ISSN 1677-5538

INTERNATIONAL BRAZ J UROL

OFFICIAL JOURNAL OF THE BRAZILIAN SOCIETY OF UROLOGY
VOLUME 42, NUMBER 4, JULY – AUGUST, 2016

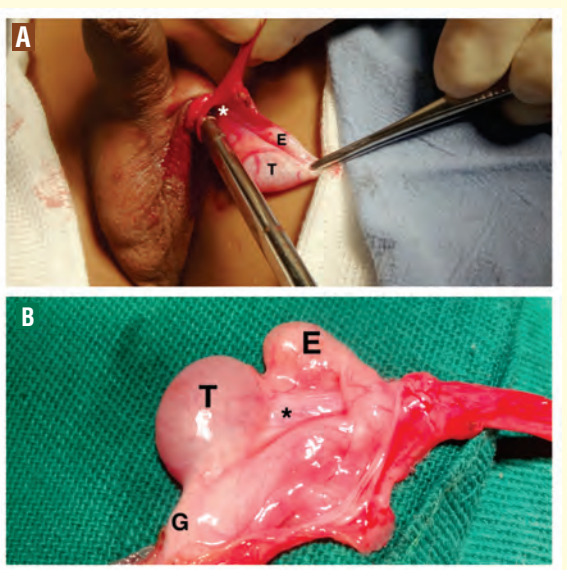

Figure 1 - Anatomic anomalies in retractile testis. A) Patient with 3 years-old with retractile testis presents complete patency of processus vaginalis (*). We can observe the surgical instrument inside the processus vaginalis. T=Testis and E=Epididymis. B) Patient with 9 years-old with retractile testis presents the epididymis attached to the testis only at the head. T = Testis; E = Epididymis; G = Gubernaculum and *Mesorquium. (Page 807)

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The paper on which the International Braz J Urol is printed meets the requirements of ANSI/NISO Z39, 48-1992 (Permanence of Paper). Printed on acid-free paper.
The International Braz J Urol is partially supported by the Ministry of Science and Technology. National Council for Scientific and Technological Development.

Editorial and Graphic Composition
DRQ Gráfica e Editora Ltd.

CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico

CAPES

The International Braz J Urol, ISSN: 1677-5538 (printed version) and ISSN: 1677-6119 (electronic version) is the Official Journal of the Brazilian Society of Urology–SBU, has a circulation of 6,000 copies per issue and is published 6 times a year (bimonthly, starting in January - February).
The issue date is up to 2 weeks after the month of issuefor the hard copy and up to 1 week after the month of issue for the electronic version.

The International Braz J Urol is indexed by: EMBASE/Excerpta Medica; SciELO, Lilacs/Latin America Index; Free Medical Journals; MD-Linx; Catálogo Latindex; SCImago, Index Medicus - NLM, PubMed/MEDLINE, ISI - Current Contents / Clinical Medicine and Science Citation Index Expanded.

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Volume 42 | number 4 | July . August, 2016 | INT BRAZ J UROL
doi: 10.1590/S1677-5538.IBJU.2016.04.01

Open retropubic prostatectomy for large prostates (Millin Surgery): Why not? It is safe! It is rapid! Complications are few and the learning curve is short!

The July-August 2016 issue of the International Braz J Urol presents original contributions with a lot of interesting papers in different fields: Urinary Incontinence, Pyelonephritis, Bladder Cancer, BPH, Prostate Cancer, Renal stones, Renal Cell Carcinoma, Uroginecology, Pediatric Urology and basic research. The papers come from many different countries such as Brazil, USA, Turkey, Italy, Israel, India, China, Iran, Thailand, Egypt, Korea and Colombia, and as usual the editor's comment highlights some papers. We decided to comment 3 papers about a very usual topic in urologic practice: Benign Prostatic Hyperplasia.

Doctor Kobayashi and collegues from Japan performed on page 740 an interesting study about the predictive risk factors of postoperative urinary incontinence following holmium laser enucleation (HoLEP). The authors evaluated 127 patients with benign prostatic hyperplasia who underwent HoLEP. The authors observed that a postoperative urinary incontinence (UI) occurred in 31 patients (24.4%), but it cured in 29 patients (93.5%) after a mean duration of 12 weeks. They concluded that longer enucleation time and increased blood loss were independent predictors of postoperative UI in patients who underwent HoLEP during the initial learning period.

Doctors Wei and Collegues from China performed on page 747 an interesting review study about the Bipolar transurethral enucleation and resection of the prostate (B-TUERP) versus bipolar resection of the prostate (B-TURP) for prostates larger than 60gr. The authors studied 270 BPH patients who underwent B-TUERP and 204 patients who underwent B-TURP for BPH. The authors observed that compared with the B-TURP group, the B-TUERP group had shorter operative time, postoperative bladder irrigation duration and hospital stay, a greater amount of resected prostatic tissue, less postoperative hemoglobin decrease, better postoperative IPSS and Qmax, as well as lower incidences of hyponatremia, urinary sepsis, blood transfusion requirement, urine incontinence and reoperation.

Doctor Pearce and collegues from USA performed on page 757 an interesting study about the Thulium vapoenucleation of large prostates. The authors studied 25 men underwent Thu-VEP, all with prostate volume >75mL. The authors shows that there were 2 intraoperative complications (8%), both cystotomies related to morcellation; Nine patients (36%) experienced a complication, all within 30 days; there were no Clavien III complications. Significant improvements were seen in Qmax, PVR, IPSS, and QoL score at each time interval to 12-months following surgery (all $p<0.05$). Of 21 patients initially in retention, all were voiding at last follow-up.

The 3 papers that we comment above are very interesting and relevant. I'm a urologist for a developed country and we do not have the same facility to achieve new

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technologies. I loved the new technologies, but in some cases we need to make some questions. The open retropubic adenomectomy (Millin surgery) is safe, rapid, cheap and had a faster learning curve. In this surgery the transfusion rate 6 %, operation duration is about 88 min., Foley catheterization duration 3.8 days, clinical results at 3 months were: IPSS decrease from 25 to 5 points, quality of life score decrease from 5 to 0.7 points, Qmax increase from 6.5 to 22 mL/sec, PRV decrease from 115 to 7.5 mL (1). In a elegant systematic review, Lucca and collegues shows that in the new techniques for BPH the length of catheter use and estimated blood loss were significantly lower, while the duration of operation was longer than in open prostatectomy (2). In a interesting metaanalysis Li and Collegues shows that the duration of operation was longer for Endoscopic prostatectomy (EP) compared with Open prostatectomy (OP). The resected tissue weight and decrease in hemoglobin were less with EP. EP was associated with fewer blood transfusions. There were no significant differences between EP and OP when comparing other complications (3).

The most important point in the papers about BPH in this number is the postoperative urinary incontinence (UI) that occurred in 24.4% of the cases, with a mean duration of 12 weeks! This is a problem for the patient. This complication do not occur with this frequency during the learnig curve of the Millin surgery. We need to think about the open surgery for large prostates.

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DIFFERENCE OF OPINION

Vol. 42 (4): 637-639, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2016.04.02

Are syntetic slings safe?

Opinion: Yes

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Keywords: Suburethral Slings; Surgical Mesh; Pelvic Floor; Prolapse

Nowadays, synthetic meshes are widely used in reconstructive surgeries of the pelvic floor. However, since the publication of the FDA warning about associated complications in 2011 (1), several discussions and contrary opinions have been published about its usefulness. The fear of court lawsuits related to side effects, common in some settings, has contributed to the widening of global discussion.

Doubtless, these slings are associated to specific complications, such as exposition and erosion, and impact on sexual performance of treated patients. However, the big question is: is the use of meshes in pelvic surgery always problematic?

a) The use of mesh to treat prolapses is equal to its use in stress urinary incontinence?

b) Is the use of these slings in the correction of prolapses of different grades and positions the same?

In other words, is it possible to expand the complications rates from one indication to others, and vice-versa?

When we evaluate the history of the use of slings in reconstructive surgery of the pelvic floor, this reasoning of generalization was used since the beginning. Slings were introduced as a minimal invasive procedure without the need of incisions to reach healthy tissues, with good results and low rate of complications at long follow up. The use of meshes was widened to include the treatment of pelvic prolapses with a valid theoretic reasoning that conventional surgeries showed high rates of recurrence (2). This fact corresponded to the beginning of use of the same materials in large scale.

Urologists and gynecologists started to progressively employ these meshes frequently with low training. After some years, the complications emerged. Publication of results of the use of meshes in the treatment of pelvic prolapses by several authors justified the positioning of FDA (1).

In that document, the agency cited 10% of exposition/erosion of meshes in patients treated for pelvic prolapses inserting the mesh vaginally after 12 months of surgery (3). However, in some studies, this rate was even higher, reaching almost 33% (4).

On the other hand, the incidence of erosion/exposition of mesh in the abdominal correction of prolapses is inferior, around 4%, in a follow up of 23 months (5), implying that the access way and not only the use of meshes is related to the high level of observed complications.

Equally, erosion rate of midurethral slings is 2%, according to FDA. Only 3 to 5% of patients evaluated by the TOMUS trial presented complications related to meshes in a follow up of 24 months (6).

In relation to sexual performance, 6.2% of women submitted to sling surgery presented dyspareunia, in a 3 year-follow up study (7). After treatment of prolapses via vaginal appliance of meshes, dyspareunia was referred by 24.4% of patients (8), emphasizing again different rates of the same disturbance according to different indications of their use.

Many of the complications related to the use of slings are not related to where they are applied. Pain, dyspareunia, recurrence, urinary infection and hematomas are also observed in conventional vaginal surgeries with native tissue. This fact was also stressed by SUFU in relation to the FDA warning (9).

In a comparative study, Nieminem et al showed a lower rate of dyspareunia in patients submitted to correction of prolapse with mesh, when compared to women submitted to conventional treatment (10). They confirmed that this complain is not exclusive of women treated with synthetic slings.

Therefore, should we make the same old mistake and generalize indications and side effects of prolapse correction and retrograde slings as was for the initial indications?

We don't think so, and other expert groups also endorse this position. American Urogynecologic Society (AUS) defended FDA positioning, but restricted it only to the use of meshes for correction of prolapses via vagina. AUS reinforced that such arguments should not be applied to slings or to the use of meshes via abdominal for the correction of prolapses (11).

Midurethral synthetic slings are still the gold standard technique for the treatment of stress urinary incontinence in women. EAU recommends them as first choice for non-complicated stress urinary incontinence in women (12). AUA guidelines describe the use of synthetic slings as an option for the treatment of stress urinary incontinence and recommends the discussion of specific complications with the patients as well as the benefits of quick recovery (13).

Therefore, in our point of view, it is equivocal to condemn in general the use of midurethral slings via vagina. General fear should not mask reality, the years of experience and published data.

As physicians, we should endorse the best available evidences. Although the significant number of complications related to the treatment of prolapses justify precaution, slings should be viewed as good alternatives, with acceptable side effects, inferior to those observed with the use of meshes via vagina to correct prolapses.

According to good practice standards, we should guide and obtain signed consent of the patients, similar to any surgical procedure involving the use of prosthesis, reinforcing that side effects are specific for this kind of treatment.

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DIFFERENCE OF OPINION

Vol. 42 (4): 640-644, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2016.04.03

Are syntetic slings safe?

Opinion: No

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Keywords: Suburethral Slings; Surgical Mesh; Pelvic Floor; Prolapse

Urinary incontinence is a highly prevalent condition affecting up to half of all women, most of whom have a component of stress urinary incontinence (SUI) (1). Approximately 10% of these women will undergo surgical treatment. While for decades the standard of care was the Burch colposuspension or autologous fascial pubovaginal sling, rapid advances in the development of augmented polypropylene products (APM) for medical use led to the widespread adoption of synthetic midurethral slings (SMUS) for the treatment of SUI.

SMUS are now the standard of care and the most commonly performed procedure for the treatment of SUI worldwide. Multiple level one randomized trials have demonstrated equivalent outcomes for SMUS to Burch colposuspension and autologous fascial slings (2). In addition to their ease of use, SMUS provide faster operative times, reduced post-operative morbidity, faster resumption of normal activity, and reduced cost (3). Patient satisfaction with the procedures has been quite high (4) with comparable durability to the older techniques.

As seen for slings, the adoption of APM products for the treatment of pelvic organ prolapse (POP) gained rapid acceptance due to perceived safety, efficacy, and durability. With increasing use, however, a growing number of severe complications came to light, prompting the FDA to release its first black box warning in 2008 (5). Such concerns continue to grow; after an expanded warning reissued in 2011 (6), the past year has seen the FDA upgrade of transvaginal mesh for the treatment of POP to a class III ("high-risk") device (7).

Transvaginally-placed mesh used in the treatment of incontinence, however, remains exempt from these warnings, despite the fact that more than half of the tens of thousands of lawsuits brought against mesh manufacturers have been from patients implanted with retropubic or transobturator SMUS (8). Of the nearly one thousand patients seen at our center over the past five years for transvaginal mesh complications, 77% (n=747) were related to SMUS placement. The last FDA safety communication from 2011 notes that almost half of the Medical Device Reports (MDRs) for urogynecological meshes in the Manufacturer and User Device Experience (MAUDE) database were associated

with SUI repairs, stating that the "FDA continues to evaluate the effects of using surgical mesh for the treatment of SUI and will report about that usage at a later date" (6).

All procedures have potential complications; any time we take scalpel to skin, the conceivable outcomes range from success to death. Risk denotes the possible range of negative outcomes following an intervention, while benefit details the potential positive outcomes to the patient. In contrast, an assessment of safety and efficacy require an understanding not just of the frequency with which these risks and benefits occur, but of their severity. Both of these are lacking for SMUS.

Multiple studies have detailed a wide range of complications after SMUS placement; this report is not meant to be an inclusive description of all the potential complications associated with SMUS placement, but instead seeks to highlight some of the limitations in the dialogue regarding SMUS complications. The common complications of clinical significance after SMUS placement include vaginal mesh extrusion, vaginal scarring/stenosis, urethral and bladder perforation, voiding dysfunction, de novo urgency and urge incontinence, recurrent infections, vaginal bleeding, dyspareunia, and chronic pain, which have been discussed in multiple comprehensive reviews (9) and studies (10). Instead, we will focus on a discussion of chronic pain as a representative example of this class of complications.

Chronic pain is probably one of the most neglected, yet prevalent complications after SMUS. Indeed, many studies only assessed pain at a single early time point in follow-up, frequently at 6 weeks after surgery. Those studies that did address chronic pain report incidences ranging from 0-31% (9); the highly variable methodologies and follow-up intervals make a comparison of these studies challenging. The Cochrane review reports an overall risk of chronic groin pain of 4.5% (2), but does not comprehensively address other sites of pain that can be affected after SMUS. It is also important to remember that the reported rates of success and adverse events frequently do not incorporate these types of complications at all. The continent patient with refractory, debilitating chronic pain developing more than one year after placement is typically considered a treatment success by multiple measures in the vast majority of clinical trials. The treatment of these patients is challenging and frustrating for both the patient and provider. No recommendations or treatment algorithms exist to guide treatment; so, many women will attempt myriad treatments before finally seeking partial or complete mesh excision. Pain is one of the most common indications for mesh removal, particularly for transobturator slings (11, 12). Even with excision, approximately one-quarter of these patients will not improve or will even worsen (13), living with constant, debilitating pain.

Compelling evidence (9, 14) suggests that the numbers of complications from SMUS are underreported, due to variability in outcome assessment methodology, reporting biases, and lack of long-term follow-up. Despite this underestimation, Blaivas et al. (9) estimate that at least one in ten (15.3%) women undergoing placement of a SMUS will experience a serious adverse event or surgical failure. A recent 5-year trial of women undergoing SMUS for SUI reported a much higher number of almost 25% (10), suggesting serious complications after SMUS are not rare.

More importantly, our understanding of the severity of complications and their impact on patient quality of life is drastically limited. A wide range of complications, such as recurrent cystitis, voiding dysfunction, de novo urgency and urge incontinence, neurologic symptoms, and chronic pain, are frequently trivialized in prospective studies as short-lived or controllable with expectant management. These studies, however, lack any long-term follow-up or quantitative assessment to support such dismissive claims. In a qualitative assessment of women with vaginal mesh complications, Dunn et al. (15) describe the degraded emotional and physical health of patients with these types of complications, particularly chronic pain. These women describe significant shame, hopelessness, regret, frustration, and anxiety impacting their personal relationships, self-image, and personal and professional productivity. In support of their findings, our anecdotal experience with over 1500 patients presenting with transvaginal mesh complications underscores the physical and psychosocial toll and the treatment-refractory nature of these complications on a subset of these patients.

The FDA states that "the safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to 1 year" (6). Recent reports indicate that many of the refractory complications of SMUS do not present until years after placement. In a recent prospective trial (10), one-quarter of all women experienced significant adverse outcomes by five years after SMUS placement; almost 20% of all women who underwent SMUS were impacted by chronic pain. Multiple retrospective reviews reveal that the majority of these complications, especially pain, overwhelmingly develop more than a year after placement (11, 16). In our series of 747 women, 61% described refractory pain symptoms; of those, the average time to presentation was greater than three years after the initial surgery. Yet in the recent updated Cochrane review, only four of the 84 included trials addressed SMUS outcomes after one year (2), meaning that determinations regarding the safety of SMUS are being made using data with only months of follow-up, which may have limited clinical relevance.

The vast majority of commercially-available SMUS use polypropylene, a substance widely used in medical implants and surgical sutures with good tolerability (17). Despite this record, data increasingly suggest that there may be something unique to transvaginal surgery that alters the risk profile of mesh implants, resulting in greater risk of complications. The vagina cannot be completely sterilized by surgical preparation (18); thus, SMUS are placed through a contaminated field. While others have observed subclinical mesh infection in patients with chronic complications (19), our preliminary studies (20) have observed the enrichment in pathogenic bacterial species of SMUS in patients with chronic pain, while sling meshes removed for urinary retention lack this colonization. These patients also exhibit a macrophage--predominant peri-mesh inflammation that again is lacking from patients with urinary retention. This correlation implicates contamination of the SMUS surface during placement in the etiology of chronic pain and explains the unique complications after transvaginal surgery.

The serious complications of transvaginal POP mesh are well recognized. Logically, it is difficult to accept that a similar composition mesh implanted a few centimeters distally would be completely insusceptible to these devastating complications. It is more plausible that the increased rates of complications with POP meshes over those seen for SMUS may reflect the larger amount of mesh. Lighter weight meshes are better tolerated than the older thicker grafts (19); thus SMUS may be better tolerated than POP mesh simply due to the smaller volume of mesh used.

As physicians, we must come back to the principal precepts of bioethics: autonomy, justice, beneficence, and non-maleficence. Non-maleficence, often popularized by the phrase "first, do no harm", purports it may be better not to do something if it risks causing more harm than good. Incontinence is a disease affecting quality of life; any treatment we prescribe should improve that quality. We must have the discussion as a discipline about whether even low incidences of severe, debilitating complications are reasonable for patients with a non-life-threatening illness, especially when equivalent, lower-risk alternatives exist.

The American Urogynecologic Society (AUGS) and the Society for Urodynamics, Female Pelvic medicine and Urogenital Reconstruction (SUFU), published a joint position statement supporting the continued use of SMUS for the treatment of SUI. This report does not intend to challenge those conclusions. We do not pursue a ban on the use of synthetic mesh for incontinence surgery; millions of patients have benefitted tremendously from its use. We seek only to highlight the limitations of our current knowledge and expand the debate regarding mesh-augmented procedures in SUI management. Even with conservative estimates, several percent of patients receiving SMUS may have devastating, irreversible complications that drastically alter their lives. We must consider whether the improvements in perioperative morbidity and recovery for SMUS over the older Burch colposuspension and autologous fascial sling procedures are justifiable in the face of these serious adverse events. If the answer is affirmative, our shaping of pre-operative expectations must reflect the seriousness of these possible poor outcomes.

While slings have been extensively studied over decades, we may not have been asking several vital questions defining long-term satisfaction, success, and adverse events. There is not as yet adequate data to address this knowledge gap; we must

perform long-term prospective studies to define the nature and severity of the range of complications following SMUS and determine how these newer techniques measure up against historical standards. Without complete data, we have allowed the scientific debate to be determined by the legal system, devolving medical practice into litigious mudslinging.

Perceived treatment failure on the part of the patient has less to do with objective or even subjective symptomatic improvement and more to do with the patient's expectations of outcomes. If we frame SMUS surgery as a quick fix for everyone with few side effects, we may continue to see a growing divide between physicians and patients and continue to contribute to the emotional and psychological devastation these patients experience.

It is hard to remember that there is a low risk of debilitating pelvic pain when you are the one affected. While slings may be effective for most patients, the past decade has seen the evolution of high-volume tertiary referral centers specializing in the treatment of mesh complications. Patients have self-organized into advocacy and support groups and have even created their own registries of complications; all of which suggests that the medical profession has failed to adequately address and acknowledge these patients' experiences. As a community we must take this public outcry seriously, acknowledge our lack of insight into these complications, and pursue a deeper understanding of the pathophysiology of poor outcomes after SMUS.

Like all new technologies, the SMUS is not perfect. But it has been beneficial to large numbers of women, restoring their ability to function in society without incontinence. The recognition, comprehensive characterization, and deeper understanding of the many complications after SMUS could lead to the development of better, lower risk implants with better durability for all patients. We owe it to them.

ABBREVIATIONS

APM = Augmented Polypropylene Mesh
AUGS = American Urogynecologic Society
FDA = Food and Drug Administration
MDR = Medical Device Reports
MAUDE = Manufacturer and User Device Experience
POP = Pelvic Organ Prolapse
SMUS = Synthetic Mid-Urethral Sling
SUFU = Society for Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction
SUI = Stress Urinary Incontinence

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REVIEW ARTICLE

Vol. 42 (4): 645-654, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0696

Semi-rigid ureteroscopic lithotripsy versus laparoscopic ureterolithotomy for large upper ureteral stones: a meta - analysis of randomized controlled trials

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ABSTRACT

Introduction: To provide a systematic review and meta-analysis of randomized controlled trials (RCT) comparing semi-rigid ureteroscopic lithotripsy (URS) with laparoscopic ureterolithotomy (LU) for the treatment of the large proximal ureteral stone.

Materials and methods: A systematic literature review was performed in June 2015 using the PubMed, Scopus, and Web of Science databases to identify relevant studies. Article selection proceeded according to the search strategy based on Preferred Reporting Items for Systematic Reviews and Meta-analysis criteria.

Results: Six RCT including 646 patients were analyzed, 325 URS cases (50.3%) and 321 LU cases (49.7%). URS provided a significantly shorter operative time (weighted mean difference [WMD] = -31.26 min; 95%CI -46.88 to -15.64; p<0.0001) and length of hospital stay (WMD = -1.48 days; 95%CI -2.78 to -0.18; p=0.03) than LU. There were no significant differences in terms of overall complications (OR = 0.78; 95%CI 0.21-2.92; p=0.71) and major complications – Clavien ≥3 – (OR = 1.79; 95%CI 0.59-5.42; p=0.30). LU led to a significantly higher initial stone-free rate (OR = 8.65; 95%CI 4.18-17.91; p<0.00001) and final stone-free rate (OR = 6.41; 95%CI 2.24-18.32; p=0.0005) than URS. There was a significantly higher need for auxiliary procedures in URS cases (OR = 6.58; 95%CI 3.42-12.68; p<0.00001).

Conclusions: Outcomes with LU for larger proximal ureteral calculi are favorable compared to semi-rigid URS and should be considered as a first-line alternative if flexible ureteroscopy is not available. Utilization of flexible ureteroscopy in conjunction with semi-rigid ureteroscopy may impact these outcomes, and deserves further systematic evaluation.

ARTICLE INFO

Keywords:
Laparoscopy; Lithotripsy; Ureter; Ureteroscopy; Urinary Calculi

Int Braz J Urol. 2016; 42: 645-54

Submitted for publication:
December 04, 2015

Accepted after revision:
January 19, 2016

INTRODUCTION

Ureteral stones may cause severe pain, lead to hydronephrosis and/or urinary tract infection, and ultimately may be the reason for renal function loss (1). Although small distal ureteral stones most commonly spontaneously pass through the ureter into the bladder, large proximal ureteral stones (>10mm) can take more than 2 - 3 weeks to pass all the way (2, 3). In a worst scenario, these stones can get impacted in the ureter, requiring surgical intervention.

Medical expulsive therapy using alpha--blockers (i.e. tamsulosin, alfuzosin) or calcium

channel blockers (i.e. nifedipine) have been used for several years in the treatment of patients suffering from ureteral stone, reportedly resulting in a higher stone-free rate and a shorter time to stone expulsion when compared to placebo (4, 5). However, a recent multicenter, randomized, placebo-controlled trial has demonstrated different outcomes and questioned the role of medical expulsive therapy (6).

Thus, surgical intervention may be the best alternative for patients with refractory pain to analgesics, and early intervention may be considered for large proximal calculi that are unlikely to pass spontaneously. Although there is consensus that ureteroscopy is the most efficient treatment for patients with distal ureteral stones, there is a debate regarding large proximal ureteral stones (7, 8). AUA (American Urological Association) and EAU (European Association of Urology) have recommended ureteroscopic lithotripsy (URS) or shockwave lithotripsy (SWL) as first option, although percutaneous nephrolithotomy (PCNL) and laparoscopic ureterolithotomy (LU) may be suitable (3, 7-9).

Currently, there is a clear tendency of less SWL and more URS in the treatment of patient with urinary stones, even in developing countries (10). As flexible ureteroscopies are not available in all services, semi-rigid ureteroscopy has been used for treatment of ureteral stones in all locations, even for those in the proximal ureter. PCNL is a procedure with inherent high-risk of surgical complications, whereas LU has gained some popularity (11). Based on these concepts, in this meta-analysis we aimed to compare the outcomes from URS with those from LU for management of large proximal ureteral stones.

MATERIAL AND METHODS

Evidence acquisition - Literature search and study selection

A systematic literature review was performed in June 2015 using PubMed, Scopus, and Web of Science databases to identify relevant studies. Searches were restricted to publications in English and in the adult population. Separate searches were done with the following search terms: laparoscopic ureterolithotomy, ureteroscopy, ureterolithotripsy, ureterolithotomy. Article selection proceeded according to the search strategy based on Preferred Reporting Items for Systematic Reviews and Meta-analysis criteria (www.prismastatement.org) (Figure-1). Only studies comparing URS and LU were included for further screening. Only randomized controlled trials (RCT) were selected and included in the study. There is only one RCT comparing flexible ureteroscopy with laparoscopy (12), therefore the study focused on semi-rigid ureteroscopy. Cited references from the selected articles retrieved in the search were also assessed for significant papers. Conference abstracts were not included because sufficient detail for the study is not available in an abstract. Two independent reviewers completed this process, and all disagreements were resolved by their consensus.

Study quality assessment

The level of evidence was rated for each included study according to the criteria provided by the Center for Evidence-Based Medicine in Oxford, UK (13). The methodological quality of RCT was assessed using the Jadad scale, which goes from 0 to 5 points (14).

Statistical analysis

A meta-analysis was performed to assess the overall outcomes of URS compared with LU. Extracted data for the analysis included operative time, length of hospital stay, need for auxiliary procedures, and postoperative complication and stone-free rates. Complications were scored according Clavien classification (15). Residual fragments or stone migration during URS or LU were not considered as complications, because these findings were evaluated by the stone-free rate. Initial stone-free rate was evaluated immediately after surgery, whereas final stone-free rate was evaluated after auxiliary procedures or spontaneous passage at least 3 weeks (3 weeks to 1 year) after the first procedure. Odds ratio (OR) was used for binary variables, and mean difference or standardized mean difference was used for the continuous parameters. For studies presenting continuous data as means and range, standard de-

viations were calculated using the methodology described by Hozo and associates (16). Pooled estimates were calculated with the fixed-effect model (Mantel-Haenszel method) if no significant heterogeneity was detected; otherwise, the random--effect model (Der Simonian-Laird method) was used. The pooled effects were determined by the z test, and $p<0.05$ was considered statistically significant. The Cochrane chi-square test and inconsistency (I^2) were used to evaluate the heterogeneity among studies. Data analysis was performed with Review Manager software (RevMan v.5.1, Cochrane Collaboration, Oxford, UK).

RESULTS

Evidence synthesis - Study characteristics

Six RCT including 646 patients were selected for the analysis, 325 URS cases (50.3%) and 321 LU cases (49.7%) Table-1 (17-22). There were no differences regarding age (40.9 vs. 41.0 years, respectively), gender (61.2% vs. 62.5% male, respectively), stone size (13.6 vs. 18.2mm, respectively) and laterality of the procedure (49.7% vs. 52.4%, respectively) between the groups. The methodological quality of included studies was medium, as they scored 2 of 5 points (17, 19, 20, 22) or 3 of 5 points (18, 21) in Jadad scale; as surgical blinded studies are hard to be conducted, two points of Jadad scale were lost in all studies (Table-2).

URS and LU were indicated for large, >10mm, proximal ureteral stone in all studies. Most of the studies performed semi-rigid URS with laser as energy source (17, 19-22), although pneumatic lithotripsy was done in two studies (17, 18). LU was performed through retroperitoneal access in 3 studies (19, 20, 22), transperitoneal access in 2 studies (17, 21), or both in 1 study (18). Double J stent was routinely left in all patients regardless the surgical approach in most of studies (19-22). In only two studies double J stent was placed according to surgeon description (17, 18). Postoperative imaging exam as control for residual stones was

Figure 1 - Preferred Reporting Items for Systematic Reviews and Meta-analysis flow of study selection.

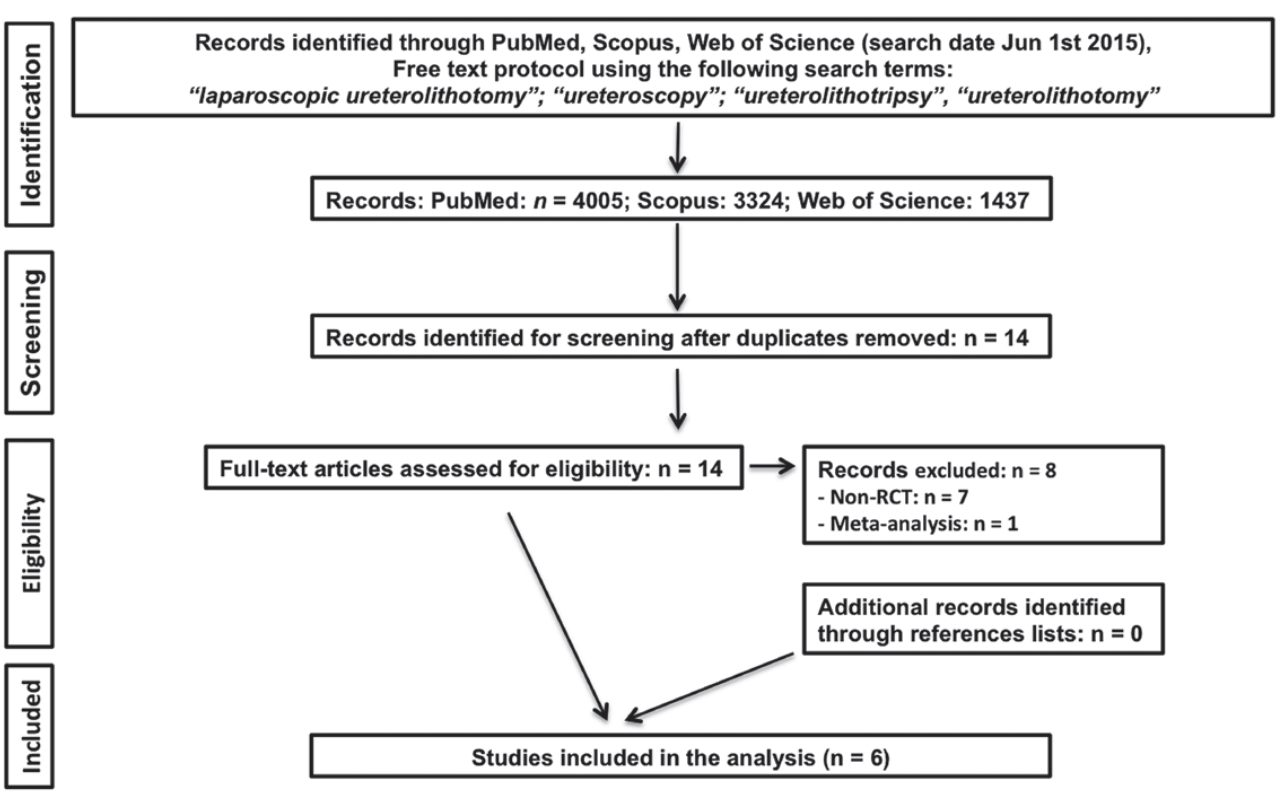


Table 1 - Demographic data.

	URS	LU	p-value
Number of cases (n)	325	321	-
Age (mean, ± SD)	40.9 ± 5.1	41.0 ± 4.7	0.936
Gender (male, %)	61.20%	62.60%	0.746
Stone size (mean, ± SD)	13.6 ± 7.8	18.2 ± 4.2	0.298
Side (right, %)	49.70%	52.40%	0.604

URS = ureteroscopic lithotripsy; **LU** = laparoscopic ureterolithotomy; **SD** = standard deviation

Table 2 - Ureteroscopic lithotripsy versus laparoscopic ureterolithotomy: summary data of randomized controlled trials.

Study	N of cases		Study period	Study Design	Level of evidence	Inclusion criteria (stone size)	Energy source of URS	LU access	Control imaging exam	Quality score*
	URS	LU								
Basiri et al.	50	50	2004 - 2006	RCT	2b	≥15 mm	Pneumatic or laser	Transperitoneal	KUB and USG	2
Lopes Neto et al.	16	15	2008 - 2010	RCT	2b	≥10 mm	Pneumatic	10 trans and 5 retroperitoneal	KUB or CT	3
Fang et al.	25	25	2008 - 2010	RCT	2b	≥10 mm	Laser	Retroperitoneal	KUB	2
Shao et al.	139	136	2009 - 2013	RCT	2b	≥12 mm	Laser	Retroperitoneal	NA	2
Kumar et al.	50	50	2010 - 2012	RCT	2b	≥ 20mm	Laser	Transperitoneal	CT	3
Liu et al.	45	45	2011 - 2013	RCT	2b	NA	Laser	Retroperitoneal	KUB	2

URS = ureteroscopic lithotripsy; **LU** = laparoscopic ureterolithotomy; **RCT** = Randomized controlled trial; **NA** = not available; **KUB** = kidney, ureteral and bladder x-ray; **USG** = ultrasound; **CT** = computed tomography
*Jadad Quality Scale for RCT studies (score from 0 to 5)

different among the studies: KUB plus ultrasound was done in 1 study (17), only KUB was done in 2 studies (19, 20), KUB or computed tomography (CT) scan was done in 1 study, while CT scan alone was done in 1 study (21). One study did not report the imaging exam used after the procedure to assess stone fragments (22) (Table-2). Stone-free was considered as absence of residual fragments in 3 studies (17-19), residual fragments ≤3 in 2 studies (20, 21) and it was not clear in 1 study (22).

Tables-3 and 4 summarize the outcomes of each study included in this meta-analysis.

Outcomes

URS provided a significantly shorter operative time (weighted mean difference [WMD] = -31.26 min; 95% CI-46.88 to -15.64; p<0.0001) and length of hospital stay (WMD = -1.48 days; 95% CI-2.78 to -0.18; p=0.03) than LU (Figures 2 and 3, respectively). There were no significant

Table 3 - Outcomes: operative time, length of hospital stay, and complications.

Study	Operative time (min)		LOS (days)		Complications (n)		Minor Complications (n)		Major Complications (n)*		LU conversions to open
	URS	LU	URS	LU	URS	LU	URS	LU	URS	LU	
Basiri et al.	42.7 ± 17.9	127.8 ± 41.8	0.53 ± 0.12	5.8 ± 2.3	0	11	0	8	0	3	2
Lopes Neto et al.	72.8 ± 42.0	215.0 ± 89.0	1.15 ± 0.55	3.15 ± 1.43	3	0	2	0	1	0	1
Fang et al.	49.0 ± 8.0	41.8 ± 8.0	2.8 ± 1.3	2.9 ± 0.8	0	0	0	0	0	0	0
Shao et al.	48.5 ± 7.7	65.6 ± 8.8	2.8 ± 0.6	4.9 ± 0.7	88	116	84	116	4	0	1
Kumar et al.	47.3 ± 8.2	49.1 ± 9.2	2.1 ± 0.6	2.2 ± 0.7	18	12	18	12	0	0	5
Liu et al.	61.1 ± 17.8	87.9 ± 18.3	5.1 ± 0.6	4.5 ± 0.48	5	3	3	3	2	0	0

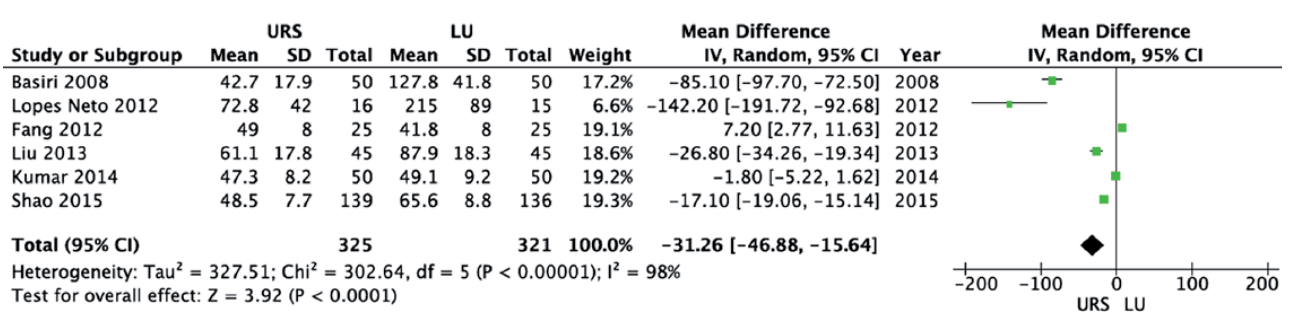
URS = ureteroscopic lithotripsy; **LU** = laparoscopic ureterolithotomy; **LOS** = length of hospital stay
* Major complication = re-operation, sepsis + intensive care unit, ureteral stenosis (Clavien ≥3)

Table 4 - Outcomes: stone-free rates and auxiliary procedures.

Study	Initial stone-free rate (n;%)		Final stone-free rate (n;%)		Auxiliary procedures (n;%)	
	URS	LU	URS	LU	URS	LU
Basiri et al.	28 (56%)	44 (88%)	38 (76%)	45 (90%)	11 (22%)	5 (10%)
Lopes Neto et al.	8 (50%)	14 (93.3%)	10 (62.5%)	14 (93.3%)	2 (12.5%)	0
Fang et al.	22 (88%)	25 (100%)	25 (100%)	25 (100%)	3 (12%)	0
Shao et al.	NA	NA	125 (89.9%)	132 (97.0%)	14 (10.3%)	4 (2.9%)
Kumar et al.	NA	NA	28 (56%)	50 (100%)	13 (26%)	0
Liu et al.	23 (51.1%)	42 (93.3%)	37 (82.2%)	45 (100%)	17 (37.8%)	0

URS = ureteroscopic lithotripsy; **LU** = laparoscopic ureterolithotomy
NA = not available

Figure 2 - Forest plot of operative time (min).



differences between URS and LU in terms of overall complications (OR = 0.78; 95% CI 0.21 to 2.92; p=0.71) and major complications – Clavien ≥3 – (OR = 1.79; 95% CI 0.59 to 5.42; p=0.30) (Figures 4 and 5, respectively) (15). Most of complications were minor; major complications were reported as re-operation, sepsis with need for intensive care unit, and ureteral stenosis. There were 8 conversions in the LU cases to open surgery due to technical difficulties.

LU led to a significantly higher initial stone-free rate (OR = 8.65; 95% CI 4.18 to 17.91; p<0.00001) and final stone-free rate (OR = 6.41; 95% CI 2.24 to 18.32; p=0.0005) than URS (Figures 6 and 7, respectively). There was a significantly higher need for auxiliary procedures in URS cases (OR = 6.58; 95% CI 3.42 to 12.68; p<0.00001) than in LU cases (Figure-8).

DISCUSSION

Interpretation of data

URS has proved to be first choice of urologists, particularly young urologists, while LU has gained some popularity in the management of stones of the upper urinary tract (24-26). These findings led us to search for the current literature available comparing URS with LU in terms of peri- and postoperative outcomes. To best of our knowledge there is no meta-analysis of RCT (level of evidence 1a) regarding this relevant issue. Though semi-rigid URS is the primary modality utilized around the world, the use of flexible URS has expanded (27). Unfortunately, only one RCT including flexible URS was identified in our search, which does not provide sufficient data for a detailed evaluation. In this study, 151 patients with ureteral stones between 1 and 2cm were ran-

Figure 3 - Forest plot of length of hospital stay (days).

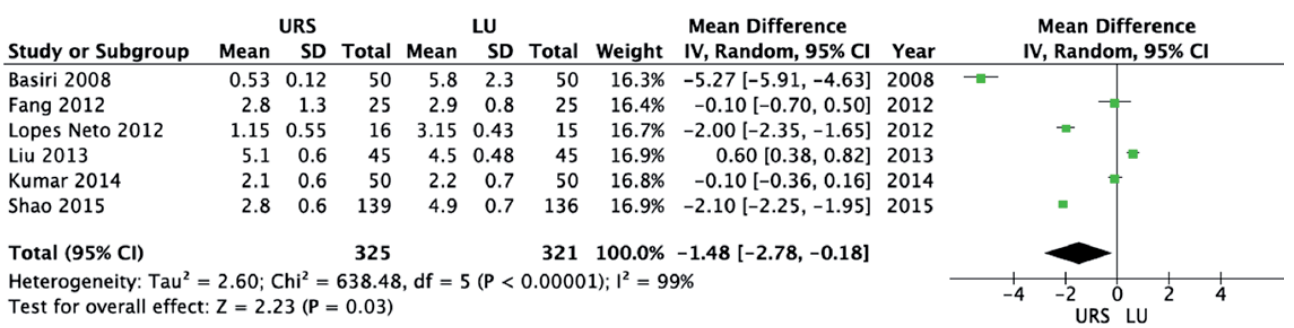


Figure 4 - Forest plot of overall postoperative complications.

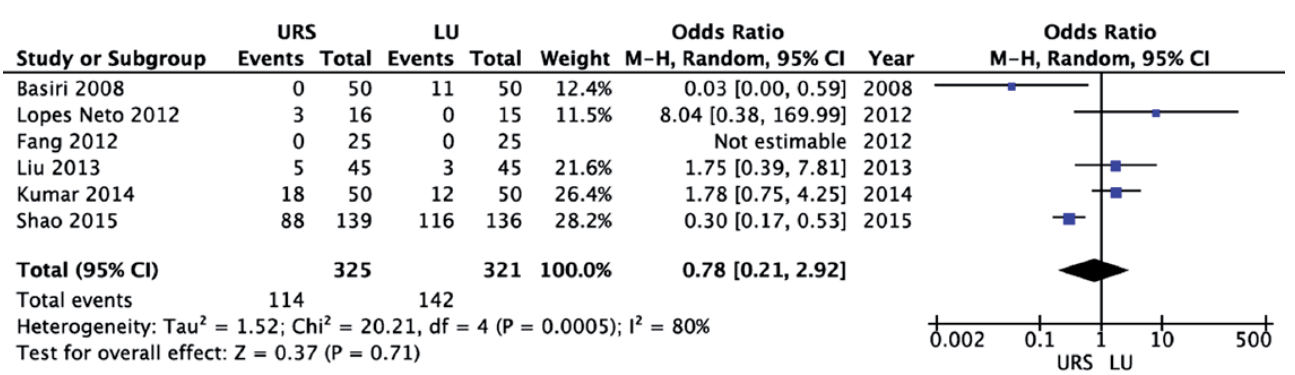


Figure 5 - Forest plot of major postoperative complications.

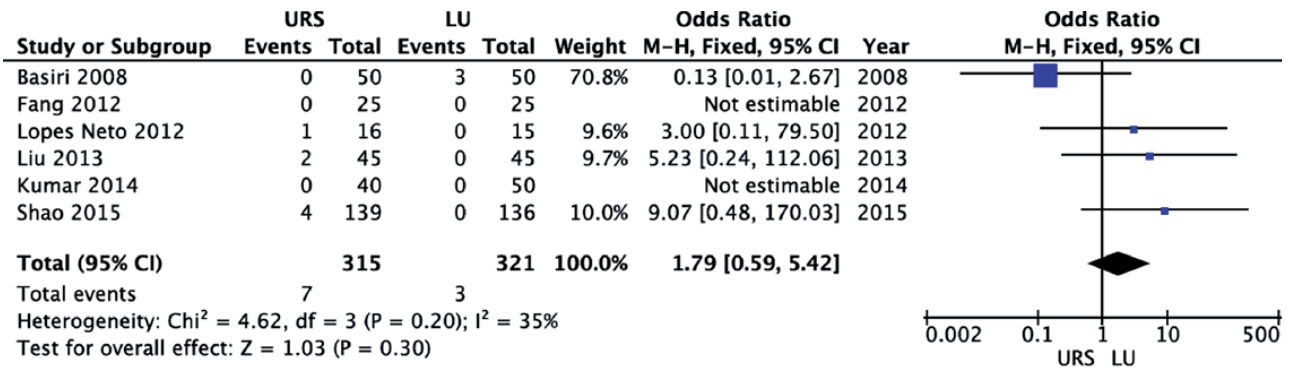


Figure 6 - Forest plot of initial stone-free rate.

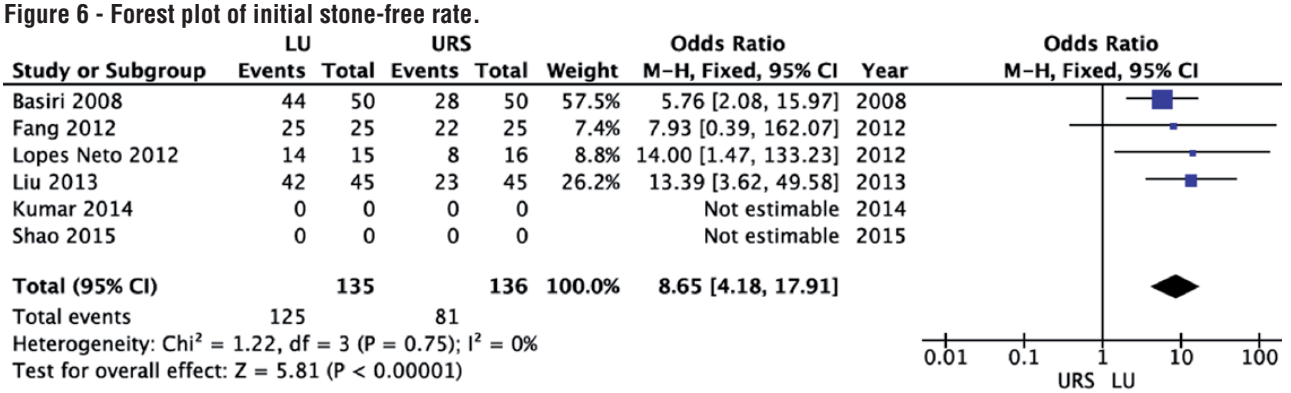
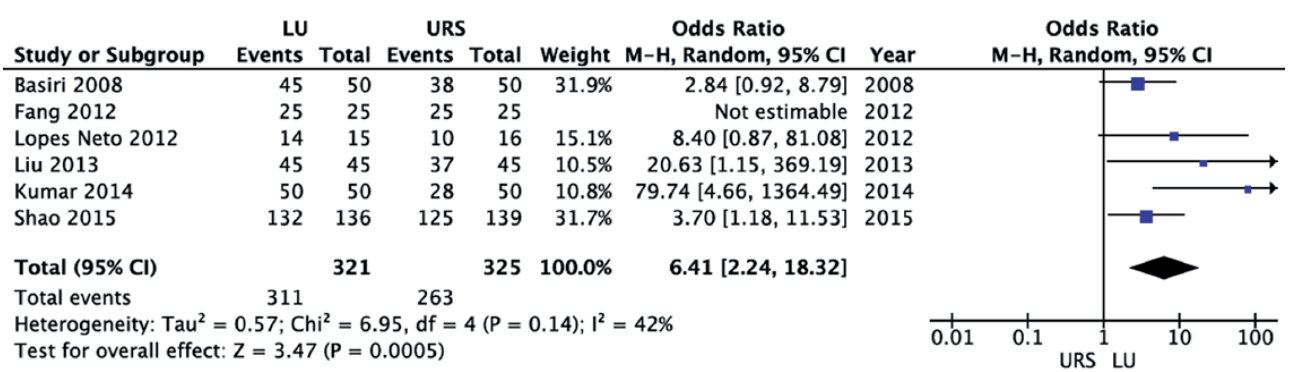


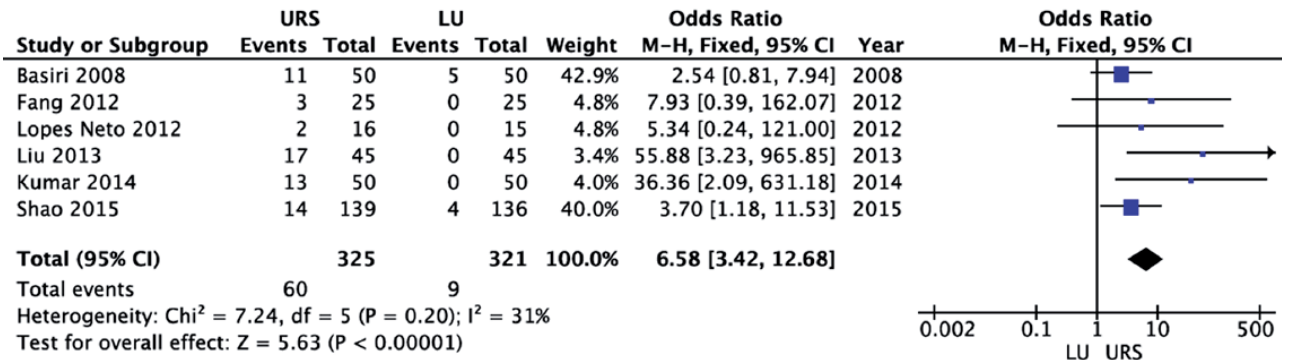
Figure 7 - Forest plot of final stone-free rate.



domized in 3 groups (52 SWL, 51 LU and 48 flexible URS). The success rates were 96%, 81% and 79% in the laparoscopy, SWL, and URS groups, respectively. The complication rates were 7.86%, 7.06%, and 4.11% in the laparoscopy, SWL, and URS groups, respectively. While the success rate was significantly higher in the laparoscopy group ($p<0.05$), the complication rate was significantly lower in the URS group ($p<0.05$) (12).

A shorter operative time with URS was reported in five of six RCT (17, 18, 20-22), which can reflect the regular practice and the familiarity of most of urologists with this procedure. In a similar way, a shorter length of hospital stay with URS was also reported in five of six RCT (17-19, 21, 22) suggesting its less invasive nature when compared to LU leads to shorter recuperation. Regarding postoperative complications, although LU

Figure 8 - Forest plot of need for auxiliary procedures.



is a more invasive procedure, the risk of complications, including severe complications (Cavien ≥3) are similar. Most of complications were mild (Clavien 1 or 2), such as pain, temporary fever, and urinary tract infection. Urinary leaking was a postoperative event described more commonly after LU, but in few cases required a surgical intervention. Major complications were rare (7 cases in the URS group and 3 cases in the LU group) and were mostly re-operation due to urinary fistula or late ureteral stenosis. These data show the low morbidity of both URS and LU procedures and probably reflect patient's characteristics, stone disease features, and surgeon's experience with URS and LU of each study. With regards to BMI impact on surgical outcomes, none study included in the meta-analysis reported and/or compared the BMI between the groups, preventing us of performing any comment about that. URS can be safely and equally performed in normal, obese, and morbid obese patients (28). To best our knowledge, there is paper no evaluating the impact of obesity / BMI on LU.

Another variable that should be taken into account when evaluating the complication rate from LU is if it was performed by transperitoneal or retroperitoneal way. There is one randomized comparison study, including 48 patients that compared transperitoneal or retroperitoneal LU. The stone-free rate was similar between the groups, however transperitoneal LU was significantly associated with more pain, ileus, and longer hospital stay than retroperitoneal LU (29). In our study, most of LU was done by retroperitoneal access (211 of 321 cases), which may have contributed for the low complication rate.

Removing the stone and relieving the pain are the main purposes of URS and LU. Initial and final stone-free rates were higher with LU in all studies, showing its high efficiency (17-22). There was a higher initial (8-fold) and final (6-fold) stone-free rate with LU. The inferiority of URS may be related to the difficulty of reaching the proximal ureter with semi-rigid scopes, as flexible ureteroscopes were not used in these RCT. Furthermore, dusting the stones can lead to stone migration to the kidney, impacting negatively on stone-free rates. Another factor that needs be taken into account is the source of energy used to stone fragmentation during URS. Two of six studies used pneumatic lithotripter instead of laser to break the stone (17, 18) which is not the gold standard and may have influenced the surgical outcomes (30, 31). However, these studies reported similar final stone-free rates when compared to the studies that utilized laser as energy source. Lastly, it is important to note that the imaging modality used to evaluate postoperative stone-free rates was not the same in all studies, varying from KUB to CT scan, which have different accuracies for residual fragments (32, 33).

The need for auxiliary procedures followed the initial stone-free rate. As it was lower with URS, auxiliary procedure had a higher indication in all studies (17-22). The most common auxiliary procedure was SWL. There was a 7-fold higher risk of need for auxiliary procedures with URS than LU.

Heterogeneity among studies was found to be high for several parameters. Difference in surgical practices, follow-up imaging exams, and outcomes definitions may explain that. Despite this heterogeneity, this meta-analysis of RCT provides strong evidence (level 1a) when comparing intra- and postoperative outcomes from URS and LU. It may help urologists when choosing between these procedures for treatment of large proximal ureteral stones, mainly young urologists that have expertise with both techniques. The main limitation of this study is that flexible ureteroscopy was not take into account, but there are few well--designed studies comparing flexible ureteroscopy to laparoscopy in the management of ureteral stones, preventing us of performing a systematic evaluation.

CONCLUSIONS

Meta-analysis of RCT suggests that LU provides a higher stone-free rate than URS in the management of large proximal ureteral stones. There are no differences regarding overall postoperative complications or major postoperative complications between the procedures. Semi-rigid URS is associated with a short operative time and length of hospital stay, however it leads to a higher need for auxiliary procedures. When counseling a patient with a large proximal ureteral stone, LU should be advised as the procedure with the higher chance of stone removal, although it is also more invasive, leading to longer operative time and length of hospital stay. Utilization of flexible ureteroscopy in conjunction with semi-rigid ureteroscopy may impact these outcomes, and deserves further systematic evaluation.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 655-662, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0608

Extraperitoneal versus transperitoneal laparoscopic radical cystectomy for selected elderly bladder cancer patients: a single center experience

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ABSTRACT

Objective: This study reports the initial experience of extraperitoneal laparoscopic radical cystectomy (ELRC) and compared with transperitoneal laparoscopic radical cystectomy (TLRC) in the treatment of selected elderly bladder cancer patients.
Patients and Methods: A total of forty male bladder cancer patients who underwent ELRC (n=19) or TLRC (n=21) with ureterocutaneostomy were investigated. Demographic parameters, perioperative variables, oncological outcomes and follow-up data were retrospectively analyzed.
Results: A significantly shorter time to exsufflation (1.5±0.7 vs 2.1±1.1 d; p=0.026) and liquid intake (1.8±0.9 vs 2.8±1.9 d; p=0.035) were observed in the ELRC group compared with the TLRC group. The incidence of postoperative ileus in the ELRC group was lower than the TLRC group (0 vs 9.5%). However, the difference had no statistical significance (p>0.05). The removed lymph node number in the ELRC group was significantly lower than the TLRC group (p<0.001). No significant differences were observed between the two groups in the overall and cancer-free survival rates (p>0.05).
Conclusions: ELRC seems to be a safe and feasible surgical strategy for the selected elderly bladder cancer patients with ≤ T2 disease. The surgical and oncological efficacy of the ELRC is similar to that of the TLRC, but with faster intestinal function recovery. Further studies with a large series including different urinary diversions are needed to confirm our results and to better evaluate the benefit of ELRC in bladder cancer patients.

ARTICLE INFO

Keywords:
Laparoscopy; Oncology; Bladder; cystectomy

Int Braz J Urol. 2016; 42: 655-62

Submitted for publication:
October 23, 2015

Accepted after revision:
January 07, 2016

INTRODUCTION

Bladder cancer is one of the most common urologic malignancies in men with an especially high incidence in the elderly patients (1). Radical cystectomy (RC) with urinary diversion is a standard surgical measure in Urology and constitutes the golden choice for muscle-invasive bladder cancer (MIBC). With the rapid advances in urological laparoscopy over the past few decades, laparoscopic radical cystectomy (LRC) has been widely used for MIBC as a minimally invasive treatment to reduce morbidity. However, in elderly patients, LRC is still a challenge due to the associated severe comorbidities and whether they can tolerate longer operation time, pneumoperitoneum, and peculiar surgical position as well as younger patients (2). Although the role of LRC in elderly patients is still debated (3, 4), some reports have shown that LRC may be performed safely in well-selected elderly patients (2, 5).

As we know, generally the LRC is performed with traditional transperitoneal approach

and the operative steps of transperitoneal laparoscopic radical cystectomy (TLRC) are basically duplicated from the open techniques. To our best knowledge, there is no report about LRC with an extraperitoneal approach by now. But with the experience of EORC and LRC, the application of extraperitoneal laparoscopic radical cystectomy (ELRC) can be available. In the present study, we describe our initial experience of ELRC and compare variables with those of TLRC done by the same surgeon in our institution.

PATIENTS AND METHODS

Patient Selection

From January 2012 to March 2015, a retrospective study of male elderly patients with MIBC or high risk NMIBC who underwent LRC was conducted in our institution. All the cases were evaluated by common preoperative examination including routine laboratory tests, abdominal ultrasonography, chest radiography, echocardiography, lung function test, computerized tomography or magnetic resonance imaging. The indication for LRC was histologically diagnosed MIBC by transurethral resection or biopsy confirmed recurrent multifocal high-grade NMIBC or bladder cancer in situ that were refractory to repeated transurethral resection with intravesical therapy. The exclusion criteria were a Body Mass Index (BMI) >30kg/m^2, American Society of Anesthesiology (ASA) >3, tumor grade >T2 and inability to provide written informed consent. Since the patients undergoing conduit diversion need the transperitoneal approach anyhow, we chose the patients who underwent ureterocutaneostomy diversion to access the safety and feasibility of ELRC. The indications for ureterocutaneostomy diversion included cases of inability to use intestinal segments due to related problems or the patient decided to undergo ureterocutaneostomy due to the decreased life expectancy with associated comorbidities. All patients had discussed the risks and benefits related to the two procedures of LRN and all kinds of urinary diversions before they made decisions. If the patient decided to undergo the LRN, the possibility of ELRC was proposed.

Study Design

Nineteen patients submitted to ELRC with ureterocutaneostomy were enrolled in the present study. For comparison purposes, twenty-one demographics-matched patients with bladder cancer of comparable tumor stage who underwent TLRC with ureterocutaneostomy were also enrolled. The two procedures were performed by a single surgeon who was proficient in both techniques. All patients gave written informed consent. The study protocol was approved by the Institutional Review Board of our hospital and was conducted in compliance with the Declaration of Helsinki.

The demographic parameters, operative variables, perioperative outcome and oncological outcomes were recorded and analyzed. Comorbidities and complications were also recorded. One day before the operation, patients were required to fast and mechanical bowel preparation with polyethylene glycol electrolye powder plus intravenous hydration and perioperative antibiotics were administered.

Statistical analysis

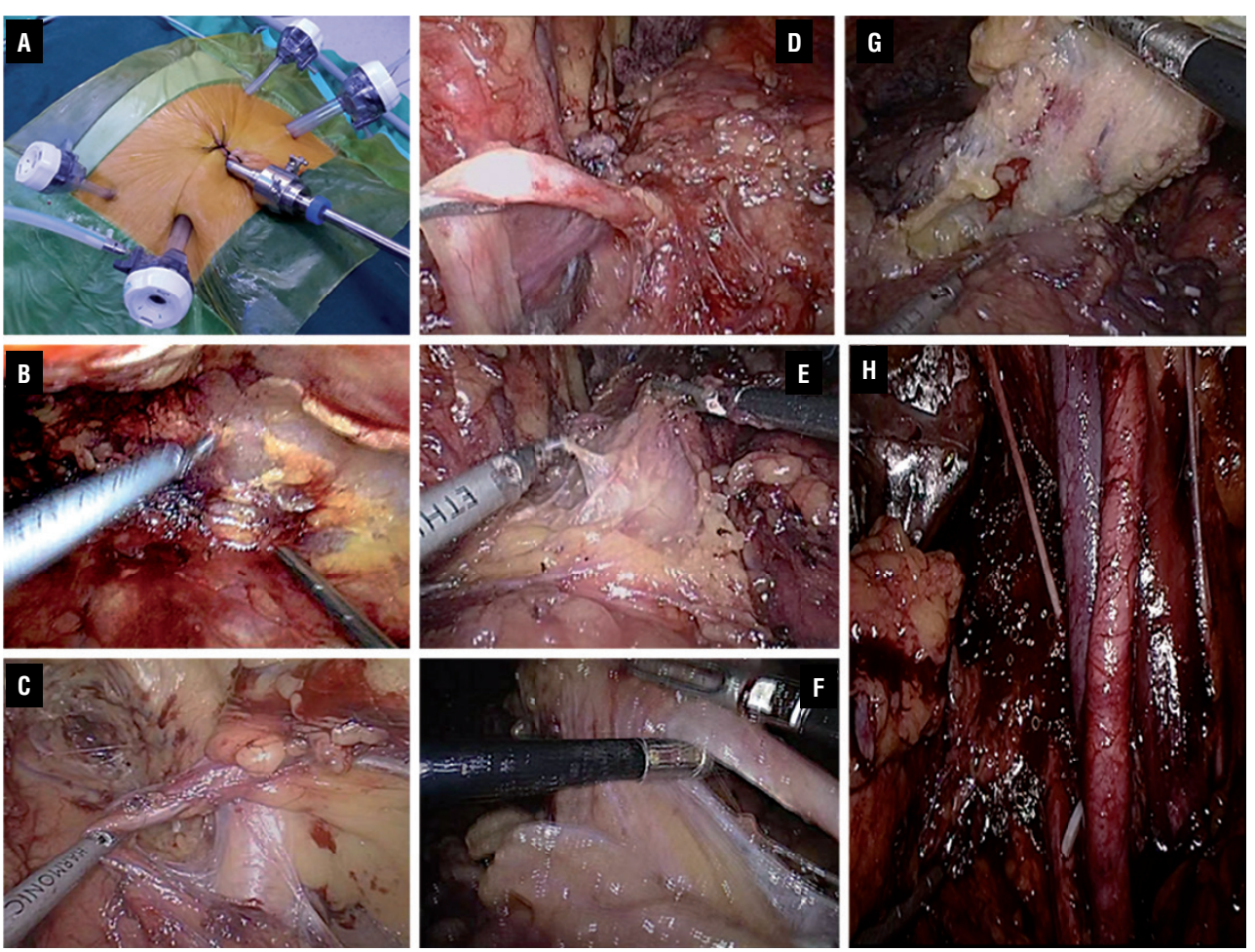
The continuous parametric data were compared using the independent samples t-test. The categorical data were compared using Pearson's χ^2-test, and Fisher's exact test was used when appropriate. The survival data were compared using Kaplan-Meier survival analysis and the log-rank test. Differences with P values <0.05 were considered significant.

Surgical technique

The procedure of TLRC was performed according to the procedures described by Matin and Gill (6). Bilateral pelvic lymphadenectomy was performed in the area of the common, external and internal iliac arteries and the obturator. In the ELRC cohort, the surgical position was similar to that of TLRC. First, a 2cm longitudinal incision under navel was used and an extraperitoneal space was created with fingers behind rectus abdominis muscle and below the arcuate line. An artificial gasbag was placed into the space with air inflation of 800 to 1000mL. The inflation was maintained for 5 minutes. The first 12mm trocar was placed

into the incision above for the 30 degree laparoscope. The other 4 trocars were placed under vision just like TLRC. The subsequent operation steps were performed by reference to the procedures of antegrade extraperitoneal approach to radical cystectomy described by Serel et al. (7). First, the spermatic cord on left side was identified and severed after ligature. The whole pelvic peritoneum was gently pushed cephalad at the level of the vasa deferentia on either side to visualize the common iliac vessels. The ureter on left side was identified and mobilized to the ureterovesical junction. The transection of the left ureter was performed after dissociating the ureterovesical junction. The same method was used to deal with the spermatic cord and ureter on the right side. The peritoneal reflection was indentified depending on the bilateral peritoneal margin as a sign. The peritoneal was separated from the anterior and apex of the bladder. The urachus was cut at the level of the umbilicus. Mobilization of the posterior wall of bladder was performed and the attachment of Denonvilliers' fascia to the rectum was released, maintaining all of its layers on the seminal vesicles. The subsequent procedures of dealing with the verumontanum, seminiferous ducts, bladder collateral ligament and prostate were similar to that of TLRC. Bilateral pelvic lymphadenectomy was carried out for pathological examination (Figure-1). According to patient's decision, ureterocutaneostomy was performed for both the groups.

Figure 1 - (A) The trocar setting of the extraperitoneal laparoscopic radical cystectomy (ELRC). (B) A retroperitoneum operation area was created. (C) The spermatic cord was identified.(D) The ureter was identified and mobilized. (E) The peritoneal was separated from the bladder. (F) The urachus was identified. (G) Mobilization of the posterior wall of bladder. (H) Pelvic lymphadenectomy was carried out for pathological examination.



RESULTS

Patient Characteristics

There was no conversion to open surgery. The patients in the ELRC and TLRC groups had comparable baseline characteristics. Data is shown in Table-1.

Operative outcomes

The operative and postoperative characteristics are shown in Table-2. The ELRC group required a significantly shorter time to exsufflation (1.5±0.7 versus 2.1±1.1d for TLRC; p=0.026) and time to liquid intake (1.8±0.9 versus 2.8±1.9d for TLRC; p=0.035). There were no significant differences in the other parameters of operative characteristics. The incidence of postoperative ileus in the ELRC group was lower than the TLRC group (0 versus 9.5%). However, the difference had no statistic significance (p>0.05). There were no significant differences in the other parameters of postoperative complications (p>0.05). The removed lymph node number in the ELRC group was significantly lower than the TLRC group (9.4±2.6 versus 13.4±3.4, p<0.001). Positive lymph node was observed in 1 patient in the ELRC group and 2 patients in the TLRC patients (Table-3). All the three patients underwent postoperative adjuvant chemotherapy.

The median follow-up was 13.8±8.0 months and 18.2±10.0 months for the ELRC group and the TLRC group respectively. There were 18 and 19 patients alive from the ELRC group and the TLRC group at the last follow-up, respectively. One patient died of pneumonia in the ELRC group and two patients died of heart attack in the TLRC group. Cancer recurrence was observed in 2 and 1 patients in the ELRC group and the TLRC group respectively. The Kaplan-Meier survival curves showed there were no significant differences between the ELRC and the TLRC group in terms of the overall and cancer-free survival rates (p>0.05, data is shown in Figure-2).

Table 1 - Patients' baseline characteristics.

	ELRC (n=19)	TLRC (n=21)	P value
Age (years)	78.4±5.7	79.0±6.1	0.739
BMI (kg/m^2)	24.9±1.8	25.3±3.2	0.742
ASA score (n%)			0.987
2	9(47.4%)	10(47.6%)	
3	10(52.6%)	11(52.4%)	
Hb (g/L)	123.8±21.3	117.0±26.3	0.379
Scr (umol/L)	96.9±29.5	97.2±29.3	0.975
Abdominal surgical history (n%)	2(10.5%)	3(14.3%)	0.719
Comorbility (n%)			
Hypertension	6(31.6%)	6(28.6%)	0.836
Cardio-vascular disease	3(15.8%)	2(9.5%)	0.549
Chronic pulmonary disease	2(10.5%)	3(14.3%)	0.719
Diabetes mellitus	4(21.1%)	3(14.3%)	0.574
Chronic renal insufficiency	1(5.3%)	2(9.5%)	0.609
Other chronic diseases	1(5.3%)	2(9.5%)	0.609

Data presented as mean±standard deviation or n (%).
ASA = American Society of Anesthesiologists; **BMI** = body mass index; **Hb** = hemoglobin; **Scr** = serum creatinine; **ELRC** = extraperitoneal laparoscopic radical cystectomy; **TLRC** = transperitoneal laparoscopic radical cystectomy.

Table 2 - Patients' operative and postoperative characteristics.

	ELRC (n=19)	TLRC (n=21)	P value
Operative time (min)	179.9±38.3	165.6±40.0	0.254
Estimated blood loss (mL)	280.0±111.1	271.9±105.0	0.814
Transfusion requirement (n%)	2(10.5%)	2(9.5%)	0.916
Time to exsufflation (d)	1.5±0.5	2.1±1.1	0.026*
Time to liquid intake (d)	1.8±0.9	2.8±1.9	0.035*
Time to canalization (d)	5.4±1.9	5.7±1.7	0.556
Hospital stay after operation (d)	8.2±1.6	9.5±3.1	0.097
Postoperative complications			
Total infection (n%)	2(10.5%)	3(14.3%)	0.719
Pyelonephritis	1(5.3%)	1(4.8%)	0.942
Pneumonia	1(5.3%)	2(9.5%)	0.609
Postoperative ileus (n%)	0	2(9.5%)	0.168
Arrhythmia (n%)	2(10.5%)	1(4.8%)	0.489
Lymphorrhagia (n%)	1(5.3%)	1(4.8%)	0.942
Clavien-Dindo classification			
Total	5(26.3%)	7(33.3%)	0.629
Grade I	1(5.3%)	1(4.8%)	0.942
Grade II#	4(21.1%)	6(28.6%)	0.583
Grade III-V	0	0	NA

Data presented as mean±standard deviation or n (%).
ELRC = extraperitoneal laparoscopic radical cystectomy; **TLRC** = transperitoneal laparoscopic radical cystectomy; **NA** = not applicable.
Transfusion requirement were not included; *p<0.05.

DISCUSSION

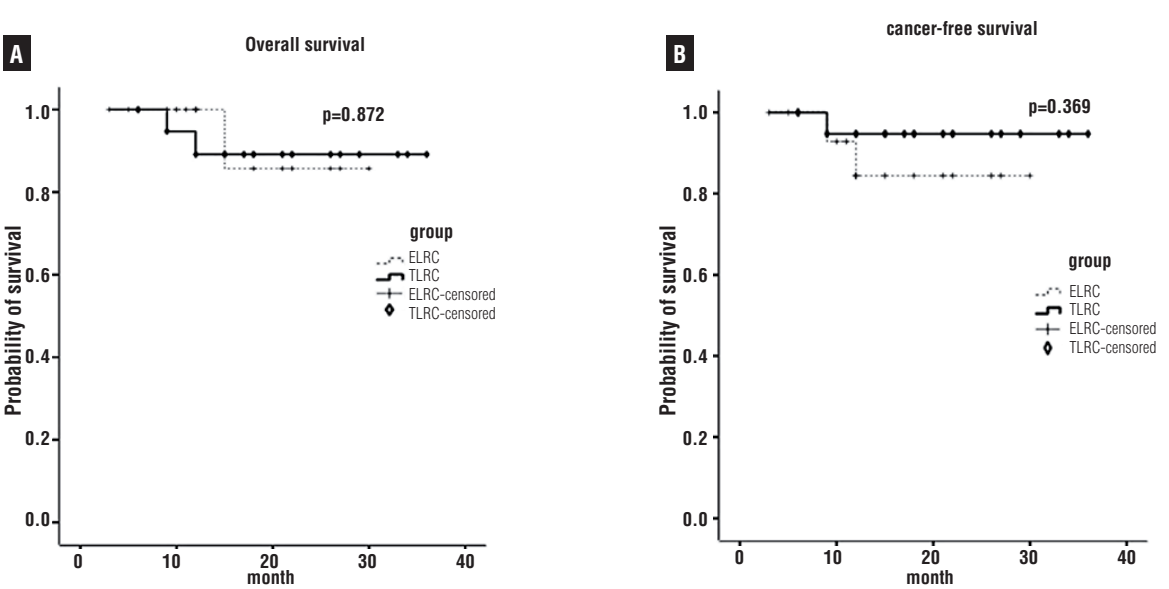
In the present study, it was observed that the ELRC group was associated with less time to exsufflation and liquid intake. The results indicated that the existence of a peritonealized pelvis in the ELRC group was benefic for the functional recovery of the bowel. In the transperitoneal radical cystectomy, the peritoneum covering is left on the bladder to allow for a wide perivesicle dissection. Surgery induced inflammatory reactions that arise between the small bowel and the deperitonealized pelvic wall will lead to small bowel palsy, obstruction, ileus, or constipation (8). The results of Zhao J et al. (9) also showed the existence of a nonperitonealized pelvis in the TLRC group adversely affected the functional recovery of the bowel, which is similar with our observations. Keeping the integrity of the peritoneal cavity can prevent the inflammatory reactions induced by the deperitonealized pelvic wall with the small bowel (10). No postoperative ileus occurred in the ELRC group in our study, which is a better outcome than the TLRC group, although the sample size in the present study was small to achieve statistical significance. Shorted time for patients to exsufflation can help them to take food as early as possible. Keeping a balanced nutrition early after surgery can also reduce the possibility of delayed recovery, which is helpful to decrease the time of the hospital stay. In our study, the hospital stay in the ELRC group was also less

Table 3 - Patients' pathological outcomes.

	ELRC (n=19)	TLRC (n=21)	P value
Tumor stage (n %)			**0.873**
T1,Tis	5(26.3%)	6(28.6%)	
T2	14(73.7%)	15(71.4%)	
Tumor grade (n %)			**0.719**
Low grade	2(10.5%)	3(14.3%)	
High grade	17(89.5%)	18(85.7%)	
Lymph node number	9.4±2.6	13.4±3.4	<0.001*
Lymph node metastasis (n %)			**0.609**
Negative	18(94.7%)	19(90.5%)	
Positive	1(5.3%)	2(9.5%)	
Positive surgical margins (n%)	0	0	NA

Data presented as mean±standard deviation or n (%).
ELRC = extraperitoneal laparoscopic radical cystectomy; **TLRC** = transperitoneal laparoscopic radical cystectomy; **NA** = not applicable.
*p<0.001

Figure 2 - Kaplan-Meier Curves for (A) Overall Survival and (B) Cancer-Free Survival among extraperitoneal laparoscopic radical cystectomy (ELRC) and transperitoneal laparoscopic radical cystectomy (TLRC). Log-rank test indicates there is no significant difference between the two groups (p>0.05).



than the TLRC group, although the difference had no statistical significance (p=0.097).

For the ELRC procedure, the first step is to create an adequate retroperitoneum operation area. The experience of extraperitoneal laparoscopic radical prostatectomy (11) and extraperitoneal laparoscopic partial cystectomy (12) had already proved the availability of the retroperitoneum operation area. The other difficult step is to mobilize the peritoneum covering the postero-superior

surface of the bladder. Sometimes the peritoneum should be removed with the bladder wall when the peritoneal reflection is hard to be identified and then the peritoneum was closed. Zhu et al. had the peritoneal covering of the bladder detached ex vivo after RC. Suspicious peritoneal lesions were sampled and random biopsies were taken. The authors found that patients with pathological stage T1-T2 bladder cancer had a very low possibility of peritoneal involvement (13). Therefore, in our study, the peritoneum covering the surface of the bladder could be kept intact. However, when the lesions were around the bladder apex or over the posterior bladder wall, we still recommend the peritoneum to be removed with the bladder wall to ensure the oncologic adequacy of the procedure.

In the present study, the number of lymph nodes removed in the ELRC group was significantly lower than the TLRC group. The extent of pelvic lymph nodes dissection (PLND) in the ELRC group was unlikely to reach the same level in the TLRC group due to the existence of peritoneum, which is the limitation of this technique. Although there was evidence which indicated that more extended PLND is associated with survival benefit (14), Jensen et al. found that the prognosis after RC and extended PLND in patients with T1–T2 disease was not significantly better than those following RC and limited PLND (15). A meta-analysis study also indicated that compared with non--extended PLND, extended PLND was associated with a better RFS rate for patients with pT3–pT4 disease, but not for patients with ≤pT2 disease (16). For patients with different age and comorbidity status, the beneficial effect of PLND was also different. Larcher et al. (17) found that RC with PLND is associated with improved cancer specific survival relative to RC alone, in younger and healthier RC candidates but not in older and sicker patients. From our study, although the number of PLND was less in the ELRC group, the lymph node status and the survival rate were similar in the two groups. Therefore, the observed benefit of PLND may not be universally applicable to all RC patients. However, we must admit that the debate of the extended PLND in radical cystectomy still goes on and for the selected elderly bladder patients with ≤T2 disease, ELRC with PLND might not necessarily be an oncologically unacceptable approach. Moreover, we propose measures to avoid offering ELRC in patients with >pT2 cases which have a significant risk of peritoneal infiltration and lymph node mestastases.

There were some limitations in this study. First, the nature of a retrospective study made it impossible to avoid the selection bias and attrition bias. Secondly, the sample size of this study was small and all the cases were performed in male patients with only ureterocutaneostomy. We have no idea of the feasibility of this method in female patients because we think the gynecologic organ in the peritoneum seems to be a disturbance for the ELRC surgery. Moreover, the ureterocutaneostomy diversion is not a procedure applicable to the majority of patients and mostly ileal conduit or neo-badder is performed. But for some elderly patients whose operation should be rapidly terminated due to the deteriorated health state, and those with decreased life expectancy due to associated comorbidities or inability to use intestinal segments owing to related problems, it is a less invasive approach and rational option (18). Furthermore, a randomized, prospective study with larger sample and different kinds of urinary diversions would better assess the feasibility of ELRC for the selected elderly bladder patients.

CONCLUSIONS

ELRC seems to be a safe and feasible surgical strategy for the selected elderly bladder cancer patients with ≤T2 disease. The surgical and oncological efficacy of the ELRC is similar to that of the TLRC, but with faster intestinal function recovery. Further studies with a large series including different urinary diversions are needed to confirm our results and to better evaluate the benefit of ELRC in bladder cancer patients.

ABBREVIATIONS

ASA = American Society of Anesthesiologists
BMI = body mass index
ELRC = extraperitoneal laparoscopic radical cystectomy
EORC = extraperitoneal open radical cystectomy
Hb = hemoglobin

LRC = laparoscopic radical cystectomy
MIBC = muscle-invasive bladder cancer
NMIBC = non-muscle-invasive bladder cancer
RC = Radical cystectomy
Scr = serum creatinine
TLRC = transperitoneal laparoscopic radical cystectomy

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 663-670, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0393

A comparison of preliminary oncologic outcome and postoperative complications between patients undergoing either open or robotic radical cystectomy

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ABSTRACT

Purpose: To compare complications and outcomes in patients undergoing either open radical cystectomy (ORC) or robotic-assisted radical cystectomy (RRC).
Materials and Methods: We retrospectively identified patients that underwent ORC or RRC between 2003- 2013. We statistically compared preliminary oncologic outcomes of patients for each surgical modality.
Results: 92 (43.2%) and 121 (56.8%) patients underwent ORC and RRC, respectively. While operative time was shorter for ORC patients (403 vs. 508 min; p<0.001), surgical blood loss and transfusion rates were significantly lower in RRC patients (p<0.001 and 0.006). Length of stay was not different between groups (p=0.221). There was no difference in the proportion of lymph node-positive patients between groups. However, RRC patients had a greater number of lymph nodes removed during surgery (18 vs. 11.5; p<0.001). There was no significant difference in the incidence of pre-existing comorbidities or in the Clavien distribution of complications between groups.
ORC and RRC patients were followed for a median of 1.38 (0.55-2.7) and 1.40 (0.58-2.59) years, respectively (p=0.850). During this period, a lower proportion (22.3%) of RRC patients experienced disease recurrence vs. ORC patients (34.8%). However, there was no significant difference in time to recurrence between groups. While ORC was associated with a higher all-cause mortality rate (p=0.049), there was no significant difference in disease-free survival time between groups.
Conclusions: ORC and RRC patients experience postoperative complications of similar rates and severity. However, RRC may offer indirect benefits via reduced surgical blood loss and need for transfusion.

ARTICLE INFO

Keywords:
Oncology Nursing; Postoperative Period; Robotics; Cystectomy; Urinary Bladder Neoplasms

Int Braz J Urol. 2016; 42: 663-70

Submitted for publication:
November 30, 2015

Accepted after revision:
January 23, 2016

INTRODUCTION

Bladder cancer is the fourth most commonly diagnosed malignancy in the United States, with a peak incidence between 50-70 years of age (1). Open radical cystectomy (ORC) has been considered the gold-standard of care for the surgical treatment of bladder cancer (2). However, following the first reported robotic-assisted laparoscopic cystectomy (RRC) more than a decade ago (2), its positive effects on reducing surgical blood loss, accelerating recovery time, and shortening surgical learning times have been reported.

A prospective, randomized trial of 124 patients failed to identify significant advantages of RRC compared to ORC in terms of 90 day complication

rates, length of stay, pathologic outcome and short-term quality of life measures (3). However, neither the rate of recurrence or time to all-cause death were compared between surgical modalities.

While these clinical data have supported the wider use of RRC (4, 5), comprehensive studies comparing clinical outcomes between patients undergoing ORC or RRC have only recently started to emerge. In addition, the majority of published reports and randomized clinical trials comparing open and robotic surgical modalities have been published from NCI comprehensive programs or from community cancer network sites, rather from patients treated at a large community hospital.

In the present study, we retrospectively compared oncologic outcome, post-operative complication rates, disease recurrence and all-cause mortality in patients who underwent either open or robotic-assisted radical cystectomy during a 10-year contemporary period.

MATERIALS AND METHODS

A retrospective review of our IRB-approved cystectomy database identified 213 patients with demographic and clinical data who underwent radical cystectomy between January 2003-December 2013. These patients were stratified on the basis of whether they underwent ORC or RRC. Four surgeons performed the open surgeries, while two surgeons performed the robotic procedures. The choice of surgery type was based upon consultation and between the patient and physician, comorbid conditions, tumor/pathologic stage, and also the availability of robotic surgical suites. In the early phase of our study period (2003-2008), >80% of cases were performed using an open procedure. In more recent years (2009-2013), however, the majority of surgeries (66%) were robotic-assisted, which is likely a reflection of surgeons becoming more confident with robotic procedures. Although in most robotic cases urinary diversion was created extracorporeally, intracorporeal urinary diversions also was created in few, more recent, cases.

Patient demographics and clinical data including preexisting comorbidities, Charlson Comorbidity Index (CCI) score, chemotherapy history and peri/postoperative complications that occurred ≤90 days post-surgery were tabulated. Follow-up intervals were every 3 months for the first 2 years, then every 6 months for the next 3 years, and annually thereafter. Complication severity was classified according to the Clavien grading system (6). Clinical tumor stage was defined from MRI/CT imaging and cystoscopy/TURBT pathology prior to surgery. The association between risk factors, comorbidities, CCI score, and patient outcomes for each surgical type were evaluated. Recurrence was primarily determined at follow-up through work up, imaging (e.g. CT scan), cytology and/or biopsy.

The incidence of complications following ORC and RRC was compared. Continuous variables were compared utilizing independent samples t-test or Wilcoxon Ranked Sum tests depending on whether assumptions concerning the underlying distributions were met. Chi-square tests of proportion were utilized to compare data for dichotomous and categorical variables. Kaplan-Meier analyses were used to determine time to disease recurrence and disease-free survival time. All statistical analyses were performed using SPSS v21.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

All cystectomy patients

A total of 213 patients who underwent either ORC or RRC procedures between January 2003-December 2013 formed the study cohort, of which 168 (78.9%) were male (Table-1). The mean age of the entire study cohort was 66.7±10.4 years. A total of 141 (66.2%) of patients were either current or former tobacco users. In addition, 39 (18.3%) of patients had pre-operative hydronephrosis. Neoadjuvant therapy was used in 59 (27.7%) patients, while adjuvant chemotherapy was utilized in 55 (25.8%) patients across both surgery types. A total of 62 (29.1%) tumors were clinically staged ≤cT1, while 144 (67.6%) were staged cT2-cT4. A total of 27 (12.7 %) patients were downstaged (≥T2 to ≤Ta/Tis) on final pathology.

Comparison of open and robotic radical cystectomy patients

Demographics: When stratified by surgical modality, a total of 92 (43.2%) and 121 (56.8%)

Table 1 - Demographic, surgical and oncologic data.

		Cystectomy procedure		
		Open	Robotic	p
Demographic data				
Number of patients (n; %)		92 (43.2)	121 (56.8)	-
Age at surgery (mean ± SD) (years)		67.8±10.4	65.9±10.4	0.176
Gender (male; %)		73 (79.3)	95 (78.5)	1.0
Tobacco use (ever smoked) (n; %)		70 (89.7)	71 (65.1)	<0.001
BMI (mean ± SD) (kg/m^2)		28.4±5.2	28.2±5.0	0.860
CCI score		4 (3-5)	4 (3-5)	0.694
ASA physical status score		3 (2-3)	3 (2-3)	0.407
Patients with pre-operative hydronephrosis (n; %)		18 (19.6)	21 (17.4)	0.722
Patients who received adjuvant chemotherapy (n; %)		21 (22.8)	38 (31.4)	0.402
Follow up time (years)		1.38 (0.55-2.7)	1.40 (0.58-2.59)	0.850
Surgical and oncologic data				
Estimated blood loss (median; IQR) (mL)		600 (450-1100)	450 (300-725)	<0.001
Patients requiring transfusion (n; %)		36 (39.1)	26 (21.5)	0.006
Operative time (median; IQR) (min)		403 (359-467)	508 (436-589)	<0.001
Length of stay (median; IQR) (days)		9 (7-13.8)	8 (7-12)	0.221
Patients with disease recurrence (n; %)		32 (34.8)	27 (22.3)	0.046
Patients with positive margins (n; %)		5 (5.6)	10 (8.3)	0.591
Lymph node-positive patients (n; %)		22 (24.4)	25 (20.7)	0.514
Median number of lymph nodes removed from all patients		11.5 (7-19)	18 (11-24)	<0.001
Positive lymph nodes removed from lymph node-positive patients		2 (1-3)	2.5 (1-4.2)	0.354
Total patients down-staged (≥T2 to ≤Ta/Tis on final pathology) (n; %)		7 (7.6)	20 (16.5)	0.062
Patients down-staged who received adjuvant chemotherapy (n; %)		4 (19.0)	11 (28.9)	0.045
Number of deaths (all causes) (n; %)		34 (37.0)	29 (24.0)	0.049
Lymphovascular invasion (n; %)	TURB specimen	17 (18.9)	23 (19.0)	1.0
	Cystectomy specimen	30 (32.6)	38 (31.4)	0.883
Type of diversion (n; %)	Ileal conduit	64 (69.6)	71 (59.2)	0.208
	Indiana pouch	5 (5.4)	13 (10.8)	
	Neobladder	23 (25.0)	36 (30.0)	

Data are shown as median (interquartile range) unless otherwise specified.

patients underwent ORC and RRC, respectively. There was no significant difference in the distribution of clinical or pathologic tumor stages between patients who underwent ORC and RRC (p=0.437 and 0.267; Tables 2 and 3). In addition, there was no significant difference in the distribution of the type of urinary diversion (i.e. ileal conduit, Indiana pouch and neobladder) utilized in ORC and RRC patients (p=0.208; Table-1).

The age of ORC and RRC patients at the time of surgery was not significantly different (67.8±10.4 versus 65.9±10.4 years, respectively; p=0.176, Table-1). ORC and RRC patients were followed for a median of 1.38 (0.55-2.7) and 1.40 (0.58-2.59) years, respectively (p=0.850). There was also no significant difference in gender distribution, BMI, CCI score and ASA score between ORC and RRC patient cohorts (p=1.0, 0.860, 0.694,

Table 2 - Outcome stratified by clinical stage.

		Cystectomy procedure		
		Open	Robotic	p
Clinical bladder cancer stage (n; %)	≤cT1	25 (27.5)	37 (30.8)	0.437
	cT2	45 (49.5)	65 (54.2)	
	cT3	15 (16.5)	11 (9.2)	
	cT4/node positive (N1/N2)	6 (6.6)	7 (5.8)	
Patients with muscle-invasive tumors (n; %)		66 (72.5)	83 (69.2)	0.649
Time to recurrence (mean; 95% CI) (months)	All stages	12.6 (9.3-15.9)	11.8 (7.7-15.9)	0.949
	≤cT1	17.3 (9.6-25.1)	13.2 (4.5-21.8)	0.858
	cT2	15.9 (10.8-20.9)	12.8 (7.8-17.8)	0.318
	cT3	5.8 (2.8-8.7)	16.0 (0.0-39.6)	0.410
	cT4/node positive (N1/N2)	5.0 (2.7-7.3)	3.3 (0.01-6.5)	0.841
Time to all-cause death (mean; 95% CI) (months)	All stages	66.9 (55.3-78.6)	68.8 (59.6-77.9)	0.301
	≤cT1	74.3 (54.7-93.9)	67.5 (57.1-77.9)	0.531
	cT2	74.4 (58.8-90.0)	72.4 (59.9-84.9)	0.416
	cT3	24.6 (14.2-35.1)	26.6 (18.5-34.8)	0.459
	cT4/node positive (N1/N2)	50.2 (16.6-83.7)	30.3 (14.4-46.2)	0.864

Table 3 - Outcome stratified by pathologic stage.

		Cystectomy procedure		
		Open	Robotic	p
Pathologic bladder cancer stage (n; %)	≤pT1	29 (31.5)	50 (41.3)	0.267
	pT2	25 (27.2)	22 (18.2)	
	pT3	25 (27.2)	28 (23.1)	
	pT4/node positive (N1/N2)	13 (14.1)	21 (17.4)	

0.407, respectively; Table-1). A total of 70 (89.7%) ORC patients had a history of tobacco use, which was significantly higher than the proportion of RRC patients who were tobacco users (p<0.001; Table-1). There was no significant difference in the utilization of either neoadjuvant or adjuvant chemotherapy between ORC and RRC patients (p=0.166 and 0.402, respectively). In addition, the proportion of patients with pre-operative hydronephrosis was not statistically different between patients undergoing ORC and RRC (p=0.722; Table-1).

Surgical and oncologic outcome: There was no significant difference in the distribution of the type of urinary diversion performed in ORC and RRC patients (p=0.208; Table-1).

There was also no significant difference in the incidence of muscle-invasive tumors between surgical groups, based on either their clinical or pathologic staging (p=0.649 and 0.154, respectively; Tables 2 and 3). Of the patients who received neoadjuvant chemotherapy, 4/21 (19.0%) of ORC and 11 (28.9%) of RRC patients were downstaged on final pathology (p=0.045).

There was no significant difference in the proportion of ORC and RRC patients with lympho-vascular invasion (based on either TURB or cystectomy specimens) (Table-1). There was also no significant difference in the number of positive margins on biopsy between surgical groups (p=0.591; Table-2), or in the proportion of lymph node-positive patients (p=0.514; Table-1). However, patients who underwent RRC had a significantly greater number of lymph nodes removed than those undergoing ORC (18 versus 11.5; p<0.001; Table-1). There was no significant difference in the number of positive lymph nodes removed from lymph-node-positive patients between ORC and RRC groups (2 versus 2.5; p=0.354).

Recurrence and mortality: A significantly lower proportion of patients who underwent RRC experienced disease recurrence than patients who underwent open surgery (22.3 versus 34.8%; p=0.046; Table-1). However, there was no significant difference in the time to recurrence between ORC and RRC patients, based on either clinical or pathologic stage (Tables 2 and 3). A significantly higher all-cause death rate was observed in patients undergoing ORC compared to RRC (37 versus 24%; p=0.049; Table-1). However, there was no significant difference in the time to all-cause death between ORC and RRC patients, when stratified by either clinical or pathologic tumor stage (Tables 2 and 3).

Comorbidities and peri/postoperative complications: Estimated blood loss during RRC was significantly lower than in patients undergoing ORC (450 versus 600mL; p<0.001; Table-1). Furthermore, a significantly lower proportion of RRC patients required transfusion compared to those undergoing ORC (21.5 versus 39.1%; p=0.006; Table-1). Estimated surgical blood loss in patients requiring a transfusion was not significantly different between open and robotic surgeries (p=0.635). However, operative time for ORC was significantly shorter than for RRC (403 versus 508 min; p<0.001; Table-1). Length of hospital stay was not significantly different between the two surgical groups (p=0.221; Table-1). There was no significant difference in the incidence of pre-existing comorbidities between ORC and RRC patient groups (Table-4).

In addition, there was no significant difference in the incidence of post-operative complications (≤90 days post-surgery) between ORC and RRC surgical groups (Table-4). We also stratified complications using the Clavien grading system into major (Clavien 3-5) and minor (Clavien 1-2) subgroups. There was no significant difference in the incidence of either major or minor complications in patients undergoing ORC or RRC procedures (p=0.726 and 0.094, respectively; Table-4).

DISCUSSION

Surgical intervention with radical cystectomy and extended pelvic lymph node dissection (ELND) is the curative treatment of choice in patients with either muscle-invasive or high-risk non-muscle invasive bladder (2) [Steven & Poulsen; Poulsen et al.; Bi et al. 2015]. In patients with invasive (T2) bladder cancer, ELND has been associated with improved survival compared to standard lymphadenectomy (7, 8). Radical cystectomy with ELND of >16 lymph nodes resulted in a 22% increase in 5-year survival compared to patients

Table 4 - Incidence of comorbidities and complications.

		Cystectomy procedure		
		Open	Robotic	p
Comorbidities (n; %)	Coronary artery disease	15 (16.3)	17 (14)	0.701
	Chronic heart failure	2 (2.2)	2 (1.7)	1.0
	Chronic obstructive pulmonary disorder	10 (10.9)	19 (15.7)	0.420
	Diabetes	17 (18.5)	23 (19.0)	1.0
	Connective tissue	10 (10.9)	12 (9.9)	0.824
	Peptic ulcer	2 (2.2)	2 (1.7)	1.0
	Renal insufficiency	7 (7.6)	8 (6.6)	0.793
	Cerebrovascular accident	3 (3.3)	6 (5.0)	0.735
	Peripheral vascular disease	4 (4.3)	4 (3.3)	0.729
	Lymphoma	0 (0)	2 (1.7)	0.507
	Myocardial infarction	9 (9.8)	4 (3.3)	0.080
	Liver	1 (1.1)	0 (0)	0.432
	Any	44 (47.8)	63 (52.1)	0.581
Complications (n; %)	Cardiac	10 (10.9)	5 (4.1)	0.064
	Respiratory	5 (5.4)	7 (5.8)	1.0
	Genitourinary	6 (6.5)	6 (5.0)	0.766
	Gastrointestinal	23 (25.0)	24 (19.8)	0.406
	Infection	13 (14.1)	16 (13.2)	0.843
	Vascular	15 (16.3)	16 (13.2)	0.560
	Nausea	5 (5.4)	3 (2.5)	0.296
	Misc. medical	7 (7.6)	5 (4.1)	0.370
	Misc. surgical	2 (2.2)	1 (0.8)	0.579
	Other	4 (4.3)	6 (5.0)	0.729
	Any	50 (54.3)	57 (47.1)	0.334
	Minor complications (Clavien 1-2)	45 (48.9)	45 (37.2)	0.094
	Major complications (Clavien 3-5)	19 (20.7)	22 (18.2)	0.726

in which <16 nodes were excised. In addition, a recent meta-analyses indicated that ELND was associated with a positive effect on recurrence-free survival compared to non-ELND patients (9, 10).

The potential for robotic-assisted surgery to drive a reduction in complication rates, morbidity and mortality associated with cystectomy surgery has received significant interest. As such, whether the use of robotic-assisted surgery compromises the pathological and oncological outcomes relative to open surgery is a key question. Furthermore, it is also important to determine whether indices of perioperative outcome, including blood loss, operative time, and length of stay, are comparable to ORC, since these factors may adversely impact morbidity and recovery time. Finally, complication rates associated with RRC, and how they compare with open surgery, is of clinical relevance. As such, we retrospectively compared these clinical indices in 213 patients who underwent either ORC or RRC over a 10-year contemporary period at our large, urban clinical practice.

Data from a prospective, randomized trial compared oncologic outcomes following open or minimally invasive cystectomy (11). While there was no indication of significant differences in oncologic outcome between surgical modalities, RRC was associated with a reduction in blood loss and shorter hospital stay (11). Looking ahead, the multicenter RAZOR (randomized open versus robotic cystectomy) trial in 320 patients (T1-T4, N0-N1, M0) will be completed in 2016-2017 (12), and will provide additional important data regarding the impact of pelvic lymph node dissection and urinary diversion on oncologic outcomes, complications and health--related quality of life over a 2-year period.

Khan et al. recently described the functional and oncologic outcomes of a small cohort of RRC patients with invasive and non-invasive bladder cancer (14 patients) over a 5-8 year follow-up period. RRC was associated with excellent local disease control, and outcomes in patients with metastatic disease were equivalent to ORC (13). A previous prospective, randomized single center study compared perioperative and pathologic data (EBL, operative time, complications, bowel function and length of stay) in 41 patients undergoing either ORC or RRC (14). The primary aim of this trial was to assess lymph node yield between open and robotic cystectomy. The node yield in both arms was lower than expected for ELND including the common iliac nodes. While this study was not adequately powered to assess secondary endpoints, surgical time was prolonged in the robotic surgery group and surgical blood loss was significantly reduced. While the study cohort was relatively small, these data illustrated that RRC was not inferior to ORC.

The greater lymph node removal in RRC patients may be related to a growing use of extended lymph node dissection and robotic surgery for bladder cancer at our clinical center over the last 3 years. Over the study period, lymph node yield during both open and robotic cystectomy procedures increased at a similar rate. These data support the general trend towards more extensive lymph node dissection that is beneficial in limiting subsequent disease recurrence. The ability to undertake more extensive lymph node removal is likely to have been facilitated by the routine use of robotic-assisted surgical systems. Furthermore, higher lymph node yields (in addition to the potential for selection bias) may be related the lower rate of recurrence in RRC patients in our study.

More recently, Tang et al. described a systematic review of the safety and efficacy of RRC compared to ORC in the treatment of bladder cancer (15). In a meta-analysis of 13 studies (one randomized controlled trial, seven prospective and five retrospective studies) ORC was found to be associated with shorter surgical times. However, patients undergoing RRC experienced significantly fewer complications, less surgical blood loss, shorter length of hospital stay, lower blood transfusion rate, less transfusion needs, shorter time to regular diet, increased lymph node yield and fewer positive lymph nodes. There was no difference in positive surgical margins between ORC and RRC surgical groups. Overall, this meta-analysis demonstrated significant advantages of RRC compared to open surgery. Wang et al. also described the perioperative and pathological outcomes in a small prospective study of 54 patients undergoing either ORC or RRC (16). The 33 patients who underwent RRC had decreased blood loss and requirement for transfusion, but increased surgical duration. The complication rates were similar between groups.

Haber et al. have also published a critical review of laparoscopic and robotic-assisted radical cystectomy surgery between 1992-2007, concluding that RRC combines the patient-recovery advantages of minimally-invasive surgery with the safety of open surgery (17). In general, laparoscopic surgery was associated with reduced blood loss, comparable rates of complications and equivalent oncological outcomes. More recently, a prospective, randomized trial comparing perioperative complications between a total of 124 patients who underwent RRC or ORC failed to identify a large advantage of robotic over open cystectomy (3). Both surgical groups had similar 90-day complication rates, length of stay, pathologic and quality of life outcomes (3).

Importantly, our data illustrate that rates of individual complications in patients undergoing RRC are equivalent to those undergoing ORC. Furthermore, the distributions of major (Clavien 3-5) and minor (Clavien 1-2) complications were not statistically different between surgical groups.

Limitations of our study include its retrospective nature and the potential for selection bias of

a patient for a particular surgical procedure. There were no absolute selection criteria for open versus robotic cystectomy. In the early part of our study period (2003-2008), relatively more cases were performed using an open procedure. However, over the study period this changed with robotic cystectomies relatively more common during the last 5 years. As such, there was likely some selection bias, particularly towards open cystectomies in the initial phase of the study period. Positive aspects of our study are that the patient cohort was sampled over a 10-year contemporary time period, and patient has sufficient length of post-surgical follow-up (median 1.4; IQR: 0.6-2.6 years) to allow us to statistically compare recurrence and mortality between surgical groups.

CONCLUSIONS

While our study was retrospective in nature, and the patient cohorts were relatively small, our data suggest that ORC and RRC patients have comparable post-surgical outcome profiles. RRC may offer additional benefits in terms of lower surgical blood loss and reducing the need for transfusion.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 671-677, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0503

Presentation and surgery outcomes in elderly with pheocromocytoma: a comparative analysis with young patients

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ABSTRACT

Purpose: To evaluate the presentation and early surgical outcomes of elderly patients undergoing adrenalectomy for phaeochromocytoma.
Patients and Methods: A retrospective search was performed of our adrenal disorders database for patients who underwent surgery for phaeochromocytoma or paraganglioma between 2009 and 2014. Patients >60 years old were classified as elderly. The clinical manifestations, intraoperative course, and early postoperative outcomes of elderly patients were compared to those of younger individuals (<60 years old).
Results: The mean (±standard deviation) age in the older (n=10) and younger (n=36) groups was 69.6±5.3 years and 34.0±12.9 years. Germ-line mutations were more common in younger patients (50.0% versus 0%; p=0.004), whereas incidental lesions were more common in the elderly (40.0% versus 5.3%; p=0.003). In both groups, surgery was most commonly performed by videolaparoscopy (90% in the elderly and 82% in the younger group), with similar intraoperative anesthetic and surgical outcomes. Postoperatively, the older group more commonly received vasoactive drugs (60.0% versus 10.5%; p<0.001) and had a longer intensive care unit stay (3.1±2.8 versus 1.4±1.0 days; p=0.014), more clinical complications (60% versus 18.9%; p=0.01), and longer hospital stay (10.2±8.4 versus 5.7±4.9 days; p=0.028).
Conclusions: Although all patients received the same preoperative preparation, the elderly group exhibited a slower and more complicated recovery after adrenalectomy. Meticulous perioperative care should be used in the elderly when treating phaeochromocytoma; nevertheless, adrenalectomy is a relatively safe procedure in this patient population.

ARTICLE INFO

Keywords:
Pheochromocytoma; Adrenalectomy; Surgical Procedures, Operative

Int Braz J Urol. 2016; 42: 671-7

Submitted for publication:
September 09, 2015

Accepted after revision:
January 07, 2016

INTRODUCTION

Phaeochromocytoma is a neuroendocrine tumor with a prevalence ranging from 0.05% to 0.1% (1, 2). Phaeochromocytomas are located in the adrenal cortex in 85% of cases (2). The main clinical manifestation of phaeochromocytomas is arterial hypertension, which is the result of uncontrolled production of catecholamines by the tumor. It is estimated that 0.1% to 0.6% of all patients with hypertension have an underlying phaeochromocytoma (2, 3). Moreover,

catecholamine-producing neoplasms can lead to hypertensive emergencies with life-threatening consequences; thus, this tumor has major clinical importance (2, 4).

Curative treatment for phaeochromocytoma requires surgical removal of the tumor, which can be challenging because of the high likelihood of hemodynamic instability during the procedure and substantial blood pressure fluctuations during the recovery period (5). Fortunately, the development of preoperative strategies for strict blood pressure control has led to an important reduction in mortality rates. Forty years ago, the perioperative mortality ranged from 30% to 45% (5), whereas in recent series, perioperative mortality decreased to 0% to 2.9% (1, 3). Surgery-related complications have also declined, but they are still frequent, occurring in one of every five patients who undergo surgery (4).

Phaeochromocytomas are frequently associated with familial syndromes; in these instances, the tumors are usually diagnosed in young adults. However, phaeochromocytomas also affect children and the elderly, with sporadic cases being more common in older patients (2). Furthermore, with recent increases in life expectancy and improvements in imaging techniques, there has been an increase in the number of incidental diagnoses of phaeochromocytoma in older individuals undergoing periodic routine check-ups (6).

As an increasing number of the elderly are being considered for surgical removal of phaeochromocytomas, concerns have arisen regarding the perioperative management of older individuals undergoing this surgery. The elderly are physically more fragile than younger adults because of their attenuated systemic response to surgical stress and the frequent presence of comorbidities. Thus, surgical outcomes in this population may be worse than in younger patients (7, 8). We therefore performed the present study to evaluate the presentation and surgical outcomes of elderly individuals with phaeochromocytoma.

PATIENTS AND METHODS

After ethics board approval, a retrospective review of the adrenal disorders database at our institution was performed, selecting patients with phaeochromocytoma and paraganglioma who underwent adrenalectomy or adrenal tumor resection between January 2009 and January 2014. The diagnosis was confirmed by histopathological analysis. Forty-nine patients were identified, three of whom were excluded because of incomplete data. Two individuals with a metachronous contralateral phaeochromocytoma underwent two operations, resulting in a total of 48 procedures. The patients were divided into two groups according to their age at surgical intervention. Individuals older than 60 years were classified as elderly, in accordance with World Health Organization (WHO) recommendations (9). These recommendations state that the age cutoff to define elderly is established by the local government, with a minimum age of 60 years.

Preoperative data were reviewed, with comorbidities classified according to the Charlson scoring system (10). The clinical presentation at tumor diagnosis was categorized as typical manifestation, atypical manifestation, incidental finding, or familial syndrome follow-up. Typical symptoms included the presence of palpitations, headaches, sweating, syncope, tremors, weight loss, and hypertensive crisis. The presence of any other symptom was considered an atypical manifestation. Incidental diagnosis was defined as the presence of tumor in an asymptomatic patient who had an unexpected adrenal mass detected on imaging examination, in the absence of a familial syndrome.

According to our institution's clinical guidelines, all patients had a thorough preoperative evaluation and only underwent surgery after their comorbidities were strictly controlled. Selective alpha-receptor blockers were administered preoperatively in all patients. Either prazosin and doxazosin were initiated at least 15 days before surgery, with the doses adjusted to achieve a blood pressure <135/85mmHg. In patients with a heart rate >100 beats/min, beta-blockers were also administered. Two days before surgery, the patients began a liquid diet, and on the evening before surgery, they received 10mg bisacodyl orally for bowel cleaning.

All surgical procedures were performed by the same experienced surgeon, supervising a urology resident. The choice of surgical modality was based on the number of previous abdominal surgeries and whether the tumor was suspected to be malignant. Transperitoneal videolaparoscopy was the first choice whenever possible; it was initiated in 40 cases, although three required conversion to an open technique. The other eight adrenalectomies were accomplished by the open approach. In patients with bilateral phaeochromocytomas, total adrenalectomy was performed first on the side with the higher tumor volume and partial adrenalectomy was performed when possible in the contralateral gland. All patients were anesthetized by the same skilled professional, who was supervising an anesthesia resident. The diagnosis of phaeochromocytoma was confirmed after analysis of the surgical specimen. Intraoperative events, including surgical and anesthesia data, were reviewed. Clinical complications, stratified by the Clavien score (11), and early postoperative events were also evaluated.

Data are presented as mean±standard deviation unless otherwise indicated. Statistical analysis was performed with the SPSS® program, with the student-test or Kruskal-Wallis test being used for continuous variables. Chi-squared or Fisher tests were used to compare categorized variables. Values were considered significant if the p value was <0.05.

RESULTS

Among the 46 patients evaluated, 10 were included in the elderly group (five males and five females) and 36 in the young adult group (nine males and 27 females). The respective mean ages of the two groups were 69.6±5.3 years and 34.0±12.9 years. Two individuals in the younger group with metachronous phaeochromocytoma underwent two operations, for a total of 38 surgeries in this group. The mean Charlson score was 3.6±1.3 in the older group and 0.89±1.0 in the younger group (p<0.0001). No genetic alterations were observed in the elderly group, whereas in the younger group, 18 individuals (50.0%) had germ-line mutations (p=0.004). Incidental diagnosis was noted in 40.0% of patients in the older group but in only 5.3% of patients in the younger group (p=0.003). Data regarding the diagnoses at presentation are shown in Table-1.

Long-term hypertension was a common finding in both groups, but it was more frequent among the elderly (80.0% versus 43.2%; p=0.039). The number of medications used to control the blood pressure preoperatively was also significantly higher among the elderly (1.7±1.2 versus 0.6±1.0; p=0.008). The mean tumor size was 5.3±2.4cm and 4.2±2.6cm in the older and younger groups, respectively (p=0.219). Metaiodobenzylguanidine-scintigraphy was performed in 34 patients; positive results were found in a similar percentage of older and younger patients (90.0% in the older group and 83.3% in the younger group; p=0.616).

Among the 40 attempted videolaparoscopic adrenalectomies (9 [90%] in the older group and 31 [82%] in the younger group), three were converted to open surgery: one in the older group because of difficulty performing the adrenal dissection, and two in the younger group because of uncontrolled bleeding. The other eight surgeries were performed by the conventional open approach.

Eleven (29%) patients in the younger group had bilateral tumors; six of these were synchronous. In these patients, bilateral adrenalectomy was performed, removing the entire gland on the side with the largest tumor and preserving approximately 1/3 of the adrenal gland on the other side. Among the patients with metachronus tumors who previously underwent total adrenalectomy, three underwent partial adrenalectomy and two underwent total adrenalectomy. There were no bilateral phaeochromocytomas in the older group. Two cases of paraganglioma were diagnosed, one in each group; the open approach was used for the younger group patient and videolaparoscopic surgery was used in the older group patient. There were two cases of malignant tumors, both of which were in the younger group (5.5%).

The early perioperative outcomes are displayed in Table-2. There were no significant differences between groups in any of the evaluated intraoperative parameters. In the postoperative period, the elderly had a higher need for

Table 1 – Pre-operative characteristics.

	Elderly	Young	p
No.	10	36	
Average age	69.6 ± 5.3	34.0 ± 12.9	
Male:Female	5:5	9:27	0.128
Mean Charlson	3.6 ± 1.3	0.89 ± 1.0	< 0.0001
Germ-line mutation (%)	0	18 (50%)	0.004
Diagnosis (%)			
Incidental	4 (40%)	2 (5.3%)	0.003
Typical symptoms	3 (30%)	16 (42.1%)	0.486
Atypical symptoms	3 (30%)	7 (18.4%)	0.422
Investigation / follow-up on familial syndrome	0	13 (34.2%)	0.030
Long-term hypertension (%)	8 (80%)	16 (43.2%)	0.039
Anti-hypertensive drugs (number)	1.7 ± 1.2	0.6 ± 1.0	0.008
Image evaluation			
Bilateral (%)	0	11/36 (30.6%)	0.045
Average lesion size (cm)	5.3 ± 2.4	4.2 ± 2.6	0.219
Positive cyntigraphy-MIBG (%)	9/10 (90%)	20/24 (83.3%)	0.616

vasopressors (60.0% versus 10.5%; p<0.001), longer intensive care unit (ICU) stay (3.1±2.8 days versus 1.4±1 days; p=0.014), and longer hospital stay (10.2±8.4 days versus 5.7±4.9 days; p=0.028). Postoperative complications occurred in 60% of the older patients but only 18.9% of the younger patients (p=0.01). According to the Clavien classification, there were five minor complications and one major complication (pulmonary thromboembolism requiring ICU admission) in the older group, whereas there were seven minor complications in the younger group (Table-3). There were no deaths in any patient.

DISCUSSION

Considering the complexity of the perioperative management of phaeochromocytomas, we hypothesized that elderly patients would have worse outcomes compared to younger patients. Our results showed that surgery in the elderly was feasible, but recovery was slower and more prone to postoperative complications.

The diagnosis of neoplasms in the elderly has increased in recent years because of the rise in life expectancy and the implementation of routine screening exams (7). Surgeons may be hesitant to perform aggressive treatment in this population because of their higher risk of perioperative complications and death (12, 13). As a consequence of aging, breathing capacity, renal function, and resting cardiac output are reduced. Moreover, baseline global metabolism declines, thereby attenuating the body's physiologic response to stress (7, 8). However, when a catecholamine-producing tumor is discovered, expectant management is not appropriate. Besides the undesirable effects of sustained elevated blood pressure, these tumors can produce hypertensive emergencies, with potentially life-threatening cardiovascular consequences (2). An autopsy study reported that 75% of deaths related to phaeochromocytoma were due to a myocardial infarction or cerebral vascular accident (14), emphasizing the importance of interventional treatment.

Surgery in the elderly requires maximum effort, focusing on strict control of comorbidities

Table 2 – Intra-operative and early post-operative outcomes.

	Elderly	Young	p
Surgery Modality (%)			
VLP	9 (90%)	31 (82%)	
Open	1 (10%)	7 (18%)	
Partial Adrenalectomy	0	9 (23.7%)	
Synchronous Bilateral Adrenalectomy	0	6 (16%)	
Intra-operative outcomes			
Surgery conversion (%)	1/9 (11.1%)	2/31 (6.5%)	0.640
Hypertension / Tachycardia (%)	9 (90%)	32 (84.2%)	0.644
Vasoactive drugs use (%)	9 (90%)	28 (73.7%)	0.274
Average Crystalloid volume (mL)	3500 ± 1130	3658 ± 1048	0.696
Average anesthesia time (min)	261 ± 73	290 ± 73	0.291
Average surgery time (min)	161 ± 47	168 ± 66	0.722
Blood transfusion (%)	1 (10%)	8 (21.1%)	0.426
Early post-operative outcomes			
ICU after surgery	8 (80%)	33 (86.8%)	0.585
Average time on ICU (days)	3.1 ± 2.8	1.4 ± 1	0.014
Need of vasoactive drugs (%)	6 (60%)	4 (10.5%)	< 0.001
Clinical complications (%)	6 (60%)	7 (18.9%)	0.010
Average hospital discharge (days)	10.2 ± 8.4	5.7 ± 4.9	0.028

Table 3 – Complications according to Clavien classification.

	Elderly	Young	p
Complications	6 (60%)	7 (18.9%)	0.010
Minor complications			
Clavien I	2	4	
Clavien II	3	3	
Major complications			
Clavien III	0	0	
Clavien IV	1	0	

and thorough surgery preparation. Associated diseases may impair surgical recovery by increasing complications and raising mortality rates (8, 13). Our findings support these observations, as both the Charlson score (3.5 versus 0.89) and rate of clinical postoperative complications (60% versus 18%) were higher in the elderly. The complication rate noted in our younger patients was similar to rates reported in the literature, which varied from 10% to 21% (4, 15, 16). The elderly also had a six times higher likelihood of receiving vasopressors postoperatively, compared to younger patients. Furthermore, during recovery, older patients had a longer duration of ICU stay and hospitalization.

However, intraoperative parameters were similar in the two groups. Bruynzeel et al. (3) also did not find a relationship between age and hemodynamic instability during surgery for phaeochromocytoma. Other previous studies have included elderly patients in their study population, but none have analyzed outcomes stratified by age.

In addition to age and comorbidities, the tumor volume and presence of familial syndromes may also influence surgical outcomes. Younger patients had a 50% rate of germ-line mutations, which are frequently associated with bilateral and malignant phaeochromocytomas (2, 4). Regarding tumor volume, a positive relationship between tumor size and higher catecholamine production has been previously described (3). The increased catecholamine release could produce more intense symptoms and more severe illness. In the present study, there was no difference in tumor size between groups, and the expected relationship between familial syndromes and worse outcomes was not observed.

Regarding preoperative care, several actions should be adopted in the elderly to facilitate a quicker surgical recovery with fewer complications. Although the use of alpha-blockers is indisputable, there is controversy regarding which alpha-blocker medication most effectively optimizes outcomes (2). Although no correlation with age has been reported, short-acting selective alpha-blockers can avoid prolonged postoperative hypotension and are thereby generally preferred for the elderly (16). Furthermore, preoperative bowel preparation should be judicious in the elderly, to prevent hydric and electrolyte disturbances and to minimize the risks of colonic bacterial translocation (17). To reduce the risk of postoperative pulmonary embolism, anti-coagulation regimens must be introduced early, as difficulty with postoperative ambulation is anticipated. Intense pulmonary rehabilitation should be instituted to reduce the risk of other postoperative pulmonary complications.

This study is subject to the drawbacks of its retrospective design, small sample size and absence of matched paired comparison. Moreover, as our department is a quaternary referral service, many patients returned to their original health care center and were lost to long-term follow-up at our institution. However, this is the first series specifically addressing the feasibility of phaeochromocytoma resection in the elderly population. Furthermore, all patients were treated by the same surgeon who had performed more than 300 adrenalectomies in the preceding 10 years.

In conclusion, our elderly population had a slower recovery and more complications after resection of phaeochromocytoma, when compared to young adults. However, most complications were minor, surgery was equally feasible and did not result in mortality in this vulnerable group of patients. Meticulous preparation for surgery is crucial among the elderly and particular attention should be focused on maintaining balance between the adrenal disease and comorbidities.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 678-684, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0397

Clinical Significance of Preoperative Neutrophil – to – Lymphocyte Ratio in Renal Cell Carcinoma

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ABSTRACT

Introduction: We investigated the prognostic significance of the neutrophil-to-lymphocyte ratio on tumor stage and Fuhrman nuclear grade in renal cell carcinoma.
Methods: The records of 432 patients with RCC who underwent radical or partial nephrectomy between 2005 and 2014 were retrospectively reviewed. Patients were classified as group lower tumor stage(T1 + T2) and higher(T3 + T4). As like tumor stage, Fuhrman nuclear grade were classified lower (G1+G2) and higher(G3+G4) too. The best NLR cut off value was 3.01.Two sample t-test or Mann–Whitney U-test used for the continuous variables and a chi-square test or Fisher's exact test used for the categorical variables.
Results: Among the 432 total patients analyzed in our study, there were 275 males (63.7%) and 157 females (36.3%). Mean laboratory values were CRP 2.73 ± 1.93 mg/dL (normal less than 0.3), neutrophil count 4,23 ± 1.46/µL, lymphocyte count 1,61 ± 0,61/µL and NLR 2.64 ± 1.24. According to our data, statistically pretreatment NLR significantly correlated with CRP ($p<0.0001$). And tumor patologic stage ($p=0.08$), tumor histologic grade ($p<0.001$) was significantly associated with NLR.
Discussion: We compared the relationship of preoperative NLR and NC parameters with RCC tumor stage and grade. And NLR were found to have statistically significant higher T stage and grade at RCC. Further studies with more patients are needed to confirm our study.

ARTICLE INFO

Keywords:
Neutrophils; Lymphocytes; Carcinoma, Renal Cell; Epithelium

Int Braz J Urol. 2016; 42: 678-84

Submitted for publication:
July 20, 2015

Accepted after revision:
January 23, 2016

INTRODUCTION

Renal cell carcinoma (RCC) is the most common renal malignancy in adults and leads to a mortality rate of over 100.000 per year worldwide. In the United States renal cell carcinoma accounts for 2.3% of all cancer deaths (1). RCC is more prevalent in men than in women and occurs most often between 50-70 years of age. Cancer involving the renal parenchyma accounts for the majority of cases, while the minority of cases derive from the renal pelvis. The predominant subtype of RCC is a clear cell type that represents 80% of RCC, and is derived from the tubular epithelium (2). The incidence and the incidental detection of RCC in asymptomatic patients have been increasing worldwide (3-5). The increase can be partly explained by the widespread usage of ultrasound, abdominal computorized tomography (CT) and magnetic resonance imaging in recent years (6).

Cancer and inflammation are inextricably linked, and cancer patients have local and systemic changes in the inflammatory parameters. These include changes in peripheral blood cell numbers

(neutrophils, lymphocytes, and neutrophil to the lymphocyte ratio [NLR]), phenotypes, and gene expression patterns, changes in the erythrocyte sedimentation rate, and alterations in the level of serum inflammatory cytokines, acute-phase proteins (C-reactive protein [CRP], fibrinogen, ferritin, albumin, and transferrin). CRP is a representative marker of a systemic inflammatory response and increased CRP is a poor prognostic factor in several cancer types, including RCC (7-9).

Another marker of systemic inflammatory response is NLR (10). It was recently reported that increased pretreatment NLR is associated with poor outcome in colorectal (11), gastric (12) and ovarian (13) cancer cases. To our knowledge, the prognostic value of NLR in RCC has not been investigated in similar studies. Therefore, the aim of this study was to evaluate the relationship between the tumor stage and grade which are commonly found in patients with renal cell carcinoma.

MATERIALS AND METHODS

After receiving approval from our institutional review boards we retrospectively analyzed the prospective kidney cancer databases of the patients who underwent radical and partial nephrectomy between 2005 and 2014 at our institution. The databases contain information on the clinical presentation, demographics, comorbidity, pathological findings, and preoperative laboratory parameters of patients. A total of 432 patients were screened for the study. The variables abstracted from the databases included age, gender, various pathological parameters, lymphocyte, and neutrophil count. The clinical presentation was categorized as symptomatic or incidental. The tumors accompanied by pain, hematuria, abdominal mass, fever, or weight loss, were categorized as symptomatic tumors. The preoperative neutrophil - to - lymphocyte ratio (NLR) was calculated by dividing the neutrophil count (NC) by the lymphocyte count (LC).

The surgical specimens were processed according to standard pathological procedures and evaluated by the pathologists at our institution. The pathologic staging was performed using the 7th edition of the American Joint Committee on Cancer (AJCC). The histologic subtype was determined according to the 1997 World Health Organization Heidelberg classification, and the tumor nuclear grading was performed according to the Fuhrman nuclear grading system (14). There are several proposed cut off points to stratify LC, NC, and NLR (15-17). The best NLR cut off value was 3.01.

Statistical analysis

The baseline characteristics of the subjects were compared using a two sample t-test or Mann–Whitney U-test for the continuous variables and a chi-square test or Fisher's exact test for the categorical variables. All the statistical tests were two-tailed, and the statistical significance was defined as $P<0.05$. All the analysis was conducted using SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Among the 432 total patients analyzed in our study, there were 275 males (63.7%) and 157 emales (36.3%). The demographic analyses and clinicopathologic characteristics are shown in Table-1. The median age at the time of surgery was 57.76 ± 10.97. Radical and partial nephrectomy was performed in 379 (87.7%) and 53 (12.3%) patients, respectively. Of the tumors, 348 were incidental and 84 were symptomatic. The tumor pathologic stage was determined at a lower stage (T1 or T2) and at a higher stage (T3 or T4) in 360 (83.3%) and 72 (16.7%) of the patients respectively. Also, the histopatologic nuclear grades were stratified as lower grade (G1 or G2) and higher grade (G3 or G4) in 332 (76.9%) and 100 (23.1%) of the patients respectively (Table-1).

Mean laboratory values were CRP 2.73 ± 1.93mg/dL (normal less than 0.3), neutrophil count 4.23 ± 1.46/µL, lymphocyte count 1.61 ± 0.61/µL, and NLR 2.64 ± 1.24. Patients were also stratified according to NLR using cutt off value 3.01. Of 360 patients with lower stage (T1 or T2), 146 were found to have NLR >3.01; while 41 patients with higher stage (T3 or T4) tumor have NLR >3.01. Additionally, of 100 patients with higher grade (G3 or G4) tumor, 71 were found to have NLR >3.01. The details were demonstrated in Table-2.

Table 1 - Patient characteristics and pathological findings.

	No. Pts(%)
Average Age	57.76±10.97
Gender	
Male	275 (63.7%)
Female	157 (36.3%)
Presentation	
Incidental	348 (80.5%)
Symptomatic	84 (19.5%)
Radical Nephrectomy	379 (87.7%)
Partial Nephrectomy	53(12.3%)
Stage	
Lower stage (T1-T2)	360 (83.3%)
Higher Stage (T3-T4)	72 (16.7%)
Nuclear Grade	
Fuhrman Grade 1 and 2	332 (76.9%)
Fuhrman Grade 3 and 4	100 (23.1%)

According to our data, no statistically difference was found in NLR value in terms of age (≥60, <60) and gender distribution. The pretreatment NLR significantly correlated with CRP (p=0.015). The tumor patologic stage (p=008), and the tumor histologic grade (p<0.001) were significantly associated with NLR. The median NC was significantly associated with the tumor stage and the Fuhrman grade (p=0.048, p=0.021), but LC was not associated (p= 0.841, p=0.774). The detailes were depicted in Table-2 and 3.

DISCUSSION

Many well-known prognostic factors exist, including the anatomical factors (the TNM stage and the tumour size), histological factors (the nuclear grade, the histological type, and the microscopic venous invasion), and clinical factors (symptoms, performance status, and anemia) (18). Molecular markers represented by carbonic anhydrase IX are also being investigated as potential

Table 2 - The neutrophil/lymphocyte ratio according to tumor parameters and markers in surgery group.

Characteristic	NLR < 3.01	NLR > 3.01	P value
Age			0.486
≥60	109	82	
<60	136	105	
Gender			0.537
Male	156	119	
Female	89	68	
CRP level			0.015 *
≥0.3	108	103	
<0.3	137	84	
Tumor Stage			0.008 *
T1+T2	214	146	
T3+T4	31	41	
Nuclear Grade			<0.001 *
G1+G2	216	116	
G3+G4	29	71	698.4

* = Statiscally meaningful

Table 3 - NC, LC and NLR associations with pathological parameters.

		Neutrophil Count		Lymphocyte Count	
	No. Pts	Median	P Value	Median	P Value
Tumor Stage			0.048 *		0.841
T1+T2	360	4.08 (3.1-6.2)		1.60 (1.2-2.3)	
T3+T4	72	5.01 (3.5-6.9)		1.71 (1.2-2.2)	
Nuclear Grade					
G1+G2	332	3.96 (3.4-5.3)	0.021 *	1.61 (1.3-2.1)	0.774
G3+G4	100	5.11 (3.4-6.3)		1.67 (1.3-2.2)	

* =Statiscally meaningful

prognostic factors for RCC, but the TNM stage and nuclear grade remain the most important prognostic factors (18, 19).

The neutrophil - to - lymphocyte ratio (NLR) is an easily measurable parameter of the systemic inflammation and stress in patients (10). Our study suggests that the pretreatment NLR may have some prognostic value for the renal cell carcinoma. In this retrospective study, the patients with the lower pretreatment NLR who underwent radical nephroctomy had a lower T stage and nuclear grade with the histopathologic results. This study shows that NLR is an independent prognostic factor after surgery for RCC.

Increasing evidence supports the involvement of systemic inflammation in cancer development and progression (20). A systemic inflammatory response can be assessed by the concentration of acute phase proteins, CRP, fibrinogen, ferritin, albumin and transferrin, or peripheral blood leukocyte components, including neutrophils and lymphocytes. CRP, which is an acute phase protein, has been widely studied as a prognostic parameter for various cancers (9, 21). Increased pretreatment CRP is associated with poor survival in patients with localized and metastatic RCC (7, 8). CRP kinetics also have an impact on the survival of patients with metastatic RCC since the decreased CRP during treatment is a predictor of a better prognosis (22). In regard to the prognostic significance of peripheral blood leukocyte components, neutrophilia and lymphocytopenia were reportedly associated with a poor prognosis in patients with metastatic RCC (23, 24). However, the prognostic significance of the peripheral blood leukocyte component in patients with localized RCC remains unclear.

A high NLR reflects an increased neutrophil and/or a decreased leucocyte ratio. It is generally accepted that the inflammatory processes in the tumor microenvironment play a crucial role in promoting proliferation, invasion, and metastasis of the malignant cells (20, 25). The infiltrating leucocytes, including neutrophils and lymphocytes, are important factors in this process (20). Neutrophilia has been associated with malignancy. However, the cause is not completely understood. Neutrophils in the peripheral blood, or in the tumor microenvironment, were shown to produce pro-angiogenic factors including the vascular endothelial growth factor to stimulate tumor development and progression (26). The cytokines involved in cancer-related inflammation, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNFα), may induce neutrophilia (27, 28). The para-neoplastic production of myeloid growth factors by the cancer cells may represent an additional cause of neutrophilia (29). Hence, a high peripheral neutrophil level may indicate a cancer-related inflammation or tumor progression, and predict a poor clinical outcome. The immune cells that infiltrate into or around the tumor engage in dynamic and extensive crosstalk with the cancer cells (30).

Over the past decade, there has been growing evidence that lymphocytes operate as crucial

components for the adaptive immune system, and are the cellular basis of cancer immunosurveillance and immunoediting (31). Furthermore, infiltrating lymphocytes have been reported to indicate the generation of an effective anti-tumor cellular immune response (32). Therefore, a low lymphocyte count may be responsible for an inadequate immunologic reaction to the tumor, and consequently a weakened defence against cancer, resulting in poor prognosis (33). Activated specific CD8+T cells were shown to control tumor growth by cytotoxic activity and inducing the apoptosis of the tumor cells (34). CD4+T cells are crucial for screening cytokines such as IL-2, which are essential for CD8+T cell growth and proliferation. Furthermore, recent reports reveal that the activation of CD4+T cells is required for the immunization of the CD8+T cells against cancer (35). In vitro studies showed that the cytolytic activity of lymphocytes and natural killer cells were suppressed when co-cultured with neutrophils, and the extent of the suppression was proportionally enhanced by the addition of neutrophils (36, 37). Accordingly, an elevated pre-treatment NLR was reported to correlate with the reduced survival in several types of cancers.

In the RCC field, the first report addressing the usefulness of NLR as a prognostic indicator was published by Ohno et al. and focused on localized RCC (15). In published studies to date, only patients with RCC (38, 39) or the subtypes were the predominantly clear cells (16, 40) included. In a multivariable model, a variable that combined a categorically coded pretreatment and posttreatment NLR, attained statistical significance. Pichler et al. validated preoperative NLR as an independent prognostic factor in 678 patients with nonmetastatic clear cell RCC (38). In a prospective study, in 83 patients categorically coded ANC and ALC were not associated with disease-free survival, but this study accrued relatively few patients (16).

This study had some deficiencies. Firstly, it is a retrospective study with the limited number of patients included. It is unavoidable to state that the post follow-up period is as important as the pathology in the follow-up of the patients involved in the study and the aggressiveness of the tumor. Secondly, our results were based on the experience of a single institution in Turkey with a <600 patients with RCC, and there are substantial differences in RCC incidence and mortality rates between Western countries and Turkey. Therefore, the relationship between RCC and NLR should be validated through massive studies worldwide. The factors that are definitely attested to be effective on RCC risk (such as smoking, obesity, hypertension, genetic susceptibility, and enviroment etc.) were not included in the study. Moreover, although there still is no agreement as to which grading system should be used, the most common system is the one proposed by Fuhrman et al. (14). The Fuhrman grade is based on the nuclear size and shape and the prominence of nucleoli, and we know that when the surgical specimens are evaluated by different pathologist there can be some differences. Thus, it would be better to work with one single pathologist.

Although it is debatable whether or not to estimate the progression of RCC based on the preoperative blood parameters; our findings are valuable as they show the value of NLR in this respect.

CONCLUSIONS

In conclusion, we have found that patients with higher T stage and grade renal cell carcinoma have elevated level of NLR which provides a positive link between RCC and inflammation. This is a practical assessment tool that can easily be used for the risk stratification and prognostic models. Further studies with more patients are needed to confirm our study findings.

ACKNOWLEDGEMENTS

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: All participants signed an informed consent form before being enrolled on the study.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 685-693, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0243

Neutrophil to lymphocyte ratio, a biomarker in non–muscle invasive bladder cancer: a single–institutional longitudinal study

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ABSTRACT

Background: Bladder cancer represents one of the most important clinical challenges in urologic practice. In this context, inflammation has an important role in the development and progression of many malignancies. The objective of the present study was to evaluate the prognostic value of pre-treatment Neutrophil to lymphocyte ratio (NLR) on the risk of recurrence and progression in patients with primary non-muscle invasive bladder cancer.

Materials and Methods: Data obtained from 178 bladder cancer patients who underwent transurethral resection of bladder tumor (TURB) between July 2008 and December 2014 were evaluated prospectively. NLR was obtained from each patient before TURB and defined as the absolute neutrophil count divided by the absolute lymphocyte count. Cox proportional hazards regression model was performed to calculate disease recurrence and progression including NLR.

Results: During the follow-up study (median: 53 months), 14 (23.3%) and 44 (37.9%) (p=0.04) patients respectively with NLR<3 and ≥3experienced recurrence and 2 (3.3%) and 14 (11.9%) experienced progression (p=0.06), respectively. At the multivariate Cox regression analysis, NLR ≥3 was associated with worse disease recurrence (HR: 2.84; p<0.01). No association was found regarding disease progression. The 5-year recurrence free survival was 49% and 62% in patients with NLR≥3 and <3 (p<0.01). The 5-year progression free survival was 77% and 93% in patients with NLR≥3 and <3 (p=0.69).

Conclusion: NLR predicts disease recurrence but not disease progression in NMIBC patients. NLR alterations may depend of tumor inflammatory microenvironment.

ARTICLE INFO

Keywords:
Urinary Bladder Neoplasms; Neutrophils; Biomarkers

Int Braz J Urol. 2016; 42: 685-93

Submitted for publication:
May 01, 2015

Accepted after revision:
October 26, 2015

INTRODUCTION

Bladder cancer represents one of the most important clinical challenges in urologic practice. At the time of initial diagnosis, approximately 70% of patients have cancers confined to the epithelium or the subepithelial connective tissue. In general, these cancers are primarily managed by endoscopic resection (TURB) (1-3). The dilemma in the management of non–muscle-invasive bladder cancer (NMIBC) still remain the risk of recurrence ranging from 30% up to nearly 80% and depending on the risk profile, up to 45% of tumors may progress to muscle-invasive disease within 5 years after initial diagnosis (4). To manage patients with NMIBC based on their individual risk, based

on the course of the disease in well-controlled prospective randomized clinical trials, the European Organization for Research and Treatment of Cancer (EORTC) has developed risk tables to predict the individual risks for tumor recurrence or progression to muscle-invasive disease (4). According to the EORTC risk table, using a scoring system based on previous recurrence rate, tumor number, tumor diameter, T category, World Health Organization (WHO) grade, and the presence of concurrent carcinoma in situ (CIS), to estimate the risk of disease recurrence and progression at 1 and 5 years, patients with bladder cancer were stratified into low-, intermediate-, and high-risk group, which may guide clinical management (5). To further improve the predictive accuracy of risk Tables, a large number of clinical, molecular, biological, and environmental factors are available that have been studied in relation to bladder cancer development, recurrence, and/or progression in NMIBC.

In this context, inflammation has an important role in the development and progression of many malignancies (6). Putative mechanisms include the increased supply of factors that promote carcinogenesis and tumor progression by cells of the innate immune systems such as neutrophils and decreased anti-tumor response by immune cells of the adaptive system such as lymphocytes (7-11).

Moreover, the neutrophil to-lymphocyte ratio (NLR), which can easily be calculated from routine complete blood counts (CBCs) with differentials, is an emerging marker of host inflammation and it has been shown to be an independent prognostic factor for a variety of solid malignancies, including the urinary tract (12-14). Although a recent study found that preoperative NLR was associated with advanced pathologic stage at the time of cystectomy, as well as increased risk for disease recurrence, cancer-specific mortality and all-cause mortality (15), there are sparse and retrospective data on the prognostic role of NLR in patients with NMIBC. The purpose of our study was to evaluate the prognostic value of pre-treatment NLR on the risk of recurrence and progression in patients undergoing TURB for primary NMIBC.

MATERIALS AND METHODS

Data obtained from 178 bladder cancer patients who underwent transurethral resection of bladder tumor (TURB) between July 2008 and December 2014 were evaluated prospectively after institutional internal review board approval was obtained. The diagnosis of bladder cancer was histologically confirmed by TURB in each patient. The clinical T stage of a bladder tumor was determined according to the 2002 Union International Contre le Cancer (UICC) TNM classification of bladder tumors. Tumor size was defined as the maximum tumor dimension estimated at the time of TURB and/or by clinical imaging. Tumors size were categorized in one group if its size was above 3cm and into another if below 3cm. The number and shape of the tumors were examined in the same manner. Concomitance of CIS was revealed in the surgical pathology of TURB. According to the pathology reports, patients were grouped as non-muscle invasive bladder cancer (NMIBC) or muscle-invasive bladder cancer (MIBC). Only patients with NMIBC were included in our study. Demographics and laboratory data, including hemoglobin (Hb) levels, platelet count, neutrophil count, lymphocyte count and serum values of neutrophil to lymphocyte ratio (NLR) were obtained from each patient before TURB. The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. Patient demographics, preoperative full blood count, operative details, and standard histologic tumor characteristics were recorded. Exclusion criteria for the present study were previous operation due to bladder tumor, ongoing treatment for bladder cancer, hematologic disorders or history of conditions that may have influenced blood cell lines such as connective tissue disease, presence of an active infection and/or immunodeficiency virus infection at the time of surgical intervention, prior or concomitant intravesical therapy with Bacille Calmette–Guérin (BCG), prior blood transfusion, and the presence of other cancer types or prior chemotherapy. Patients with non-urothelial cancer or for primary prostatic urothelial carcinoma were also excluded in order to maintain a homogenous cohort.

A second TURB was routinely performed in patients who had a T1 or high-grade tumor on initial TURB. Patients received post-operative intra-vesical instillations based on tumor characteristics, and at the discretion of the treating urologist. Postoperative follow-up consisted of cystoscopy and upper urinary tract imaging performed every three months for the first 2 years, every 6 months 2 to 5 years after surgery, and annually thereafter. Patients with a suspected recurrence underwent TURB. Disease recurrence was defined as the first pathologically confirmed tumor relapse in the bladder, regardless of the tumor stage. Disease progression was defined according to the International Bladder Cancer Group consensus definition for progression in NMIBC, in the presence of an increase in T category from CIS or Ta to T1 (lamina propria invasion), development of≥T2 or lymph node (N+) disease or distant metastasis (M1), or an increase in grade from low to high.

All participants provided written informed consent before enrolment and the study was conducted in accordance with regulatory standards of Good Clinical Practice and the Declaration of Helsinki (1996). The study was approved by our Institutional Research Ethics Committee.

Statistical analysis

All statistical analyses were completed using SPSS versus 19 software (SPSS Inc, IBM Corp, Somers, NY, USA). The qualitative data were tested using the chi-square test or Fisher's exact test as appropriate and the continuous variables, presented as median, were tested by Mann-Whitney U-test.

The significance of the clinic and pathological variables associated with disease recurrence and progression were assessed using the Cox proportional hazards regression model, including age, stage, grade, tumor size, focality, BMI, gender, diabetes, Cis and NLR. Based on the ROC curve, we used a cut-off of 3 for the NLR with the best balance between sensitivity (50%) and specificity (76%) (area under the curve 0.60, 95% confidence interval [CI] 0.51-0.69; p<0.05).

Curves were tested with the log-rank test. Predictive accuracy of the model was assessed in term of the area under the curve (AUC) value, incorporating all significant and independent predictors. AUC values were also calculated by applying base model to the study cohort. The areas under the curve were compared via the Mantel-Haenszel test. For all statistical comparisons significance was considered as p<0.05. One thousand bootstrap resamples were used for all accuracy estimates and to reduce overfit bias. P-value<0.05 was considered as an indicator of statistical significance.

RESULTS

Table-1 lists the baseline characteristics of the cohort. This study included 148 (83.1%) male and 30 (16.9%) female patients. The median age of all 178 patients enrolled in the study was 69.27 (IQR: 63.78-79.44), with a median follow-up of 53 months (IQR: 33.0-76.25). Patients with NLR≥3 were older (74.45 versus 67.94; p=0.02) and exhibited significant differences in term of pathological stage (26.6% versus 20.33%; p<0.05), number of multifocal tumors (53.4% versus 23.72; p=0.04) and Cis (50.0% versus 16.94%; p<0.05) if compared with those with NLR<3 (Table-2).

During the follow-up study, 14 (23.3%) and 44 (37.9%) (p=0.04) patients respectively with NLR<3 and ≥3 experienced recurrence and 2 (3.3%) and 14 (11.9%) experienced progression (p=0.06), respectively. At the multivariate Cox regression analysis, NLR≥3 was associated with worse disease recurrence (HR: 2.84 [IQR: 1.50-5.75]; p<0.01). Pathological stage pT1 (p<0.01), high grade (p<0.01), no. of tumors (p<0.01) and smoking status (p<0.01) were independently predictors of disease recurrence. No association was found between NLR≥3 and disease progression at the multivariate Cox regression analysis (Table-3). The 5-year recurrence free survival was 49% and 62% in patients with NLR≥3 and <3 (p<0.01) (Figure-1). The 5-year progression free survival was 77% and 93% in patients with NLR≥3 and <3 (p=0.69).

The bootstrapping calculations generally confirmed the p-values of the conventional Cox-regression analysis with larger ranges of 95% CI of the ORs (data not shown). After one thousand

Table 1 - Baseline characteristics of the patients.

	Total (n=178)
Age, year, median (IQR)	69.27 (63.78-79.44)
Gender, no. (%)	
Female	30 (16.9)
Male	148 (83.1)
BMI, median (IQR)	27.29 (24.2-29.4)
Hypertension, no. (%)	108 (60.7)
Diabetes, no. (%)	54 (30.3)
Dyslipidemia, no. (%)	36 (20.2)
NLR, median (IQR)	2.41 (1.69-3.62)
Pathologic stage, no. (%)	
pTa	138 (77.5)
pT1	40 (22.5)
Pathologic grade, no. (%)	
Low grade	126 (70.8)
High grade	40 (22.5)
Concomitant CIS, no. (%)	
No	128 (71.9)
Yes	50 (28.1)
No. of tumours (%)	
1	118 (66.3)
2-7	54 (30.3)
≥ 8	6 (3.4)
Tumour size, cm, no. (%)	
< 3 cm	96 (53.9)
≥ 3 cm	82 (46.1)
Smoking status	
Never	18 (10.1)
Former	74 (41.6)
Current	86 (48.3)
EORTC Recurrence	
Low	48 (27.0)
Intermediate	126 (70.8)
High	4 (2.2)
EORTC Progression	
Low	58 (32.6)
Intermediate	82 (46.1)
High	38 (21.3)

IQR = interquartile range; **BMI** = body mass index; **NLR** = neutrofil-to-lymphocyte ratio; **CIS** = carcinoma in situ

bootstrapping resampling, the derived ROC of the base model was 0.75, while when incorporating the NRL to this model the derived AUC value resulted in 0.78. However, the gain in accuracy (3%) was not statistical significant.

DISCUSSION

Non-muscle invasive bladder cancer (NMIBC) represents a heterogeneous group of tumors with different rates of recurrence, progression, and disease-related mortality. NMIBC are initially treated with TURB after which adjuvant therapy should be considered according to tumor-based risk stratification that helps identify the appropriate treatment for each group of patients based on their risk for recurrence or progression (3). To further improve the ability to select the appropriate treatment for each individual patient, especially in doubtful cases such as patients at intermediate or high risk for recurrence or progression, additional, independent pretreatment predictors of outcome may help to further individualize treatment options within each risk group (5, 16). In recent years, the host inflammatory response has gained increasing attention in oncology research. In fact, increasing evidence showed the association of inflammation and cancer. While initially thought to represent an anti-tumor response, immune cells, particularly those of the innate immune system, also exhibit effects that promote carcinogenesis and cancer progression. Proposed mechanisms include increased supply of growth factors, survival factors, pro-angiogenic factors, extracellular matrix-modifying enzymes and inductive signals that may lead to epithelial-to-mesenchymal transition (7, 17). Recently, several inflammatory parameters obtained from blood tests, including C-reactive protein, NLR, platelet-lymphocyte ratio, and albumin levels, were associated with the treatment outcome of several malignancies (18). In this context, there is a biological rationale for using NLR, the ratio of circulating neutrophils (immune cells of the innate system) to lymphocytes (immune cells of the adaptive system), as a measure of the systemic host response when evaluating the association between inflammation and cancer outcomes. In fact, an enhanced neutrophil

Table 2 - Clinical characteristics of the patients according to neutrophil-to-lymphocyte ratio.

	NLR < 3 (n=118)	NLR ≥ 3 (n= 60)	p-value
Age, year, median (IQR)	67.94 (63.33-76.97)	74.45 (44.75-80.41)	0.02
Gender, no. (%)			0.96
Female	20 (16.9)	10 (16.7)	
Male	98 (83.1)	50 (83.3)	
BMI, median (IQR)	27.29 (24.22-32.44)	27.15 (24.20-28.39)	0.44
Hypertension, no. (%)	70 (59.3)	38 (63.3)	0.60
Diabetes, no. (%)	32 (27.1)	22 (36.7)	0.19
Dyslipidemia, no. (%)	22 (18.6)	14 (23.3)	0.46
NLR, median (IQR)	1.94 (1.57-2.41)	4.02 (3.55-4.82)	<0.01
Pathologic stage, no. (%)			0.03
pTa	103 (87.28)	44 (73.3)	
pT1	15 (12.72)	16 (26.6)	
Pathologic grade, no. (%)			0.22
Low grade	90 (76.27)	36 (60.0)	
High grade	28 (23.73)	24 (40.0)	
Concomitant CIS, no. (%)			0.01
No	98 (83.05)	24 (40.0)	
Yes	20 (16.94)	36 (60.0)	
No. of tumours (%)			0.04
1	90 (76.28)	28 (46.6)	
2-7	28 (23.72)	26 (43.4)	
≥ 8	0 (0)	6 (10.0)	
Tumour size, cm, no. (%)			0.60
< 3 cm	67 (56.78)	29 (48.33)	
≥ 3 cm	51 (43.22)	31 (51.66)	
Smoking status			0.06
Never	12 (10.2)	6 (10.0)	
Former	63 (53.4)	11 (18.3)	
Current	43 (36.4)	43 (71.7)	
EORTC Recurrence			0.34
Low	32 (27.1)	16 (26.7)	
Intermediate	86 (72.9)	40 (66.6)	
High	0 (0.0)	4 (6.7)	
EORTC Progression			0.15
Low	39 (33.0)	19 (31.7)	
Intermediate	62 (52.5)	20 (33.3)	
High	17 (14.5)	21 (35.0)	
Chemotherapy instillation	90 (76.27)	40 (66.6)	0.17
Immunotherapy instillation	10 (8.5)	9 (15.0)	0.18

IQR = interquartile range; **BMI** = body mass index; **NLR** = neutrofil-to-lymphocyte ratio; **CIS** = carcinoma in situ

Table 3 - Multivariate Cox-regression analysis for predictors of disease recurrence and progression adjusted for BMI and intravesical therapy.

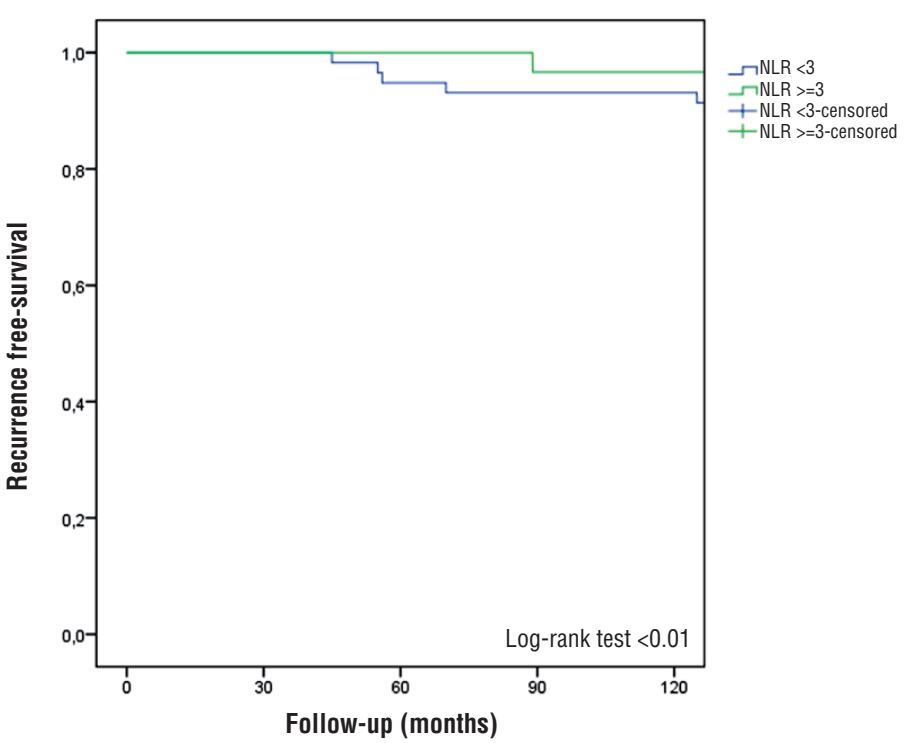
	Disease Recurrence		Disease Progression	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age, year			1.02 (0.94-1.11)	0.60
Gender, female vs. male	0.48 (0.15-1.53)	0.22	0.30 (0.10-0.50)	0.98
Diabetes, yes vs. no	1.25 (0.64-2.42)	0.50	1.20 (0.19-7.54)	0.84
Pathologic stage				
pTa	1.00 (Ref.)		1.00 (Ref.)	
pT1	4.18 (1.87-9.35)	<0.01	5.75 (0.54-60.99)	<0.05
Pathologic grade				
Low grade	1.00 (Ref.)		1.00 (Ref.)	
High grade	2.88 (1.33-6.18)	<0.01	2.96 (0.46-18.86	<0.05
Concomitant CIS				
No	1.00 (Ref.)		1.00 (Ref.)	
Yes	2.20 (0.82-5.88)	0.11	7.27 (1.01-14-76)	<0.05
No. of tumours				
1	1.00 (Ref.)		1.00 (Ref.)	
2-7	2.25 (1.25-4.07)	<0.01	5.33 (0.69-41.25)	0.11
≥ 8	1.62 (0.67-7.12)	<0.01	0.98 (0.60-1.20)	0.98
Tumour size, cm				
< 3 cm	1.00 (Ref.)		1.00 (Ref.)	
≥ 3 cm	1.57 (0.84-2.92)	0.15	2.26 (0.42-12.27)	0.34
Smoking status				
Never	1.00 (Ref.)		1.00 (Ref.)	
Former	3.13 (1.20-8.78)	<0.01	1.14 (0.30-3.04)	<0.05
Current	1.78 (0.95-3.30)	<0.01	5.62 (1.32-9.45)	<0.05
NLR				
< 3	1.00 (Ref)		1.00 (Ref.)	
≥ 3	2.84 (1.50-5.75)	<0.01	5.35 (0.39-73.70)	0.21

response and/or suppression of lymphocyte leading to a high NLR might promote carcinogenesis and inhibit anti-tumor immune response (18, 19). Several studies have shown that a pretreatment high NLR was associated with worse disease-specific and overall survival in muscle–invasive bladder cancer and the upper urinary tract (14, 15, 18, 20). Similarly, a correlation between high NLR levels and muscle-invasive disease at TURB was found by other studies (2, 18). The role of negative predictor of recurrence-free survival and cancer specific survival of elevated NLR was also confirmed in a recent meta-analysis including 17 studies involving 3159 cases with urinary cancers (21). However, most previous studies which evaluated the predictive value of NLR in bladder cancer, were retrospective and included a mixed and heterogeneous group of patients with muscle-invasive and high risk non-muscle invasive tumors. Besides heterogeneity, divergence may result from many other factors, including age distribution, gender, lifestyle and so on. Herein we found an association between high NLR levels and worse disease recurrence-free survival even after

adjustment for common risk factors but not for progression free-survival as recently reported by a retrospective study (18). These findings are consistent with previous reports that found an association between greater NLR and unfavorable tumor characteristics, worse recurrence-free, disease specific and overall survival in patients with muscle-invasive bladder cancer or high--risk patients with NMIBC (2, 18). However, on the contrary to recent report (18), our study did not found association between higher NLR and disease progression at the multivariate analysis. We recognize that our study is limited by its small sample size and non-randomized nature. Furthermore, we acknowledge the relative arbitrary cut point of NLR ratio used for the analyses in our study, nevertheless, this threshold allows our data to be contextualized in light of previously published analyses, which, likewise, dichotomized NLR (2, 7, 15). In addition, despite the use of standard treatment protocols, information regarding the use of intra-vesical maintenance treatment, which may have influenced outcomes, was lacking. Furthermore, Ta and T1 category tumors are distinct diseases that may be associated in a different manner with NLR. Larger cohorts are required to evaluate NLR separately in both these groups. Finally, we recognize that these data are from a single, tertiary referral institution and, as such, require external validation. Nevertheless, within the limitations of a nearly-phase study for marker assessment, our findings suggest that NLR is a potential prognostic marker for prediction of disease recurrence in NMIBC and may better risk-stratify patients in the pre and postoperative settings in order to guide treatment strategies.

It could be also postulated that NLR alterations in NIMBC patients mainly depends of tumor inflammatory microenvironment and cancer biology raising new opportunities for therapeutic interventions (22). The near future of NLR application could be also directed into the interpretation of immune response of BCG therapy. It should be in fact taken into account that NLR is an expression of the immune system, a marker that can be also associated with immunotherapy and considered as a potential predictive factor of BCG response.

Figure 1 - Kaplan-Meier estimates of recurrence-free survival stratified by NLR.



Further prospective, well-controlled clinical studies of diverse patients in multiple institutions are required to validate the role of NLR as a prognostic marker, which may improve current risk stratification tools and treatment outcome in this group of patients.

CONCLUSIONS

In conclusion, NLR is an inexpensive hematologic test based on commonly measured parameters that may predict disease recurrence, T1 category, concomitant Cis and high tumor grade in a cohort of patients with NMIBC. Whereas our results suggest that NLR may have a role as a prognostic biomarker, further studies are needed to maximize the clinical utility of NLR in patients with NMIBC.

ABBREVIATIONS

NLR = Neutrophil to lymphocyte ratio
NMIBC = Non muscle invasive bladder cancer
TURB = Transurethral resection of bladder tumor
AUC = Area under the curve

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 694-703, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0226

Sunitinib treatment in patients with advanced renal cell cancer: the Brazilian National Cancer Institute (INCA) experience

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ABSTRACT

Purpose: The aim of this study was to assess the impact of sunitinib treatment in a non-screened group of patients with metastatic renal cell cancer (mRCC) treated by the Brazilian Unified Health System (SUS) at a single reference institution.
Material and Methods: Retrospective cohort study, which evaluated patients with mRCC who received sunitinib between May 2010 and December 2013.
Results: Fifty-eight patients were eligible. Most patients were male 41 (71%), with a median age of 58 years. Nephrectomy was performed in 41 (71%) patients with a median interval of 16 months between the surgery and initiation of sunitinib. The most prevalent histological subtype was clear cell carcinoma, present in 52 (91.2%) patients. In 50 patients (86%), sunitinib was the first line of systemic treatment. The main adverse effects were fatigue (57%), hypothyroidism (43%), mucositis (33%) and diarrhea (29%). Grade 3 and 4 adverse effects were infrequent: fatigue (12%), hypertension (12%), thrombocytopenia (7%), neutropenia (5%) and hand-foot syndrome (5%). Forty percent of patients achieved a partial response and 35% stable disease, with a disease control rate of 75%. Median progression free survival was 7.6 months and median overall survival was 14.1 months.
Conclusion: Sunitinib treatment was active in the majority of patients, especially those with low and intermediate risk by MSKCC score, with manageable toxicity. Survival rates were inferior in this non-screened population with mRCC treated in the SUS.

ARTICLE INFO

Keywords:
Neoplasm Metastasis; Kidney Neoplasms; sunitinib [Supplementary Concept]; Retrospective Studies

Int Braz J Urol. 2016; 42: 694-703

Submitted for publication:
April 20, 2015

Accepted after revision:
January 03, 2016

INTRODUCTION

Renal cell cancer (RCC) represents 2-3% of all cancers. Patients are diagnosed with locally advanced (stage III) or metastatic (stage IV) disease in approximately 33%, and 40% of those treated with curative intent surgery experience recurrence (1). Without treatment, the prognosis for metastatic renal cell cancer (mRCC) patients is restricted, with a median survival ranging from 6 to 12 months and a survival rate in two years between 10 and 20% (2). Immunotherapeutic agents, such as interleukin-2 (IL-2) and interferon-alpha (IFNα), were historically the only therapeutic options

available for mRCC, despite the low response rates and a limited impact on overall survival (OS) (3-6).

The better understanding of the biological mechanisms related to carcinogenesis and intracellular signaling pathways enabled the creation of new treatment strategies for mRCC, with the introduction of targeted therapies. Sunitinib was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor 1 receptor (CSF-1R), and the glial cell line-derived neurotrophic factor receptor (RET). The inhibition of these tyrosine kinase (TK) receptors affects cellular signal transduction, thus influencing the processes involved in tumor growth, systemic dissemination and angiogenesis (7, 8).

The biological rationale for the use of VEGF pathway blocking agents for RCC is explained by the fact that the RCC is a highly vascularized tumor with high levels of VEGF and VEGFR expression. Furthermore, RCC is associated with mutations and/or defects in Von Hippel-Lindau (VHL) gene function and hypoxia-inducible genes, resulting in increased production of hypoxia-inducible factor (HIF), VEGF and PDGF (8, 9).

Motzer et al. randomized 750 treatment-naive RCC patients to receive sunitinib or IFNα in a prospective, phase III trial. Sunitinib treatment was associated with a higher objective response rate (47% versus 12%, p<0.001), leading to a median progression-free survival (PFS) of 11 months in the sunitinib arm, compared to 5 months in IFNα arm (p<0.001). The overall survival (OS) was 26.4 months in sunitinib arm and 21.8 months in IFNα arm (HR 0.82 p=0.051) (10, 11). Cella et al. demonstrated gain in quality of life for sunitinib, when compared to IFNα, and that the patients achieving a better quality of life had a longer progression-free survival, while the presence of hepatic metastases and a higher number of risk factors, as per Memorial Sloan Cattering Cancer Center (MSKCC) risk score, at the start of study were correlated with a shorter progression-free survival (12-14). Patients in the sunitinib arm experienced the following events as most common grade 3-4 toxicities: systemic hypertension occurred in 12% of the patients, fatigue in 11%, diarrhea in 9% and hand-foot syndrome in 9%.

The purpose of this study was to assess the impact of sunitinib treatment in terms of OS, PFS, and toxicity in a non-screened group of patients with mRCC treated by the Brazilian Unified Health System (SUS) at a single reference institution, while assessing the reproducibility of the clinical trial results in patients from routine clinical practice.

MATERIALS AND METHODS

Between May 2010 and December 2013, 65 consecutive patients provided informed consent for the treatment of metastatic renal cell carcinoma with sunitinib at our institution (Clinical Oncology Service – Brazilian National Cancer Institute (INCA) – Rio de Janeiro, Brazil) and had their medical records reviewed. This study was approved by the Ethics in Human Research Committee of INCA and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

We performed a retrospective cohort study. Clinical data including demographics, Eastern Cooperative Oncology Group (ECOG) performance status (PS), Memorial Sloan Kettering Cancer Center (MSKCC) risk classification for mRCC, stage, histology, previous therapies, and the toxicity related with sunitinib therapy were collected.

Response to treatment was assessed using clinical and, especially, radiological criteria as follows: complete response (CR), partial response (PR), progressive disease (PD), and stable disease (SD). The radiological evaluation was based on the Response Evaluation Criteria in Solid Tumors, version 1.1 (15), with a frequency determined by the assistant physician. The medium interval between the radiological evaluations was 3 months.

In our institution we standardized the evaluation of toxicities by the National Cancer Institute Common Toxicity Criteria, version 3.0, every month (16).

Exclusion criteria included patients without sufficient records to fill the questionnaire and another primary neoplasm except non-melanoma skin cancer.

Patients who were treated with other first line therapy than sunitinib and subsequently received the referred drug were not evaluated for PFS and OS, as well patients with histology of non-clear cell carcinoma. Toxicities were evaluated in all patients independent of histology and line of treatment.

Overall survival was estimated from the time of the first palliative treatment day until death or, for living patients, the last available follow-up, and PFS was measured from the date of the sunitinib treatment beginning to either first progression or death or the date of last contact for patients who were alive and progression-free, in both cases using the Kaplan-Meier method. Survival curves were compared by Log-Rank test. Association between response rate and MSKCC risk classification was analyzed by Fisher's Exact test. All analyses were performed with the SPSS software, version 18.0.

RESULTS

Sixty-five patients were evaluated for this analysis; however, only 58 were eligible: 7 patients were excluded due to insufficient data in their records for the application of the research protocol.

Most of eligible patients were male – 41 (71%), with a median age of 58 years (18-80) and the majority underwent previous nephrectomy – 41 (71%), with a median interval between surgery and treatment beginning of 16 months (1-180). The most prevalent histological subtype was clear cell carcinoma, present in 52 (91.2%) patients.

The other histological subtypes found were: chromophobe cell in 1 patient (1.8%) and papillary cell in 3 patients (5.3%). One patient had a mixed tumor with papillary and clear-cell renal carcinoma characteristics (1.8%). Two patients from this cohort had partial responses and three had stable disease with sunitinib treatment.

The most frequent metastatic sites were lung, present in 42 patients (72%), followed by bone in 26 patients (45%), lymph nodes in 21 patients (36%) and liver in 9 patients (15%). Table-1 summarizes patients and tumor characteristics.

The standard dose of sunitinib used was 50mg orally once daily for four weeks, with two-weeks intervals (scheme 4:2). There was a change in the dose or regimen due to side effects in 24 patients (41%): 19 patients (33%) used 50mg in 2:1 scheme, three patients (5%) used the every-other-day scheme and 2 patients (3%) used 25mg a day on a continuous basis.

Nine patients began the treatment with 50mg in 2:1 scheme due to their borderline PS.

All the patients were assessed for toxicity. The most common adverse effects found were fatigue (57%), hypothyroidism (43%), diarrhea (29%), skin changes such as yellowing of the skin and rash (29%), mucositis (33%), hand-foot syndrome (HFS) (29%), hypertension (24%) and nausea (24%). Grade 3 and 4 adverse effects were infrequent: fatigue (12%), hypertension (12%), thrombocytopenia (7%), neutropenia (5%) and HFS (5%). Only one patient of those who experienced severe neutropenia had fever associated, with the need for hospital admission. Table-2 describes the treatment toxicities.

Rare adverse effects, possibly related to the use of the medication, that were not described in the tables below were: one acute coronary syndrome (G4), one transaminases elevation (G2), one nephropathy (G1), two deep vein thrombosis with pulmonary thromboembolism (G3, G3) and one anastomosis dehiscence (G3).

With the objective of avoiding confounding factors in the main analysis, only patients with renal clear cell carcinoma who were exposed to sunitinib as the first line of palliative treatment were evaluated for response, PFS and OS. A total of 45 (76%) patients were included in this analysis. Eighteen (40%) had partial response (PR), sixteen (35.6%) stable disease (SD) and 11 (24.4%) progressive disease (PD). Thus, approximately, 75% of the patients obtained clinical benefit with sunitinib treatment. The response rates were also assessed according to MSKCC risk groups, outlined in Table-3.

We performed the PFS estimative in the 45 patients eligible to analysis and according to MSKCC risk groups of these patients. The global PFS was 7.69 months. When applying MSKCC criteria, patients with favorable, intermediate and high risk had a PFS of 8.9 months, 5.1 months and 2.6 months, respectively, with statistically significant difference between favorable and high risk groups (Figure-1). The median OS

Table 1 - Patients characteristics.

	n	%
Age, years		
Median	58.0	
Range	18–80	
ECOG PS		
0-1	37	64
2	12	20
Histology		
Clear cell	52	91
Non-clear cell	6	9
Previous nephrectomy	41	71
Metastatic sites		
Lung	42	72
Bone	26	45
Lymph nodes	21	36
Liver	9	15
Adrenal glands	5	9
Pancreas	4	7
Locoregional	4	7
Pleura	3	5
Brain	2	3
Previous systemic therapy [a,*]		
No previous systemic therapy	50	86
Antiangiogenic [b]	3	5
Cytokine	7	12
mTOR inhibitor [c]	2	3
Risk group according MSKCC criteria [d]		
Low risk	19	33
Intermediate risk	23	38
High risk	16	28
Total	**58 patients**	

[a] Includes 3 (7%) patients that participated in clinical trials
[b] Include sorafenib and bevacizumab.
[c] Include everolimus and temsirolimus.
[d] The MSKCC modified risk factors are PS ECOG ≥2, anemia, hypercalcemia, increased lactate dehydrogenase and time between nephrectomy and treatment shorter than 12 months [5]. MSKCC: Memorial Sloan-Kettering Cancer Center.

Table 2 - Prevalence and grade of adverse effects (%)*

Adverse effect	Grade			
	All	1	2	3
Fatigue	57	21	24	12
Diarrhea	29	9	17	3
Skin changes	29	11	16	2
Mucositis	33	17	16	NA
Hand-foot syndrome	29	19	5	5
Hypertension	24	3	9	12
Nausea	24	15	9	NA
Anemia	19	3.5	12	3.5
Thrombocytopenia	15	3	5	7
Epistaxis	9	3.5	3.5	2
Neutropenia	10	2	3	5
Edema	5	2	3	NA
Neuropathy	5	3	2	NA
Change in Taste	5	3	2	NA
Constipation	5	2	3	NA
Bleeding	5	2	3	NA

* Considering valid information
NA, Not applicable

Table 3 - Response rates assessed according to MSKCC risk groups.

			Response			
			Total	PR	SD	PD
MSKCC criteria	Favorable risk	Number of patients	**16**	10	5	1
		(%)	**35.6%**	55.6%	31.3%	9.1%
	Intermediate risk	Number of patients	**16**	6	7	3
		(%)	**35.6%**	33.3%	43.8%	27.3%
	High risk	Number of patients	**13**	2	4	7
		(%)	**28.9%**	11.1%	25.0%	63.6%
Total		**Number of patients**	**45**	**18**	**16**	**11**
		(%)	**100%**	**40%**	**35.6%**	**24.4%**

p-value = 0.003 by Fisher's Exact test; **PR** = partial response; **SD** = Stable disease; **PD** = Progressive disease **MSKCC** = Memorial sloan cattering cancer center (MSKCC)

was 14.1 months, without statistically significant variation among risk groups.

Among the 45 eligible patients for PFS and OS analysis, we found six with PFS greater than 20 months. Three (50%) had MSKCC low risk, two (33.3%) intermediate risk and one (16.7%) high risk. The most common metastatic sites in this subset of patients were: lymph nodes (50%), lungs (50%), bones (33%) and loco-regional (16.7%).

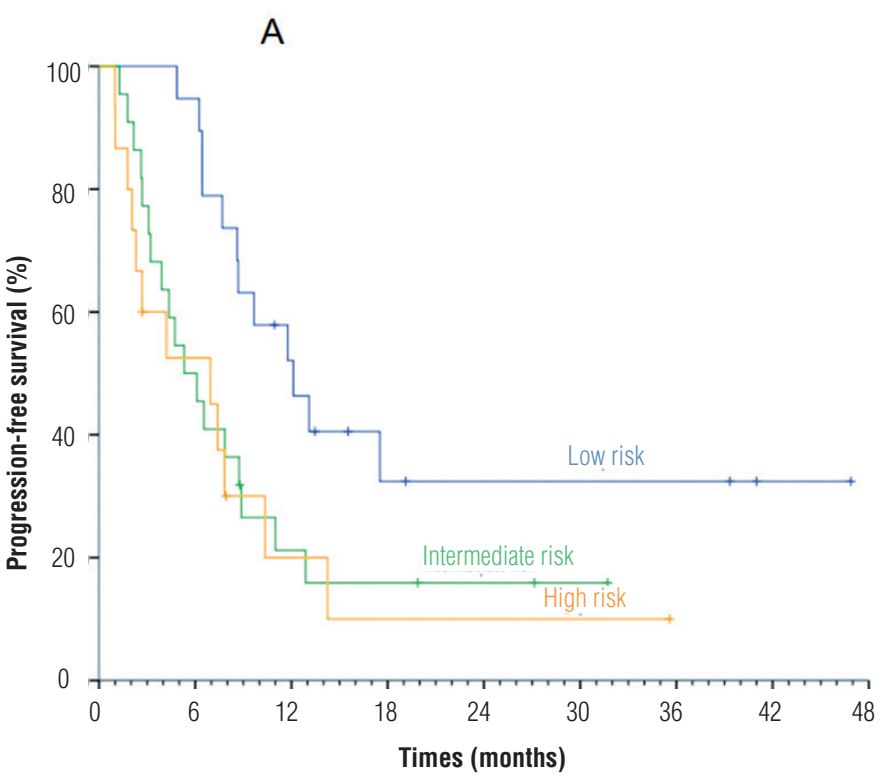
In eight patients (14%), sunitinib was the second or third line of systemic treatment. Among those who underwent previous treatment, four patients had partial response, one stable disease and two progressive disease with sunitinib treatment. Seven patients received interferon alpha, two received the combination of everolimus and bevacizumab in a clinical trial, one patient was treated with IFN and sorafenib and one patient sorafenib and one patient with temsirolimus.

Only 9 (16%) patients underwent a subsequent line after sunitinib treatment. m-TOR inhibitors were the most frequently used agents: 2 patients received temsirolimus and 5 patients everolimus. Furthermore, one patient received sorafenib and another pazopanib. The low rate of treatments after sunitinib progression occurred because at Brazilian public health facilities like INCA, second or third line treatments for mRCC are not routinely available.

DISCUSSION

We reported a retrospective analysis of the use of sunitinib in advanced renal cell cancer patients treated at INCA's clinical oncology outpatient department. All patients were treated at the public health setting under the Brazilian Unified Health System (SUS).

Figure 1 - Progression free survival according to MSKCC risk groups.



p-value = 0.029 by Log Rank test

The retrospective nature of this study raises the possibility of bias once some clinical details were not identified on the medical chart reviews. It is important to emphasize that our data express INCA's reality and, probably, the reality of other Brazilian and Latin America health institutions. So, the data in this article is of a great value and can help other institutions to organize their budget.

Firstly, the population is representative of the daily clinical practice in the public oncology services in Brazil. The population has characteristics that are different from the patients represented in prospective clinical trials. A higher proportion of factors associated with a poorer prognosis is seen, such as MSKCC high risk group, higher proportion of elderly patients and patients with performance status equals to or higher than 2 and/or who did not were submitted to previous nephrectomy.

The safety and tolerability was similar to that described in the medical literature (11, 12, 17-19). Most adverse events were mild and did not prevent the continuity of sunitinib treatment. Approximately 41% of the patients had their therapeutic regimens changed due to intolerance or by decision of the physician in charge, probably related to the performance status and comorbidities. Most of them were treated with regimen adjustment (50mg with a 2:1 interval), keeping the dose intensity. The rates of dose change are similar to literature data (17-19).

Sunitinib was a well-tolerated drug for most patients with 0-2 performance status; however, in patients with PS≥3, it had more harmful effects and severe toxicities, including death.

The median PFS and OS were lower than prospective data, probably because the population was non-screened, with a higher frequency of poor prognosis factors and lower frequency of second-line treatments. Nevertheless, a high response and clinical benefit rate (>75% of patients) was found. There is a risk that such data is overestimated by the methodology used in this study. Not surprisingly, patients with low risk, as per MSKCC score, had a higher rate of partial response and stable disease, as well a trend towards longer overall survival and a statistically significant better progression-free survival compared with high risk patients. We suggest that, in our population of patients with mRCC, clear cell histology and MSKCC low to intermediate risk, sunitinib is an active agent for first line therapy. Nevertheless, in MSKCC high risk patients, because response to sunitinib was poor, alternative treatments like temsirolimus need also to be considered (20).

Table-4 compares the results of this study with the results of studies performed in other countries and the controlled prospective study performed by Motzer et al. (11), which led to the approval of the drug.

Another factor that could be involved in the inferior survival is the absent information on second or third line therapies, as these therapies are not available for patients in the Brazilian Unified Health System (SUS), and most of the patients received only one line of treatment for metastatic disease. So, agents like everolimus, sorafenib and axitinib were not routinely prescribed (21-23). These agents showed activity in patients who failed to VEGF targeted therapies increasing progression free survival, but without impact in overall survival. Some reasons that could explain why OS benefit was not achieved in the studies evaluating the drugs described above are: study design and PFS as primary endpoint instead of OS, crossover between study groups and sequential treatments. Escudier et al. showed overall survival benefit of 3.5 months with sorafenib when post-crossover placebo survival data were censored, reinforcing our hypothesis (22).

CONCLUSIONS

Sunitinib treatment was active in the majority of patients, especially those with low and intermediate risk by MSKCC score, with manageable toxicity. Furthermore, patients categorized as low-risk exhibited a trend towards higher response rate, longer progression-free survival and overall survival. Overall and progression-free survival for our patient's cohort were inferior when compared to phase 3 trials probably because the present study evaluated a non-screened population with mRCC treated at the Brazilian public health system.

Table 4 - Comparison among studies evaluating sunitinib treatment in metastatic renal cell cancer.

Site	N	Prognostic factors	G3-4 Toxicities	Response Rate	PFS (m)	OS (m)
Coelho et al.	58	28.9% MSKCC high risk, 36% PS≥2, 27% ≥ 65 years old, 29 % without nephrectomy	12% fatigue, 12% hypertension, 7% thrombocytopenia, 5% neutropenia, 5% hand-foot syndrome.	Assessed in 45 patients: 40% partial response, 35.6% stable disease	7.6	14.1
Motzer et al. (11, 12)	375	10% without nephrectomy, 6% MSKCC high risk, PS 0-1, median age of 62 years	12% hypertension, 11% fatigue, 9% hand-foot syndrome and 9% diarrhea.	47%	11	26.4
Gore et al. (16)	4564	11% without nephrectomy, 9% MSKCC high risk, 14% PS≥ 2, 32% age ≥ 65 years	8% fatigue, 8% thrombocytopenia, 6% neutropenia, 6% asthenia, 6 % HFS, 5 % diarrhea	1% complete response, 16% partial response, 59% stable disease	10.9	18.4
Ansari et al. (17)	56	14 % without nephrectomy, 18% PS≥2, median age of 61 years, 50% received interferon alpha as previous treatment	21 % mucositis, 14% leucopenia, 13% neutropenia, 9% thrombocytopenia, 7% increased creatinine, 5% diarrhea, 5% hypertension, 5% HFS	Assessed in 49 patients: 41% partial response, 37% stable disease	12.2 no difference between patients receiving and not receiving immunotherapy	18.2 no difference between patients receiving and not receiving immunotherapy
Hong et al. (18)	76	Median age of 57.5 years, 10.5% PS =2, 10% MSKCC high risk, 4.3% without nephrectomy	38.2% thrombocytopenia, 10.5 % fatigue, 10.5% mucositis, 9.2 % HFS	27.6% objective response and 84.2% with controlled disease	7.2	22.8

ACKNOWLEDGEMENTS

We would like to thank Pfizer for providing Sunitinib.

LIST OF ABBREVIATIONS

INCA = The Brazilian National Cancer Institute
RCC = Renal cell cancer
mRCC = Metastatic renal cell cancer
IL-2 = Interleukin-2
IFNα = Interferon-alpha
OS = Overall survival
PFS = Progression-free survival
PDGFRA AND PDGFRB = Platelet-derived growth factor receptors
VEGFR1, VEGFR2 AND VEGFR3 = Vascular endothelial growth factor receptors

KIT = Stem cell factor receptor
FLT3 = Fms-like tyrosine kinase-3
CSF-1R = Colony stimulating factor 1 receptor
RET = Glial cell line-derived neurotrophic factor receptor
TK = Tyrosine kinase
MSKCC = Memorial sloan cattering cancer center
SUS = Brazilian unified health system
HFS = Hand-foot syndrome

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 704-709, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2014.0598

Does an asymmetric lobe in digital rectal examination include any risk for prostate cancer? results of 1495 biopsies

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ABSTRACT

Introduction: Despite the well-known findings related to malignity in DRE such as nodule and induration, asymmetry of prostatic lobes, seen relatively, were investigated in a few studies as a predictor of prostate cancer so that there is no universally expected conclusion about asymmetry. We aimed to compare cancer detection rate of normal, asymmetric or suspicious findings in DRE by using biopsy results.

Materials and Methods: Data of 1495 patients underwent prostate biopsy between 2006-2014 were searched retrospectively. Biopsy indications were abnormal DRE and or elevated PSA level(>4ng/mL). DRE findings were recorded as Group 1: Benign DRE, Group 2: Asymmetry and Group 3: Nodule/induration. Age, prostatic volume , biopsy results and PSA levels were recorded.

Results: Mean age, prostate volume and PSA level were 66.72, 55.98 cc and 18.61ng/mL respectively. Overall cancer detection rate was 38.66 % (575 of 1495). PSA levels were similar in group 1 and 2 but significantly higher in group 3. Prostatic volume was similar in group 1 and 2 and significantly lower in Group 3.

Malignity detection rate of group 1,2 and 3 were 28.93%, 34.89% and 55.99% respectively. Group 1 and 2 were similar (p=0.105) but 3 had more chance for cancer detection.

Conclusion: Nodule is the most important finding in DRE for cancer detection. Only an asymmetric prostate itself does not mean malignity.

ARTICLE INFO

Keywords:
Prostate; Neoplasms; Digital Rectal Examination

Int Braz J Urol. 2016; 42: 704-9

Submitted for publication:
January 12, 2015

Accepted after revision:
April 05, 2016

INTRODUCTION

Digital rectal examination (DRE) for prostate is an important diagnostic procedure for both benign and malignant diseases. Prostate specific antigen (PSA) and DRE are the best-known predictive factors for positive prostate biopsies (1). Although there is an increase in cancer detection with PSA, transrectal ultrasonography (TRUS) and magnetic resonance imaging (MRI) modalities, DRE is the most frequently used and the first-preferred tool for cancer detection in prostate. Indications for prostate needle biopsy (PNB) include elevated serum prostate-specific antigen (PSA) and/or abnormal DRE (2). In some studies (3), suspicious DRE findings were described as nodule, induration and asymmetry. In other studies, only induration or nodule were considered suspicious for cancer. The asymmetry, i.e. one lobe having higher volume than the other one, was defined as benign finding (4). While there are well-known findings associated with malignancy in DRE such as nodule and induration, the contour alterations or asymmetry of prostatic lobes, seen relatively, were also investigated in a few studies as predictors of prostate cancer (5, 6), so there is no universally expected conclusion regarding asymmetry.

The aim of our study was to compare the cancer detection rates of normal, asymmetric or suspicious prostate such as nodule in DRE by using TRUS guided prostate biopsy results of 1495 patients.

MATERIALS AND METHODS

Following the approval of local ethics committee, data belonging to 1495 patients who had undergone TRUS guided tru-cut prostate biopsy in our institution between 2006 and 2014 were screened retrospectively. Biopsy indications included abnormal DRE findings such as nodule or induration identified by an urologist at our department, elevated PSA levels (>4ng/mL), increased PSA velocity (>0.7ng/mL), low free/total PSA percentage (<18%) and density. Exclusive asymmetry finding was not considered as an abnormal DRE finding for biopsy indication. Patients with asymmetric prostatic lobe had biopsy due to high PSA level or increased PSA velocity. Initial biopsies included 12 cores in most of the patients. Eighteen or 24 cores were taken from patients who had history of recurrent biopsies and larger volumes of prostate (>60cc). DRE findings were grouped as follows: group 1: patients with benign DRE, group 2: patients with asymmetric prostatic lobe, group 3: patients with nodule and/or induration by palpation. If a lobe is found to be larger than the other in DRE, it is considered as asymmetry. The asymmetric lobes did not have any additional suspicious lesions such as nodule or induration. Age, prostatic volume on TRUS, pathology results of biopsies, and PSA levels were also recorded. Then, DRE findings, biopsy results, PSA levels and prostatic volumes of all groups were compared.

Statistical methods

SPSS for Windows version 16.0 (SPSS Inc Chicago Illinois USA) was used for data analysis. One-Way ANOVA test and Tukey's post-hoc test were used for comparison of continuous data in multiple groups, and chi-square test was used for comparison of categorical data of any two groups. P<0.05 level was considered as significant in all analyses.

RESULTS

Mean age of patients enrolled in this study was 66.72, mean prostatic volume on TRUS was 55.98cc and mean PSA level was 18.61ng/mL. Overall cancer detection rate was 38.66% (575/1495) (Table-1). 819 of 1495 (54.78%) patients had benign DRE findings, 484 (32.37%) patients had suspicious DRE findings such as nodule or induration, and 192 (12.84%) patients had asymmetric lobe in DRE and asymmetry was confirmed by TRUS assessment. All asymmetric lobes in DRE had higher volume than counter lobes in TRUS assessment.

When we compared the groups for age, the mean age for benign and asymmetry groups was similar (p=0.607), nodule group had higher age average than benign and asymmetry groups (p=0.027, p=0.043).

PSA levels were similar in groups 1 and 2, however group 3 had significantly higher PSA levels than the others (Table-2).

Prostatic volume was statistically similar in groups 1 and 2 (p=0.359). Group 3 had significantly lower prostatic volume compared to others (p=0.027).

We could not obtain data for asymmetric side in 16 patients (8.33%). 106 of 192 asymmetric lobes were on the right side (55.2%), and 70 were on the left side (36.45%). 67 of 192 (34.89%) patients with asymmetric lobe had cancer somewhere in whole prostate. Remaining 125 (65.10%) did not have malignancy. Asymmetric lobe included malignancy in 46 of 67 (68.65%)

Table 1 - Patients' data.

DRE findings	Benign	819 (54.78%)
	Asymmetry	192 (12.84%)
	Nodule/induration	484 (32.37%)
Mean age		66.72
Mean PSA (ng/dL)		18.61
Mean Prostatic volume (cc)		55.98
Mean biopsy cores		16.4
Overall cancer detection rate (%)		38.66

Table 2 - Mean PSA level and prostatic volume of 1495 patients.

	Benign (Group 1)	Asymmetry (Group 2)	Nodule (Group 3)	ANOVA
Mean PSA (ng/dL)	8.71±21.70	7.67±6.81	27.56±99.0	p1-2=0.973 p2-3<0.001*
Mean Prostatic Volume (cc)	56.57±29.15	59.97±31.90	53.16±32.60	p1-2=0.359 p2-3=0.027*
n	819	192	484	1495

*statistically significant

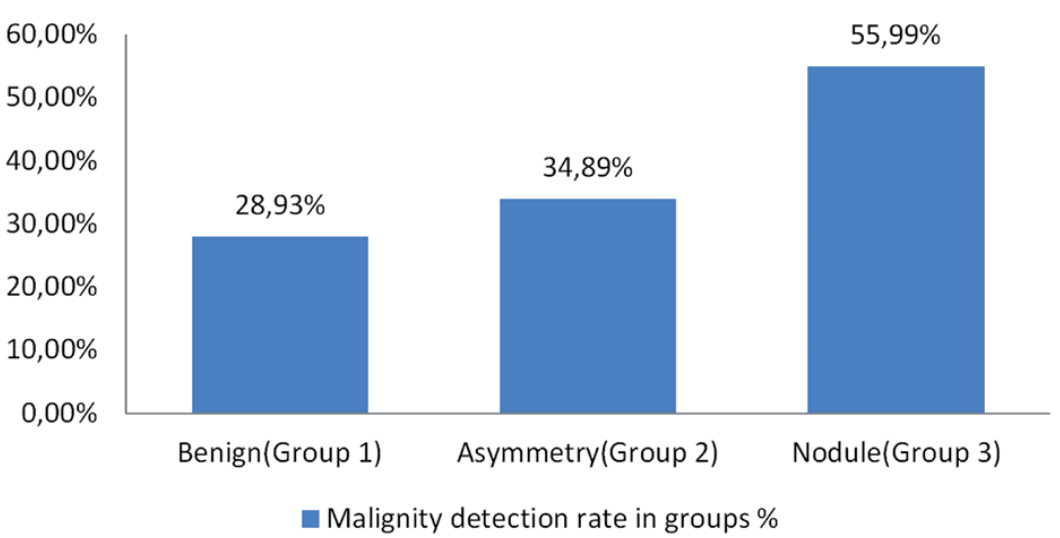
patients. Remaining 21 (31.34%) patients had malignancy in opposite side of asymmetry. 271 of 484 (55.99%) patients with nodule had malignancy in their prostate. Nodule and malignancy were concurrent in the same lobe in 232 of 271 patients (85.60%). 213 (44%) patients with nodule had benign results. According to biopsy results, 819 patients in total had benign DRE findings and 237 (28.93%) of them had malignancy (stage T1c).

Malignancy detection rate for benign, asymmetry and nodule findings in DRE were 28.93%, 34.89% and 55.99% respectively. Benign and asymmetry findings were similar (p=0.105), but nodule finding had greater possibility to detect cancer compared to the other two (p=0.001) (Figure-1). Sensitivity and specificity for cancer detection for benign, asymmetry and nodule in DRE were 41.21%/36.74%, 11.65%/86.41% and 47.13%/76.84%, respectively (Figure-2).

DISCUSSION

Despite the availability and popularity of PSA, an abnormal DRE alone is still considered an absolute indication for prostate biopsy (7). Furthermore, DRE remains an essential part of a routine physical examination, and it is useful to understand and quantify its diagnostic power for cancer

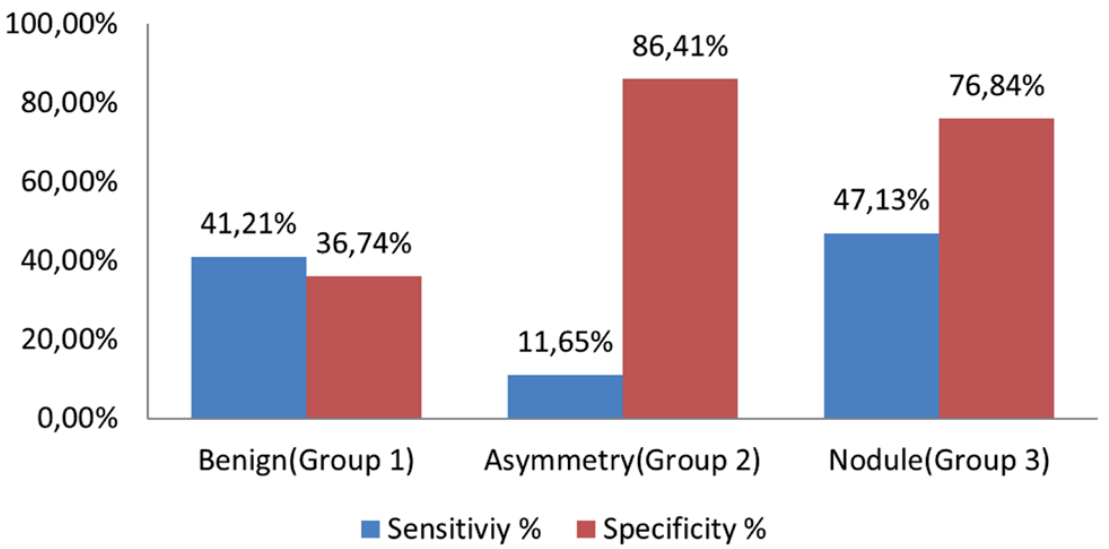
Figure 1 - Malignancy detection rate of DRE findings.



*p (Groups 1-2) = 0.105 *p (Groups 1-3) = 0.001** *p (Groups 2-3) = 0.001**

*Chi-square test **Statistically significant

Figure 2 - Sensitivity and specificity for cancer detection of three groups.



detection of different findings such as benign, asymmetry and nodule. The result of DRE is usually stated as abnormal, i.e. nodularity or induration suspicious for prostate cancer, or as normal (8) the diagnostic value of different DRE findings (benign, nodule/induration and asymmetry) as a predictor of prostate cancer has not been thoroughly evaluated in the past. Our study is the first one that evaluated the prediction value of DRE findings, especially asymmetry, in prostate cancer according to biopsy results.

Asymmetry of a prostate was defined as asymmetric growth of lateral lobes without any other suspicious findings such as nodule or induration, as assessed by DRE. Although this finding is quite often in routine prostate control, its predictive value for cancer detection is not so clear. There are only a few studies about asymmetry and its predictive value in prostate cancer in literature (5). Hansen et al. followed 963 men with no clinical evidence of prostate cancer by using PSA, and prostate biopsies were taken from men in case their PSA levels started to get increased, then asymmetry in DRE was evaluated for cancer detection among those patients they concluded that this finding was not an independent cancer predictor. Kiyoshima et al. (6) evaluated asymmetrical contours in 114 radical prostatectomy specimens and concluded that the 34% asymmetry findings were caused by cancer, and cancer-associated asymmetries showed significant correlations with aggressive signs such as cancer volume, Gleason score, positive surgical margin, and extraprostatic extension.

We evaluated the patients who had undergone prostate biopsy at our department retrospectively. Our study included all DRE findings, i.e. benign, nodule and asymmetry. Although the patients with asymmetry had somewhat more cancer detection rate than benign DRE, the difference could not reach a statistically significant level, therefore, as Hansen et al. did, we also concluded that asymmetry does not carry significant additional risk for prostate cancer. In our study, the most important and critical DRE finding for cancer detection was nodule. We only evaluated the effect of DRE findings on cancer detection of non-cancer features such as aggressiveness or extention, as biopsy results may not be enough to make such decisions.

One of the most accepted tools for prostate cancer screening and detection is PSA. When we compared the groups in terms of PSA levels, nodule group had highest correlation level with biopsy results and it was statistically significant.

Although asymmetry group had higher PSA than benign group, the difference could not reach statistically significant level. PSA level findings indicated that the most important DRE finding for cancer detection is nodule, asymmetry may be deemed as benign. As prostatic volume can affect PSA level (9-11), we compared the groups in terms of prostatic volume. Benign and asymmetry group were similar according to volume but nodule group had smaller prostate significantly. It showed that detecting higher PSA level in nodule group was not influenced by prostatic volume.

It is known that prostate cancer incidence increases with advanced age (9). We also found for all groups that all of our patients who had malignancy, were older than the patients who did not have cancer. This result was consistent with PSA and biopsy results.

The cause of asymmetric growth of prostate has not been clearly understood. There may be some local factors that act differently in asymmetric lobe such as androgen receptor level or increased response to growth factors, or decreased apoptosis (12-14). In contrast with nodule (15), we cannot definitely say that cancer causes asymmetry. The most important question is whether the reason of asymmetry is malignancy or not. Although our results were not able to demonstrate that asymmetry is an apparent sign of cancer, we found that if there is malignancy in somewhere of the asymmetric prostate, the localization of this malignancy is probably in asymmetric side in an insignificant matter. Therefore, additional studies are required to come to a conclusion on the importance of asymmetry.

Normally, equal number of cores are taken from both lobes, unless suspicious areas are seen in TRUS imaging during biopsy procedure (16). That is, if a lobe is bigger than the other, more core samples may be necessary to sample both lobes equally. By doing that, the malignancy detection rate of asymmetric lobes may increase.

DRE is a subjective examination due to variability in inter-examiner findings (17). We diagnosed the asymmetry not only with DRE but also with TRUS by measuring the craniocaudal and horizontal diameters of both lobes individually. As a result, subjectivity of DRE with asymmetry was minimized. But other findings such as benign and nodule were not verified by TRUS or another examiner. This is one of the limitations of our study. Another limitation may be the retrospective nature of the study. This study only evaluated patients who underwent biopsy, meaning we do not know about patients with cancer, but have not been diagnosed with biopsy due to absence of indications such as abnormal PSA level and DRE findings. So making an exact conclusion for predictive value of DRE findings, more prospective studies may be necessary. The asymmetry in DRE has a endency to be benign based on patient's age, PSA level and biopsy result. Within our knowledge, our study is the first one that Evaluate age and PSA level in relation with cancer detection in asymmetric prostates.

CONCLUSIONS

We found that nodule is the most important finding in DRE for cancer detection. According to our results, an asymmetric prostate itself cannot be accepted as a cancer sign. Some additional studies may be useful to come to an exact conclusion about asymmetry in prostate.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol.42(4):710-716,July-August,2016
doi: 10.1590/S1677-5538.IBJU.2014.0291

Complete supine PCNL: ultrasound vs. fluoroscopic guided: a randomized clinical trial

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ABSTRACT

Introduction and Hypothesis: To compare complications and outcomes of complete supine percutaneous nephrolithotomy (csPCNL) with ultrasound guided and fluoroscopically guided procedure.

*Materials and Methods: I*n this randomized clinical trial study from January 2009 to September 2010, 26 of 51 patients with renal stones underwent csPCNL with ultrasonographic guidance in all steps of the procedure (group A), and the other 25 patients underwent standard fluoroscopically guided csPCNL (group B). All of the patients underwent PCNL in the complete supine position. Statistical analysis was performed with SPSS16 software.

Results: Mean BMI was 28.14 in group A and 26.31 in group B (p=0.30). The mean stone burden was 26.48 and 30.44 in groups A and B, respectively (p=0.20). The stone free rate was 88.5% in group A and 75.5% in group B, that was no significant (p=0.16). Overall 2 patients (7.7%) in group A and 6 patients (24%) in group B had complications (p=0.11). Mean operative time in group A was 88.46 minutes, and in group B it was 79.58 minutes (p=0.39). Mean hospital stay was 69.70 and 61.79 hours in group A and B, respectively (p=0.22). There was no visceral injury in groups.

Conclusions: This randomized study showed that totally ultrasonic had the same outcomes of fluoroscopically csPCNL. Ultrasonography can be an alternative rather than fluoroscopy in PCNL. We believe that more randomized studies are needed to allow endourologists to use sonography rather than fluoroscopy in order to avoid exposition to radiation.

ARTICLE INFO

Keywords:
Nephrostomy, Percutaneous; Ultrasonography; Fluoroscopy; Supine Position

Int Braz J Urol. 2016; 42: 710-6

Submitted for publication:
June 15, 2014

Accepted after revision:
October 12, 2015

INTRODUCTION

Percutaneous nephrolithotomy (PCNL) is a common method for treatment of kidney stones (1, 2). All of the steps in PCNL should be performed with proper image guidance. The imageless PCNL should never be applied because it is dangerous to vital structures (3).

The popular imaging of PCNL is fluoroscopy, so the patient and surgical team are exposed to some level of radiation by fluoroscopy during PCNL. The side effects of extensive radiation are well known. Thus, the ultrasound-guided PCNL can be an alternative method to decrease the radiation exposure hazard to the surgeon (4-6).

The purpose of present study is to compare complications and outcomes in patients who underwent complete supine percutaneous nephrolithotomy (csPCNL) with these two methods and to share the experience of the authors with totally

ultrasound-guided csPCNL procedure with the urological community.

MATERIAL AND METHODS

In this randomized clinical trial study from January 2009 to September 2010, 51 patients with renal stones were selected for csPCNL. All participants were informed about the surgical method and consent. We used totally ultrasonographic guidance in all steps of the procedure during csPCNL in 26 of our patients (group A), whereas the other 25 patients underwent standard fluoroscopically guided csPCNL (group B). All patients in both groups performed PCNL in the complete supine position without any towel under the patient's flank and with no change in leg position. For all patients, routine blood and urine tests, coagulation profile and imaging series, including intravenous urogram and ultrasonography, were carried out and medical conditions were studied.

Inclusion criteria were patients with single large pelvic stone, lower caliceal stone, stones in the pelvis and lower calyx, middle caliceal stones, and non-opaque stones (staghorn stones) with hydronephrosis.

Exclusion criteria's in this study were multiple stones in multiple calyxes, staghorn stones (except non-opaque stones), urinary tract anomalies, single kidney and morbid obesity and non-opaque stones (staghorn stones) without hydronephrosis.

All of the patients underwent general anesthesia, and a 5F ureteral catheter was placed transurethrally for injection of saline or contrast media. Injection of saline obtained mild dilatation of collecting system and this was useful especially for the totally ultrasound-guided PCNL group.

In group A, ultrasonography was used to observe the location of the kidney, needle entrance point, urinary tract dilatation and to check for residual stone at the end of csPCNL. Because the Rouch guidewire is more rigid, and in order to not miss the access, we used this type of guidewire, although the guidewire was clearly visible but the Amplatz dilatators and the Amplatz sheath were not exactly visible by ultrasonography.

In group B, we performed all the above steps of csPCNL with the guidance of fluoroscopy. Our technique was a one-shot dilatation in both groups.

In this study, the items including side of renal unit, stone burden, stone-free rate, complications (extravasation, colon injury, fever, etc.), and the history of previous open renal surgery or previous ESWL, mean hospital stay, mean operative time, body mass index (BMI), serum creatinine before the operation, and hemoglobin before and after the csPCNL were studied.

In group A, after removal of the stone(s), ultrasonography was used to detect any residual stones, hematoma, or extravasation of urine outside of the kidney.

In the fluoroscopic group, residual stones and extravasation were checked by fluoroscopy. We performed tubeless PCNL except in patients with severe extravasation, ureteral obstruction, severe hemorrhage, or large residual stone.

Statistical analysis was performed with SPSS16 software. A P value of less than 0.05 was considered statistically significant.

This study was approved by ethical review committee of Guilan University of Medical Science and the trial registered at http://www.irct.ir (IRCT138805251853N3).

RESULTS

Total number of patients in both groups was 51 (26 patients in group A and 25 patients in group B). Demographic data and stone characteristics of two groups are shown in Table-1. In group A, mean age was 48.41 years and in group B it was 51.17 years (p=0.46). Mean BMI was 28.14 in group A and 26.31 in group B (p=0.30). The mean hemoglobin level before operation was 12.81 and 13.38 in groups A and B, respectively (p=0.23). The mean stone burden was 26.48 and 30.44 in groups A and B, respectively (p=0.20). The stone burden was detected on the basis of maximum diameter of stones on the KUB or ultrasonography. 4 patients (15.4%) in group A and 7 patients (28%) in group B had coexisting disease (p=0.44). All of

Table 1 - This table showed the demographic data of two groups according to method of study.

	Ultrasonographic Group	Fluoroscopic Group	P_Value
Total N	26	25	-
Sex			
Male (%)	17 (65.4)	15 (60)	0.69
Female (%)	9 (34.6)	10 (40)	
Age (Year)	48.41	51.17	
Mean (SD)	(13.22)	(11.82)	0.46
BMI (Kg/m^2)	28.17	26.31	
Mean (SD)	(4.17)	(5.88)	0.30
Serum Cr. before the Operation,	1.45	1.16	
Mean (SD)	(1.60)	(0.28)	0.38
Hb before the Operation,	12.81	13.38	
Mean (SD)	(1.78)	(1.56)	0.23
Stone Size (mm),	26.48	30.44	
Mean (SD)	(10.90)	(11)	0.20
Number of Stones,	1.42	1.58	
Mean (SD)	(0.50)	(0.50)	0.26
Side,n (%)			
Right	15 (57.7)	17 (68)	0.51
Left	10 (38.5)	8 (32)	
Co-existing Disease,n (%)			
Yes	4 (15.4)	7 (28)	0.44
No	22 (84.6)	19 (76)	
Previous open or percutaneous surgery, n (%)			
Yes	6 (23.1)	7 (28)	0.68
No	20 (76.9)	18 (72)	
Previous ESWL, n (%)			
Yes	11 (42.3)	13 (52)	0.48
No	15 (57.7)	12 (48)	

the patients underwent general anesthesia and the access was sub costal in all patients. Intra and postoperative parameters of the two groups are shown in Table-2. The stone free rate was 88.5% in group A and 75.5% in group B, that was no significant (p=0.16). Overall, 2 patients (7.7%) in group A and 6 patients (24%) in group B had complications (p=0.11). In group A, 1 patient (3.8%) had fever, and in group B, 4 patients (16%) needed transfusion and 2 patients (8%) had fever (Grade I and II of the Clavien Classification of Surgical Complications). Mean operation time in group A was 88.46 minutes, and in group B, it was 79.58 minutes (p=0.39). Mean hospital stay was 69.70 and 61.79 hours in groups A and B, respectively (p=0.22). There was no complications compatible with Grade III to V of the Clavien Classification of Surgical Complications in both groups.

Table 2 - This table showed the comparison of results after the procedure between two groups.

	Ultrasonographic Group	Fluoroscopic Group	P_Value
Total N	26	25	-
Stone free rate (%)			
Stone free	20 (77)	17 (71)	
Residual stone<5mm	3 (11.5)	1 (4.5)	0.16
Residual stone>5mm	3 (11.5)	6 (27.3)	
Complications			
Yes	2 (7.7)	6 (24)	0.1
No	24 (92.3)	19 (76)	
Nephrostomy tube			
Yes	2 (8.7)	1 (4.3)	0.55
No	21 (91.3)	22 (95.7)	
Duration of access to target calyx (sec)	14.36	14.78	0.08
Mean (SD)	(14.84)	(25.54)	
Duration of entrance to target calyx (sec)	84.87	41.22	0.07
Mean (SD)	(112.83)	(48.51)	
Duration of 9Fr dilator dilatation (sec)	22.48	23.39	0.78
Mean (SD)	(26.7)	(37.7)	
Duration of Amplatz dilator dilatation (sec)	32.72	15.57	0.77
Mean (SD)	(82.45)	(15.94)	
Duration of Amplatz sheath insertion (sec)	17.46	12.41	0.28
Mean (SD)	(26.72)	(15.67)	
Hb Drop after the operation	1.11	1.14	
Mean (SD)	(1.35)	(1.52)	0.93
Operating time, min	88.46	79.58	
Mean (SD)	(39.49)	(32.6)	0.39
Hospital stay, hour	69.70	61.79	
Mean (SD)	(18.87)	(25.22)	0.22
Extravasation (%)	0	0	-
Pseudo aneurism (%)	0	0	-
Fever, n (%)	1(3.8)	2(8)	-
Colon injury (%)	0	0	-

DISCUSSION

The scope of endourology despite its short age has been widened. The first step in percutaneous procedures is to access to the collecting system, usually performed by fluoroscopy, ultrasonography, or computed tomography (CT) guidance (7-9).

To reduce the risk of radiation exposure, using ultrasonography for PCNL can be an alternative imaging method to fluoroscopy as the first and standard imaging technique (10, 11).

Some studies reported that PCNL under ultrasonography guidance in the flank or prone position has high success rates and limited complications and can be a safe and effective alternative to fluoroscopy in experienced hands (11-18).

Ultrasound-guided PCNL without fluoroscopy has some advantages and disadvantages. Advantages: Avoidance of X-ray exposure, no necessity of lead shield, all organs on the way of access are visible, search for residual stones at the end of the procedure especially for non-opaque stones. Disadvantages: Endourologists are unfamiliar with ultrasonography, and poor echogenicity of the Amplatz dilatator and Amplatz sheath (11, 12, 19, 20).

Nowadays, PCNL is considered a generally safe management option with a low incidence of complications and is the method of choice for treatment of renal stones (11, 21, 22).

PCNL is done in the prone, flank, semi-supine, and csPCNL positions. We performed csPCNL in our patients due to better control of the airway, better tolerance for patients especially with cardiopulmonary disease, easier to perform ureteroscopy or TUL, better drainage and evacuation of stones by the Amplatz sheath, possibility to change regional anesthesia to general anesthesia, and probably less risk of colon injury. These are some advantages of csPCNL (13).

Because of levitation of the colon in the abdominal cavity in the supine position it is less affected to injury when puncture site is in the posterior axillary line (23).

The access to the kidney is important in PCNL and usually is performed by fluoroscopy, ultrasonography, or computed tomography guidance with rates of success of 86.7-100% (9, 11, 20, 24-26). The success rate in achieving access in our study was 100% in both groups. The gaining access to the collecting system under ultrasonographic guidance was similar to the fluoroscopic--guided access.

Some studies showed that the stone-free rate in percutaneous nephrolithotomy with ultrasonography guidance varied from 66.6 to 94.7% (5, 7, 12, 18, 20, 27). Other studies showed that primary stone-free rate and total stone-free rate with ultrasound-guided percutaneous nephrolithotomy were 45.7 - 69.6% and 82.6 - 96.5%, respectively (21, 26). In our study, similar to the others, the stone-free rate was 88.46% and 72%, without any significant statistical difference in groups A and B, respectively (p=0.16).

The mean operative time was 120±68 minutes (range 45-350) in one study. The real-time ultrasound can be used to guide the percutaneous puncture (26). In another study mean (range) of operative time was 111 (70-180) minutes. They emphasized that ultrasonographic - guided PCNL is feasible but fluoroscopy must be present in the operating room (27). Mean operative time was reported as 88.92 and 79.28 minutes in sonographic and fluoroscopic groups, respectively (20). In the current study mean operative time was similar to other studies without any significant statistical difference (p-value=0.39).

Hospital stay was 3.6 days (range 2-8 days) in one study and other studies reported 2.7 to 4.1 days (5, 12, 20 24, 27). In our study, hospital stay was similar to other studies without any significant difference (p=0.22).

Although we had seen more complications in fluoroscopic group, they were not significant.

In this study we found no extravasation in both groups. This result was similar to others (20, 21). Some studies reported 4-9% with postoperative fever (12, 18). Other studies reported 26.3-27.6% postoperative fever and the patients responded to antibiotics (21, 27). In this study fever had no effect on the results of our study. All of the patients with fever were cured with appropriate antipyretics and antibiotics. Septic shock was not a major complication in our patients.

In other studies, like ours, no severe complications such as colon damage, pneumothorax or hydrothorax or any adjacent injuries occurred (24, 26). We had no patient with injury to adjacent organs during csPCNL till now.

Totally ultrasound-guided PCNL is feasible and safe in patients with a history of renal surgery (28).

In current study mean BMI was similar to the other studies without any significant statistical difference between the two groups (p-value=0.3); therefore, BMI had no effect on the results of our

study. We achieved access in all patients and we believe that ultrasound-guided csPCNL in obese patients is more difficult but it is safe and feasible. Sometimes it was imperative to draw up the fatty abdomen with a strip band for preventing any encumbrance during the procedure.

PCNL is feasible and safe in the supine position (13, 29-32).

CONCLUSIONS

This randomized study showed that totally ultrasonic csPCNL had the same outcomes of fluoroscopically-guided csPCNL. We believe that more randomized studies are needed to allow endourologists to use sonography rather than fluoroscopy to avoid exposing the radiation.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 717-726, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0481

Using an abdominal phantom to teach urology residents ultrasound-guided percutaneous needle placement

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ABSTRACT

Introduction: To assess the effect of a hands-on ultrasound training session to teach urologic trainees ultrasound-guided percutaneous needle placement.
Materials and methods: University of California, San Francisco (UCSF) urology residents completed a time trial, placing a needle into a phantom model target under ultrasound guidance. Participants were randomized into three educational exposure groups: Group 1's time trial occurred prior to any teaching intervention, group 2's after experiencing a hands-on training module, and group 3's after exposure to both the training module and one-on-one attending feedback. Needle placement speed and accuracy as well as trainees' perceived confidence in utilizing ultrasound were measured.
Results: The study cohort consisted of 15 resident trainees. Seven were randomized to group 1, three to group 2, and five to group 3. All residents reported minimal prior ultrasound experience. Their confidence in using ultrasound improved significantly after completing the training module with the most significant improvement seen among junior residents. Time to needle placement was fastest after receiving attending feedback (46.6sec in group 3 vs. 82.7sec in groups 1 and 2, $p<0.01$). Accuracy also improved with attending feedback, though the number of repositioning attempts did not differ significantly between groups.
Conclusions: A hands-on training module and use of an abdominal phantom trainer increased resident confidence and skill in their use of ultrasound to guide percutaneous needle positioning. Attending feedback is critical for improving accuracy in needle guidance toward a target. Ultrasound-guided needle positioning is a teachable skill and can be applicable to multiple urologic procedures.

ARTICLE INFO

Keywords:
Education, Percutaneous Nephrolithotomy, Ultrasonography

Int Braz J Urol. 2016; 42: 717-26

Submitted for publication:
August 21, 2015

Accepted after revision:
February 29, 2016

INTRODUCTION

Percutaneous needle placement into the kidney is a skill of great utility for the practicing urologist. It is commonly used for percutaneous renal access to facilitate nephrostomy tube placement and percutaneous nephrolithotomy (PCNL) and also is applicable for renal biopsies and percutaneous ablation of renal masses (1, 2). All of these procedures are reliant on image-guided, accurate needle placement into different areas of the kidney. While ultrasound guidance is commonly used by interventional radiologists and nephrologists to position needles into the kidney for nephrostomy tube placement, renal biopsy, and tumor ablation (3), urologists may be less familiar with using renal ultrasonography to guide procedures.

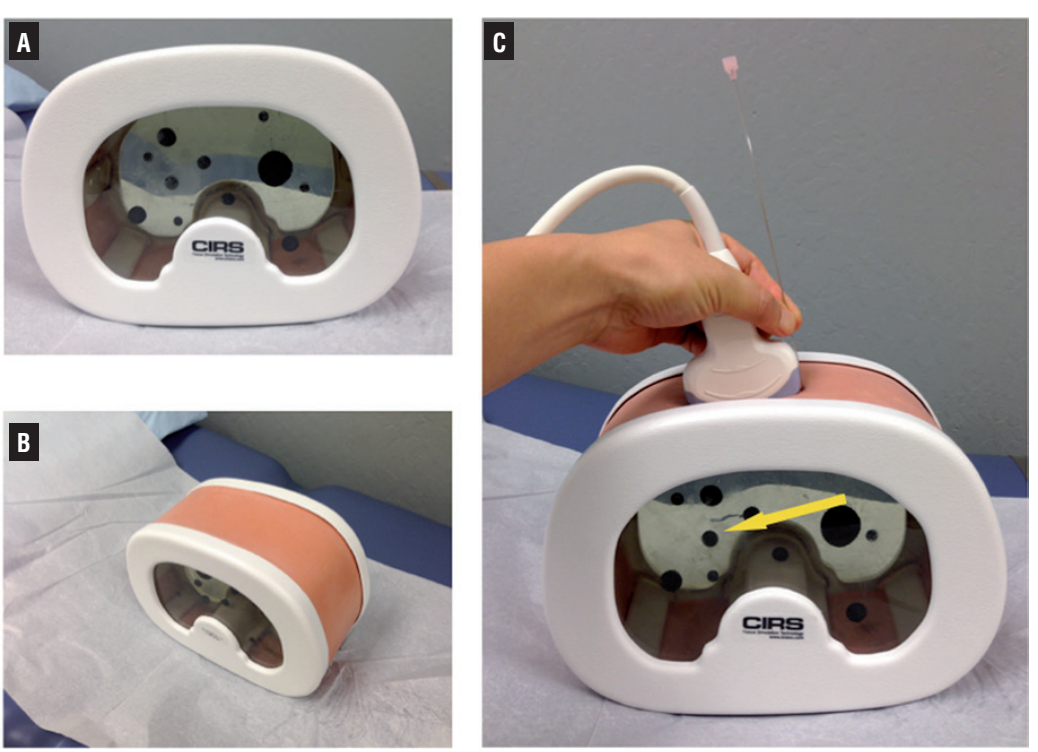
Applying ultrasound (US) -guided needle placement to renal access during PCNL has been shown to result in decreased overall radiation exposure for patients and providers, as well as decreased blood loss during the procedure compared to fluoroscopy (4). Distinguishing posterior from anterior calyces is also an easier task using ultrasonography compared to fluoroscopy given the orientation of the US probe relative to the renal collecting system (5). Despite these benefits, the majority of urologists in the United States and around the world do not utilize ultrasound to guide needle placement for renal access during PCNL. This is likely due in part to the minimal emphasis placed on teaching renal US imaging during residency training (6). The goal of this study was to demonstrate that US-guided needle placement is a teachable skill for urologic trainees. We examined trainee experience level with US use for urologic procedures and evaluated the effect of an easily implementable teaching module on residents´ accuracy and precision in guiding a needle toward a target under US guidance in a simulated learning environment using an abdominal phantom trainer.

MATERIAL AND METHODS

Resident trainees post-graduate year (PGY) 1-6 who were current members of the University of California, San Francisco Department of Urology residency program in December 2014 formed the study cohort. All trainees consented to study participation. After consulting with the institutional Committee on Human Research, this study was deemed exempt from approval.

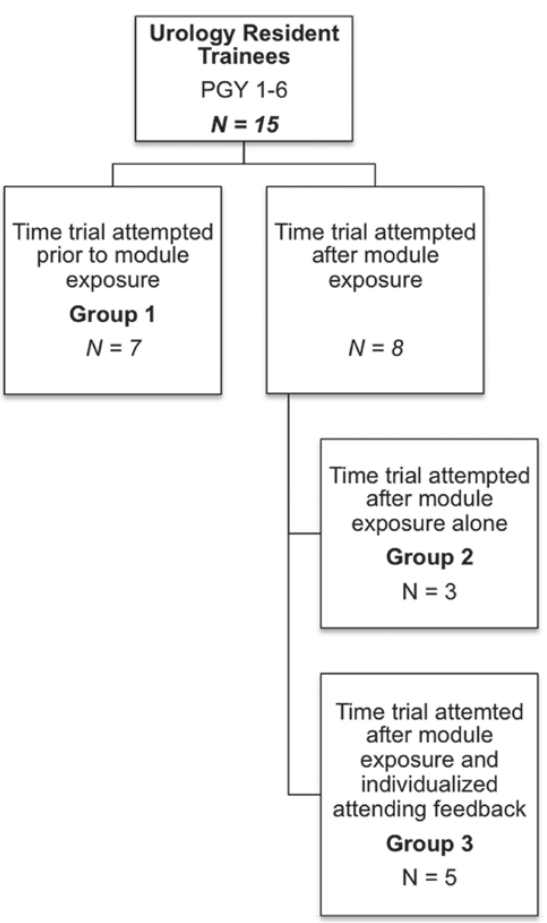
Trainees were invited to participate in a training session and then randomized into three exposure groups. All participants were tasked with the objective of completing a time trial of placing a needle into a phantom target under US guidance (Figure-1). Group 1's time trial occurred prior to any intervention, group 2's time trial occurred after listening to a training module presented by

Figure 1 - Abdominal training phantom used for ultrasound-guided needle placement time trial. The model has randomly distributed targets, visible in lateral (A) and oblique (B) views. Panel C demonstrates positioning of the ultrasound probe and needle used during the time trial. Participants were asked to place the needle into the black circular target indicated by the arrow.



an attending endourologist, and group 3's time trial occurred after exposure to both the training module and individualized attending feedback given during a hands-on experience with the US console and abdominal phantom (Figure-2). Participants in Groups 2 and 3 were both permitted to use the model for practice prior to their time trial, and Group 3 participants did so under the tutelage of an attending. For an effect size, we anticipated a three fold change in confidence level and two fold change in needle placement accuracy for participants in this study (7). Therefore, a sample size calculation dictated a minimal sample size of 4 participants in each exposure arm for this study design to achieve significance with a probability threshold of 0.05. Participants were randomized to each exposure group using an envelope randomization strategy. Opaque envelopes chosen by participants contained a paper marked with the word 'before' or 'after', determining whether or not the time trial would take place before or after module exposure. Furthermore, participants in the 'after' group underwent secondary envelope randomization by the study administrators to receive attending feedback or not. Residents were overall anticipated to be mostly naïve to prior use of ultrasound-guided procedures and were therefore not block randomized by seniority. The training module provided a general overview of how renal US imaging is performed, different hand hold positions used for the US probe, how US guidance can be applied to renal tract access during PCNL, and several videos of renal percutaneous access performed under US guidance. These materials were designed by the authors to be practical and focused on skill acquisition. In addition, trainees had the opportunity to perform renal US imaging on one another as a part of this training module. Individualized attending feedback consisted of an endourology-focused attending experienced in renal US and US-guided needle placement providing instruction and immediate feedback to each trainee on the use of US while the trainee attempted to image and place a needle into a target in the phantom model. Two attendings provided ultrasound instruction. One (TC) who had recently begun performing PCNL under ultrasound guidance and one (JL) who had performed more than 8000 PCNL procedures under ultrasound guidance (8).

Figure 2 - Description of UCSF urologic trainee cohort teaching exposures in each intervention arm.



The phantom model (model 071A, CIRS, Inc., Norfolk, VA) is an abdominal US training phantom consisting of a housing containing 11 randomly positioned circular target lesions encased with a self-healing gel as well as a simulated spine and ribs. This phantom has been previously published and validated as a model for teaching image-guided biopsy technique (9).

The sizes of the targets embedded in the phantom range from 8-12mm, comparable to renal caliceal diameters in the moderately dilated collecting system. For this study, during the time trial, one of the medium-sized 10mm targets was pointed out to the trainee. The trainees were instructed to use US guidance to place a 15cm long,

18-gauge needle (Cook Echotip, Cook Medical, Bloomington, IN) into the indicated target (Figure-1). Time until the trainee felt the needle was placed into the intended target, number of needle repositioning attempts and needle placement accuracy (whether the phantom target was hit or not) were measured. Trainees took a survey before and after their training session which assessed trainee confidence in interpreting US images as well as using US to guide needle positioning during a procedure (Tables 1 and 2). Additional self-reported data regarding trainee characteristics (resident year, quantity of urologic procedures done under fluoroscopic guidance, and quantity of previous experience with US imaging) was also collected. Statistical analyses were performed using Student's t-test and Fisher's exact test using Stata 12.0 (StataCorp, College Station, TX).

RESULTS

Fifteen trainees participated in this study; seven were randomized to group 1, three to group 2 and five to group 3. Neither the distribution of junior (PGY1-3) and senior (PGY4-6) residents nor trainee experience with US within group 1 differed significantly compared to groups 2 and 3. 100% of trainees reported doing less than five percutaneous renal procedures under US guidance during their training. 87% (N=13) of trainees reported using US for suprapubic tube placement less than five times. The majority of residents (73%, N=11) reported using US for renal imaging less than five times throughout their training. Residents reported the most experience with using US to image areas other than kidneys, with 53% (N=8) of residents reporting using US for this purpose over 20 times throughout their training (Table-1).

Table 1 - Trainee demographics and ultrasound experience.

Trainee characteristic	Value	Group 1	Group 2 and 3	P-value
		Teaching module taken after attempt (n=7)	Teaching module taken before attempt (n=8)	
Resident year, n (%)	Junior resident (PGY 1-3)	5 (71)	3 (38)	0.32
	Senior resident (PGY 4-6)	2 (29)	5 (62)	
Number of percutaneous renal procedures done using fluoroscopic guidance, n (%)	0-5	5 (71)	2 (24)	0.27
	6-10	0 (0)	3 (38)	
	>10	2 (29)	3 (38)	
Number of percutaneous renal procedures done under US guidance, n (%)	0-5	7 (100)	8 (100)	1.00
	>5	0 (0)	0 (0)	
Number of suprapubic tubes placed under US guidance, n (%)	0-5	6 (86)	7 (88)	1.00
	6-10	1 (14)	1 (12)	
	>10	0 (0)	0 (0)	
Number of times performing renal US for imaging, n (%)	0-5	6 (86)	5 (63)	0.71
	6-10	0 (0)	2 (25)	
	>10	1 (14)	1 (12)	
Number of times using US to image areas other than kidneys, n (%)	0-5	3 (43)	2 (25)	0.78
	6-10	1 (14)	1 (12)	
	>10	3 (43)	5 (63)	

Table 2 - Trainee confidence scores (whole group) before and after ultrasound teaching module.

Confidence Level (Scale 1-10)	Value (N=15)	Before teaching module	After teaching module	P-value
		mean (SD)	mean (SD)	
How confident do you feel that you could accurately interpret renal US imaging not performed by you (i.e. by a radiologist or technician)?	Junior resident	2.6 (1.9)	5.3 (1.7)	<0.01
	Senior resident	6.3 (3.0)	7.9 (0.9)	0.17
	All residents	4.3 (3.1)	6.5 (1.9)	<0.01
How confident do you feel that you could accurately identify renal calyces using an US device?	Junior resident	3.3 (1.5)	5.0 (1.4)	0.01
	Senior resident	6.0 (2.2)	7.0 (1.5)	0.23
	All residents	4.5 (2.3)	5.9 (1.8)	<0.01
How confident do you feel that you could accurately identify renal stones using an US device?	Junior resident	3.9 (1.9)	5.9 (1.9)	0.01
	Senior resident	5.4 (2.6)	7.0 (1.9)	0.03
	All residents	4.6 (2.3)	6.4 (1.9)	<0.01
How confident do you feel that you could accurately place a needle into a target under US guidance?	Junior resident	2.3 (1.8)	5.0 (2.3)	0.06
	Senior resident	4.4 (2.6)	7.8 (1.6)	0.03
	All residents	3.3 (2.4)	6.3 (2.4)	<0.01
Total confidence score (out of 40)	Junior resident	12.1 (6.2)	21.1 (6.4)	<0.01
	Senior resident	22.1 (9.8)	29.7 (4.1)	0.04
	All residents	16.8 (9.3)	25.1 (6.9)	<0.01

Perceived confidence in their ability to perform and interpret US imaging was compared amongst junior and senior level trainees, as well as amongst all participants before and after completion of their training session. Overall confidence scores of all participants improved after completing the training session (Figure-3). Total confidence scores (scale: 1-40; 40=most confident) were significantly increased for all trainees after their training session (16.8 before vs. 25.1 after, p<0.01). This improvement was most significant for junior residents, PGY1-3 (12.1 vs. 21.1, p<0.01). Individual question scores (scale: 1-10; 10=most confident) also showed significantly improved perceived confidence after completing the training module across a variety of skills, with residents feeling more confident in interpreting renal imaging (6.5 after vs. 4.3 before, p<0.01), identifying renal calyces (5.9 vs. 4.5, p<0.01), identifying renal stones (6.4 vs. 4.6, p<0.01), and accurately placing a needle into a target under US guidance (6.3 vs. 3.3, p<0.01). Senior residents, PGY4-6, felt improved confidence in their ability to accurately place a needle into a target under US guidance (7.8 vs. 4.4, p=0.03) whereas junior residents felt statistically significantly improved confidence in all question areas except for this one (5.0 vs. 2.4, p=0.06). Senior residents felt more confident interpreting renal US imaging not done by them and identifying renal calyces following completion of the training module, though changes in these question scores were not statistically significantly different (Table-2).

When comparing accuracy of placing a needle into a phantom target under US guidance during a time trial among participants, time to perceived target acquisition, number of attempts utilized and whether the needle actually landed in the target improved the most for group 3, who received one-on-one training with attending feedback prior to their time trial (Table-3). Time to perceived needle placement was significantly faster after attending feedback was given (46.6sec in group 3 vs. 82.4sec in groups 1 and 2, p=0.04).

Figure 3 - Kernel density distribution of total confidence scores for trainees before and after ultrasound teaching module.

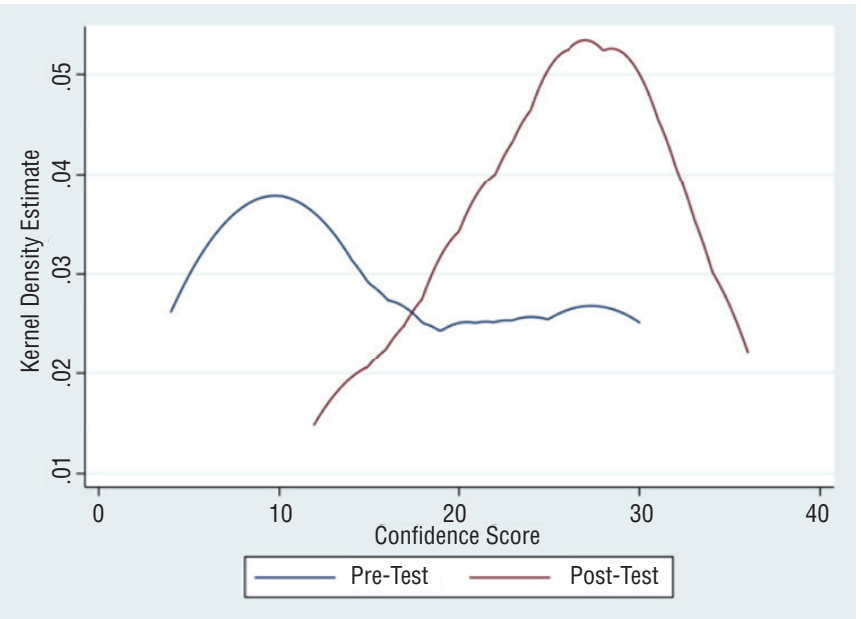


Table 3 - Univariate analysis of needle placement accuracy comparing trainees who made their attempt before or after being exposed to ultrasound teaching module and attending feedback.

Accuracy		Group 1 and 2 n=10	Group 3 n=5	P value
Time to target in seconds, mean (SD)		82.7 (32.1)	46.6 (21.5)	0.04
Number of attempts, mean (SD)		6.9 (5.4)	4.0 (2.6)	0.28
Needle successfully placed in target, n (%)	Yes	4 (43)	4 (80)	0.36
	No	6 (57)	1 (20)	

The number of needle attempts needed to reach the target decreased following attending feedback, though this difference did not reach statistical significance (4.0 needle attempts vs. 6.9, p=0.28). In addition, the percentage of needles successfully placed into the target increased following individualized attending feedback, though this difference was not statistically significant (80% success vs. 43% success, p=0.36).

DISCUSSION

Renal ultrasound is a tool used to facilitate percutaneous renal procedures. These include obtaining percutaneous renal access for PCNL and nephrostomy tube placement (10), performing percutaneous renal biopsies (11), and placement of needles for focal lesion ablation (1). All of these procedures rely on accurate use of imaging to guide needle placement within the kidney into the desired location. Ultrasonography is an ideal imaging platform for needle guidance and a simulation environment provides a means for trainees to increase their familiarity with ultrasound techniques in a safe, low pressure learning environment (7). Our study demonstrates that with the use of an abdominal phantom, resident trainees can garner confidence and acquire skills to support their clinical training for ultrasound-guided percutaneous procedures.

The use of PCNL is considered the minimally invasive standard of care for surgically removing large renal stones (12, 13). There are several technical challenges for the practicing urologist to overcome in order to perform this procedure effectively. Precise puncture into the appropriate calyx is paramount, and achieving successful collecting system needle access has been quantified as significantly contributing to the steep learning curve attributed to PCNL. De la Rosette et al. quantified the learning curve for gaining access during PCNL utilizing fluoroscopic guidance, and recommended a minimum of 24 PCNLs during training in order to attain good surgical proficiency, and a total of 60 to achieve competency (14). Current Accreditation Council for Graduate Medical Education (ACGME) urologic residency training standards require a minimum of ten percutaneous renal endourology procedures performed in order to successfully complete residency training (15). Thus, reaching the minimum number of PCNL procedures residents are required to perform during residency to meet ACGME competency requirements may not be sufficient for proficiency in gaining percutaneous renal access for this procedure by a graduating urologist, much less utilizing US to gain access.

Along with the overall infrequent use of and training in US needle guidance during PCNL, another disadvantage for training urologists in this modality lies in the nature of the overall procedure itself. What has been quantified as the most difficult and arguably most important part of the procedure to learn-gaining access into the appropriate calyx of the kidney-is only done once per PCNL in the absence of the need for multiple access tracts. Thus, training opportunities in the operating room are naturally diminished by the nature of the procedure.

US has been shown in previous studies to be an excellent adjunct tool to aid in gaining percutaneous access into the collecting system (16). Using US guidance for this purpose allows visualization of the vasculature of the kidney, which can contribute to decreased blood loss during PCNL (5). Additionally, the harms of significant ionizing radiation exposure to the patient and providers are decreased when using US-guided access during training. Jagtap et al. found that trainees utilizing US guided access during PCNL had less radiation exposure during renal access than those using fluoroscopy alone (17). Despite the benefits of US guidance, this study shows that urologic residents at our institution are not receiving significant exposure to using renal US as an imaging tool during their training. This experience is likely reflected across most training programs in the United States.

Several studies have shown that the use of virtual reality simulators improves urology trainee skills in areas such as endoscopy and robotics, but the use of US trainers as a part of urologic education has not been thoroughly evaluated (18). This study demonstrates the effect of a teaching module and attending feedback on the US skills and perceived confidence levels of urology residents. Our results highlight the fact that US imaging and needle guidance are skills that can be effectively taught to trainees through hands-on training during residency with tangible improvement in resident skill and confidence.

We examined hands-on simulator training as an alternative to in vivo experience for the training of urologic residents in the skill of needle positioning and guidance with US. This training session only required one hour of time for each trainee, incorporating visual information on how to use US, a brief didactic lecture, and a hands on experience, but was found to significantly improve resident confidence scores in using US as a tool to aid in target access, as well as significantly improve confidence in interpreting US. This improvement was particularly significant among junior residents, suggesting that this type of education may be most useful if done early in urologic training.

When looking at the effect of this training session on US skill, one-on-one attending teaching and feedback was found to be the most critical piece for improving trainee accuracy in being able to guide a needle toward a target. Though some improvement was seen in the group who received the education module before attempting their time trial compared to those who did not receive the module before the attempt, the most significant improvement in time to reaching the target occurred in the group that received attending feedback and teaching. Improved confidence and skill acquisition support trainees to move forward with continuing

to perform procedures when they leave the training environment (7, 11). Teaching interventions like the one described in our study that not only facilitate skill acquisition but also improve the learner's confidence may therefore translate to improved procedure performance in a real world setting. This is particularly relevant for the teaching of percutaneous nephrolithotomy, the procedure most commonly performed by urologists to which percutaneous renal needle positioning is applicable.

One major limitation for our study was the small overall group and subgroup sizes. Based on our sample size calculations, since a large effect size was anticipated, an adequate number of participants were enrolled to detect differences in confidence and skill levels between groups. Despite this, the small sample size may have decreased our power to detect differences in performance between groups that may otherwise not be readily apparent. Accuracy and number of needle placement attempts improved with attending feedback, though not significantly. This difference in significance may have been confounded by the small sample size. Also, due to the small sample size, no multivariate analysis of the effect of the teaching module on resident skill could be performed to control for factors such as resident experience level or quantity of US experience. Despite limited sample sizes, however, others have validated the effects of simulated training on resident learning with studies where small sample sizes were utilized (19, 20). Therefore, while our sample size was small, it was not outside of a reasonable range to be expected for this type of study.

In addition, this study evaluated the experience and confidence levels within a single residency training program, one in which urology residents have had very little prior exposure to the use of ultrasound. To date, the majority of PCNL procedures had been done under fluoroscopic guidance at our program, and this cohort of residents therefore had little training in the use of ultrasonography outside of transrectal ultrasound. These study results thus focus on urologists who are early in there training, but already committed to urology. Ideally multiple institutions could be surveyed in the future for a more in-depth look at training in US-guided renal access to gain a more generalizable understanding of how urology residents receive training in the United States. Future studies might also include medical students as well as more experienced urologists to see if these types of simulator training sessions have similar effects on trainees of different levels.

We also utilized a non-validated set of questionnaires to evaluate trainee confidence levels. Specific to the tasks examined in our study, no validated questionnaires exist, leading us to create a set of questions that were resultant of a discussion between members of the research team. These questionnaires were intended to capture trainee confidence and experience and query their experiences related to ultrasound and percutaneous needle placement but could be made to be more comprehensive and generalizable during future studies. Based on our study results, appropriately powered studies across multiple institutions could be planned to validate and confirm our findings.

Lastly, this study looked at the effect of a training session on the ability of participants to place a needle into a target within an abdominal phantom and on their perceived confidence in using US. For a urologist in training, clinical performance in real-life situations is the ultimate measure of how impactful a training session is for their overall ability to care for patients. While our study demonstrated that participants performed better on a needle placement task in a training environment and felt that they could better image the kidney in future settings, we did not measure the impact of this training session on actual clinical performance. Several challenging factors are inevitably present in real patients that are difficult to simulate in the training environment when relying on phantoms as training models. These include the movement of the kidney with respiration, the variation of kidney depth relative to body habitus, and the presence of small caliceal puncture targets in the context of the non-dilated collecting system. Our phantom facilitated a training environment that provides the trainee with tools to learn ultrasound guided needle placement, but these more complex situations were not simulated with our training phantom.

In clinical practice, to overcome some of these complex situations, needle guides are sometimes used to increase the accuracy of needle pla-

cement. These are particularly popular during percutaneous renal biopsy procedures. In practice, our clinical team routinely performs percutaneous renal access without a needle guide, but recognizes that their use is certainly not unreasonable. However, needle guides can be limiting in some circumstances where the angle of entry needed for the needle to enter the skin and the kidney lies outside of what the needle guide permits. For example, if the patient's kidney has a particularly sharp infundibulopelvic angle, it might be advantageous to enter the kidney with a very shallow angulation relative to the skin. A needle guide might not facilitate this angle of entry, despite some guides having multiple possible positioning angles available for use. Therefore, in order for a trainee to apply ultrasound guidance to any variety of clinically relevant scenarios, we feel that the most critical skill for the trainee to acquire is the coordinated ability to track movement of the needle under real time ultrasound imaging.

To this end, the clinical relevance of our results warrants particular consideration as the study was performed in a simulated environment. Our results demonstrate that trainees can learn how to image a needle and coordinate their hands so that they can guide needle placement toward a target and that their confidence in this skill improves with a single, relatively easily implemented teaching encounter. We think that these results have clinical relevance from several perspectives. Our study demonstrated that the physical skill of ultrasound guided needle placement is learnable. Performing this feat relies on two technical skills. First, the imaging hand must maintain a steady image of the target and the desired path to that target. Second, the needle hand must advance the needle within the imaging plane in order to achieve needle insertion into the target. While these are the only two technical skills requiring mastery in order to learn ultrasound guided needle access, they rely on two hands gaining independent skills and then coordinating those skills between the two hands and the visual image seen on the screen. A simulated environment is therefore an ideal arena in which to acquire these technical skills, without which, needle guidance in a clinical setting would not be easy to accomplish. Our study focused on the acquisition of these technical skills, and therefore lays the foundation for clinical translation of these skills to procedural use. In addition, literature supports the idea that if trainees feel more confident in performing a skill, they are more likely to continue utilizing that skill after completing their training (7). In today's practice environment, the majority of urologists do not obtain their own percutaneous renal access for PCNL (6). We contend that if ultrasound needle guidance can be taught in a manner that is adoptable and facilitates urologic trainee's confidence in that skill set, they may be more likely to obtain their own renal access or perform percutaneous ultrasound-guided procedures in practice after completing their training. We hope that this might eventually lead to urologists obtaining their own percutaneous renal access for PCNL, which might facilitate safer procedures in the future. This current study, centered around teaching of the technical skill itself, was limited in our ability to evaluate these latter hypotheses. However, it lays the groundwork to future studies that will show the relevance of simulated ultrasound guided needle placement training to clinical practice, including both the urologist's ability to apply these skills to clinical practice as well as the adoption of these skills into their routinely used arsenal of patient care tools.

Ultimately, the goal of this present study was to demonstrate the concept that ultrasound guidance for needle placement, which could also be applied to percutaneous renal mass biopsy and ablation as well as percutaneous nephrolithotomy, is an easily teachable skill for urologic trainees. Indeed, these training sessions generated increased confidence and enthusiasm for these skills within the participating trainees, and these are effects that we hope will carry over into future aspects of each resident's training and clinical practice. We consider these present results as early steps toward more widespread adoption of ultrasound training for urology residents. Based on our current findings, we believe that ultrasound needle guidance is a teachable, learnable skill. We plan that future studies will expand on whether these simulated skills translate to application in a real world procedural setting.

CONCLUSIONS

This educational exposure study shows that a short, formalized training session in US use can be readily implemented in urologic trai-

ning to improve resident skill and confidence. US-guided percutaneous needle positioning is a teachable, achievable skill that is effectively taught with a combination of didactics, hands-on training, and, most importantly, one-on-one attending feedback.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 727-733, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0570

Doxazosin oral intake therapy to relieve stent – related urinary symptoms and pain: a prospective, randomized, controlled study

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ABSTRACT

Objective: To assess the impact of Doxazosin Oral Intake Therapy on urinary symptoms and pain in patients with indwelling ureteral stents

Patients and Methods: A total of 239 patients with ureteral stone-related hydronephrosis who underwent a double-J stent insertion after ureteroscopic lithotripsy were enrolled. Patients were randomized to receive doxazosin cotrolled release 4 mg once daily for 4 weeks or matching placebo. Patients completed the brief-form Chinese version Ureteric Stent Symptom Questionnaire (USSQ) and quality of life (QoL) score 2 weeks and 4 weeks after stent placement and 4 weeks after stent withdrawal. The analgesic use was also recorded during the stenting period.

Results: Patients in Doxazosin Oral Intake Therapy group, in the first 2 weeks and second 2 weeks with the stent in situ, expressed significant lower daytime frequency (p=0.028 and p=0.038), nocturia (p=0.021 and p=0.008) and urgency (p=0.012 and p=0.014), respectively. Similarly, flank pain score, QoL score and analgesic use were also significant less in the stenting period. There was no significant difference in scores of urinary symptoms, pain and QoL during the post-stent period between two cohorts.

Conclusions: Doxazosin Oral Intake Therapy reduced stent-related urinary symptoms, pain and the negative impact on QoL.

ARTICLE INFO

Keywords:
Quality of Life; Doxazosin; Lower Urinary Tract Symptoms

Int Braz J Urol. 2016; 42: 727-33

Submitted for publication:
October 05, 2015

Accepted after revision:
December 06, 2015

INTRODUCTION

More than four decades have passed since the first description of an indwelling ureteral stent by Zimskind et al. (1). Placement of ureteral stent after ureteroscopic procedure remains common practice. However, morbidity associated with the stent has been well documented. In particular, general health and work performance were impacted by bothersome urinary symptoms in 80% cases and pain in 78% (2, 3).

Several studies have demonstrated α-blockers, such as alfuzosin and tamsulosin, improving stent-related symptoms (4-7). However, the results showed some fluctuations (7). Doxazosin Oral Intake Therapy has been shown to offer enhanced delivery rate, pharmacokinetic profile and compliance in patients with benign prostate hyperplasia (BPH) (8, 9). In addition, it might interact with α1-adrenergic receptor subtype located in central nervous system (CNS) for producing maximum benefit (9, 10). Herein, we firstly perfor-

med a double-blind, randomized, placebo controlled study to assess the impact of Doxazosin Oral Intake Therapy on stent-related urinary symptoms and pain.

PATIENTS AND METHODS

This study was conducted with the institutional review approval. From June 2013 to February 2015, patients with unilateral hydronephrosis associated with ureteral stone to be treated with ureteroscopic lithotripsy and an indwelling ureteral stent insertion for 4 weeks were assumed for enrollment in the study. After documentation of informed consent, patients were randomized (using a Table with random number) to 1 of 2 treatment groups: doxazosin controlled release 4mg daily for 4 weeks (Carduran XL®, Pfizer Pharmaceuticals, Vega Baja) or matching placebo once daily for 4 weeks. Both investigators and patients were blinded to the randomization scheme and medication. Patients were asked to take 1 tablet on postoperative day 1.

Patients with bilateral stones, pregnancy or probable pregnancy, nursing, symptoms of BPH, urinary tract infection, chronic pain history, α-blocker or anticholinergic use in previous 3 months, hypotension or orthostatic hypotension history (resting blood pressure less than 100/70mmHg), age less than 18 years and other contraindications indicated in package insert were excluded.

Ureteroscopic lithotripsy was initially conducted with a Wolf 8F/9.8F semirigid ureteroscope in all patients. Stones were fragmented to less than 2mm using 0.8J 10Hz Holmium: YAG laser and a 200μm fiber. When flexible ureteroscope was required, a 12/14F dual lumen ureteral access sheath (Flexor® DL, Cook Urologic, Spencer, IN) was introduced over a working guidewire. A 6Fr indwelling double-J stent (Inlay optima®, Bard Medical, Convington, GA) was placed under fluoroscopic and cystoscopic control. Appropriate length was evaluated according to patient height. Stent position was examined radiographically.

The primary endpoints were the assessment of urinary symptoms and pain. The secondary endpoints included QoL, analgesics use and treatment emergent adverse event (TEAE). To assess urinary symptoms and pain associated with ureteral stent, patients were asked to complete the brief-form Chinese version USSQ 2 weeks and 4 weeks after stent placement and 4 weeks after stent withdrawal (11). The outcomes obtained at 4 weeks after stent withdrawal were proposed to be the baseline data without the impact of ureteral stone and related hydronephrosis (6). Patients received a prescription for diclofenac sodium 50mg×10 suppositories. A log sheet of analgesic use was kept during the stenting period.

The brief-form Chinese version USSQ, a simplified condition-specific questionnaire for evaluation of stent-related urinary symptoms and pain in the past 2 weeks, was adopted from the validated International Prostate Symptom Scale (IPSS) (11). The procedure of back translation was performed to verify the utility for covering the urinary symptoms section and pain section of the original USSQ initiated by Joshi et al. (11, 12). Accordingly, QoL of IPSS was also assessed in our study (13). The individual index has a score ranging from 0 to 5 (or QoL score of 6), with high scores corresponding to worse outcomes.

A sample size of 218 patients was calculated based on a power of 80% and a significant level of 0.05 to detect 30% difference in flank pain scores and 26% difference in frequency scores in the first 2 weeks with the stent in situ (11). Descriptive statistics included mean±SD for continuous variables, number and percentage for categorical variables. Student t test, chi-square test and non-parameter Wilcoxon test were used, as appropriate. Analyses were performed on full per-protocol set population as it was determined more appropriate to exclude those who failed to complete the study. A p value <0.05 was considered significant. Statistic analyses were conducted using computer software (Package for Social Science 19.0, SPSS Inc., Chicago, IL).

RESULTS

A total of 239 patients were enrolled, 231 of whom were randomly assigned to either Doxazosin Oral Intake Therapy or placebo group. The total number of patients that completed the study

at 2 weeks and 4 weeks after stent placement and 4 weeks after stent withdrawal were 219, 212 and 201, respectively. The main reasons for discontinuation were loss during follow-up, protocol deviation, withdrawal of consent and TEAE.

Patient demographics are listed in Table-1. Average patient age was 45.7 years (range 26 to 66), and the overall distribution of female and male was 29% and 71%, respectively. There was no significant difference in age, gender, stone size, stone location, height and length of stent between 2 cohorts.

The overall study results are presented in Table-2. Patients receiving Doxazosin Oral Intake Therapy expressed significant lower daytime frequency (p=0.028 and p=0.038, respectively), nocturia (p=0.021 and p=0.008, respectively) and urgency (p=0.012 and p=0.014, respectively) in the first 2 weeks and second two weeks with the stent in situ when compared to the placebo group. Similarly, there were marked decreases in flank pain and abdominal pain that were associated with Doxazosin Oral Intake Therapy. Mean analgesics use and QoL scores were also significant lower in Doxazosin Oral Intake Therapy group during the stenting period.

There was no significant difference in scores of urinary symptoms, pain and QoL in the post-stent period between two groups, which were considered as the baseline characteristics.

Four patients in Doxazosin Oral Intake Therapy experienced mild TEAE (dizziness in 3

Table 1 - Patient characteristics.

Variables	Doxazosin	Placebo	P value
No. of Patients	112	107	NA
Age (y), Mean±SD (Range)	44.7± 9.4 (26-64)	46.6 ± 8.2 (30-66)	0.12*
Gender, n (%)			0.46†
Female	35 (31)	28 (26)	
Male	77 (69)	79 (74)	
Laterality, n (%)			0.13†
Left	53 (47)	39 (36)	
Right	59 (53)	68 (64)	
Stone size (mm),Mean ±SD	8.2 ± 3.5	7.8 ± 2.5	0.27*
Stone location, n (%)			0.56†
Upper	19 (17)	13 (12)	
Middle	20 (18)	18 (17)	
Lower	73 (65)	76 (71)	
Height (cm) , Mean ± SD	164.4 ± 6.5	163.6 ± 6.2	0.31*
Length of stent, n (%)			0.35†
24 cm	50 (45)	55 (51)	
26 cm	62 (55)	52 (49)	

NA not applicable
* Student t test
† Chi-square test

Table 2 - Overall study results.

Variables	Doxazosin	Placebo	P value
Daytime Frequency			
First 2 weeks	2.18 ± 1.80	2.68 ± 2.00	0.028
Second 2 weeks	1.98 ± 1.64	2.48 ± 1.81	0.038
Post-stent	1.08 ± 1.24	1.33 ± 1.41	0.266
Nocturia			
First 2 weeks	1.35 ± 1.46	1.88 ± 1.74	0.021
Second 2 weeks	1.05 ± 1.18	1.66 ± 1.62	0.008
Post-stent	0.42 ± 0.83	0.49 ± 0.90	0.749
Urgency			
First 2 weeks	1.33 ± 1.67	1.93 ± 1.74	0.012
Second 2 weeks	1.13 ± 1.33	1.67 ± 1.57	0.014
Post-stent	0.68 ± 1.26	0.77 ± 0.97	0.083
Urge incontinence			
First 2 weeks	0.09 ± 0.32	0.14 ± 0.46	0.676
Second 2 weeks	0.06 ± 0.23	0.08 ± 0.27	0.510
Post-stent	0.00	0.02 ± 0.14	0.232
Hematuria			
First 2 weeks	1.20 ± 1.62	1.26 ± 1.52	0.644
Second 2 weeks	0.86 ± 1.28	1.05 ± 1.25	0.141
Post-stent	0.27 ± 0.56	0.16 ± 0.43	0.196
Flank pain			
First 2 weeks	1.13 ± 1.46	1.83 ± 1.92	0.007
Second 2 weeks	0.93 ± 1.18	1.45 ± 1.54	0.014
Post-stent	0.18 ± 0.55	0.31 ± 0.67	0.140
Abdominal pain			
First 2 weeks	1.03 ± 1.30	1.60 ± 1.74	0.015
Second 2 weeks	0.80 ± 1.08	1.50 ± 1.55	0.001
Post-stent	0.13 ± 0.39	0.29 ± 0.66	0.074
Urethral pain			
First 2 weeks	1.07 ± 1.33	1.45 ± 1.82	0.236
Second 2 weeks	0.72 ± 1.02	1.27 ± 1.56	0.021
Post-stent	0.18 ± 0.54	0.21 ± 0.52	0.610
QoL			
First 2 weeks	2.79 ± 1.05	3.27 ± 1.32	0.003
Second 2 weeks	2.69 ± 0.97	3.00 ± 1.07	0.024
Post-stent	1.44 ± 0.95	1.57 ± 0.69	0.273
Analgesics use			
First 2 weeks	0.30 ± 0.79	0.74 ± 1.29	0.005
Second 2 weeks	0.20 ± 0.62	0.53 ± 1.02	0.006

Values in both treatment groups are presented by mean ± standard deviation
Mann-Whitney U test was used for all statistical analyses.

and orthostatic hypotension in 1), and two of them discontinued medication, and symptoms disappeared after discontinuation.

DISCUSSION

To our knowledge, this is the first double-blind, placebo controlled study to demonstrate the effectiveness of Doxazosin Oral Intake Therapy in reducing ureteral stent-related discomforts. A range of patient urinary symptoms and pain were improved, including frequency, nocturia, urgency, flank pain, abdominal pain. Patients QoL seemed to be better preserved also. The sample size per group in the study was the biggest in relevant literature. The same type of stent and indication were controlled to minimize related biases.

Although there have been lots of advances in ureteral stent composition and constructions design directed at improving biocompatibility and patient relevant symptoms, the ideal biomaterial for stent has yet to be discovered (14, 15). In contrary to stent engineering research, several studies suggested that α-blockers would be effective (4-7).

Deliveliotis et al. firstly reported that alfuzosin improved a subset of urinary symptoms and pain in patients with an indwelling double-J stent using USSQ 4 weeks after stent insertion (4). Then another two studies elucidating the efficacy of alfuzosin and tamsulosin on stent symptoms were performed by Buddingfield et al. and Damino et al., respectively (5, 6). Meta-analyses also showed that α-blockers are associated with improvements in stent symptoms (16, 17).

Recently, Dellis et al. reported that tamsulosin and alfuzosin reduced stent-related symptoms in patients with hydronephrosis associated ureteral stone who underwent stent placement, routinely for 4 weeks, after extracorporeal shock wave lithotripsy (SWL, n=106) or ureteroscopic lithotripsy (n=44) using the USSQ as originally intended by Joshi et al. 1 week and 4 weeks after stent placement and 4 weeks after stent removal (7). In our study, we assessed patient's morbidity in the first two week and second two weeks with the stent in situ and during the post-stent period using the brief--form Chinese version USSQ, which covers stent--related condition in recent two weeks. (11).

The pathophysiology of stent-related symptoms may be associated with irritation of the trigone, smooth muscle spasm in ureter and bladder, reflux of urine to kidney, or a combination of them (18). α1-adrenergic receptors are expressed in ureter, bladder body, bladder neck, urethra and prostate. The benefits of selective α1-blockers are 2-fold: inhibition of α1-adrenergic receptors in bladder neck and prostate to decrease outlet resistance and reflux of urine, and concurrent inhibition of α1-adrenergic receptors in bladder body and ureter to decrease bladder overactivity and ureter spasm, thereby improving both urinary symptoms and pain (19).

Doxazosin is a long-acting selective α1-adrenergic receptors antagonist with a half life of 16-20 hours. Doxazosin Oral Intake Therapy has been shown to offer enhanced pharmacokinetic profile, delivery rate and tolerability (8, 9). It may also improve lower urinary tract symptoms more completely via additional α-adrenergic receptors in CNS than tamsulosin (9, 10).

The beneficial effect of Doxazosin Oral Intake Therapy on stent symptoms was primarily shown in the first two weeks with the stent in situ. The results in the second two weeks with the stent in situ further indicated the efficacy of Doxazosin Oral Intake Therapy on stent symptoms, which were less dependent on patient surgical complications, preoperative condition and postoperative recovery. The outcomes obtained at 4 weeks after stent withdrawal were proposed to be the baseline data without the impact of ureteral calculi and related hydronephrosis (6). However, we still noted a trend for higher abdominal pain in the placebo group after stent removal; this finding might demonstrate the residual effects of the treatment or the prevalence of symptoms in background population (3).

Our study has several limitations. Firstly, we didn't evaluate all aspects of stent-related morbidity using USSQ initiated by Joshi et al., because the whole USSQ was not trans-

lated, adapted and validated in Chinese population. Secondly, Doxazosin Oral Intake Therapy was not compared with other α-blockers such as alfuzosin and tamsulosin. Thirdly, though the sample size per group was big enough for daytime frequency and flank pain, it might be relatively small to detect small differences of other parameters between two cohorts. Finally, since the brief-form Chinese version USSQ is used to assess symptoms associated with ureteral stent in previous 2 weeks, the discomforts were not evaluated on postoperative day 3 or 1 week after surgery when the outcomes were thought to be more relevant (5).

Future randomized study with larger patient population using validated USSQ is warranted to further ascertain the efficacy of Doxazosin Oral Intake Therapy on stent-related morbidity and find the best way to address those discomforts by comparison between Doxazosin Oral Intake Therapy and other drugs already studied, such as tamsulosin or anticholinergics.

CONCLUSIONS

The administration of Doxazosin Oral Intake Therapy 4mg once daily reduced stent-related urinary symptoms, pain and the negative impact on QoL.

ABBREVIATIONS USED

USSQ = Ureteric Stent Symptom Questionnaire
QoL = Quality of Life
TEAE = Treatment Emergent Adverse Event

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 734-739, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0275

Predicting procedural pain after ureteroscopy: does hydrodistention play a role?

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ABSTRACT

Purpose: To identify perioperative predictors of immediate pain after ureteroscopy, specifically evaluating the impact of hydrodistention from irrigation on pain.
Materials and Methods: We retrospectively identified patients who underwent ureteroscopy for the treatment of calculi. Data recorded for these patients included their maximum pain score in the post-anesthesia care unit (PACU), average flow rate of irrigant used during the procedure, patient and stone characteristics, operative procedure, and details of patients' immediate, post-operative course. Spearman's rho was used to determine the relationship between non-parametric, continuous variables. Then, a linear regression was performed to assess which variables could predict the peak pain score.
Results: A total of 131 patients were included in the study. A non-parametric correlation analysis revealed that maximum pain score was negatively correlated with being male ($r = -0.18$, $p=0.04$), age ($r = -0.34$, $p<0.001$), and post-op foley placement ($r = -0.20$, $p=0.02$) but positively correlated with the preoperative pain score ($r = 0.41$, $p<0.001$), time in the PACU ($r = 0.19$, $p = 0.03$), and the morphine equivalent dose (MED) of narcotics administered in the PACU ($r = 0.67$, $p<0.001$). On linear regression, the significant variables were age, preoperative pain score, and stent placement. For every ten-year increase in age post-operative pain score decreased by 4/10 of a point ($p = 0.03$). For every 1 point increase in preoperative pain score there was a 3/10 of a point increase in the maximum pain score ($p = 0.01$), and leaving a stent in place post-operatively was associated with a 1.6 point increase in the maximum pain score.
Conclusions: Hydrodistention does not play a role in post-ureteroscopy pain. Patients who are younger, have higher preoperative pain scores, or who are stented will experience more post-operative pain after ureteroscopy.

ARTICLE INFO

Keywords:
Pain; Postoperative Period; Ureteroscopy; Ureteral Calculi; Kidney Calculi; Surgical Procedures, Operative

Int Braz J Urol. 2016; 42: 734-9

Submitted for publication:
May 19, 2015

Accepted after revision:
October 15, 2015

INTRODUCTION

Pain is the most common complication following ureteroscopy as well as the most common reason for hospital admission after the procedure (1-3). The cause of this post-operative pain has been studied extensively but has yet to be determined. In general, pain of renal origin is thought to be secondary to distention of the renal capsule and the overlying nerve endings (4, 5). Studies from the 1950s showed that increasing pressures in or near the renal pelvis caused increased pain (6). Other potential sources of pain include ureteral spasm (7, 8), mucosal irritation, ischemia, inflammation, and activation of chemoreceptors (9, 10).

During ureteroscopy, forced irrigation causes distention of the renal collecting system. We

have empirically observed petechial hemorrhage of the urothelium with forced irrigation of the upper tract; similar to what is seen with hydrodistention of the bladder. Therefore, we hypothesized that more irrigation would lead to more hydrodistention and more pain. To this end, we evaluated the impact of irrigant flow rate on post-ureteroscopy in patients who were treated for calculi. We also examined which factors, if any, were predictive of immediate post-operative pain.

MATERIALS AND METHODS

After institutional review board approval, we retrospectively identified patients who underwent ureteroscopic removal of calculi (CPT 52351-52354, 52344). Patients and stone characteristics were obtained from the electronic medical record. Stone size was defined as the maximum diameter of the largest stone measured by preoperative CT scan, which was used also to document the stone location.

All procedures were performed by one of two endourologists at our institution, and general endotracheal intubation with inhalation agents was used for all cases. Semi-rigid ureteroscopy was utilized for distal and mid-ureteral pathology, while flexible ureteroscopy with the routine use of a ureteral access sheath was used for proximal ureteral and intrarenal pathology. Both surgeons employed a fragmentation and basketing strategy as opposed to dusting. Depending on surgeon preference, pressurized irrigation using a hand-held syringe (Boston Scientific Single-Action Pump System) or pressurized bags (100-200mmHg) was utilized for all procedures. The number of 3000mL irrigation bags used during each procedure was determined from patient-billing records.

Pain scores were quantified by patients, using a self-administered visual pain analog table. The preoperative pain score was defined as the last recorded pain score before the patient entered the operating room. The maximum pain score was the highest pain score the patient reported while in the Post-Anesthesia Care Unit (PACU). In the PACU, patients were queried by the nurses regarding their pain, starting from when they first gained consciousness, and were reassessed at regular intervals or after the administration of medications.

Patients who underwent additional procedures at the time of ureteroscopy, with the exception of cystoscopy or retrograde pyelograms, were excluded from the study. Total procedure time was defined as the time from the insertion of the cystoscope to the insertion of the postoperative urethral catheter as documented in the electronic medical record. To better approximate the pressures inside the renal collecting system during the procedure, we created a predictor variable, flow, defined as the volume of fluid used per minute.

Results were expressed as a proportion or as the mean and standard deviation. Spearman's test was used to determine the relationship between non-parametric, continuous variables. Then, a linear regression was performed to assess which variables could predict peak pain score. Statistical analysis was performed with SPSS, version 22.0 (SPSS Inc., Chicago, IL) and the significance level was set at $p<0.05$.

RESULTS

A total of 131 patients were included in this study. There was an equal gender distribution (50% male). The mean age was 54 ± 15 years and the mean BMI was $31\pm7.6 kg/m^2$. The average diameter of the largest stone was 7.2 ± 3.7mm and 43% of these were in the ureter. A more detailed description of patient and stone characteristics can be found in Table-1. The average flow of irrigant was 130 ± 76mL/min and 84% of patients were stented. The average maximum pain score was 3.7 ± 3.1 and ranged from 0-10 (Table-2). A non-parametric correlation analysis revealed that the maximum pain score was negatively correlated with being male ($r=-0.18$, $p=0.04$), age ($r=-0.34$, $p<0.001$), and post-op Foley placement ($r=-0.20$, $p=0.02$) but positively correlated with both the preoperative pain score ($r=0.41$, $p<0.001$), time in the PACU ($r=0.19$, $p=0.03$), and the morphine equivalent dose (MED) of narcotics administered in the PACU ($r=0.67$, $p<0.001$).

Multiple linear regression analysis was performed to identify variables that were predictive of the maximum pain score. Explanatory va-

Table 1 - Patient and Stone Characteristics.

	Stone Patients (n=134)		
	Mean±STD or Number (%)		Range
Age	53.4±14.6		21-87
20-40	30 (22.4)		
41-60	57 (42.5)		
>60	47 (35.1)		
Gender (male)	50%		
BMI (kg/m^2)	30.8	7.65	18.8-59
Preadmission narcotic use	50 (37)		
History of ureteroscopy	64 (48)		
History stent placement	79 (59)		
Stone size (mm)	7.1	3.65	1-24
Stone location			
Ureter	75 (56)		
Renal	59 (44)		
Stone composition			
Calcium oxalate	89 (66.4)		
Calcium phosphate	32 (29.3)		
Uric Acid	6 (4.5)		
Magnesium Ammonium Phosphate	1 (0.7)		
Mixed	6 (4.5)		

Table 2 - Operative Procedures, Post-Operative Exerience and Pain.

Stone Patients (n=134)			
Operative time (min)	60.3	31.7	15-192
Procedure			
Ureteroscopy	28 (21)		
Nephroureteroscopy	106 (79)		
No. laser used	87 (65)		
No. basket used	132 (98)		
No. dilator us d	20 (15)		
No. stent used	111 (83)		
Bilateral procedures			
Ureteroscopy	8 (6)		
Stent Placement	4 (3)		
Bags of irrigant	2.1	0.63	1-5
Preo-operative pain score	1.7	2.6	0-10
High pain score	3.8	3.1	0-10
Time in PACU (min)	199	122	47-979
Narcotics given in PACU (MEDs)	27.6	35.9	0-193

riables included in the model were age, sex, BMI, preoperative pain score, preadmission narcotics consumption, basket or laser use, stent placement, ureteral dilation, use of a ureteral access sheath, use of a rigid cystoscope, stone location, stone size, time spent in the PACU, narcotics administered in PACU, post-operative Foley catheter insertion, and previous history of a stone, ureteroscopy or stent. After linear regression sex, post-operative Foley placement, and time spent in the PACU were no longer significantly associated with the pain score. The variables that were found to be predictive were age, preoperative pain score, stent placement, and narcotics administered in the PACU. For every ten-year increase in age, post-operative pain score decreased by 4/10 of a point (p=0.03). For every 1 point increase in preoperative pain score there was a 3/10 of a point increase in the maximum pain score (p=0.01). Leaving a stent in place post-operatively was associated with a 1.6 point increase in the maximum post-operative pain score (p=0.05). The amount of post-operative pain correlated with the amount of post-operative narcotics required; for each MED administered in the PACU the predicted maximum pain score increased by 1/3 of a point (p<0.001) (Table-3).

DISCUSSION

Renal colic is thought to be caused in part by increased pressure in the renal pelvis and ureters, leading to dilation of these structures, stretching of the nerve endings, and resulting in pain (4-6, 10, 11). Indeed, pain associated with hydro-

Table 3 - Linear Regression for Predictors of Post-Ureteroscopy Pain.

Patients (n=131)			
Variable	B	SE	P-value
Age	-0.39	0.17	0.03*
Sex (Male)	-0.92	0.53	0.09
BMI	0.03	0.03	0.38
Preoparative pain score	0.27	0.10	0.01*
Home narotic use	-0.28	0.54	0.60
Laser	0.10	0.66	0.88
Basket	3.43	2.00	0.08
Dilator	-0.52	0.72	0.48
Stent	1.6	0.79	0.05*
Rigid scope	-0.17	0.65	0.79
Sheath used	0.02	0.75	0.98
History of stone	-0.02	0.56	0.97
History of ureteroscopy	0.02	0.67	0.98
History of stent placement	-0.73	0.59	0.22
Diameter of largest stone	-0.02	0.07	0.74
Locatin of largest stone (kidney)	-0.40	0.54	0.46
Flow (volume irrigant/op time)	0.00	0.00	0.50
Post-procedure foley	-0.98	0.60	0.10
Time in PACU (min)	0.00	0.00	0.43
Narcotics given in PACU (MEDs)	0.03	0.01	<0.001*

R square = 0.46

distention can be severe in patients with interstitial cystitis (12). We hypothesized that patients who received more irrigant per minute of their procedure, and therefore experienced more dilation and hydrodistention of their urinary tract, would suffer more post-operative pain.

However, we found that the rate of irrigation flowing into the collecting system during ureteroscopy was not correlated with maximum pain score. The independent predictors of maximum pain score were age, preoperative pain score, stent insertion and MEDs given. The relationship between the preoperative and the postoperative pain score is difficult to discern. It is possible that high levels of preoperative pain impact an individual's sensory perception of post-operative pain. It is also possible that those who report worse preoperative pain have a lower pain tolerance or more difficulty with pain management.

The relationship noted between MEDs administered in the PACU and postoperative pain is likely a causal one; those in more pain received more narcotics. To check the robustness of our results, we performed another regression in which MEDs administered in the PACU was used as a proxy for post-operative pain, and again flow rate was not a significant variable.

There have been other studies examining pain following ureteroscopy, including the relationship between age, stent placement and pain, with disparate results (13-15). Schuster et al. reported that stones located in the kidney and longer operative times were predictive of increased pain 48 hours after surgery but sex, stone size, stent placement, and ureteral dilation were not (1). Others, however, found a statistically significant relationship between age, basket use, stone size, operative time and post-operative pain (15, 16).

The role of stent placement in post-operative pain is particularly contested. As mentioned above, Schuster et al. did not find a relationship between pain and stent placement. Others, including Borboroglu et al., found that at 48 hour patients with stents had more overall pain than patients who were not stented. Similar to our results, however, they did not find a relationship between intraoperative ureteral dilation or laser lithotripsy and either pain or narcotic consumption (17). The dubious role of stent insertion in post-ureteroscopy pain was emphasized in a recent meta-analysis, which found that there was so much heterogeneity in the results of studies examining the relationship between stent placement and pain scores, in the immediate post-postoperative period, the data could not be pooled for analysis (18).

Our study has some limitations. We did not directly measure the pressure within the ureter and renal pelvis. Instead, we used average flow rate of irrigation during the procedure as a proxy for hydrodistention. Secondly, we were unable to isolate the volume of irrigant used for the cystoscopy portion of the procedure (placement of a safety wire) from the volume of irrigant used during ureteroscopy. In addition, since this is a retrospective analysis some confounders may exist; however, a multivariate analysis with linear regression was performed to decrease the effect of potential bias. Future prospective or randomized control trials would be useful to further examine the relationship between hydrodistention of the renal collecting system and immediate pain following ureteroscopy, looking specifically at regulated pressures during irrigation.

CONCLUSIONS

To our knowledge, no other studies have attempted to study the relationship between hydrodistention of the renal collecting system and post--ureteroscopy pain. Hydrodistention of the kidney and ureters from pressurized irrigation during ureteroscopy is not correlated with immediate postoperative pain. On linear regression, the predictors of immediate postoperative pain after ureteroscopy were the preoperative pain score, age, and stent placement. It should be anticipated that those patients with higher levels of pain prior to ureteroscopy will require greater amounts of narcotics in the PACU. Indeed, the use of adjuncts such as parenteral ketorolac or acetaminophen may be targeted to these patients.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 740-746, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0477

Predictive risk factors of postoperative urinary incontinence following holmium laser enucleation of the prostate during the initial learning period

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ABSTRACT

Purpose: To determine the predictive factors for postoperative urinary incontinence (UI) following holmium laser enucleation of the prostate (HoLEP) during the initial learning period.

Patients and Methods: We evaluated 127 patients with benign prostatic hyperplasia who underwent HoLEP between January 2011 and December 2013. We recorded clinical variables, including blood loss, serum prostate-specific antigen levels, and the presence or absence of UI. Blood loss was estimated as a decline in postoperative hemoglobin levels. The predictive factors for postoperative UI were determined using a multivariable logistic regression analysis.

Results: Postoperative UI occurred in 31 patients (24.4%), but it cured in 29 patients (93.5%) after a mean duration of 12 weeks. Enucleation time >100 min (p=0.043) and blood loss >2.5g/dL (p=0.032) were identified as significant and independent risk factors for postoperative UI.

Conclusions: Longer enucleation time and increased blood loss were independent predictors of postoperative UI in patients who underwent HoLEP during the initial learning period. Surgeons in training should take care to perform speedy enucleation maneuver with hemostasis.

ARTICLE INFO

Keywords:
Blood Loss, Surgical; Lasers; Learning; Prostatic Hyperplasia; Urinary Incontinence

Int Braz J Urol. 2016; 42: 740-6

Submitted for publication:
August 29, 2015

Accepted after revision:
November 22, 2015

INTRODUCTION

Transurethral resection of the prostate (TURP) is considered a standard procedure for treating benign prostatic hyperplasia (BPH). In recent years, several laser systems and applications have been applied to the endoscopic surgical treatment of BPH. Holmium laser enucleation of the prostate (HoLEP) is one such type of laser treatment. It was first reported by Gilling et al. (1) and several studies have documented its efficacy and safety (2-4). This minimally invasive technique enables complete prostate resection even in cases with a large prostate volume (5, 6). In addition, it is reported to provide better short-term urinary functional outcomes, shorter duration of Foley catheter use, and shorter hospital stay than TURP (7). HoLEP is expected to become the new gold standard technique for treating BPH. However, difficulties of surgical techniques and high frequency in postoperative urinary incontinence (UI) remain to be significant problems for unexperienced urologists.

HoLEP required a certain surgical learning curve. Some studies have reported that urologists

need a threshold of at least 20-50 cases to gain acceptable efficacy (8, 9). Although HoLEP is one of the established surgical procedures, not a few urologists hesitate to introduce HoLEP techniques. A multicenter prospective study showed that almost half of centers which introduced HoLEP chose to terminate the operation due to longer operative time and difficulty of enucleation of the prostatic lobe (10).

Postoperative UI is mainly classified as either stress or urge UI. These UI occurred after BPH surgery by several factors, the etiology still remains to be elucidated. Transient stress UI after HoLEP is similar to that observed after TURP according to a meta-analysis comparing HoLEP and TURP (7). On the other hand, short-term urge UI after HoLEP is more frequent than those of TURP (4). Almost all UI cases improved after a few weeks, but persistent UI occurs in 1%–2% patients (2, 4, 11).

There is little available data on the relationship between perioperative variables including surgical parameters and UI following HoLEP (11, 12). To disseminate and continue with the technique of HoLEP, it is important to determine the cause of postoperative UI. Thus, in the present study, we evaluated the clinical characteristics that can significantly predict postoperative UI following HoLEP, particularly during the initial learning period.

PATIENTS AND METHODS

The present study was approved by the institutional review board of our hospital. A total of 146 initial patients who underwent HoLEP between January 2011 and December 2013 were identified using a prospectively collected database. The HoLEP procedure was performed either of two surgeons who were skilled in endourological procedures. We excluded 12 patients of conversion to TURP due to capsular perforation or uncontrolled bleeding. We also excluded patients who were unable to answer the questionnaires regarding their UI because of dementia (n=2) and those who presented with UI preoperatively (n=5). Thus, a total of 127 patients were eligible for the present study.

Subjective symptoms of the International Prostate Symptom Score (IPSS) and quality of life (QoL) scores, objective parameters of uroflowmetry, and post-void residual urine (PVR) were measured pre- and post-operatively. The total prostate volume was determined by transrectal ultrasonography. Transperineal prostate biopsy was performed to exclude prostate cancer when serum prostate-specific antigen (PSA) >4.0ng/mL. IPSS, QoL scores, uroflowmetry, and PVR were determined at 3 months after HoLEP and were compared with preoperative data.

Our HoLEP technique was based on the procedure described in detail by Gilling et al. (1). We used a 100W holmium: YAG laser source (VersaPulse PowerSuite, Lumenis, Yokneam, Israel), a 550μm laser fiber (SlimLine, Lumenis, Yokneam, Israel), and a 26Fr continuous-flow resectoscope (Karl Storz, Tuttlingen, Germany). We placed the patients generally under spinal anesthesia and dissected and enucleated the median, left, and right lobes of the prostate one by one in a retrograde fashion. We performed morcellation of the 3 enucleated lobes using a tissue morcellator (VersaCut, Lumenis, Yokneam, Israel). After the procedure, a 20Fr Foley catheter was placed and the urinary bladder was continuously irrigated until the next day. The patient was typically discharged after the removal of the Foley catheter on postoperative day 2.

We evaluated preoperative variables in all patients, including age, body mass index (BMI), diabetes mellitus, serum PSA levels, use of medication including antiplatelet agents, history of acute urinary retention, and total prostate volume (Table-1). In patients receiving antiplatelet therapy, these agents were usually terminated 7–10 days before HoLEP, and then resumed 1–2 days after surgery. We also noted surgery-related variables, including operative time, enucleation time, morcellation time, total energy, occurrence of bladder injury, enucleated prostate volume and blood loss (Table-1). The difference in hemoglobin levels between before surgery and on postoperative day 1 was used to estimate blood loss. The postoperative PSA levels were obtained at the 3-month follow-up visit, and the percentage reduction in PSA levels was calculated using serum PSA levels

Table 1 - Baseline characteristics of 127 patients.

	Mean ± SD or N
Preoperative variables	
Age, year	72 ± 6
BMI, kg/m^2	23.2 ± 2.9
Diabetes mellitus	
Yes	20
No	107
PSA, ng/mL	7.0 ± 6.3
Antiplatelet agents	
Yes	9
No	118
History of acute urinary retention	
Yes	41
No	86
Total prostate volume, mL	69 ± 33
Surgery-related variables	
Operative time, min	127 ± 50
Enucleation time, min	93 ± 38
Morcellation time, min	14 ± 12
Total energy, KJ	133.0 ± 47.8
Bladder injury	
Yes	6
No	121
Enucleated prostate volume, g	40 ± 27
Blood loss, g/dL	1.4 ± 1.2
Postoperative variables	
PSA reduction, %	82.8± 14.0

BMI = body mass index; **PSA** = prostate-specific antigen; **SD** = standard deviation.

obtained before and after surgery. We observed the patients for postoperative complications such as acute urinary retention, blood transfusion, UI, urethral stricture, and urinary tract infection for 90 days after HoLEP.

All patients were asked about the presence or absence of UI at every outpatient visit before and after HoLEP. Stress UI was evaluated on the basis of medical interview. Urge UI was assessed by using the overactive bladder symptom score, the symptom assessment questionnaire of overactive bladder: daytime frequency, nocturia, urgency, and urge incontinence (13). On the basis of the responses to questions, we excluded patients with preoperative UI, and we collected information regarding the type of UI (stress UI, urge UI, or mixed UI) and the total number of pads used per day. Continence was defined as complete dryness or 1 pad used prophylactically per day.

All variables were analyzed for statistically significant differences using the Mann-Whitney U test for continuous variables and the chi-square and Fisher exact tests for categorical variables. To identify the risk factors for the incidence of postoperative UI following HoLEP, a logistic regression analysis was used, and odds ratios (ORs) and 95% confidence intervals (CI) were determined. P values <0.05 on a univariate analysis were included in a multivariate logistic model. The statistical analyses were performed using JMP version 9.0 (SAS Institute Inc., Cary, NC, USA). All p values <0.05 were considered significant.

RESULTS

Table-1 illustrates the clinical characteristics of all 127 patients. The mean blood loss was 1.4g/dL. Nine patients continued antiplatelet therapy during surgery. Mean IPSS (p<0.0001), mean QoL scores (p<0.0001), and mean PVR rate (p<0.0001) had significantly decreased from baseline, respectively. Similarly, mean Qmax rate significantly increased (p<0.0001). We evaluated the correlations between blood loss and clinical variables. When patients were divided into groups on the basis of a blood loss >2.5g/dL (n=18) and other parameters (n=109), larger total prostate volume (p<0.0001), longer operative time (p=0.0098), longer morcellation time (p=0.0002), and larger enucleated prostate volume (p<0.0001) were significantly correlated with a blood loss >2.5g/dL. In contrast, blood loss was not correlated with the status of antiplatelet drug use and the percentage reduction in PSA.

The mean follow-up was 13 months (range, 3–53 months). A total of 31 patients (24.4%) developed postoperative UI as follows: 17 with stress UI, 9 with urge UI, and the remaining 5 with mixed UI. After pelvic floor exercises and/or anti-

cholinergic drugs introduced in these patients, UI disappeared in 29/31 (93.5%) patients at a mean duration of 12 weeks (range, 2–28 weeks). Two patients with mixed UI had persistent incontinence until the last follow-up visit (>2 year).

Overall, perioperative complications occurred in 22 (17.3%) patients. Superficial bladder mucosal injury during morcellation, urethral stricture, febrile urinary tract infection, and postoperative acute urinary retention developed in 6, 7, 7, and 1 patient, respectively. One patient who had a prostate volume of 202mL required a blood transfusion. After HoLEP, his hemoglobin level decreased from 13.0g/dL to 8.3g/dL on postoperative day 1. When his hemoglobin level was 7.4g/dL on postoperative day 2, we transfused 2 units of packed red blood cells without any adverse events.

Further, we assessed the clinical parameters that were significantly associated with postoperative UI. Univariate analysis revealed that enucleation time >100 min, enucleated prostate volume >50g, and increased blood loss >2.5g/dL were significantly associated with postoperative UI. We found no significant difference between both surgeons and incidence of postoperative UI (data not shown). On multivariable logistic regression analysis, enucleation time >100 min (OR, 2.54; 95% CI, 1.03–6.30; p=0.043) and increased blood loss >2.5g/dL (OR, 3.62; 95% CI, 1.12–11.99; p=0.032) were identified as independent and significant predictors of postoperative UI (Table-2). In sub-analysis of associations between two types of UI and clinical parameters, univariate analysis revealed that enucleated prostate volume >50g (p=0.030), and increased blood loss >2.5g/dL (p=0.017) were associated with stress UI, and increased blood loss >2.5g/dL was only identified as a significant parameter associated with urge UI (p=0.030).

COMMENTS

There is still limited data regarding the predictive factors for stress UI in patients following HoLEP. Detrusor dysfunction, sphincter incompetence, and mixed incontinence have been considered as the main etiological factors for stress UI after prostatectomy. Long-term urinary bladder outflow obstruction leads to detrusor instability, and any damage to the urethral sphincter during surgery results in sphincter incompetence (14). Elmansy et al. (12) demonstrated that total prostate volume, operative time, and percentage reduction in PSA levels were significantly associated with stress UI after HoLEP. One possible explanation for the incidence of stress UI is that large prostate volumes are associated with longer operative times. This is associated with longer durations during which the sheath is manipulated across the urethral sphincter, which may cause sphincter incompetence (12). Another possible explanation is that more complete prostate tissue removal creates a large prostatic fossa and causes short-term urine trapping and leakage during stress maneuvers (15). A greater percentage reduction in PSA levels may be a surrogate marker of less residual adenoma following BPH surgery, which could lead to the incidence of stress UI seen after HoLEP.

There are several hypotheses regarding the mechanism of postoperative urge UI. Patients with preoperative terminal detrusor overactivity are more likely to develop high overactive bladder

Table 2 - Changes in clinical parameters after HoLEP.

	Preoperative	Postoperative	
	Mean ± SD	Mean ± SD	p
IPSS	18.5 ± 8.3	5.9 ± 5.8	<0.0001
QoL	4.7 ± 1.3	1.6 ± 1.5	<0.0001
Qmax, mL/sec	9.3 ± 4.3	21.8 ± 11.2	<0.0001
PVR, mL	144.2 ± 266.1	17.9 ± 29.1	<0.0001

IPSS = International Prostate Symptom Score; **PVR** = post-void residual urine; **Qmax** = maximal flow rate; **QoL** = quality of life; **SD** = standard deviation

symptom scores and persistent urge UI after TURP (16). On the other hand, detrusor overactivity is not associated with urge UI following HoLEP, and the presence of bladder injury during morcellation was the only predictive factor for urge UI (11). Although it is important to provide hemostasis for a clear endoscopic view for avoiding bladder mucosal injury during morcellation, we did not identify a significant difference between intraoperative bleeding and bladder mucosal injury in our cohort.

Surgical technique of HoLEP during the learning period is one major predictor of postoperative UI (Table-3). Although HoLEP has become increasingly utilized for the treatment of BPH, the technical challenge of HoLEP is greater than those of TURP and requires longer training periods (8). The occurrence of postoperative UI after HoLEP was 4.9–12.5% with even expert surgeon who operated more than 900 cases (2, 12). The possible technical causes of developing stress UI during the learning phase are thought to be violate operative planes, enucleation too deep, and over-dissection at the level of apex (17). In particular, appropriate apical dissection is considered an important point for avoiding urinary sphincteric injury during HoLEP procedure (18). In the present study, surgery-related variables such as enucleation time and blood loss were associated with postoperative UI, whereas all preoperative variables were not. This result indicated technical improvement possibly contributes to reduce postoperative UI. Indeed, Endo et al. (19) revealed that the procedure of anteroposterior dissection (a surgical procedure where adenoma is dissected antegradely) could decrease postoperative stress UI. Further studies are warranted to assess the association between surgical technique and postoperative UI.

Table 3 - Univariate and multivariate logistic regression analysis for predicting postoperative urinary incontinence.

	Univariate analysis		Multivariate analysis	
Variables	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Age, y (>75 vs ≤75)	1.16 (0.47–2.73)	0.74		
BMI, kg/m^2 (>25 vs ≤25)	0.99 (0.39–2.37)	0.99		
Diabetes mellitus (yes vs no)	0.74 (0.20–2.23)	0.61		
PSA, ng/mL (>4 vs ≤4)	1.06 (0.46–2.53)	0.89		
Antiplatelet agents (yes vs no)	0.88 (0.13–3.87)	0.87		
History of acute urinary retention (yes vs no)	1.00 (0.41–2.34)	0.99		
Total prostate volume, mL (>80 vs ≤80)	2.12 (0.88–5.04)	0.092		
Operative time, min (>160 vs ≤160)	1.70 (0.68–4.12)	0.25		
Enucleation time, min (>100 vs ≤100)	2.81 (1.21–6.58)	0.017	2.54 (1.03–6.30)	0.043
Morcellation time, min (>20 vs ≤20)	1.11 (0.40–2.85)	0.84		
Total energy, KJ (>170 vs ≤170)	1.92 (0.73–4.86)	0.18		
Bladder injury (yes vs no)	0.61 (0.03–3.96)	0.64		
Enucleated prostate volume, g (>50 vs ≤50)	3.56 (1.51–8.51)	0.0039	2.13 (0.78–5.61)	0.14
Blood loss, g/dL (>2.5 vs ≤2.5)	5.24 (1.85–15.34)	0.0019	3.62 (1.12–11.99)	0.032
PSA reduction, % (>85 vs ≤85)	1.89 (0.79–4.80)	0.15		

BMI = body mass index; **CI** = confidence interval; **PSA** = prostate-specific antigen

Our results generate the hypothesis that blood loss may serve as a predictive factor for the incidence of postoperative UI. Although surgical techniques for controlling bleeding in prostatectomy procedures have been established, blood transfusion is still required in some patients. Martin et al. (20) reported that 8 of 130 patients (6.7%) required postoperative blood transfusions. Intraoperative poor visibility attributed to bleeding increased the risk of misfiring the laser or using excessive compression with the beak of the resectoscope sheath on the external urinary sphincter. This may have resulted in sphincter damage, which lead to stress UI. Moreover, prostatic capsule was exposed to excessive laser energy for stop bleeding during surgical procedure, that may also be attributed to development of urge UI. Thus, we supposed that meticulous hemostasis, without blind laser application, and careful blunt dissection can achieve less bleeding and lead to a decrease in the incidence of postoperative UI.

The present study had several limitations. First, it enrolled a relatively small number of patients; therefore, further evaluation and validation of our study findings is required. Second, HoLEP was not performed by a single surgeon. Although the incidence of postoperative UI was not significantly different between both surgeons, surgical technique potentially influenced functional outcomes. Third, the objective assessment of the presence of detrusor overactivity or sphincter disorders was limited because this study was retrospective in nature, and urodynamic tests other than uroflowmetry were not performed routinely.

CONCLUSIONS

Our data demonstrated that HoLEP could gain good functional outcomes regardless of duration of the initial learning period. Longer enucleation time and increased blood loss were significantly associated with postoperative UI following HoLEP. Although postoperative UI is usually transient and resolves within a few months, prolonged, severe UI occurred in some patients. Thus, surgeons in training should take care to achieve speedy enucleation with meticulous hemostasis during surgical procedures, and technical improvement of surgery might provide decrease of the incidence of UI.

ABBREVIATIONS

BMI = body mass index
BPH = benign prostatic hyperplasia
CI = confidence intervals
HoLEP = Holmium laser enucleation of the prostate
IPSS = International Prostate Symptom Score
ORs = odds ratios
PSA = prostate-specific antigen
PVR = post-void residual urine (PVR)
QoL = quality of life
TURP = Transurethral resection of the prostate
UI = urinary incontinence

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 747-756, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0225

Bipolar transurethral enucleation and resection of the prostate versus bipolar resection of the prostate for prostates larger than 60gr: A retrospective study at a single academic tertiary care center

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ABSTRACT

Objective: To evaluate the efficacy and safety of bipolar transurethral enucleation and resection of the prostate (B-TUERP) versus bipolar transurethral resection of the prostate (B-TURP) in the treatment of prostates larger than 60g.
Material and Methods: Clinical data for 270 BPH patients who underwent B-TUERP and 204 patients who underwent B-TURP for BPH from May 2007 to May 2013 at our center were retrospectively analyzed. Outcome measures included operative time, decreased hemoglobin level, total prostate specific antigen (TPSA), International Prostate Symptom Score (IPSS), maximal urinary flow rate (Qmax), quality of life (QoL) score, post void residual urine volume (RUV), bladder irrigation duration, hospital stay, and the weight of resected prostatic tissue. Other measures included perioperative complications including transurethral resection syndrome (TURS), hyponatremia, blood transfusion, bleeding requiring surgery, postoperative acute urinary retention, urine incontinence and urinary sepsis. Patients in both groups were followed for two years.
Results: Compared with the B-TURP group, the B-TUERP group had shorter operative time, postoperative bladder irrigation duration and hospital stay, a greater amount of resected prostatic tissue, less postoperative hemoglobin decrease, better postoperative IPSS and Qmax, as well as lower incidences of hyponatremia, urinary sepsis, blood transfusion requirement, urine incontinence and reoperation ($P<0.05$ for all).
Conclusions: B-TUERP is superior to B-TURP in the management of large volume BPH in terms of efficacy and safety, but this finding needs to be validated in further prospective, randomized, controlled studies.

ARTICLE INFO

Keywords:
Prostatic Hyperplasia; Transurethral Resection of Prostate; Prostate

Int Braz J Urol. 2016; 42: 747-56

Submitted for publication:
April 20, 2015

Accepted after revision:
February 01, 2016

INTRODUCTION

Transurethral resection of the prostate (TURP) has long been considered the gold standard for treatment of symptomatic benign prostatic hyperplasia (BPH) when medical therapy fails (1, 2). Conventional TURP uses a monopolar electrocautery system in which distilled water or a variety of solutions other than normal saline are used as an irrigant (3). Although monopolar TURP has a high success rate (90%-95%), it is associated with a morbidity rate of 15% to 18% and a mortality rate of 0.001% (4). Bipolar TURP (B-TURP), with the use of normal saline as irrigant, significantly eliminates the risk of transurethral resection syndrome (TURS) (3-5). B-TURP is asso-

ciated with significantly less fluid absorption than monopolar TURP, but the operative duration and the weight of resected prostatic tissue are similar between the two procedures (6). In addition, postoperative bleeding, blood transfusion requirements, early and late complications such as clot retention, urinary retention, bladder neck stenosis and urethral stricture did not significantly differ between the two procedures (7-10). There is still a need to upgrade this technique to improve its efficacy and safety.

Transurethral enucleation and resection of the prostate (TUERP) is a recently developed procedure created by Liu et al. (11), in which the prostate is transurethrally enucleated and resected using a bipolar plasma kinetic resectoscope (12). Studies have suggested that TUERP is a safe and feasible treatment for BPH with few complications (12-15). Although several studies have demonstrated better clinical benefits for TUERP than for other treatments (13, 16), this procedure has not been widely accepted. This study aimed to compare the efficacy and safety of B-TUERP versus B-TURP in the management of prostates larger than 60g.

MATERIAL AND METHODS

Patients and study protocol

The study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Fujian Medical University. All patients provided written informed consent. The clinical data for 298 consecutive patients who underwent B-TUERP and 225 consecutive patients who underwent B-TURP for BPH from May 2007 to May 2013 at our center were retrospectively analyzed. All operations were performed mainly by one surgeon (Xue X-Y), who has more than twenty years of experience with these procedures. The type of operation was selected according to the patient's preference after detailed explanation by the surgeon regarding the procedures, outcomes, and complications of each option. All the patients had histologically proved BPH and only those with prostate volume larger than 60g on transrectal ultrasound were included (9, 17). Any patient with a previous history of prostatic or urethral surgery, urethral stricture, neurovesical dysfunction and/or prostate cancer was excluded. Indications for surgery were a preoperative International Prostate Symptom Score (IPSS) ≥12 points, a maximal urinary flow rate (Qmax) <15mL/s, urine retention, upper tract dilatation, renal insufficiency and recurrent urinary tract infection. B-TUERP or B-TURP was done according to patient's preference. Age, IPSS, quality of life (QoL) score, prostate specific antigen (PSA), prostatic volume (PV) and post-void residual urine volume (RUV) were compared preoperatively between the two groups. A total of 474 (90.6%) of 523 patients were followed for two years, and the others were lost to follow-up.

Operative techniques

Both bipolar resection procedures were performed using the Gyrus bipolar plasmakinetic resection system, with the power set at 200W for cutting and at 100W for coagulation. Normal saline was used as irrigant, and the irrigation pressure ranged from 80 to 100mH_2O. Cystostomy was not performed in all cases. Under general or spinal anesthesia, the patient was placed in the lithotomy position. A 27-Fr resectoscope was placed in the bladder under video assisted endosurgical system guidance.

B-TURP was performed as previously described (18). Transurethral resection of prostatic hyperplasia tissue was performed along the direction from the mouth of the urethra to the prostate apex and from the urethra to the prostatic capsule.

B-TUERP was conducted also as previously described (12). Briefly, an incision was created close to the verumontanum in order to incise the urethral mucosa deep to the level of the surgical capsule. After dissecting the distal mid lobe and mucosa in a retrograde fashion toward the bladder neck and detaching adenoma of the distal mid lobe from the surgical capsule, the denuded supply vessels and hemorrhage spots on the capsule surface were identified and coagulated to block the lobe blood supply. The bilateral lobes along the surgical capsule were then detached and all supply vessels were coagulated. The adenoma was finally resected. When resec-

tion was completed, all adenoma fragments were extracted using an Ellik evacuator, and a 20-F 3-way Foley catheter was placed and connected to straight drainage until hematuria sufficiently resolved.

Outcome measures

Operative time, pre-and postoperative hemoglobin levels (on the first postoperative day), weight of resected prostatic tissue, bladder irrigation duration, hospital stay, IPSS, Qmax, QoL score, RUV, and TPSA were calculated. Perioperative complications such as TURS, hyponatremia (at the end of operation, defined as serum sodium less than 135mmol/L), blood transfusion, bleeding requiring surgery to stop bleeding, postoperative acute urinary retention, urine incontinence and urinary sepsis were observed.

Follow-up

Patients in both groups were followed for two years. One independent investigator performed the follow-up at 1, 6, 12, and 24 months. Postoperative outcome measures, including Qmax, PSA, IPSS, RUV, and QoL score, were recorded at each follow-up visit. Urethral stricture, bladder neck stenosis, urine incontinence and postoperative acute urinary retention, as well as postoperative recurrence requiring reoperation were also recorded during the follow-up period.

Statistical analysis

Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA). Data following a normal distribution are presented as mean±standard deviation and were compared using the t-test, while data not following a normal distribution are presented as median (range) and were compared using the Wilcoxon rank-sum test for two independent samples. Categorical data (percentages) were compared using the chi-square test or the Fisher's exact probability test. P-values <0.05 were considered statistically significant.

RESULTS

Baseline patient characteristics

The baseline characteristics of the included patients are shown in Table-1. There were 270 patients in the B-TUERP group and 204 patients in the B-TURP group. Preoperatively, the two groups had comparable mean age, IPSS, QoL score, TPSA, PV and RUV (P>0.05 for all).

Table 1 - Baseline characteristics of the included patients.

	B-TUERP	B-TURP	P
No. of cases	270	204	-
Age (year)	68.0±8.6	68.4±7.9	0.588
IPSS	25.4±5.2	25.0 ± 5.7	0.431
QoL score	3.5±1.4	3.5 ± 1.6	0.806
Median preoperative TPSA (interquartile range)	3.70 (2.52-6.25)	3.67 (2.39-6.19)	0.748*
PV (mL)	80.1 ± 11.1	80.7 ± 12.5	0.578
Qmax (mL/s)	5.7±2.6	5.3±2.3	0.089
RUV (mL)	140.1±43.4	136.5±41.0	0.369

B-TUERP = bipolar transurethral enucleation and resection of the prostate; **B-TURP** = bipolar transurethral resection of the prostate; **IPSS** = International Prostate Symptom Score; **Qmax** = maximal urinary flow rate; **QoL** = quality of life; **TPSA** = total prostate specific antigen; **PV** = prostatic volume; **RUV** = residual urine volume. *Mann-Whitney test.

Perioperative and postoperative outcomes

All procedures were successful, and no conversion to open surgery was required. There were no perioperative cardiovascular or cerebrovascular accidents following the two procedures. Perioperative outcomes in the two groups are summarized in Table-2. The B-TUERP procedure required significantly shorter operative time than the B-TURP procedure (P<0.05). Postoperative hemoglobin decrease was more significant in the B-TURP group compared with the B-TUERP group (P<0.05). The weight of resected prostatic tissue was greater in the B-TUERP group (P<0.05). In addition, postoperative bladder irrigation duration and hospital stay were significantly shorter in the B-TUERP group than in the B-TURP group (P<0.05 for both).

Postoperative QoL score and RUV at all follow-up time points were similar between the two groups (P>0.05 for all), but postoperative IPSS at 1, 6 and 12 months and Qmax at all follow-up time points were significantly better in the B-TUERP group than in the B-TURP group (P<0.05 for both) (Figures 1-4).

Perioperative and postoperative complications

Perioperative and postoperative complications in the two groups are presented in Table-3. No TURS occurred in either group. Six patients in the B-TURP group developed hyponatremia, while only two patients developed hyponatremia in the B-TUERP group (P<0.05). The number of patients requiring blood transfusion was significantly lower in the B-TUERP group than in the B-TURP group (P<0.05). At one month, urinary incontinence rate was significantly lower in the B-TUERP group than in the B-TURP group (P<0.05), but this resolved within three months. However, there were no significant differences in the incidence of urethral stricture, bladder neck stenosis, bleeding requiring surgery or postoperative acute urinary retention.

DISCUSSION

In recent years, B-TURP has been advocated as an alternative to monopolar TURP-the gold standard for the surgical treatment of BPH (19).

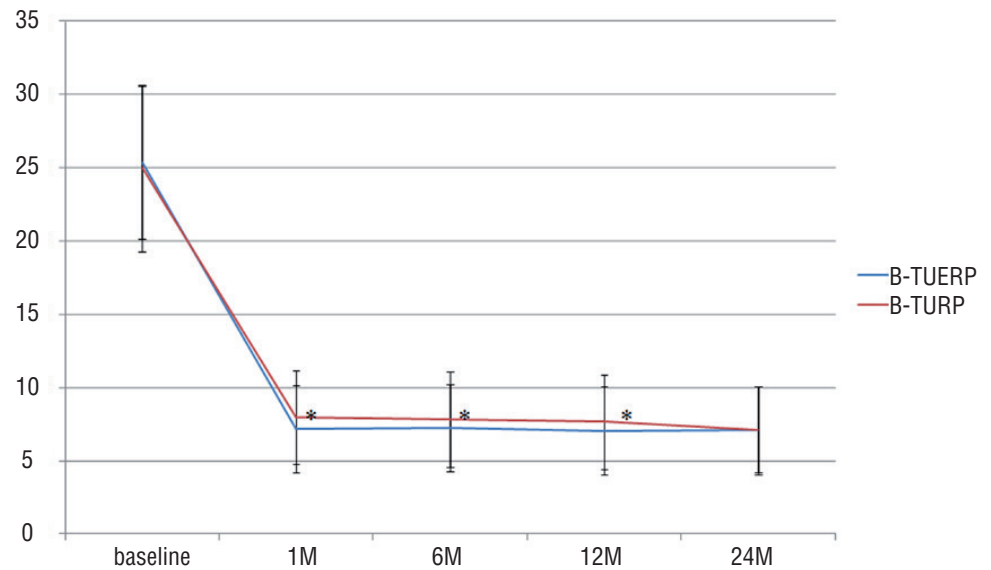
Table 2 - Perioperative outcomes in the two groups.

	B-TUERP	B-TURP	P
Operative time (min)	73.37 ± 19.99	83.77 ± 20.89	<0.001
Hospital stay (d)	4.0	5.0	<0.001*
(interquartile range)	(4.0-5.0)	(5.0-6.0)	
Decreased hemoglobin (g/L)	1.79 ± 0.51	2.35 ± 0.63	<0.001
Postoperative bladder irrigation duration (h)	32.56 ± 8.97	58.92 ± 12.93	<0.001
Weight of resected prostatic tissue (g)	43.2±12.9	40.4±11.6	0.013

B-TUERP = bipolar transurethral enucleation and resection of the prostate; **B-TURP** = bipolar transurethral resection of the prostate.*Mann-Whitney test.

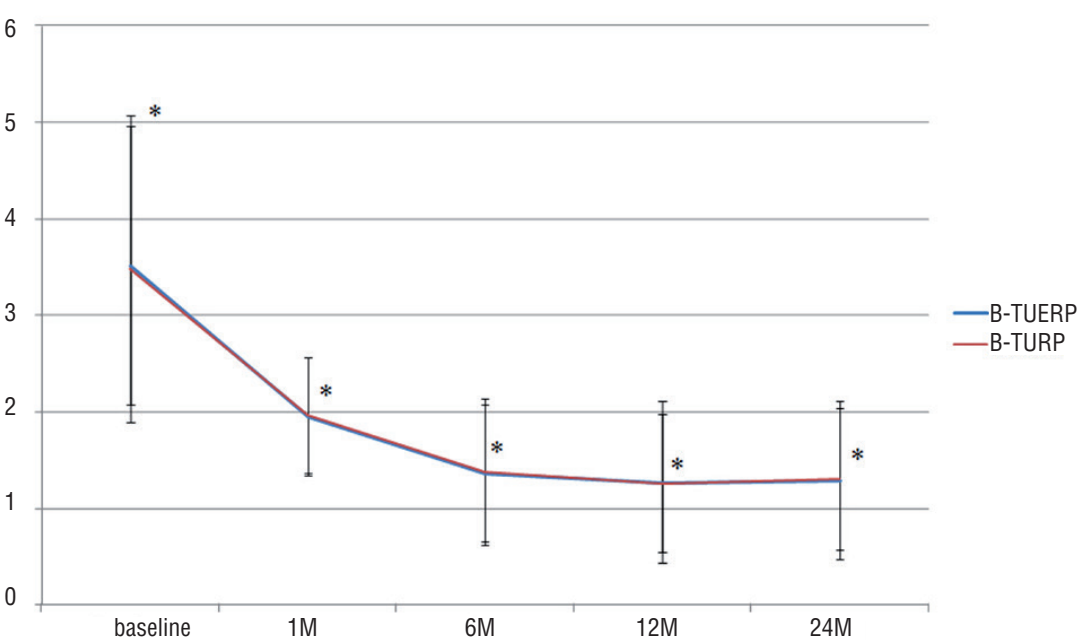
However, since the B-TURP technique is not substantially different from the monopolar technique and the amount of resected prostatic tissue did not differ significantly between the two procedures, the functional results of B-TURP are similar to those of monopolar TURP (20). A meta-analysis of 16 randomized, controlled-trials involving 1406 patients showed no clinically relevant difference in short-term efficacy between monopolar and B-TURP procedures (21). In contrast, the TUERP technique replicates the open enucleation of prostatic adenomas in an endoscopic fashion and combines the benefits of complete enucleation and a minimally invasive approach to BPH (16), allowing for

Figure 1 - Mean IPSS scores before and after treatment.



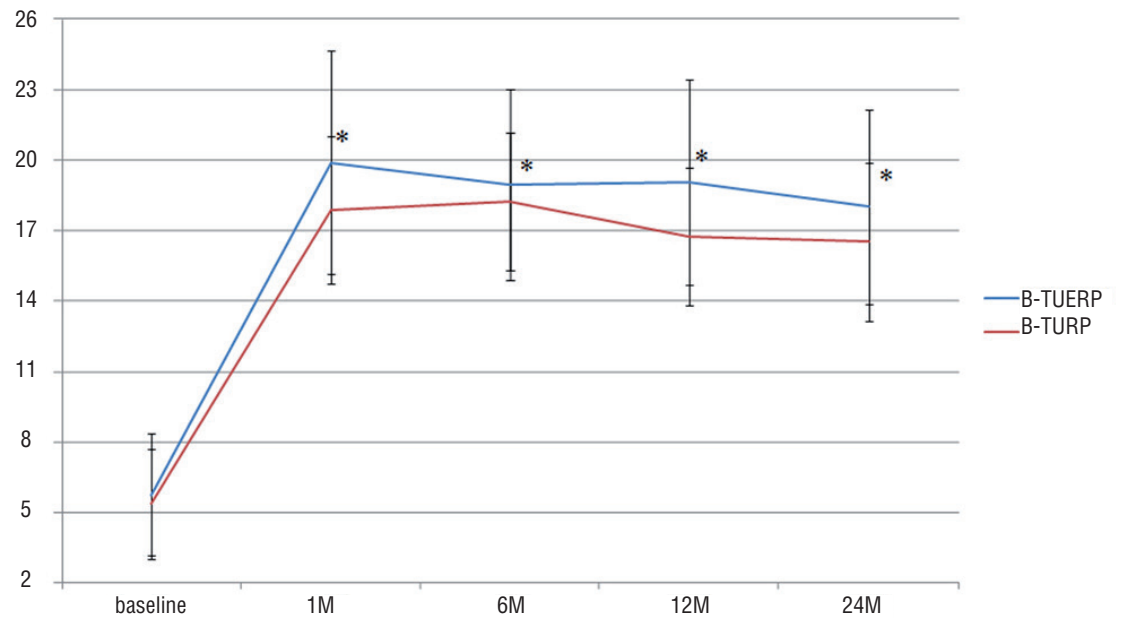
* *P*<0.05,IPSS=Internacional Prostate Symptom Score

Figure 2 - Mean QoL scores before and after treatment.



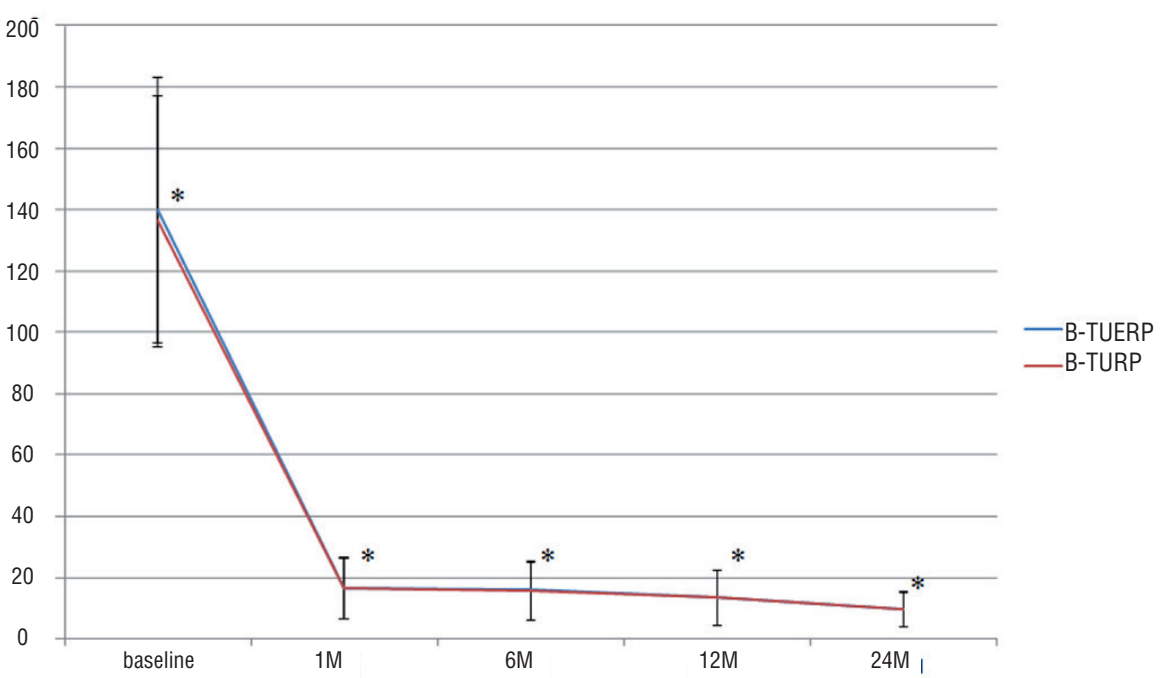
* *P*>0.05, QoL=Quality of Life

Figure 3 - Mean Qmax scores before and after treatment.



* *P*<0.05,Qmax=Maxima Urinary Flow Rate

Figure 4 - Mean RUV scores before and after treatment.



* *P*>0.05, RUV=Residual Urine Volume

Table 3 - Complications of B-TUERP and B-TURP classified according to the modified Clavien system.

Complications	B-TUERP	B-TURP	P
Grade I, n(%)	19 (7.0%)	34(16.7%)	0.001
Hyponatremia, n(%)	2 (0.7%)	6(2.9%)	0.139
Postoperative urinary sepsis, n(%)	0 (0%)	4(2.0%)	0.071*
Postoperative acute urinary retention, n(%)	2 (0.7%)	2(1.0%)	1.000*
Bladder neck stenosis, n(%)	1(0.4%)	1(0.5%)	1.000*
Incontinence at 1 month, n(%)	14(5.0%)	21(10.3%)	0.035
Grade II, n(%)	0 (0%)	3(1.5%)	0.079*
Blood transfusion requirement, n(%)	0 (0%)	3(1.5%)	0.079*
Grade III, n(%)	0 (0%)	7(3.4%)	0.003*
Bleeding requiring surgery, n(%)	0 (0%)	3(1.5%)	0.079*
Urethral stricture, n(%)	0 (0%)	1(0.5%)	0.430*
Postoperative recurrence requiring reoperation#, n(%)	0 (0%)	3(1.5%)	0.079*
Grade IV, n(%)	0 (0%)	0 (0%)	
Grade V, n(%)	0 (0%)	0 (0%)	
Total, n(%)	**19 (7.0%)**	**44(21.6%)**	**<0.001**

B-TUERP = bipolar transurethral enucleation and resection of the prostate; **B-TURP** = bipolar transurethral resection of the prostate; **TURS** = transurethral resection syndrome.*Fisher's exact test; #due to inadequate resection in the first procedure

more complete adenoma removal. We therefore in the present study compared the efficacy and safety of B-TUERP versus B-TURP in the management of prostates larger than 60g. Unsurprisingly, we found that when compared with the B-TURP procedure, B-TUERP was associated with shorter operative time, postoperative bladder irrigation duration and hospital stay. Furthermore, there was a greater weight of resected prostatic tissue, less postoperative hemoglobin decrease, better postoperative IPSS and Qmax, and lower incidences of hyponatremia, urinary sepsis, blood transfusion requirement and reoperation. All these suggest that B-TUERP is safe and feasible in the treatment of prostates larger than 60g.

After the adenoma was detached from the surgical capsule during TUERP, the blood supply to the adenoma was cut off and hemostasis was performed by coagulation under endoscopic monitoring (12). Therefore, the resection of the detached adenoma is virtually bloodless (15). In contrast, during TURP the vessels are repeatedly cut until the surgical capsule is reached (16). Therefore, intraoperative blood loss will be less in the B-TUERP procedure than in the B-TURP procedure (12, 16). Consistent with this previous observation, we found that postoperative hemoglobin decrease and the numbers of patients requiring blood transfusion and those developing bleeding requiring surgery differed significantly in favor of the TUERP procedure. Due to improved operative field visibility, decreased capsular perforation and more rapid, complete tissue removal (16), the operative time, postoperative bladder irrigation duration and hospital stay were significantly shortened in the TUERP procedure compared with the TURP procedure.

Excessive intraoperative absorption of irrigation fluid may lead to the occurrence of TURS, and the use of saline for irrigation can reduce the fluid absorption-associated morbidity and eliminate the risk of TURS (22, 23). In the current study, no TURS occurred in either the B-TURP group or the B-TUERP group, because both procedures used normal saline as irrigant. However, we found that the incidence of hyponatremia was significantly higher in the B-TURP group than in the B-TUERP group. This discrepancy may be explained by longer operative

time and greater intraoperative blood loss associated with the B-TURP procedure.

Since BPH patients often develop urinary retention and urinary tract infections, bacteria in urine can spread via blood vessels or perforated prostatic capsule and induce urinary sepsis (24). When the adenoma is enucleated during B-TUERP, hemostasis is performed by coagulation. Thus, the chance of prostatic capsular perforation and the incidence of urinary sepsis are greatly reduced. In the present study, four patients in the B-TURP group developed urinary sepsis, whereas no patients in the B-TUERP group developed this complication.

Studies have shown that the incidences of urethral stricture and bladder neck stenosis are not different significantly between the bipolar and monopolar TURP procedures (7). In this study, we found that the incidences of urethral stricture, postoperative acute urinary retention and bladder neck stenosis did not differ significantly between the bipolar TUERP and TURP procedures, suggesting that resection type is not a significant predictor of the risk of these complications.

Ideal TURP should involve accurate, complete removal of the adenoma. However, when performing traditional TURP, it is difficult to accurately judge the boundary between outer and inner glands and the depth of excision. This often results in excessive resection which may induce capsular perforation, or results in insufficient removal of the adenoma (18). Particularly, when the volume of the prostate gland is large, e.g., significantly above the level of the verumontanum, the surgeon often does not cut enough prostatic tissue at the apex due to serious concern about damaging the urethral sphincter and causing incontinence (12). As a result, recurrence often develops. Since the B-TUERP allows the removal of the adenoma accurately and completely (12, 15, 16), there is often little residual hyperplasia tissue. Unsurprisingly, although four patients in the B-TURP group needed reoperation during the 2-year follow-up period, no patients in the B-TUERP group required reoperation because of recurrence.

Our study has several limitations. The nonrandomized retrospective nature of the study is associated with a high risk of bias and may influence the interpretation of our data. In this single-center study, the relatively small sample size and short follow-up duration might lead to low statistical power and limit the strength of our conclusions. Furthermore, the inability to measure intraoperative blood loss and postoperative PV is another limitation of our study. Due to the resected cavity, the size of the residual adenoma cannot be exactly measured. Larger studies conducted in multiple centers will be required in future to confirm the findings of the present study.

In conclusion, our findings suggest that B-TUERP is superior to B-TURP in the management of prostates larger than 60g in terms of shorter operative time, postoperative bladder irrigation duration and hospital stay. There is also a greater weight of resected prostatic tissue, less postoperative hemoglobin decrease, better postoperative IPSS and Qmax. There are lower incidences of hyponatremia, bleeding, urinary sepsis, blood transfusion requirement, transitory incontinence and reoperation. However, longer-term and larger studies are needed to validate these results.

ABBREVIATIONS

BPH = benign prostatic hyperplasia
B-TUERP = bipolar transurethral enucleation and resection of the prostate
B-TURP = bipolar transurethral resection of the prostate
IPSS = International Prostate Symptom Score
PV = prostatic volume
Qmax = maximal urinary flow rate
QoL = quality of life
RUV = residual urine volume
TPSA = total prostate specific antigen
TUERP = transurethral enucleation and resection of the prostate
TURP = transurethral resection of the prostate
TURS = transurethral resection syndrome

ACKNOWLEDGEMENTS

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These authors contributed equally to this work.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 757-765, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0424

Outcomes following Thulium vapoenucleation of large prostates

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ABSTRACT

Introduction: Thulium laser VapoEnucleation of the prostate (ThuVEP) is an evolving surgical technique for BPH. Most studies have focused on outcomes in small to medium sized prostates and have originated from Europe and Asia. We sought to describe our experience with ThuVEP for very large prostates in a North American cohort.
Materials and Methods: From December 2010 to October 2014, 25 men underwent ThuVEP using the CyberTM® (Quantastem, Italy) thulium laser, all with prostate volume >75mL. Data collected included patient demographics, comorbidities, intraoperative parameters, complications, and post-operative outcomes including maximum flow rate (Qmax), post-void residual (PVR), International Prostate Symptom Score (IPSS), and quality of life score (QoL) in one year of follow-up. Statistical analysis was done using Wilcoxon signed-rank test.
Results: At baseline, mean age was 70±9 years and prostate size was 163±62g. Most patients (84%) were in retention and 10 (40%) patients were on anticoagulation. Seven (28%) patients went home the day of surgery (mean hospital stay: 1.2±1.2d). There were 2 intraoperative complications (8%), both cystotomies related to morcellation. Nine patients (36%) experienced a complication, all within 30 days. There were no Clavien ≥III complications. Significant improvements were seen in Qmax, PVR, IPSS, and QoL score at each time interval to 12-months following surgery (all $p<0.05$). Of 21 patients initially in retention, all were voiding at last follow-up.
Conclusions: Our findings suggest that ThuVEP is an effective treatment for BPH in patients with large prostates with sustained results for one year.

ARTICLE INFO

Keywords:
Prostatic Hyperplasia; Thulium; Quality of Life; Treatment Outcome; Urinary Tract

Int Braz J Urol. 2016; 42: 757-65

Submitted for publication:
January 28, 2016

Accepted after revision:
February 01, 2016

INTRODUCTION

Benign prostatic hyperplasia (BPH) and associated lower urinary tract symptoms (LUTS) are common problems, affecting 28% to 43% of men over age 60 and accounting for over $1 billion in health care costs (1). For men who fail medical management or experience sequelae of bladder outlet obstruction, the current gold standard surgical therapy remains transurethral resection of the prostate (TURP) for smaller prostates or open prostatectomy for very large organs (2). Traditional TURP is efficient and highly effective, however, it is associated with significant complications such as TUR syndrome, and blood transfusion rates remain significant at 2% to 8% in contemporary series (3, 4). Simple prostatectomy carries an even greater risk of perioperative morbidity and

mortality (5). In 2009, McCullough et al. reported a 28% and 29% rate of post-operative hemorrhage in laparoscopic and open simple prostatectomy, respectively (6).

Modern laser therapy for BPH has advantages over TURP including decreased blood loss and minimal serum electrolyte changes resulting in fewer cardiovascular complications, decreased catheter time, shorter hospital stay and the ability to treat patients on anticoagulation (4, 7). Because of these potential advantages, there has been a shift in practice patterns with laser procedures accounting for 57% of surgical interventions for BPH, compared to traditional TURP which accounted for only 39% of interventions in 2005 (8).

Among laser therapies for prostate enucleation, holmium laser enucleation (HoLEP) has been studied most extensively, and found to provide similar clinical outcomes and decreased morbidity compared to simple prostatectomy for men with large prostates (9, 10). Widespread adoption of laser enucleation techniques has been hampered by a steep learning curve particularly in large prostates, which is supported by a recent multicenter trial identifying a steep learning curve for HoLEP exceeding 20 cases, with nearly half of participating centers choosing to abandon or not continue with the technique (11).

Use of the high-powered continuous-wave thulium laser for treatment of BPH was first described in 2005, followed by multiple case series describing the use of the laser for both prostate vaporization (ThuVP) and enucleation (ThuVEP) procedures. ThuVEP has produced favorable clinical outcomes with minimal side effects in several studies from Europe and Asia (12-14). Rausch et al. recently reported improvements in International Prostate Symptom Score (IPSS), quality of life (QOL), post void residual (PVR) and maximum urine flow at 24 months in a series of 234 patients who underwent ThuVEP with a mean prostate size of 85mL (15). Interestingly, they found that small prostate size (<80mL) was a predictor of complications and treatment failure.

Initial experiences with ThuVEP have been positive, but highlighted the question of patient selection. Laser vaporization procedures appear to be supplanting TURP for treatment of smaller prostates. However, few studies have examined the outcomes of ThuVEP in men with larger prostates, when the alternative treatment would be simple prostatectomy. This study was performed to assess the feasibility, safety, and efficacy of ThuVEP in men with large prostates at two teaching hospitals in the United States.

MATERIALS AND METHODS

Institutional review board approval was obtained, and the medical records of 25 men who underwent ThuVEP from December 2010 to October 2014 by a single surgeon at two teaching hospitals were retrospectively analyzed. The surgeon had extensive previous experience with TURP, laser vaporization of the prostate, and HoLEP techniques, however, this was the surgeon's initial experience with the ThuVEP technique. All patients had an estimated prostate volume >75mL. Indications for surgery were history of urinary retention (23 or 92%) and LUTS unresponsive to medical management (2 or 8%). Baseline data were collected on demographics, medications, and comorbidities including American Society of Anesthesiologist Physical Status classification (ASA) and age-adjusted Charlson Comorbidity Index (CCI).

Preoperative urologic evaluation included a complete history, physical exam, digital rectal exam (DRE), IPSS, IPSS-QoL Index, PVR, uroflowmetry, serum prostate-specific antigen (PSA), urine culture, transrectal ultrasound and cystoscopy. Urodynamics was performed in select patients with comorbidities or incontinence, according to International Continence Society Guidelines (16-18). In appropriately aged patients at risk of clinically significant prostate cancer, based on a concerning DRE or elevated PSA, a 14-core transrectal ultrasound guided biopsy of the prostate was performed preoperatively to exclude malignancy. Anti-platelet agents such as high-dose aspirin and clopidogrel were either held or continued based on cardiovascular risk assessment by internal medicine specialists. Patients taking warfarin were bridged to enoxaparin or heparin during the perioperative period.

ThuVEP was performed using a 26F continuous flow cystoscopy with a laser bridge. We

used the CyberTM® laser (Quanta System, Italy) with an 800 or 1000µm laser fiber. Vapoenucleation was performed in a systematic fashion. All patients were under general or spinal anesthesia in the dorsal lithotomy position. Following identification of the ureteral orifices, with the laser set at 80W, incisions were made at the 5 and 7 o'clock positions starting at the bladder neck and extending to the level of the verumontanum. The incisions were connected distally and the median lobe was then enucleated at the level of the surgical capsule of the prostate from distal to proximal. The distal extent of the lateral lobe to be enucleated was then marked. Incisions were made at the 2 and 10 o'clock positions from bladder neck connecting to the previously made distal markings. Similar to the median lobe enucleation, the lateral lobes were then enucleated from distal to proximal. Anterior tissue, between the 10 and 2 o'clock position, and any irregularity in the prostate bed was then vaporized with laser set to 120W down to the level of the surgical capsule. Any excess tissue at the apex near the verumontanum was vaporized on a setting of 80W. Meticulous hemostasis was obtained with a laser power of 40W to 60W. Tissue morcellation was then performed through a 26F nephroscope using the Piranha® morcellation system (Wolf). A 20F two-way Foley catheter was inserted and manually irrigated to confirm adequate hemostasis. Continuous bladder irrigation was routinely performed in our early experience (n=8), but was later deemed to be unnecessary. Patients were typically discharged on the day of surgery or on post-operative day one depending on comorbidities, patient wishes, degree of hematuria, and access to care. The catheter was typically removed at the first post-operative clinic appointment.

Perioperative parameters included operative time, laser time (exact amount of time laser was active), laser energy, enucleation specimen weight, post-operative serum hemoglobin and serum sodium, length of stay and catheterization time. Post-operative functional outcomes were assessed at 1 month, 3 months, 6 months and 12 months including IPSS, QoL, Qmax and PVR. PSA was performed at baseline and at post-operative months 3 to 12. All complications were classified according to the Clavien-Dindo grading system (19). All statistical analysis was performed using Stata®, version 13 (Statacorp, College Station, TX). The Wilcoxon signed-rank test was used to analyze changes in outcome measures between time points, and a p-value of <0.05 was considered statistically significant.

RESULTS

Twenty-five patients underwent ThuVEP and were included in analysis. Table-1 describes the baseline characteristics of the study participants. The mean age was 70±9 years and mean BMI was 28±6kg/m^2. Mean ASA was 2.6±0.6 and age-adjusted CCI was 4.2±2.0, with coronary artery disease and diabetes mellitus present in 20% (n=5) and 32% (n=8) of patients, respectively. Ten patients (40%) were on anticoagulation peri-operatively including aspirin alone (n=7), aspirin plus clopidogrel (n=2), and warfarin bridged to enoxaparin (n=1).

The mean prostate volume was 163±62mL and mean PSA was 7.4±4.7ng/mL. Baseline IPSS was 19.3±7.3, QoL was 5.2±1.3, Qmax was 4.2±4.2mL/sec and PVR was 355±274mL. Four patients (16%) had a history of previous bladder outlet procedure and all were in retention preoperatively, having failed previous voiding trials. Eighteen (72%) were taking 5α-reductase inhibitors preoperatively and 23 (92%) were taking an α-blocker prior to surgery. Urodynamics was performed in twenty patients (80%) and the mean Bladder Outlet Obstructive Index was 87±48. Among patients who underwent urodynamics, thirteen (65%) were diagnosed with detrusor overactivity.

Operative outcomes and perioperative data are summarized in Table-2. The mean operative time was 204±58 minutes with mean 63±20 minutes of laser time. The total mean laser energy used was 347±123 kilojoules. The mean enucleated tissue weight was 47±29g with a mean morcellation time of 25±17 minutes. One patient (4%) was found to have incidental prostate cancer (Gleason score 3+3) on final pathology and the remaining 24 (96%) had benign tissue. Postoperative serum sodium concentration did not change significantly from baseline (p=0.7), but there was a decre-

Table 1 - Baseline Characteristics.

Parameter (n=25)	Mean±SD (range)
Age	70±9 (53-90)
BMI (kg/m2)	28±6 (18-42)
CCI (age adjusted)	4.2±2.0 (2-11)
ASA	2.6±0.6 (1-4)
Urinary retention (N [%])	23 (92)
On anticoagulation (N [%])	10 (40)
IPSS	19.3±7.3 (8-30)
QoL	5.2±1.3 (2-6)
Qmax (mL/sec)	4.2±4.2 (1-18)
PVR (mL)	355±274 (21-1000)
PSA (ng/mL)	7.4±4.7 (0.6-18)
Prostate Volume (mL)	163±62 (77-327)
Bladder Outlet Obstructive Index	87±48 (11-220)

BMI = body mass index; **IPSS** = international prostate symptom score; **QoL** = quality of life; **Qmax** = maximum flow rate; **PVR** = post-void residual; **PSA** = prostate-specific antigen; **CCI** = age-adjusted Charlson Comorbidity Index

Table 2 - Operative and Perioperative Outcomes.

Outcome	Mean±SD (range)
Operative time (min)	204±58 (124-332)
Laser time (min)	63±20 (28-104)
Laser energy (kJ)	347±123 (163-639)
Morcellation time (min)	25±17 (8-60)
Enucleation Weight (g)	47±29 (10-130)
Change in serum sodium (mM)	0.0±3.1 (-9-5)
Change in serum hemoglobin (g/dL)*	-0.6±1.1 (-2.8-1.5)
Hospital stay (days)	1.2±1.2 (0-5)
Catheter time (days)	6.5±2.7 (3-16)
Mean postoperative PSA (ng/mL)*	2.9±2.3 (0.7-8.2)

*p<0.05 postoperative hemoglobin and PSA compared to baseline

ase in serum hemoglobin (-0.6±1.1, p=0.01). Eight patients (32%) were placed on continuous bladder irrigation as per routine early in our experience, but this practice was eventually felt to be unnecessary. The majority of patients were discharged on the day of surgery (n=7, 28%) or on postoperative day one (n=13, 52%), and the mean length of stay was 1.2±1.2 days. The catheter was typically removed at the first postoperative follow-up appointment with a mean catheter time of 6.5±2.7 days. The mean postoperative PSA was 2.9±2.3ng/mL at a mean of 6.8±3.6 months after surgery, which was significantly decreased from baseline (7.4±4.7ng/mL, p<0.01).

Functional outcome measures including objective voiding parameters and subjective patient reported outcomes are shown in Table-3. With respect to subjective measures, significant improvements from baseline were observed for IPSS and QoL at all time points (p<0.05). Similarly, Qmax and PVR demonstrated improvements from baseline at one-, three-, six-, and twelve-month follow-up visits (p<0.05). All 20 patients initially in retention were voiding at last follow-up.

We observed 2 intraoperative complications (8%) are described in Table-4, which were both cystotomies that occurred due to inadvertent engagement with the bladder wall during morcellation. Both were identified intraoperatively, managed successfully with catheter drainage alone and resulted in no further adverse sequelae. A total of 9 patients experienced 30-day complications (36%) including 10 complications overall. There were 9 Clavien grade I complications, 1 grade II complication and no grade ≥III complications. The grade I complications included 5 culture-proven UTIs (20%), all of which resolved with oral antibiotic treatment, 3 patients failed initial voiding trial (12%) requiring re-catheterization and 1 patient (4%) experienced gross hematuria with clot retention requiring bladder irrigation. The grade II complication was a single blood transfusion for a patient who had significant cardiac comorbidity and was anemic preoperatively with serum hemoglobin of 9.6g/dL. Postoperative serum hemoglobin was 10.0g/dL. He became tachypneic and tachycardic in the recovery room and was transfused based on cardiology and anesthesiology recommendations. No complications were observed after 30-days.

DISCUSSION

Laser enucleation techniques such as ThuVEP and HoLEP have emerged over the last 10 years as viable treatment options for BOO based on evidence from prospective clinical trials. HoLEP has been more extensively studied and is considered to be a comparable alternative to simple prostatectomy in patients with large prostates and to TURP in patients with prostates <75mL (9, 10). The thulium laser is a relatively new technology with several potential advantages over alternative lasers for the treatment of BPH such as favorable hemostatic properties, a relatively shallow depth of thermal damage (20) and the ability to perform hybrid procedures utilizing both vaporization and resection properties of the laser (21, 22). Bach et al. first described the ThuVEP technique in 2009 as a safe and durable procedure (23), and since then multiple case series from Europe and Asia have reported outcomes, with the majority of publications coming from a few centers (13, 15, 21, 24-29).

In our patient cohort with a very large mean prostate size (163mL), significant comorbid disease (mean CCI 4.2 and ASA 2.6) and clinical evidence of BOO (84% in retention), ThuVEP offers improvement in voiding parameters with a favorable morbidity profile. To our knowledge, this is the first study to evaluate the safety, feasibility, and efficacy of ThuVEP in a North American patient population, supporting the technique as a possible alternative to TURP and simple prostatectomy for the surgical management of BPH. Our findings also support several potential advantages of ThuVEP over these traditional approaches including fewer electrolyte changes, less blood loss, and shorter length of stay.

We demonstrated an improvement in objective and subjective voiding parameters out to 1 year of follow-up. The observed improvement in obstructive voiding after ThuVEP is comparable to HoLEP (30), Greenlight laser vaporization (31), TURP (32) and simple prostatectomy (33). At 12 months follow-up, IPSS and QoL scores improved by 14.6 and 4.0 points, respectively. Objective voiding parameters also improved, with a 15.9mL/sec increase in mean Qmax and a 305mL reduction in PVR. Our reported improvement in postoperative voiding parameters is similar to results in other

Table 3 - Functional outcome measures.

Outcome (mean±SD [range])	Baseline	1 month*	3 months*	6 months*	12 months*
IPSS	19.3±7.3 (8-30)	6.5±4.4 (1-16)	5.8±4.1 (0-12)	5.4±5.6 (1-20)	4.7±4.6 (0-13)
QoL	5.2±1.3 (2-6)	1.7±1.4 (0-5)	2.3±2.0 (0-7)	1.2±1.0 (0-3)	1.2±1.3 (0-4)
Qmax (mL/sec)	4.2±4.2 (1-18)	14.6±8.5 (3-32)	17.7±7.2 (5-31)	15.0±9.9 (4-32)	20.1±10.4 (3-37)
PVR (mL)	355±274 (21-1000)	107±169 (0-737)	67±93 (0-284)	102±175 (0-581)	50±58 (0-159)

*p<0.05 for all outcomes at each time point compared to baseline

Table 4 – Complications.

Complication	Frequency (%)
Intraoperative	2 (8)
Any 30-d complication	9 (36)
UTI	5 (20)
Urinary retention requiring re-catheterization	3 (12)
Clot retention	1 (4)
Transfusion	1 (4)
Late complication (30d-12mo)	0 (0)

ThuVEP series, supporting the effectiveness of the procedure (25). Additionally, no patients in our series required reoperation, which is consistent with the 0% to 2.4% overall revision rates reported in other ThuVEP series with at least 1 to 2 years of follow-up (25). The 61% reduction in postoperative PSA from preoperative baseline PSA is similar to reductions seen in other early ThuVEP experiences, providing further evidence for the efficacy of the procedure (23, 26). While there was a discrepancy between the mean prostate volume (163mL) and the enucleation weight (46g) in our series, this was likely related the large amount of tissue vaporized during ThuVEP.

In regard to safety, we reported an intraoperative complication rate of 8% and a 30-day complication rate of 36%, which is comparable to the rate (overall complication rate of 30.9%) reported by Gross et al. in a large (n=1080), prospective evaluation of complications after ThuVEP using an operative technique similar to the present study (29). When analyzing the severity of complications, the vast majority of complications were Clavien grade I. UTI (20%) and urinary retention after initial decatheterization (12%) represented the most common complications, similar to previous reports by Gross et al. (29). Interestingly, they reported a 41.7% overall complication rate during their first 216 cases, which improved to 19.4% during the last 216 cases. They also demonstrated that transfusion rates and urinary retention decreased over time, but the rate of postoperative UTI remained stable. Our initial morbidity profile compares favorably to this large study, particularly when taken in the context of a well demonstrated learning curve for ThuVEP (27) and the similar HoLEP technique (34, 35).

In our series, there was a statistically significant drop in serum hemoglobin from baseline (12.6g/dL) to postoperative (12.0g/dL), however, this did not seem to be clinically significant as only one patient (who may have required transfusion even preoperatively) received a postoperative blood transfusion. Additionally, this patient actually had a small increase in hemoglobin from baseline to immediately following surgery. The 0.6g/dL decrease in serum hemoglobin is similar to the change seen by Gross et al. after ThuVEP (1.1g/dL) and multiple series after Greenlight laser vaporization (0.7-1.2g/dL) (29, 31, 36). Despite ongoing oral anticoagulation in 40% of our patients, blood loss was minimal, transfusion rate was appropriately low and few intraoperative complications were observed. Additionally, the serum sodium concentration in our study did not change significantly from baseline to after surgery, suggesting that ThuVEP is not generally associated with major electrolyte disturbances.

Our study is unique in that 28% of our patients were treated as outpatient, and 52% stayed in the hospital just for one night, which resulted in a mean length of stay and catheterization time of 1 day and 7 days, respectively. While our hospital stay is significantly shorter and catheterization time is somewhat longer than other HoLEP and ThuVEP series (29, 30), this likely represents geographic variation in practice patterns in the United States compared to China and Europe. For example, in the German health system, reimbursement is by case-based lump sums, requiring a minimum of two overnight hospital stays for full reimbursement. Additionally, many European studies describe routinely keeping the patient in the hospital until the catheter is removed and the patient has voided normally. Our preferred practice, particularly later in the experience, was to discharge patients home on the day of surgery and remove the catheter at the first postoperative follow-up appointment.

Our early experience suggested ThuVEP was safe and effective in men with large prostates (mean prostate volume 163mL), even in the setting of ongoing oral anticoagulation. The mean prostate size in the present series is significantly greater than other large ThuVEP series (51-110mL) (15, 29, 37). We confirmed that ThuVEP appears to be a size independent procedure with significant improvements in all voiding parameters and minimal perioperative morbidity in a patient cohort with the largest mean preoperative prostate size in the literature. Rausch et al. recently examined prostate size as a predictor of adverse surgical outcomes after ThuVEP in a total of 234 patients with a mean preoperative prostate size of 85mL (15). They found that prostate size <80mL was associated with treatment failure, and prostate size

<50mL independently predicted complications. While we cannot comment on risk factors for adverse outcomes because of a relatively small sample size, no patients experienced treatment failure (defined as reoperation or placement of indwelling catheter) and the thirty-day complication rate for patients with a prostate volume ≥149mL (median in our series) was 31%, which is comparable to the rate in the entire cohort (36%). A recent large multicenter study evaluated the outcomes of photoselective vaporization of the prostate (PVP) using the 180W-XPS system in men with prostate volume ≥80mL (n=387) compared to prostate volume <80mL (n=739) (38). They concluded that the XPS system was safe and effective for men with prostate size ≥80mL (median 108mL) producing similar improvements in symptoms and retreatment rates at 2 years follow-up compared to men with prostate volume <80mL. However, men with larger prostates were at a higher risk of intra-operative conversion to TURP likely due to obscured vision from bleeding. The mean prostate volume in our study was notably larger than this study and no patients in our series required conversion to traditional TURP.

Taken as a whole, our results suggest that ThuVEP is safe and effective in highly comorbid patients, including many who were on anticoagulation peri-operatively and in urinary retention at baseline. The procedure was effective in men with very large prostates and produced improvement in patient reported outcomes and objective voiding parameters with 1 year of follow-up. We demonstrate that ThuVEP can be performed in a North American patient population on an outpatient basis.

Limitations of our study include its retrospective nature, relatively small sample size, lack of a comparison group and short follow-up. As a single surgeon series, our results may not be applicable to all settings. Larger comparative studies are needed.

CONCLUSION

Thulium enucleation of the prostate is effective and yields improvement in patient reported outcomes and objective voiding parameters out to 1 year for the treatment of BPH in men with very large prostates.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 766-772, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0292

Optimal bladder diary duration for patients with suprapontine neurogenic lower urinary tract dysfunction

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ABSTRACT

Purpose: To identify the minimum bladder diary's length required to furnish reliable documentation of LUTS in a specific cohort of patients suffering from neurogenic urinary dysfunction secondary to suprapontine pathology.

Materials and Methods: From January 2008 to January 2014, patients suffering from suprapontine pathology and LUTS were requested to prospectively complete a bladder diary form for 7 consecutive days. Micturitions per day, excreta per micturition, urgency and incontinence episodes and voided volume per day were evaluated from the completed diaries.

We compared the averaged records of consecutive days (2-6 days) to the total 7 days records for each patient's diary, seeking the minimum diary's length that could provide records comparable to the 7 days average, the reference point in terms of reliability.

Results: From 285 subjects, 94 male and 69 female patients enrolled in the study. The records of day 1 were significantly different from the average of the 7 days records in every parameter, showing relatively small correlation and providing insufficient documentation. Correlations gradually increased along the increase in diary's duration. According to our results a 3-day duration bladder diary is efficient and can provide results comparable to a 7 day length for four of our evaluated parameters. Regarding incontinence episodes, 3 days seems inadequate to furnish comparable results, showing a borderline difference.

Conclusions: A 3-day diary can be used, as its reliability is efficient regarding number of micturition per day, excreta per micturition, episodes of urgency and voided volume per day.

ARTICLE INFO

Keywords:
Urinary Bladder; Pathology; Neurogenic Bowel; Lower Urinary Tract Symptoms

Int Braz J Urol. 2016; 42: 766-72

Submitted for publication:
May 31, 2015

Accepted after revision:
October 12, 2015

INTRODUCTION

Lower Urinary Tract Symptoms (LUTS) secondary to neurological disorders appear to be a major health problem affecting patients worldwide (1). Voiding dysfunction has a remarkably negative impact on the quality of life and may lead to significant and life threatening complications (2), increasing simultaneously the economic burden for patients and health providers. The usual history-taking in patients with neurological disorders seems inadequate for the assessment of LUTS due to subjective factors. Several clinical trials targeting a more objective and accurate evaluation of LUTS have employed urinary diaries in order to identify voiding patterns and to quantify response to treatment. According to the International Continence Society, three types of urinary diaries

have been defined (3): Micturition Chart, Frequency Volume Chart and Bladder Diary (BD).

Nevertheless, a validated standardized bladder diary in terms of diary format, duration and evaluated parameters, has not yet been established (4). As a result, a BD with an optimum duration, which may ensure reliable results having simultaneously an acceptable level of patient's compliance, remains a dispute.

Recent and former literature has studied mostly non-neurogenic populations, having only rare references focusing on neurogenic lower urinary tract dysfunction in patients suffering from suprapontine pathology. So, the aim of our study was to determine the optimal length of a BD in terms of test reliability in this special cohort of patients. Analyzing the data derived from a 7-day bladder diary we evaluated five parameters seeking the optimal length for each one, assuming that the 7-day duration urinary diary is the reference point in the assessment of LUTS (5, 6).

MATERIALS AND METHODS

Type of the study

Prospective, quantitative survey from January 2008 to January 2014, involving 285 consecutive patients.

Inclusion/exclusion criteria

Inclusion criteria were treatment-naive patients of both genders, older than 20 years, suffering from suprapontine pathology caused either by traumatic brain injury or by cerebrovascular accident (CVA). Patients should be mentally fit with the ability to understand and communicate and the appearance of their LUTS should prelude at least 2 weeks before the integration on this study. For the mental evaluation of our subjects, Mini Mental State Examination was used (7). Exclusion criteria were multiple sclerosis, confused state, depression, dementia, bladder cancer, pregnancy, bladder stones, bladder outlet obstruction, diabetes, and urinary tract infection. Furthermore, subjects with a previous history of stress incontinence were also excluded from this study, in order to avoid the real cause of present LUTS to be confused and mixed. Additionally, male individuals over 50 years of age were excluded, considering that the co-existing benign prostate hyperplasia might interfere and distort our results. Moreover, after a proper vaginal examination, female patients suffering from any kind of vaginal prolapse were also excluded from the study, since vaginal prolapse might cause bladder outlet obstruction distorting our results.

Process

All patients at the initial visit were clinically evaluated with physical examination, history report, urine analysis and urine culture, abdominal ultrasound and post-void residual volume evaluation. Patients received a bladder diary form and were requested to complete it for 7 consecutive days beginning with the first morning void. Patients were advised to record the precise time and volume of each void. The beginning of every day was defined at 08.00a.m. and the end at 07.59a.m. next morning (8).

Additionally, the episodes of urgency and incontinence have also been recorded. The evaluated parameters of our study were: micturitions per day (voiding frequency), excreta per micturition (mL per void), episodes of urgency and incontinence and voided volume per day.

Statistical analysis

At the second visit, we analyzed the diaries and averaged the records over 2 to 7 days. The records of each subject were considered as dependent scale parameters and the total average of the 7 days records as the reference point of our comparisons in terms of test reliability.

As a result we used paired t-tests, in order to compare the averaged records of different days (2-6 days) to the total 7 days records for each patient's diary. We sought to identify which day's mean had no statistically significant difference with the 7 days average in terms of each assessed parameter. In all comparisons p value<0.05 was considered as statistically significant. SPSS version 20.0 was used for the statistical analysis.

RESULTS

From the total of 285 patients, 122 (42%) patients were excluded while 163 subjects (58%) met the inclusion criteria and were prospectively enrolled in the study. Among the 122 patients, 12 (9%), 31 (25%) and 30 (24%) were excluded from the study due to urinary infection, diabetes and mental instability respectively. In addition, 40 (32%) male patients over 50 years old were also excluded. The 94 male and 69 female patients enrolled in our study ranged in age from 23 to 68 years, with a mean age of 43.6 years.

The data retrieved from the diaries were summarized, averaged and the descriptive statistics along with the general characteristics of our cohort are provided in Tables 1a and 1b. Correlations gradually increased along the increase in the diary's duration reaching the maximum on the day 6. Table-2 summarizes the correlations of the different diary's duration records with the 7 days average.

According to our test results, a 1-day and 2-day length bladder diary could not provide results comparable to a 7-day diary in any parameter, since the differences that arose using the paired t-test between these durations were statistically significant. Thus, regarding micturitions per day, excreta per micturition, urgency episodes and total voided volume the 3-day records were not significantly different than the 7 days records ($p>0.05$). This absence of statistical significance was interpreted as a failure to establish a true difference between the 3-day length and the 7-day length records for 4 of the 5 evaluated parameters. As a result, the 3-day diary could provide data comparable to the 7-days in terms of these parameters. As for the incontinence episodes the 3-days length was borderline significantly different from the 7-day length ($p=0.044$), becoming statistically non significant from day 4 and on. Table-3 summarizes the results of the comparisons between the different diary's lengths. Comparisons between 1-day to 7-day and

Table 1a - Descriptive statistics of the cohort. Average data derived from the completed diaries.

	Number of patients	Mean	Std. Error	Std. Deviation
Av. Micturitions	163	9.92	0.19	2.44
Av. Excreta/micturition (mL/void)	163	121.83	1.45	18.44
Av. Urgency Incidents	163	5.10	0.06	0.73
Av. Incontinence episodes	163	4.99	0.07	0.92
Av. Total voided volume (mL)	163	1140.41	13.14	167.30

Table 1b - Patient's general characteristics

	Male	Female	Total
Patients (n)	94	69	163
Mean age (yrs)	30.3	61.7	43.6
Brain trauma (n)	59	26	85
Cerebrovascular accident (n)	35	43	78

Table 2 - Correlations of different diary's length with the 7-day duration diary for the evaluated parameters (r values).

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Micturitions	0,832	0,800	0,929	0,974	0,972	0,947
Excreta/micturition	0,745	0,866	0,891	0,839	0,970	0,990
Urgency episodes	0,609	0,669	0,822	0,922	0,961	0,979
Incontinence episodes	0,664	0,707	0,798	0,906	0,968	0,969
Total Urine	0,823	0,955	0,956	0,902	0,973	0,980

Table 3-Results of the comparisons between different diary's length (comparison day1 versus day 7 and day 6 versus day 7 were omitted from the Table). Mean difference, 95% confidence intervals and P value of each comparison are provided.

		Day 2 vs. Day 7	Day 3 vs. Day 7	Day 4 vs. Day 7	Day 5 vs. Day 7
Micturitions	Mean diff.	-0.29	0.13	-0.012	0.049
	95% CI	(-0.522, -0.056)	(-0.014, 0.274)	(-0.1, 0.075)	(-0.041, 0.138)
	P value	0.016	0.077	0.776	0.282
Excreta per micturition (mL/void)	Mean diff.	2.50	-1.75	-0.27	0.07
	95% CI	(0.252, 4.757)	(-3.551, 0.035)	(-1.956, 1.413)	(-0.619, 0.778)
	P value	0.03	0.055	0.75	0.822
Urgency episodes	Mean diff.	0.12	0.06	-0.03	0.01
	95% CI	(0.013, 0.237)	(-0.005, 0.126)	(-0.084, 0.022)	(-0.021, 0.045)
	P value	0.028	0.071	0.254	0.489
Incontinence episodes	Mean diff.	0.16	-0.11	-0.06	0.027
	95% CI	(0.019, 0.306)	(-0.207, -0.031)	(-0.126, 0.003)	(-0.009, 0.065)
	P value	0.027	0.044	0.061	0.141
Voided volume (mL)	Mean diff.	-12.15	-9.32	-8.65	4.30
	95% CI	(-22.628, -1.633)	(-17.062, 0.473)	(-21.402, 4.092)	(-0.701, 10.304)
	P value	0.024	0.064	0.182	0.159

6-day to 7-day duration were omitted from the Table in order to become less complicated. Mean differences along with 95% confidence intervals and P values of each comparison, between durations, are presented in the Table.

DISCUSSION

BD's are widespread used by clinicians in the assessment of voiding dysfunction, providing real-time documentation of LUTS and voiding habits in the patient's environment during everyday life. BD's reduce the recall bias (9-11) that affects questionnaires like history-taking, providing simultaneously objective evidence for the evaluation of several therapeutic interventions. Urodynamic studies (UDS) have been considered as the mainstay in the diagnostic approach of patients suffering from LUTS and cannot be replaced by a diary. Nevertheless, voiding diaries are a useful tool in the initial management of LUTS providing information of daily bladder function, contributing to a more integrated interpretation of the UDS' results, particularly in terms of the functional bladder capacity (12).

No consensus has been reached yet for the optimal duration of BD since no sufficient data could be found in the literature. In several published reports, diaries' duration varies from 24 hours to 14 days. Wyman et al. (9) was the first who recommended that 7-day duration was sufficient to provide reliable documentation of urinary frequency and incontinence episodes in women. The most commonly recommended duration in literature is the 7-day diary (5, 6, 9, 13-15), covering both leisure and working activities. Nevertheless, several studies reported that a diary with less duration than 7 days could furnish comparably reliable results (16).

Nygaard and Holcomb (17) have suggested that a 3-day length is appropriate for trials evaluating stress incontinence, while Brown et al. (18) reported that, in patients suffering from urgency urinary incontinence, a 3-day duration diary could furnish reliable results in terms of daytime frequency, nocturia, urgency and incontinence episodes. In 2005, Dmochowski et al. (19) analyzed, reviewed and compared two large-scale randomized phase III clinical trials with patients suffering from overactive bladder, treated with transdermal oxybutynin. In both trials patient's symptoms were evaluated through voiding diaries with different durations. In trial A 520 patients documented their symptoms with a 7-day diary, while in trial B 361 patients documented their symptoms with a 3-day diary. Comparing the different durations, they concluded that 3-day diary appears to be equally effective to the 7-day, increasing potentially patient's compliance in clinical trials. Our results appear to be in accordance to the conclusion of the previously mentioned studies. Although the design and the cohort of our study was totally different, our results indicate that a 3-day diary length is adequate, effective and comparable to 7-day, providing credible results in patients suffering from suprapontine pathology in terms of the majority of the evaluated parameters.

Despite protracting the duration of the charts leads to an enhancement of the test reliability, prolonged studies might increase patient's burden leading to decreased compliance, a term described as "diary fatigue" (6, 20). Tincello et al. (21) announced that 90.7% of the patients completed a 3-day diary compared to only 50% who completed a 7-day diary, respectively. Shick et al. (16) reported that patient's compliance in BDs follows a logarithmic curve, in contrast to the reliability of the results which follows a bell-shaped curve. The intersection of these two curves represents the minimum duration of a diary which simultaneously provides acceptable reliability of the results.

In 2004, Ku et al. (22) prospectively enrolled 193 patients with incontinence and LUTS in a trial targeting to determine the appropriate duration of a diary assessing patient's compliance and burden. According to their results patient compliance was not compromised by the 7-day diary while patient's burden increases along the increase in the duration of the chart. Although patient's burden was not an evaluated parameter in the design of our study, we should mention the fact that the majority of our patients complained at the second visit about the duration of the BD, claiming that was rather inconvenient.

The majority of previous reports, focusing on the ideal duration of a BD, enrolled patients

suffering from LUTS caused by several different conditions (diabetes, benign prostate hyperplasia, overactive bladder). In contrast to them, our study population was totally homogenous, since all subjects suffered from neurogenic urinary dysfunction secondary to suprapontine pathology. Thus, the data provided in the literature for this specific population are deficient and sparse. To the best of our knowledge, this is one of the first attempts enrolling such a pure cohort. In such cohort, the neurologic condition of patients is mainly responsible for their urinary dysfunction. As a result, patients' storage and voiding function are less influenced from social, behavioural or environmental factors. The clinical assessment of such patients could be very strenuous due to their neurological pathology and their consequent mobility problems. The majority of patients might be hospitalized for a long time; making their evaluation with the "classic" diary pattern, which includes leisure and working activities, unsuitable. According to our results a 3-day duration bladder diary is efficient and can provide results comparable to a 7-day length for 4 of our evaluated parameters. Only regarding incontinence episodes, 3 days seems inadequate to furnish comparable results, showing a borderline difference. In conclusion, 3-day bladder diary appears to be a quite useful and valuable tool in the evaluation of LUTS in this specific group of patients.

Nevertheless, our study has some limitations. Although it was prospective, we had not designed a second completion of the diaries by the same subjects, as a retest. This could have added concurrent validity to our results (23). Total fluid intake and patient's burden were not evaluated in the study. Moreover, we have to mention that our patients were not evaluated by UDS and that our study was based on the use of a self-recorded diary (20). Finally, we have to point out that the results of the current study cannot be applied to other voiding dysfunctions as only suprapontine neurogenic disorders were included.

CONCLUSIONS

Three-day duration for bladder diary is as effective and sufficient as the 7-day, in at least 4 out of 5 evaluated parameters, in patients suffering from neurogenic urinary dysfunction due to suprapontine pathology. Thus, a 4-day length BD can provide comparable results in all parameters. In conclusion, the reliability of results was not compromised by the reduction in the number of days, clearly suggesting that the 7-day diary is unnecessarily protracted. Nevertheless, since LUTS derived from several different clinical conditions, it seems necessary that a validated standardized bladder diary in terms of diary format, duration and evaluated parameters needs to be developed in the future.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 773-778, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0656

Uterine preservation for advanced pelvic organ prolapse repair: Anatomical results and patient satisfaction

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ABSTRACT

Objective: The aims of the current study were to evaluate outcomes and patient satisfaction in cases of uterine prolapse treated with vaginal mesh, while preserving the uterus.
Materials and Methods: This is a retrospective cohort study that included all patients operated for prolapse repair with trocar-less vaginal mesh while preserving the uterus between October 2010 and March 2013. Data included: patients pre-and post-operative symptoms, POP-Q and operative complications. Success was defined as prolapse < than stage 2. A telephone survey questionnaire was used to evaluate patient's satisfaction.
Results: Sixty-six patients with pelvic organ prolapse stage 3, including uterine prolapse of at least stage 2 (mean point C at+1.4 (range+8–(-1)) were included. Mean follow-up was 22 months. Success rate of the vaginal mesh procedure aimed to repair uterine prolapse was 92% (61/66), with mean point C at -6.7 (range (-1) - (-9)). No major intra-or post-operative complication occurred. A telephone survey questionnaire was conducted post-operatively 28 months on average. Ninety-eight percent of women were satisfied with the decision to preserve their uterus. Eighteen patients (34%) received prior consultation elsewhere for hysterectomy due to their prolapse, and decided to have the operation at our center in order to preserve the uterus.
Conclusions: Uterine preservation with vaginal mesh was found to be a safe and effective treatment, even in cases with advanced uterine prolapse. Most patients prefer to keep their uterus. Uterus preservation options should be discussed with every patient before surgery for pelvic organ prolapse.

ARTICLE INFO

Keywords:
Pelvic Organ Prolapse; Vagina; Autonomic Nervous System; Uterus

Int Braz J Urol. 2016; 42: 773-8

Submitted for publication:
November 17, 2015

Accepted after revision:
January 19, 2016

INTRODUCTION

The prevalence of symptomatic pelvic organ prolapse (POP) is difficult to estimate because of lack of standardized methods to evaluate symptomatic prolapse, and lack of data concerning the proportion of women with POP who do not seek medical aid (1). Nevertheless, it is possible to estimate the prevalence of symptomatic POP by the number of patients who choose to undergo surgical repair. It has been estimated that the lifetime risk for American or Australian women to have an operation for POP is 11% and 19% respectively (2, 3). Among the prolapsed compartments, the anterior compartment is the most common prolapse, three times more common than posterior compartment and twice as common as apical prolapse (uterus or vaginal vault). But POP is dynamic and about two thirds of women with prolapse have genital prolapse of more than one compartment (4-6).

In the last decade, several authors have claimed that it is preferable to treat POP while

preserving the uterus, even if future pregnancy is not desired and in the postmenopausal period. Advances in vaginal mesh surgery have resulted in new techniques for preserving the uterus (7, 8). At the same time, treatment of POP with synthetic mesh has become common (9). Some safety concerns for the use of grafts in POP repair have led the US Food and Drug Administration (FDA) to publish a safety notification in 2011, and subsequently guidelines for the use of vaginal meshes (10, 11).

There are several reasons for uterine preservation, apart from the early and late complications of hysterectomy. These include cultural beliefs, personal preferences, sexual identity, and reproductive preservation in young patients (12).

The EndoFast system (Allium-IBI, Israel) is a vaginal mesh kit for single-incision POP repair (13). The posterior kit is designed for apical prolapse repair and the arms of the mesh are fixated to the sacrospinous ligament with a metallic spider fastener. The body of the posterior mesh can be used or removed depending on concomitant advanced posterior compartment prolapse.

The aims of the current study were to evaluate the outcome of uterine preservation with the EndoFast system in cases of advanced POP and uterine prolapse and to assess patient satisfaction with the decision to preserve the uterus and with the operative procedure in general.

MATERIALS AND METHODS

This is a retrospective cohort study, including a telephone questioner. The study was approved by the hospital ethics committee. We included all patients who underwent POP repair with uterine preservation at Ziv Medical Center between October 2010 and March 2013, using the EndoFast system (Allium-IBI, Israel).

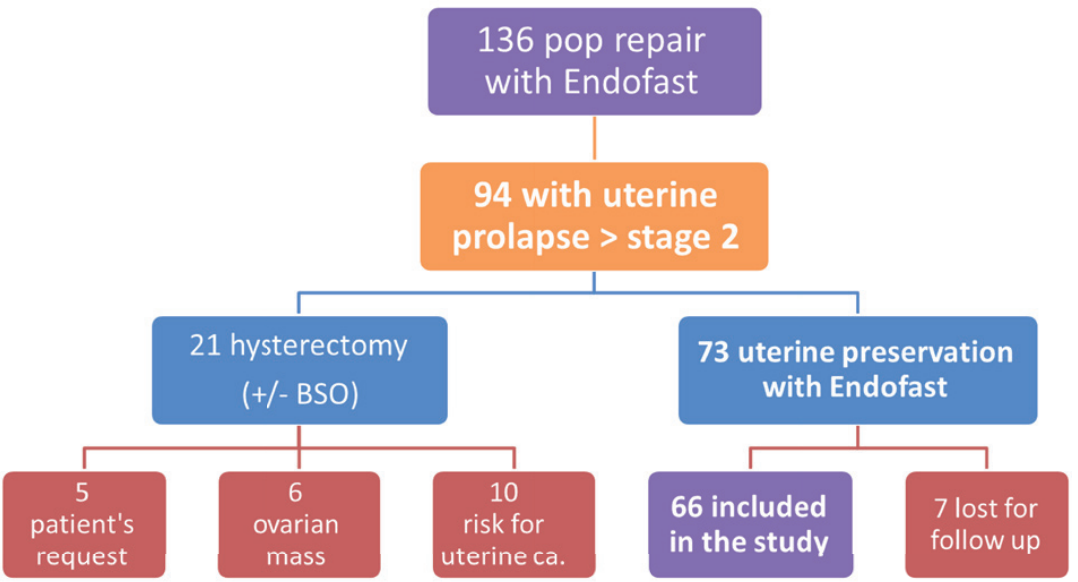
At Ziv Medical Center, the POP repair protocol does not include routine hysterectomy. Patients with advanced POP are admitted for surgical repair with synthetic mesh. The patients undergo an evaluation for pre-malignant and malignant disease of the uterus, including personal and family history of cancer. If there is no contraindication, patients are advised to preserve the uterus.

All patients included in the study had at least symptomatic uterine prolapse stage 2. All patients included underwent apical repair with the posterior kit of the EndoFast system, with or without additional anterior or posterior repair, while preserving the uterus. Data were collected from computerized archive files. Data included demographic features such as age, parity, BMI, medical history, previous gynecological operations, and family history of POP. Pre-operative evaluation included patient's symptoms for bulge, pain, dyspareunia, voiding dysfunction, urgency, urinary incontinence, nocturia, constipation, dysphasia, POP-Q examination, and stress urinary incontinence (SUI) (obvious or occult). The stage of the prolapse was determined based on the most prolapsed compartment. Data regarding the operation included intra-operative and immediate post-operative complications. Each patient was examined after the surgery at 6 weeks, 6 months and 1 year with continuous follow-up once a year. At each visit, data were collected for patient's symptoms, POP-Q examination, and complications such as pain, de novo dyspareunia, mesh erosion, de novo urgency, voiding dysfunction, and de novo SUI. Success was defined as no bulge symptoms and prolapse < than stage 2. Additionally, a phone interview was conducted to estimate patient satisfaction with the consultation they had before the surgery, with the decision to preserve the uterus, and with the entire process (Appendix 1). Validated questionnaires for this subject are lacking. We formulated the questionnaire in a manner that does not hint at any possible advantage or disadvantage of the process.

RESULTS

During the study period, 136 patients with POP were treated with the EndoFast system while preserving the uterus and 66 met our inclusion criteria and were included in the study (Figure-1). Fifty-one patients (77%) had additional anterior mesh placement for anterior compartment repair. Mean age was 61 (range: 43-82), mean parity was 4.31 (range: 1-12), mean BMI was 27.9 (range: 19.1-37.8), and mean follow-up at the clinic was 22 months (range: 6-42).

Figure 1 - Patient selection for the study.



Risk for uterine cancer was consider as a patient with breast cancer, currently under tamoxifen treatment

Before the surgery, 5, 57, and 4 patients had symptomatic POP stage 2, 3, and 4, respectively. All patients had at least uterine prolapse stage 2, with mean point C at +1.4 (range: + 8 - (-1)) (Table-1).

No intra-operative complications were reported. Immediate post-operative complications included one case of fever due to hematoma, which was self-resolved, and two cases of urinary tract infection. Long-term complications included (a) two cases of small erosions in the anterior mesh, of less than 5mm, which were treated locally with estrogen. (b) One case of metallic fastener removed from the rectum 2 months after the operation, without further sequel. Consistent pain or dyspareunia were not observed. Patient symptoms and functional results are shown in Table-2. All symptoms improved after the repair.

Operative success rate for uterine prolapse was 92% (61/66), with mean point C at - 6.7 (range (-1) - (-9)) and mean point D at -8.2 (range 0 - (-12)). Four women (6%) had recurrence of uterine prolapse within the first 6 months (> stage 1), but only 2 were symptomatic and required recurrent surgery. One patient had isolated elongation of uterine cervix without uterine prolapse.

Table 1 - Mean pre- and post-operative (at last visit) POP-Q.

	Pre-op	Post-op
Ba	1.4 (+10 - (-3))	-2.1 (+3 - (-3))
Bp	-1.6 (+7 - (-3))	-2.8 ((-2) - (-3))
C	1.4 (+8 - (-1))	-6.7 ((-1) - (-9))
D	-1 (+7 - (-6))	-8.2 (0 - (-12))

Table 2 - Pre-operative symptoms and post-operative functional results (at last visit).

	SUI	De novo SUI	Dyspareunia	De novo dyspareunia	Urgency	De novo urgency
Pre-op	34		12		34	
Post-op	8	1	6	0	12	2

Pre-and post-operative POP-Q measurements are shown in Table-1.

Telephonic interviews were conducted on average 28 months after the surgery (Appendix 1). Fifty-three patients out of 66 (80%) were interviewed. When asked about the pre-operative consultations before the decision to preserve the uterus: 18 patients (34%) received prior consultation elsewhere for hysterectomy because of their prolapse, and decided to undergo the surgery at our center in order to preserve the uterus. Forty-eight patients (91%) reported the operation to have been successful, and 52 out of 53 patients (98%) were satisfied with the decision to preserve their uterus. In general, 49 patients (92%) were satisfied [17] or very satisfied [32] with the overall process.

DISCUSSION

Hysterectomy is the second most frequently performed surgical procedure, after cesarean section, for US women. Approximately 400.000 hysterectomies are performed annually (14). Routine hysterectomy for uterine prolapse is no longer mandatory, and many recent studies support uterine preservation. The uterus can be preserved through vaginal route correction, with or without mesh, and is usually fixed to the sacrospinous ligament. The uterus can also be preserved using an abdominal or laparoscopic approach, such as sacrohysteropexy, which has produced good results (7, 8).

There are several medical reasons for preserving the uterus: (a) avoiding early and late complications of hysterectomy; (b) decreasing the rate of mesh erosion if a mesh is used at the time of hysterectomy (8); (c) reducing the cost of surgery with a shorter operation and hospitalization time (15); and (d) risk of vault prolapse, which is greater in women who had previous hysterectomy, especially after vaginal hysterectomy due to prolapse, as shown in several studies (16, 17). Other reasons for patient's desire to preserve the uterus include desire to sustain fertility, maintaining personal identity, cultural and religious considerations (18). Preservation of the uterus was shown to contribute positively to patient's self-esteem, body image, confidence, and sexuality (15).

In the past, several uterine preservation methods have been developed for selected young women suffering from uterine prolapse who desire to remain fertile. The Manchester procedure, mainly for cervical elongation, was developed already in the late 1890s. It is a good method for uterine preservation, but recurrence rate increases when the prolapse is more advanced. It is also associated with cervical stenosis, and therefore not recommended today for fertile women (7). Sacrospinous hysteropexy was first described by Richardson in 1989 (19). It involves sacrospinous fixation with suture or sutures, unilateral or bilateral. Several studies have demonstrated its success rate and pregnancy rate (7). In the 1950s, a large series in which the uterus was preserved in young women by suturing to the abdominal wall, demonstrated a high success rate, with non-negligible pregnancy rate after the surgery (20).

Since the introduction of the vaginal mesh, at the beginning of the current century, many series have demonstrated good results of its use in preserving the uterus (8). This concept has led to a new approach in which the uterus can be preserved not only for purposes of fertility, but in any prolapse. Women often ask to preserve the uterus, an option that should always be discussed before surgery. Previous studies that examined patient satisfaction with hysterectomy in non-malignant situations, such as heavy bleeding and prolapse,

have found a high rate of satisfaction with the operation (21, 22). But this may be the result of the fact that in the past patients were given no choice, as the only option for POP repair was vaginal hysterectomy and native tissue repair; patient satisfaction, therefore, may have been due to the relief from symptoms. Studies evaluating women's preference before the operation are lacking. Frik et al. examined 220 patients evaluated for the presence of POP. Sixty percent stated that they would prefer preserving their uterus if a good alternative was available (23). Another study examined 213 patients who had POP and desired prolapse repair. 36% preferred uterine preservation as opposed to only 20% who chose hysterectomy, assuming similar outcomes in both procedures (18). In our study, we have found that 18 patients (34%) had pre-consultation for hysterectomy elsewhere and decided to undergo the surgery at our center in order to avoid hysterectomy.

To estimate the patient satisfaction with the overall process, we conducted a phone survey 28 months on average after the surgery. The survey showed that 91% of patients evaluated the results as successful. We were also able to evaluate patient satisfaction with the decision to preserve the uterus. We have found that 98% of patients were satisfied with the decision to preserve the uterus. Unfortunately, women are still being advised that hysterectomy is the only solution to their prolapse. In our study, one third of the women sought an alternative.

The limitations of this study include its retrospective nature and the use of telephone survey and not validated questionnaires. Moreover, our center protocol to avoid routine hysterectomy may cause bias discussion around patient satisfaction as one-third of the patients were seeking preservation pre-op. Large RCTs are required in order to overcome surgeons and patients bias so the results can be applicable to the population in general. At the same time, the study is strengthened due to the focus on patients with advanced uterine prolapse while excluding those with non significant uterine prolapse and by included a large population of patients with detailed pre-and post-operative physical evaluations and a long thorough follow--up. In addition, all patients were operated by the same surgeon (MN) in the same institution thus neutralizing inter-surgeons differences.

CONCLUSIONS

Uterine preservation in patients with significant uterine prolapse undergoing POP repair with trocar-less vaginal mesh is safe and effective. Most patients in our study preferred to preserve their uterus even in their post-reproductive age and were satisfied with the operative results. Uterus preservation options should be discussed with every patient before surgery for POP.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 779-786, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2014.0580

Training through gametherapy promotes coactivation of the pelvic floor and abdominal muscles in young women, nulliparous and continents

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ABSTRACT

Introduction and objectives: several studies have been investigated co-activation can enhance the effectveness of PFM training protocols allowing preventive and therapeutic goals in pelvic floor dysfunctions. The objective of the present study was to investigate if an abdominal-pelvic protocol of training (APT) using gametherapy would allow co-activation of PFM and transversus abdominis/oblique internal (TrA/OI) muscles.
Patients and methods: Twenty-five nulliparous, continent, young females, with median age 24.76 (±3.76) years were evaluated using digital palpation (DP) of PFM and surface electromyography of PFM and TrA/OI simultaneously, during maximal voluntary contraction (MVC), alternating PFM and TrA/OI contraction requests. All women participated on a supervised program of APT using gametherapy, that included exercises of pelvic mobilization associated to contraction of TrA/OI muscles oriented by virtual games, for 30 minutes, three times a week, in a total of 10 sessions. Electromyographic data were processed and analyzed by ANOVA – analysis of variance.
Results: When MVC of TrA/OI was solicited, it was observed simultaneous increase of electromyographic activity of PFM (p=0.001) following ATP. However, EMG activity did not change significantly during MVC of PFM.
Conclusion: Training using gametherapy allowed better co-activation of pelvic floor muscles in response to contraction of TrA, in young nulliparous and continent women.

ARTICLE INFO

Keywords:
Pelvic Floor; Abdominal Muscles; Electromyography

Int Braz J Urol. 2016; 42: 779-86

Submitted for publication:
January 31, 2016

Accepted after revision:
February 01, 2016

INTRODUCTION

Pelvic floor muscles (PFM) are responsible for urinary and fecal continence mechanisms, and participate at sexual relations and delivery (1, 2). They also are important for pelvic stabilization, along with abdominal and lumbar muscles. Some studies (3-5) have demonstrated an intimate relation between PFM and the abdomen, particularly transversus abdominis muscle (Tra) whose impact on continence mechanisms and on pelvic floor functionality is being investigated in different phases of female vital cycle. Pereira et al. (5) have identified co-activation of those muscles in young

asymptomatic nulliparous women, but not among pregnant and puerperal primiparous.

It is already known that any anatomic, biomechanical or neuromuscular alteration can trigger functional imbalancies with consequent urogynecologic disorders (6). Dysfunctions of pelvic floor are usually multifactorial. Age, pregnancy, delivery, hormonal alterations of female cycle as well as biomechanical and postural modifications (7) can influence PFM function.

Accordingly, it is assumed that reeducation of abdominal-pelvic compartment can be beneficial to prevent and or treat female pelvic floor dysfunction (7), justifying the proposal of protocols that include abdominal muscle training, mainly Tra muscle (3, 5, 8, 9).

The objective of the present study was to identify simultaneous electrical activity of PFM and transversus abdominis/oblique internal (TrA/OI) in order to verify if a protocol of abdominal training (PAT) using gameteraphy would provide co-activation of those muscles.

METODOLOGY

Study type

Prospective, clinical study.

Sample

From January to June 2014, 25 young nulliparous continent women were recruited (median age 24.7±3.7 years) through an informative lecture at Physiotherapy and Nurse schools of the Federal University of Alfenas - UNIFAL/MG. The study was approved by the ethical committee of the University of Campinas Medical School - UNICAMP (CAAE protocol: 19625113.5.0000.5404), and all participants signed a free consent form according to Helsinki Declaration. The study was authorized to be realized at the UNIFAL-MG.

Inclusion criteria

Nulliparous young female were included, with 18 to 35 years old, without any micturition complaints (score zero according to Portuguese validated question form International Consultation on Incontinence Questionnaire Short Form - ICIQ UI-SF) (10).

Exclusion criteria

Exclusion criteria included virgin women (impossibility to apply electromyographic evaluation with endovaginal sensors); previous abdominal-pelvic surgeries; metabolic disorders (high blood pressure and diabetes); presence of myopathies and collagen diseases, neurologic alterations, cognitive disturbance and physical limitations that prevented participation; previous PFM training (supervised by a health professional); grade zero contractility of PFM, according to the Modified Scale of Oxford (11), without evident contraction of PFM.

Evaluation procedures

The study was performed by two investigators (VS and JM). Evaluations and revaluations were performed by a single researcher (JM) and the training protocol was applied by the main author (VS) who was unaware of the clinical conditions of the participants.

The participant was held in orthostatic position and the abdominal region was cleaned with 70% alcohol; adherent and dischargeable sensors were positioned above the topography of TrA/OI muscles (2cm away from the antero-superior iliac spine towards pubis). The participants were instructed to correctly contract TrA/OI during expiratory phase, in dorsal decubitus with inflected inferior limbs.

Evaluation of PFM was initially performed by digital palpation, in order to graduate contractility according to Modified Scale of Oxford (11) and to orientate the participant on how to effectively contract PFM. Participants were asked to contract PFM while the evaluator pushed the fingers cranially during expiratory phase (12, 13) avoiding the use of gluteus and adductor muscles (5).

Electromyographic activity of PFM and TrA/OI was recorded using an EMG equipment (EMG System do Brasil®), consisting of a signal conditioner with a filter with frequencies of 20-500HZ, amplifier of 1000x and rejection of common proportion of >120Db. Also, a conversion plate of A/D signal of 12 bit was used to convert analogic signs to digital signs, with sample frequency of filter 2.0khz and entrance band of 5mv. All data

were transmitted in microvolts (μv) to the equipment software (AqData®) connected to a notebook processed in Root Mean Square (RMS) making sure that all electric equipments were turned off from electric network during collection of data (5).

PFM EMG was recorded using an endovaginal sensor (Physio-Med Services®), manually introduced by the researcher with the aid of a hypoallergenic gel, positioned at the lateral wall of the vagina. Reference electrode was positioned at the right fist (between the radius and the styloid process of the ulna) (14).

Electromyographic evaluation protocol consisted on the recording of simultaneous collection of PFM (channel 1) and TrA/OI (channel 2), at rest, for 15 seconds, in order to use them during normalization of the electromyographic data, followed by three MVC (maximal voluntary contraction) of PFM, with simultaneous record of electromyographic response of TrA/OI.

After that, three MVC of TrA/OI with simultaneous recording of PFM response were performed. Each MVC was performed following a rest period of three minutes in order to avoid muscular fatigue (14).

Abdominal - pelvic training program

The protocol consisted of ten individual sessions of 30 minutes, supervised by the main investigator (physiotherapist) three times a week.

The exercises were performed emphasizing the abdominal-pelvic compartment using virtual games. This protocol was based on the work proposed by Martinho (2014), (15-17). It was used the Wii™ console and the game Wii Fit Plus™, using the sub-games: Lotus Focus, Penguin Slide, Table Tilt and Balance Bubble. The protocol was developed in order that the participant played seated on a Wii Balance Board platform positioned over an adjustable bench, allowing the knees and hips to form a flexion angle of 90o. In order to execute the games, many pelvic exercises that demanded trunk control using the abdominal muscles (TrA/OI) without active contraction of PFM were used (anteversion, retroversion, lateral pelvic inclination) (Figure-1).

Figure 1 - Movements are performed over the platform, during virtual games.

Anteversion movement (A), retroversion (B), lateral pelvic inclination (D)

Data processing and analysis

Initially, five seconds of each MVC were selected, considering the medium of three RMS (expressed in μv) for each participant. In order to investigate simultaneous electromyographic activity of PFM and TrA/OI (co-activation) it was calculated the percentage variation of activation related to rest of booth muscles, according to the following formulae (Figure-2):

Figure 2 - Calculus of percentage of variation in relation to rest.

$$\text{Percentage activation} = \frac{\text{average of 3 CVM - repose value}}{\text{repose value}} \times 100$$

Statistical analysis was performed using ANOVA (analysis of variance), using the software SAS System for Windows (Statistical Analysis System), version 9.2. SAS Institute Inc, 2002-2008, Cary, NC, USA. Significance level was set at 5%.

RESULTS

Table-1 presents clinical and social-demographic characteristics of participants.

During evaluation of PFM contractility using digital palpation, it was observed that most women presented contractions grade 3 or 4 according to Modified Scale of Oxford (11) (Table-2).

The main objective of this study was to investigate the presence of co-activation of PFM and TrA/OI before and after a program of ATP, using gametherapy. Table-3 present the results showing an increase of co-activation of PFM when it was solicited a maximal voluntary contraction of TrA/OI after training.

DISCUSSION

PFM training has been recommended to prevent and treat female pelvic floor dysfunctions since 1948, when Arnold Kegel (18) introduced the practice of repeatedly and singly contract those muscles.

Historically, PFM training programs oriented women to not contract abdominal, gluteus and adductor muscles, for those were considered accessory muscles (19). Until now, few anatomic

Table 1 - Social-demographic and clinical characteristics of participants.

Social-demographic characteristics	
Color of the skin* (%)	
White	92
Non white	8
Schooling* (%)	
Complete/incomplete higher education	100
Marital status* (%)	
Single	84
Married/stable union	16
Work (%)**	
No labor	76
Labor	24
Income revenue* (%)	
1-2 times a week	16
3-4 times a week	20
>4 times a week	64
Clinical characteristics	
Age (years) (M±SD)	24.76 (3.76)
Body Mass Index (Kg/m²) (M±SD)	22.34 (3.70)
Physical activity (%)	
Sedentaries	52
Active	48
Sexual activity (%)	
Absent	32
Present	68
Stool movements (%)	
Less than 3 times a week	20
Higher than 3 times a week	80

Table 2 - Evaluation of contractility of PFM by digital palpation, before and after training.

Modified Scale of Oxford	Before training (f-%)	After training (f-%)	Time P-value*
1	1 (4)	0 (0)	
2	4 (16)	2 (8)	
3	13 (52)	13 (52)	0.0001
4	7 (28)	9 (36)	
5	0 (0)	1 (4)	

Table presents distribution of participants according to Modified Scale of Oxford (presented data in absolute frequency-fe percentage-%) and comparison between the time of evaluation before and after training.
*Wilcoxon test.

Table 3 - Co-activation of muscles in response to maximal voluntary contraction, before and after training.

	Before training	After training	Time P-value*
Co-activation PFM (MVC TrA/OI)	127.27	147.84	0.01
Co-activation TrA/OI (MVC PFM)	234.19	196.72	0.1

Table presents muscular response (co-activation) following MVC of PFM or TrA/OI, comparing the time of evaluation before and after training. Values expressed in percentage (5). Note increase of co-activation of PFM when MVC was solicited to TrA/OI
PFM = pelvic floor muscles
MVC = maximal voluntary contraction
TrA/OI = transversus abdominis/oblique internal
***ANOVA** for repeated measures with transformation by posts.
Power of sample: 0.06

and functional studies (20, 21) showed the true relation among muscles that form abdominal-pelvic compartment.

According to Piret and Beziers (2002) (20), transversus abdominis muscle is inserted in the same layer of transverse muscle of perineum. Delancey et al. (2004) (21) reported that in normal women increase of abdominal pressure promotes contraction of elevator anus muscle diminishing the genital hiatus. On the other hand, Junginger et al. (2010) (22) observed that bladder neck is elevated only when PFM contractions are higher than intra-abdominal pressure.

Caufriez (1997) (23) developed the hypo--pressure gymnastics technique that stimulates the recruitment of PFM following activation of abdominal muscles associated to diaphragmatic aspiration. But only after the studies of Sapsford & Hodges (2001) (8) the investigation of the relationship of those muscles were intensified and demonstrated that there is a co-activation of PFM during electrical activity of Tra (3-5). Neumman and Gil (2002) (3) showed that relaxing abdominal muscles prevents efficient contraction of PFM, suggesting a strong relationship among them.

Stupp et al. (2011) (24) in order to investigate if hypo-pressure gymnastic technique could trigger activation of both muscles-PFM and TrA--showed that MVC of TrA and PFM simultaneously is as efficient as isolated contraction of PFM.

In the present study, when co-activation of those muscles was analyzed, it was observed a significant increase of electrical activity of PFM following training, when MVC of TrA/OI was solicited. One of the hypothesis to explain that fact is the solicitation of maintenance of TrA contraction during the execution of exercises induced by virtual games, favoring co-activation of PFM; the performance of exercises in a virtual environment allows the participant to interact and feedback the

real time activities. In this context, the use of gametherapy is been quite explored as biofeedback for physiotherapy treatment (15-17).

Kamel et al. (2012) (25) proposed training of abdominal muscles and observed significant improvement of PFM pressure evaluated by vaginal perineometer, suggesting indirect action of abdominal muscles on PFM activation, providing coordination, support and resistance. Rogers (2008) (26) described improvement of PFM perception following a training program justifying increase of co-activation of PFM.

On the other hand, in the present study it was not observed significant co-activation of TrA during MVC of PFM. Similar results were presented by Perschers et al. (2001) (27). Some factors could influence muscle synergy such as position of evaluation, which normally is different than the adopted position of daily activities, as well as the influence of posture in the order of muscular activation, also cited by Madill (2009) (28).

Specially in nulliparous young women, Pereira et al. (2013) (5) observed significant co-activation of both TrA/OI and PFM when MVC was solicited to both; however, co-activation was not observed in pregnant and puerperal women, suggesting the existence of other factors that influence the behavior of those muscles.

The study has some limitations, such as the small sample and reduced number of sessions. In spite of the fact that there is no consensus in literature regarding the ideal time of training to improve PFM functionality, Bø et al. (1990) (29) suggest improvement following six months of training.

Most studies investigate the effects of training in general in symptomatic women. Very few information is known regarding the pattern of muscular behavior of asymptomatic young women, who do not suffer interference of age, hormonal alterations, obesity, pregnancies and deliveries, as well of urogynecological signals and symptoms, one of the most important aspects of the present study.

Also, it is difficult to stablish in which condition it is more probable to observe positive results: while treating young asymptomatic women, with more probability of "normal" muscular performance or those with urogynecological symptoms who respond to treatment. These aspects can influence treatment adherence and follow-up. In our study we observed good adherence. Participants reported satisfaction with the training, for it was innovative and stimulated PFM. No side effect was reported after training.

One of the challenges in this area is to introduce these trainings involving abdominal muscles for prevention, particularly PFM and TrA, in order to prevent overload of pelvic floor during daily activities. Pre-contraction of these muscles during daily activities that involve increase of intra-abdominal pressure (for example, sports or gymnastic) may be fundamental to prevent future dysfunctions, with improvement of quality of life and consequent reduction of treatment costs (30). Other studies must be performed in young and healthy populations to elucidate the effects of different kinds of training on anatomic and functional aspects of that population.

CONCLUSIONS

Abdominal-pelvic training using gametherapy improved co-activation of pelvic floor muscles in response to contraction of transversus abdominis and oblique internal, in young, continent nulliparous women.

ABBREVIATIONS

ANOVA = Analysis of variance
MVC = Maximal Voluntary Contraction
SP = Standard Deviation
EMG = Surface Electromyography
ICIQ-UI SF = International Consultation on Incontinence Questionnaire Short-Form
PVM = Pelvic Floor Muscles
OI = Oblique Internal
RMS = Root-mean-square
APT = Abdomino-pelvic Training
TrA = Transversus abdominis
μV = microvolts

ACKNOWLEGEMENTS

We thank CAPES ("Coordenação de Aperfeiçoamento de Pessoal de Nível Superior") and

FAPEMIG ("Fundação de Amparo à Pesquisa do Estado de Minas Gerais") (APQ-02199-15).

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 787-792, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0453

Low serum Insulin Like Growth Factor – 1 in patients with Stress Urinary Incontinence

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ABSTRACT

Objective: SUI, involuntary loss of urine, occurs when intra abdominal pressure exceeds urethral pressure in women. Recent animal study has shown that there are therapeutic effects of Insulin-like growth factors (IGF-1) on stress urinary incontinence in rats with simulated childbirth trauma. IGF-1 is an important mediator of cell growth, differentiation and transformation in various tissues and stimulates fibroblast proliferation and enhances collagen synthesis. The purpose of the current study was to determine the association between IGF-1 levels and SUI.

Materials and Methods: All patients were evaluated for SUI and divided into two groups: 116 women with SUI and 76 women without SUI. Diagnosis of SUI was based on the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF). Levels of IGF-1 were measured in serum by enzyme-linked immunosorbent assay. The relationship between IGF-1 levels and SUI in patients was evaluated statisticaly.

Results: The mean age of patients wiyh SUI was 49.9±8.6 and 48.7±7.8 in control group. Plasma IGF-1 levels were significantly lower in SUI than in control group (106.5±26.4 and 133.3±37.1ng/mL, respectively, P <0.001). Body mass indexes were higher in women with SUI than women without SUI.

Conclusion: In this study lower serum IGF-1 levels were found to be associated with SUI. Serum IGF-1 level appears to be a specific predictor of SUI, and it may be used in early prediction of SUI in female population.

ARTICLE INFO

Keywords:
Urinary Incontinence, Stress; Enzyme-Linked Immunosorbent Assay; Insulin-Like Growth Factor I

Int Braz J Urol. 2016; 42: 787-92

Submitted for publication:
August 17, 2015

Accepted after revision:
November 22, 2015

INTRODUCTION

Stress urinary incontinence (SUI) is assosiated with high financial, social and emotional costs. SUI affects quality of life as well as sexual function in women (1). SUI is defined as the involuntary loss of urine during increase of abdominal pressure in the absence of bladder contractions; it is the most common type of urinary incontinence in women older than middle age (2). SUI is the most common form of urinary incontinence, occurring in pure or mixed forms in nearly 80% of women with incontinence, according to two European studies (3, 4). One out of every three women will experience SUI at some point in their life. Too many of them "just live with" the condition, too

embarrassed to seek help or thinking that it is a "normal" part of aging and having children. The pathogenesis of SUI is thought to be the result of urethral hypermobility secondary to a weakening or disruption of the pelvic floor musculature and/or pubourethral ligament, with a subsequent loss of pressure transmission from the bladder to the urethra upon provocation (5, 6). Previous studies have discovered that numerous factors, including age, obesity, diabetes mellitus, hypertension, menopausal status, parity, pregnancy, psychological factors, and the physical health status of women, could affect their chances of having SUI (7).

Insulin-like growth factors-1 (IGF-1), a peptide hormone that is structurally related to insulin and synthesized by almost all tissues, is an important mediator of cell growth, differentiation and transformation in various tissues (8). IGF-I is a potent mitogen and inhibitor of apoptosis for cell types and exerts all of its known physiologic effects by binding to the IGF receptor (IGF-1R) (9). IGF binding activates IGF-IR, which in turn phosphorylates phosphatidylinositol 3-kinase (PI-3K) and Ras/Raf/mitogen-activated protein kinase (MAPK). Ras/Raf/MAPK and PI-3K play important roles in IGFIR-induced cellular proliferation and inhibition of apoptosis (10). IGF-1 has been shown to stimulate fibroblast proliferation and enhances collagen synthesis (11). IGF-1 also accelerates the growth and differentiation of striated muscle precursor cells in the human urethral sphincter (12). However, to our knowledge the role of IGF-1 has not been explored yet in humans with SUI.

Because of the wide range of their biologic effects and their therapeutic potential, the IGFs have become the focus of research by an increasing number of investigators. The aim of this study was to determine whether any relationship exists between SUI and the level of IGF-1.

MATERIAL AND METHODS

We performed a prospective cross-sectional study of participants who visited Okmeydani Training and Research Hospital from February 2011 to January 2013. All women were evaluated for SUI and menopausal period. The women were divided into two groups: 116 women with SUI and 76 women without SUI (control). Postmenopausal status was defined as the cessation of menses for at least 1 year, and perimenopausal status as skipped menstruation with perimenopausal symptoms. Premenopausal women who have regular menses were assessed. 65 women were postmenopausal and 51 women were premenopausal in study group. Also, 40 women were postmenopausal and 36 women were premenopausal in control group. We used the International Consultation on Incontinence Questionnaire-Short Form (ICIQ-SF) to evaluate SUI and the question: "During the past 12 months, have you leaked or lost control of even a small amount of urine with activity like coughing, lifting, or exercise?" defined stress UI. Also, we assessed the women for SUI at gynecologic position and we determined cough stress test. In the calculations, contiinence was defined as no incontinence at all. The urodynamic study was used in patients with symptoms of mixed urinary incontinence and in cases of clinically suspicious diagnosis. Exclusion criteria were: urge incontinence, mixed urinary incontinence with dominant urge component, intrinsic sphincter deficiency, neurogenic bladder (multiple sclerosis, meningomyelocele, spinal cord injury), genital surgery history, severe mental illness and severe physical handicap. Patients who were pregnant were excluded.

IGF-1 was quantified via an enzyme-linked immunosorbent assay (ELISA) using the Immulite Analyzer kit (Diagnostic Products Corp., Caernarfon, Gwynedd, UK).

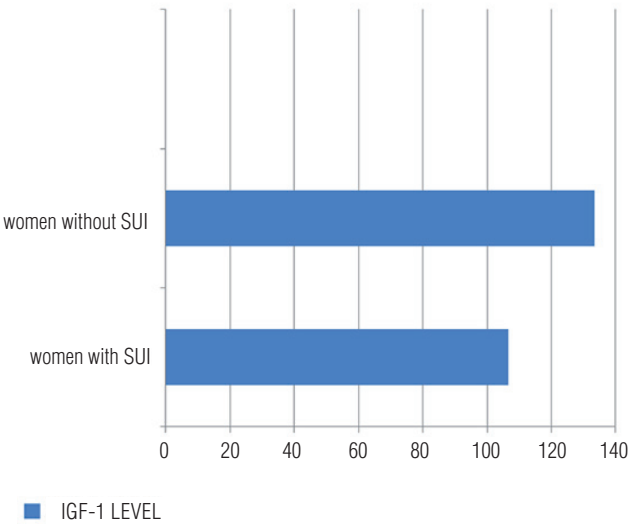
Statistical analysis

Statistical analyses were performed by the Statistical Package for Social Sciences, version 15.0, software (SPSS Inc., Chicago, IL, USA). The quantitative demographic values were evaluated by student's t or Mann Whitney U tests whether the parameters were suitable for normal distribution or not. If the parameters were qualitative chi-square test was used. Spearman correlation test was performed to analyse the association between SUI and IGF-1 level. All tests were performed using a 2-tailed analysis, and a P value of <0.05 was considered statistically significant.

RESULTS

192 women were included in the study and were divided into two groups: 116 women with SUI and 76 women without SUI (control). The baseline characteristic properties of study patients are demonstrated in Table-1. The mean age was 49.9±8.6 in women with SUI and 48.7±7.8 in women without SUI; no statistical difference were found for age between groups. There was no statistical difference between groups for weight, height, parity. Number of parity was 3.1±1.4 in patients with SUI and 2.9±1.1 in patients without SUI. Body mass indexes (BMI) were higher in women with SUI than women without SUI. There was statistically difference for BMI between women with SUI and control group (p<0.001). Also DM was higher in women with SUI than control group but there was no difference for DM between groups (p=0.15). We compared the IGF-1 levels between groups. Our results showed that women with SUI have lower IGF-1 levels than control group (Figure-1). Mean IGF-1 level was 106.5±26.4 in women with SUI and 133.3±37.1 in control goup, respectively. There was statistically difference for IGF-1 levels between women with SUI and control group (p<0.001)). The IGF-1 levels were negatively correlated with ICIQ-SF score (r=-0.583, P <0.01).

Figure 1 - Serum IGF-1 levels between study and control group.



The distribution of IGF-1 levels between study and control group(106.5± 26.4 ng/mL women with SUI; 133.3± 37.1 women without SUI respectively, P < 0.001).

DISCUSSION

The purpose of this investigation was to examine the association between IGF-1 levels and SUI in women. The results of this study showed

Table 1 - Characteristics of women with or without SUI.

	Women with SUI (n=116)	Women without SUI (n=76)	P value
Age (mean±sd)	49.9± 8.6	48.7± 7.8	0.08
Height(cm, mean±sd)	158± 5.7	160± 4.9	0.18
Weight(kg, mean±sd)	74.6± 13.1	73.2± 12.3	0.1
BMI (mean±sd)	29.8± 5.7	27.3± 4.3	< 0.001*
Parity (mean±sd)	3.1± 1.4	2.9± 1.1	0.06
DM(%)	29	25	0.15
IGF-1 (ng/mL,mean±sd)	106.5± 26.4	133.3± 37.1	< 0.001*

*: P < 0.05 was accepted as statistically significant.

BMI = Body mass index; **DM =** Diabetes mellitus; **IGF-1 =** Insulin like growth factor-1

that the patients with SUI had significantly lower IGF-1 levels than control group. Moreover, our study revealed that there was a negative correlation between IGF-1 levels and ICIQ-SF score. To our knowledge, this is the first study that shows the serum levels of IGF-1 in SUI patients. This study suggested that IGF-1 might contribute to the pathophysiology of SUI in patients. In a previous study, IGF-1 levels were lower in diabetic women (13). Also, we found that IGF-1 levels were lower in women with SUI; however in our series, DM prevalence was similar between women with and without SUI. In this context, IGF-1 levels were lower in women with SUI independently of DM.

An effective closure of the female urethra in stress situations depends on an integrated action of various anatomical intra and extraurethral structures. The most important extraurethral structures are the suburethral vaginal wall, the pubourethral ligaments, the pubococcygeus muscles, and the periurethral connective tissue. Fibrous connective tissue is mainly composed of collagen and structural glycoproteins and forms an important part of the supportive structures of the genitourinary region (14). Female urinary incontinence is a common problem that disables many women, especially after menopause. Recent research has focused on functional changes on the pelvic floor and the condition of the fibrous connective tissue, which is their main constituent as factors that play a significant role in the development of SUI (15).

The mechanical and supportive properties of the pelvic connective tissue are determined by the structure of the main molecules that constitute the tissue (collagen, elastin, proteoglycans and glycoproteins), their interactions with each other and their overall proportions. Alterations in the quantity and organization of collagen fibers significantly affect the tensile strength of the endopelvic fascia and consequently determine an attenuation in the support that provide to the bladder neck and bladder base, resulting in urethral hypermobility that causes 80–90% of SUI. Menopause and aging serve as important factors for the onset of SUI, also for the mechanism for how they affect the metabolic processes within the connective tissue (16). The main constituent of the connective tissue in the ligaments and the suburethral-vaginal wall is collagen. Collagens of type I and type III are the predominant components in this kind of connective tissue and are responsible for the tensile strength of the tissue (17). Several studies have been reported that total collagen reduction of the paravaginal fascia is associated with the development of SUI. In several papers, in incontinent women a decreased expression in collagen type I or in collagen III has been demonstrated. For example, Ulmsten and Ekman (18) showed that collagen content in biopsies from skin and ligamentum rotundum of women with a long history of stress incontinence, compared with that of continent controls, was 25-40% less than that of continent women. Also Chen et al. (19) demonstrated 60% less collagen content in the vaginal wall of women with SUI compared to age-matched continent women. Falconer et al. (20) suggested that women with SUI have an altered connective tissue metabolism causing decreased collagen production. Liapis et al. (14) have shown a significant reduction amount of type I collagen in about 53% patients with SUI. Kean et al. (21) showed that the nulliparous women with SUI had significantly less collagen in their tissues compared with the continent controls. In addition, they demonstrated a decreased ratio of type I to type III collagen in women with SUI. In relation to collagen type III content Bergman et al. (22) showed that it was significantly reduced in specimens from patients with SUI.

Metabolic processes that occur within the connective tissue seem to play an important role in regulating collagen concentrations in the periurethral region (3). Several factors, such as age, mechanical stress, hormones, enzymes and their inhibitors, growth factors and cytokines, are involved in these processes (19). Collagen production is primarily regulated by fibroblasts under the influence of specific growth factors such as IGF-1. Previous studies have shown that IGF-I is essential for collagen production by fibroblasts (23). The activation of the MAPK signalling pathway in connective tissue by autocrine production of IGF-1 is essential for collagen expression.

In a previous study, the inhibition of IGF-1 signalling pathway such as Akt-1, MAPK and c-Raf may lead to a decrease in fibroblast proliferation and subsequent reduction in collagen deposition (24). In our study, IGF-1 levels were significantly lower in patients with SUI compared to control group ($p < 0.001$). Higher IGF-1 levels may prevent SUI by increasing collagen production. Also, hormonal changes in reproductive period may affect collagen production such as estrogen. The reduction of estrogen levels in postmenopausal period contributes to the development of SUI also affecting collagen content and metabolism in the supportive pelvic connective tissue (16). On the other hand, about 44% of the study group consists of premenopausal patients. This finding can define that IGF-1 level is more effective than estrogen level on collagen production.

Therapeutic effects of IGF-1 on SUI have been studied in animal experiments in a recent study. IGF-1 treatment showed significant improvement in leak point pressure, urethral baseline pressure and urethral responses. IGF-1 treatment increased Akt phosphorylation and induced cellular proliferation and antiapoptotic effects in the urethral tissue. IGF-1 treatment may accelerate recovery from SUI in rats (25). In English literature there is no clinical study concerning the role of serum IGF-1 in SUI patients. To the best of our knowledge this is the first clinical study with humans in literature.

There are some limitations in our study. Small sample size was the major limitation in this study.

In conclusion, this study was conducted to determine a relationship between serum IGF-1 level and SUI. Serum IGF-1 level appears to be a specific predictor of SUI, and it may be used in early prediction of SUI in female population. Furthermore, molecular medical treatment of SUI with IGF-1 may be possible and effective. However, further large scale clinical and molecular studies are needed to confirm the pathophysiological role of IGF-1 in SUI patients.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 793-797, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0568

Craniofacial anomalies associated with hypospadias. Description of a hospital based population in South America

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ABSTRACT

Introduction: Hypospadias is a congenital abnormality of the penis, in which there is incomplete development of the distal urethra. There are numerous reports showing an increase of prevalence of hypospadias. Association of craniofacial malformations in patients diagnosed with hypospadias is rare. The aim of this study is to describe the association between hypospadias and craniofacial congenital anomalies.
Materials and Methods: A retrospective review of the Latin-American collaborative study of congenital malformations (ECLAMC) data was performed between January 1982 and December 2011. We included children diagnosed with associated hypospadias and among them we selected those that were associated with any craniofacial congenital anomaly.
Results: Global prevalence was 11.3 per 10.000 newborns. In this population a total of 809 patients with 1117 associated anomalies were identified. On average there were 1.7 anomalies per patient. Facial anomalies were present in 13.2%. The most commonly major facial anomaly associated to hypospadias was cleft lip/palate with 52 cases. We identified that 18% have an association with other anomalies, and found an association between craniofacial anomalies and hypospadias in 0.59 cases/10.000 newborns.
Discussion: Hypospadias is the most common congenital anomaly affecting the genitals. Its association with other anomalies is rare. It has been reported that other malformations occur in 29.3% of the cases with hypospadias. The more proximal the meatus, the higher the risk for having another associated anomaly.
Conclusion: Associated hypospadias are rare, and it is important to identify the concurrent occurrence of craniofacial anomalies to better treat patients that might need a multidisciplinary approach.

ARTICLE INFO

Keywords:
Hypospadias; Craniofacial Abnormalities; South America; Population Groups

Int Braz J Urol. 2016; 42: 793-7

Submitted for publication:
January 18, 2016

Accepted after revision:
January 23, 2016

INTRODUCTION

Hypospadias is one of the most common birth defect among newborn males worldwide. The prevalence rate varies greatly; in Australia it was calculated as 35.1 per 10.000 (1). In Colombia it affects around 1.7/1000 male live births (2). It is a congenital abnormality of the penis in which there is an incomplete development of the anterior urethra, resulting in the abnormal urethral opening on the ventral surface of the penis (3). Severity depends on the location of the urethral opening, which increases as the opening approaches the base of the penis (4). In most cases the cause is unknown; however, endocrine, environmental and genetic factors have been found to be involved in the etiology of hypospadias (3).

To date, there have been numerous reports indicating a higher incidence of associated anomalies in patients diagnosed with hypospadias. These abnormalities can be divided into genital, urinary tract and extra urinary; the latter including craniofacial and cardiothoracic alterations (5). Although most of the current data describe associations with urinary tract abnormalities, a study by Friedman et al. in 2008 showed an increased incidence of facial dysmorphic such as cleft palate, microphthalmos and high arched palate that had not been seen before.

Due to the fact that most of the associations of hypospadias reported in the literature have been presented as clinical case reports, it is difficult to establish the clinical repercussions of these associations and their epidemiology. This has created the need for population-based epidemiologic data in order to have a better understanding of the malformation phenotypes that co-occur with hypospadias (3). Furthermore, studies regarding co--occurring malformations can aid in the discovery of risk factors and provide new insight into the etiology of these malformations. The purpose of the present paper is to present the description of a large-scale multicenter study presenting information about the co-occurrence of hypospadias and craniofacial anomalies.

MATERIALS AND METHODS

Database description

Our study is based on the Latin-American collaborative study of congenital malformations (ECLAMC) initiative which is a multicenter international collaboration designed to identify associated risk factors and potential causes of congenital anomalies (CA). As mentioned on the ECLAMC methodology we followed a nested case-control design, analyzing information forwarded from each participating center. A retrospective review of data was performed between January 1982 and December 2012. The aim of our search included children diagnosed with associated hypospadias.

Data collection and Quality Management

Data collection followed a standardized methodology for the entire study period. A daily surveillance was conducted on each participating center looking for detectable CA in all newborns. For every detected case, the following information was collected: mother's demographic data, prenatal and delivery information, and exposure to medications and toxics during pregnancy. This process was done by trained personnel in the ECLAMC methodology. For every enrolled case the immediate next newborn of the same sex was included as a control, collecting the same information.

Inclusion Criteria

Hypospadias (IH) cases were strictly defined as newborns with an ectopic urethral meatus located along the ventral aspect of the penis. Depending on the location, these were further categorized as glanular (glans), coronal, penile and scrotal (6). Megameatus intact prepuce variants were included in the glanular hypospadias. Associated scrotal findings were also recorded. Associated anomalies were separately labeled. Each one of the associated anomalies was described in detail following the ECLAMC protocol for each of the different anomalies. Specifically for the craniofacial anomalies, an anatomical classification was followed according to the ECLAMC's methodology.

Statistical analysis

For all cases we analyzed the distribution of each abnormality and its association to the grade of hypospadias. Also for the demographic information, we compared non-associated cases of hypospadias to co-occurring hypospadias with craniofacial anomalies. In order to standardize the assessment, we segregated associated anomalies by affected systems: genitourinary tract (GUT), gastrointestinal tract (GIT), limbs, facial anomalies (FA), cardiovascular (CV) and nervous system (CNS), abdominal wall (ABD), and others.

RESULTS

During the analysis period, a total of 159 centers in 6 countries participated in the study. The surveillance was conducted on 4.020.384 newborns; from these a total of 4.537 hypospadias cases were detected, with a global prevalence of

11.3 per 10.000 newborns. A total of 809 patients with 1117 associated anomalies were identified. On average there were 1.38-1.7 anomalies per patient. Facial anomalies were present in 13.2%.

When analyzing and comparing the severity of hypospadias and its relation to other anomalies, we found that proximal ones were significantly associated to other anomalies (penile hypospadias RR=1.64 [95%CI=1.33–2.03] and scrotal hypospadias RR=2.49 [95% CI 1.80–3.47]). The distal cases failed to show association. No differences were identified when comparing non-associated to co-occurring craniofacial – hypospadias cases with regards to mother's age, gestational age, weight at birth.

In this population, 5128 cases of cleft lip/palate were identified, with a prevalence 12.2 cases per 10.000 newborns associated to hypospadias. For micrognatia a rate of 74 cases per 10.000 newborns was identified. 11% were associated to other anomalies, and the cases of hypospadias were selected.

The facial anomalies that were detected and its distribution according to the severity of hypospadias are shown in Table-1. The most commonly major facial anomaly associated to hypospadias was cleft lip/palate with 52 cases.

DISCUSSION

Although hypospadias is the most common congenital anomaly affecting the genitals, its association with other anomalies is rare. It has been previously reported that other malformations can coexist in 29.3% of the cases with hypospadias. In our group we identified that 18%

Table 1 - Associated anomalies and its distribution by severity of hypospadias.

Malformation	Glanular n(%)	Coronal n(%)	Penile n(%)	Scrotal n(%)	Total	Prev/1000	%
Cleft lip and/or palate	21	23	3	5	52	11.5	21.8
Micrognatia	15	21	7	3	46	10.1	19.2
Low ear implantation	19	18	5	1	43	9.5	18.0
Preauricular pit	16	16	3	0	35	7.7	14.6
Microtia	10	14	5	1	30	6.6	12.6
Microphthalmus	4	2	0	1	7	1.5	2.9
Preauricular fistula	1	6	0	0	7	1.5	2.9
Leucoma	4	0	0	0	4	0.9	1.7
Hyperthelorism	0	2	1	1	4	0.9	1.7
Blefaroptosis	1	1	1	0	3	0.7	1.3
Neonatal teeth	2	0	0	0	2	0.4	0.8
Single narine	0	1	0	1	2	0.4	0.8
Macroglosia	0	1	0	0	1	0.2	0.4
Microglosia	1	0	0	0	1	0.2	0.4
Prognatism	0	0	1	0	1	4.5	0.4
Retrognatia	0	1	0	0	1	0.2	0.4
TOTAL (%)	**94 (39.3)**	**106 (44.4)**	**26 (10.9)**	**13 (5.4)**	**239**	**52.7**	

have an association with other anomalies. There is limited data on malformation phenotypes that coexist with hypospadias (3-7). Associations such as cryptorchidism are common and belong to the gonadal dysgenesis syndrome. Also, associations with urinary tract anomalies as part of the WAGR syndrome are commonly seen. But it has been demonstrated that other affected organs or systems in association with hypospadias are rare (3).

After analyzing the severity of hypospadias and the different craniofacial anomalies we did not find any significant trends with regards to severity of the craniofacial anomaly and hypospadias severity. The distribution was very homogeneous being most frequently associated with distal hypospadias.

Information about craniofacial anomalies that co-occur with hypospadias is limited. In our population we found an association between craniofacial anomalies and hypospadias in 0.52 cases/1000 newborns. Nassar et al. (4) reported 0.3 cases per 10.000 newborns.

Not many syndromes have been described where the two systems are affected. It can be associated with MID1 gene defects which interacts with MID2 (8), and are implicated in midline anomalies (9, 10). The Toriello Carey syndrome has the co-occurrence of hypospadias and facial anomalies. Others are the Mowat-Wilson Syndrome, the Opitz-Kawegia Syndrome and the hypertelorism-hypospadias syndrome described in 1969 (11-17). In our population we identified 4 cases (1.7%) of patients diagnosed with hypertelorism whom also had hypospadias. Other authors have identified a prevalence of 15.3% of associated cases of hypospadias-hypertelorism (5). Of those, two were proximal. It seems that these cases are inherited as an X-linked or autosomal dominant trait (18).

Some authors have reported the association between deletion of 13.q33.2 and the presence of hypospadias and craniofacial anomalies. Unfortunately, our database does not include information about karyotype.

With regards to cleft lip, previous reports have shown an association prevalence with hypospadias of 5.6/1000 (19). In our population we identified a prevalence of 11.5/1000 cases of hypospadias. Although this is one of the malformations that is easily diagnosed, we do not consider that it can be overestimated in our population.

According to our experience, and many other authors, most of the congenital anomalies if detected and treated appropriately and soon enough, the future disabilities and prognosis will improve significantly. Most of the craniofacial anomalies and hypospadias need to be approached by experienced personal. For that reason, it is important for this patients to be evaluated by a multidisciplinary approach (20-23).

CONCLUSION

Our novel results indicate the importance of evaluating thoroughly all patients diagnosed with hypospadias. The prevalence of craniofacial anomalies is not increased in patients with proximal hypospadias. Or the prevalence of other anomalies is not increased in hypospadias patients who have craniofacial anomalies. Although syndromic hypospadias are rare and represent less than 20% of cases, it is important to identify the co-occurrence of craniofacial anomalies because it might help the identification of syndromic hypospadias in order to give a better care for patients and their families.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 798-802, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0579

Enuresis and overactive bladder in children: what is the relationship between these two conditions?

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ABSTRACT

Objective: Evaluate clinical aspects associated with the presence of nocturnal enuresis (NE) in children with a diagnosis of overactive bladder (OAB).
Material and Methods: A data base of 200 children who were evaluated by a structured questionnaire was analysed retrospectively . OAB was defined as the presence of urinary urgency (n=183 cases) and/or daytime urinary incontinence associated with holding maneuvers (n=168 cases). Inclusion criteria were a confirmed diagnosis of OAB, age 5-16 years, and no anatomical or neurological alterations of the urinary tract. Patients were divided into enuretics and non-enuretics. The two groups were compared with respect to sex, age, skin color, presence urinary infection, urgency, urge incontinence, non-urge incontinence, pollakiuria, urinary dysfunction, nocturia, holding maneuvers, number of episodes of enuresis and bowel alterations. In a univariate analysis, the chi-square test was used to compare proportions, with p-values <0.05 being considered significant. A multivariate analysis was conducted to identify independent predictive factors.
Results: Enuresis was diagnosed in 141/200 children. The two groups were similar with respect to sex, age and skin color. No difference was found in relation to urinary infection, non-urge incontinence, urinary dysfunction, nocturia, encopresis or constipation. The two groups were significantly different with regard to some symptoms related to OAB such as urgency (p=0.001), urge incontinency (p=0.001) and holding maneuvers (p=0.033). Following multivariate analysis, only holding maneuvers (p=0.022) remained as an independent predictive factor.
Conclusion: The only independent predictive factor for resolution of enuresis in children with OAB, as detected in the multivariate analysis, was holding maneuvers.

ARTICLE INFO

Keywords:
Urinary Bladder; Enuresis; Child; Urinary Incontinence

Int Braz J Urol. 2016; 42: 798-802

Submitted for publication:
October 09, 2015

Accepted after revision:
January 26, 2016

INTRODUCTION

The International Children's Continence Society classifies enuresis as monosymptomatic (MSE) when bedwetting is the only symptom and non-monosymptomatic (non-MSE) when lower urinary tract symptoms (LUTS) are present (1). Enuresis is a common condition in children, affecting around 15-20% of 5-year olds, 5-10% of 7-year olds, 5% of 10-year olds and 1-3% of children of 15 years of age (2-4). Older studies have reported daytime LUTS in around 15-40% of cases of enuresis (5, 6). However, more recent data suggest that LUTS such as daytime incontinence, urgency,

frequency and voiding postponement are present in 50-80% of cases (3, 7). Daytime incontinence has been found more often in girls than in boys, whereas enuresis is more common in boys (8). In many cases, LUTS go unrecognized in patients with enuresis because doctors fail to ask about them or because parents are far more concerned about bedwetting (9, 10). Because enuresis tends to have a greater effect on family dynamics than LUTS, it may be more perceptible to parents.

Differentiating between the types of enuresis (MSE and non-MSE) is relevant because the physiopathology and management may not be the same for the two conditions. Non-MSE is more commonly associated with urinary tract infections (UTI), vesicoureteral reflux, constipation and behavioral problems (11, 12). Parents often believe that their child's treatment has failed entirely when enuresis persists even though complete resolution of LUTS was achieved. Since recognizing each condition individually is important, patients with enuresis should be investigated for LUTS and patients with LUTS should be asked about the presence of enuresis. Although OAB is commonly associated with enuresis, the clinical relationship between these two conditions remains to be clarified. In fact, identifying the characteristics of these patients is a crucial step towards gaining a better picture of the clinical scenario, prognosis and management of both conditions. Therefore, the objective of the present study was to evaluate the clinical aspects associated with enuresis in children and adolescents with OAB.

MATERIAL AND METHODS

A database of 200 children who were evaluated by a structured questionnaire was analyzed retrospectively. OAB was defined as the presence of urgency (n=183 cases) and/or daytime incontinence (n=168 cases). The inclusion criteria were a confirmed diagnosis of OAB, age between 5 and 16 years and the absence of any anatomical alterations or neurogenic disorders of the lower urinary tract. Patients for whom the database information was incomplete, and those who had recorded fewer than 4 voids per day in the bladder diary were excluded from the study. The internal review board of the Escola Bahiana de Medicina e Saúde Pública approved the study protocol under reference number 12141113.0.0000.5544.

A structured questionnaire was administered to all the patients to obtain the following information: demographic data (age, sex and skin color), number of voids, the presence of nocturnal enuresis (and its intensity), daytime incontinence (and its intensity), nocturia, urgency, straining, holding maneuvers, constipation (in accordance with the Rome III criteria), and a history of UTI confirmed by culture. Daytime incontinence was classified as urge or non-urge incontinence. Daytime incontinence and enuresis were classified according to intensity as daily, three times a week or more, less than three times a week or occasional.

Holding maneuvers were considered present when the child's parents reported typical body posturing such as squeezing the genitals, crossing the legs, going on tiptoe or squatting on the heel (Vincent's curtsy). All patients underwent uroflowmetry plus electromyography. Dysfunctional voiding was defined as an abnormal voiding pattern in the uroflow curve and activity on electromyography (flat curve plus activity on electromyography, staccato and interrupted voiding). Only 85 patients completed a 3-day bladder diary. The association between enuresis and the number of voids, the presence of daytime incontinence, and constipation was evaluated. Patients with and without enuresis were compared with respect to the presence of all the aforementioned clinical variables.

The SPSS software program, version 20.0 was used throughout analysis. In a univariate analysis, the chi-square test was used to compare proportions, with p-values <0.05 being considered statistically significant. Multivariate analysis was conducted for identifying the independent predictor variables. The variables that were significant in the univariate analysis were consecutively added to a multivariate hierarchical model, which started with a simple predictor.

RESULTS

Of the 200 children with a diagnosis of OAB, 84 were boys (42%) and 116 girls (58%).

Age ranged from 5 to 16 years, with a mean of 8.6±2.9 years. NE was diagnosed in 141 children (70.5%). Of these children, 83 (58.9%) were female. The mean age of the children with enuresis was 8.6±2.7 years, while the mean age of those without enuresis was 8.6±3.2 years (p=0.831). In 112 patients (80.6%), NE occurred at least three times a week. NE rate of 68% (n=87) in children ≤9 years and 75% (n=54) in those 10 years of age or older.

Regarding the demographic characteristics of the enuretic and non-enuretic patients with OAB (Table-1), no statistically significant difference was found between the two groups with respect to sex, age or skin color.

The clinical characteristics of both groups are showed in Table-2. The symptoms associated with the presence of NE were urgency (p=0.001), urge incontinence (p=0.001) and holding maneuvers (p=0.033). There was no difference in relation to the presence of febrile or afebrile urinary infection, nocturia, constipation, straining or abnormal urine flow. In addition, there was no statistically significant difference between those patients with severe enuresis (≥3 episodes/week) and the non-enuretic patients in relation to any of these factors. Following multivariate analysis, only one independent predictive factor was identified: the presence of holding maneuvers (p=0.022).

Table 1 - Demographic characteristics of the enuretic and non-enuretic children.

Variable	Non-Enuretics (n)	Enuretics (n)	P-value
Male	26	58	
Female	33	83	p=0.702
Age ≤ 9 years	41	87	
Age ≥ 10 years	18	54	p=0.295
Skin color not black	14	29	
Skin color black	27	80	p=0.363
Total	**59**	**141**	

Table 2 - Urinary symptoms in enuretic and non-enuretic children.

Variable	Non-Enuretics (n/%)	Enuretics (n/%)	P-value
UTI without fever	24 (42.9)	45 (36.9)	p=0.448
UTI with fever	24 (44.4)	50 (40.7)	p=0.637
Urgency	**48 (81.4)**	**135 (95.7)**	**p=0.001**
Urge incontinence	**37 (63.8)**	**120 (85.7)**	**P=0.001**
Pollakiuria	27 (46.6)	**83 (60.6)**	**p=0.071**
Dysfunctional urination	23 (39.0)	44 (31.2)	p=0.288
Nocturia	19 (33.3)	35 (24.8)	p=0.223
Holding maneuvers	**34 (59.6)**	**102 (75.0)**	**p=0.033**
Non-urge incontinence	30 (51.7)	70 (50.4)	P=0.861

UTI = urinary tract infection

DISCUSSION

Few studies have dealt with the subject of non-monosymptomatic NE. Since the principal complaint of families generally concerns nocturnal enuresis, daytime complaints are often undervalued and forgotten, hampering the implementation of appropriate treatment. In some cases, parents may even be unaware of daytime symptoms, since the frantic rhythm of modern life tends to leave parents with less time to participate in the day-to-day routine of their child's life. Nocturnal enuresis causes problems with socialization, resulting in low self-esteem and stress both of the child and the family. In addition, NE has been found to be associated with behavioral alterations such as attention-deficit/hyperactivity disorder (13).

In the present sample, enuresis was shown to be a common symptom in patients with OAB, occurring in 70.5% of cases. Despite the extent to which NE distresses parents, little attention has been paid to factors potentially associated with NE in patients with LUTS. A better understanding of this relationship may help identify possible factors associated with more severe conditions. Consequently, physicians will be able to act more effectively by implementing more individualized treatments. When performing the clinical assessment of NE, physicians have frequently neglected daytime symptoms. To the best of our knowledge, this study is innovative in that an inverse analysis was used, i.e. the presence of enuresis was investigated in patients with symptoms of OAB.

In this series of patients, both the daytime urinary symptoms and enuresis were more common in girls. This finding in children with overactive bladder differs from cases of monosymptomatic NE, which tend to be more common in boys. In a study conducted with a group of 51 patients, Naseri et al. confirmed an association between enuresis and daytime incontinence, and reported twice as many girls being affected as boys (14). In the present group of 141 children with enuresis associated with OAB, the proportion of girls to boys was 1.45 to 1.

The frequency of monosymptomatic enuresis tends to decrease progressively with age until reaching a rate of 0.5 to 1% in adults. In cases of non-monosymptomatic enuresis, however, some studies have shown that this does not occur, with the frequency of enuresis tending to remain the same in older children, possibly as a consequence of the mechanisms involved in overactive bladder (11, 12, 15). Accordingly, the present study also failed to detect any reduction in enuresis with increasing age in non-monosymptomatic enuresis.

Children and adolescents with symptoms of overactive bladder should be investigated for nocturnal enuresis, principally in the presence of holding maneuvers. The present results suggest that one of the principal mechanisms involved in non-MSE is nocturnal overactive bladder, given that the above-mentioned symptoms are characteristic of this condition. The hypothesis that these children may have more difficulty waking up than non-enuretic children has to be investigated, since the involvement of assorted physio-pathological mechanisms cannot be discarded. Furthermore, the psychological impact of NE in children with OAB, and the influence of NE in rendering prognosis poorer in these patients are factors that remain to be evaluated. It is important to note that it has been found a higher rate of psychiatric disorders in children who postpone voidind with holding maneuvers (11). Further studies should be performed in order to evaluate if it is also true for patients with non-monosymptomatic enuresis.

Constipation and bowel problems are often associated with urinary tract abnormalities and 90 (46.4%) of the patients in this series had at least one complaint. Nevertheless, the groups of enuretic and non-enuretic patients were not significantly different with respect to these symptoms. None of the other clinical characteristics of the patients with lower urinary tract dysfunction were found to be associated with NE. Factors such as the presence of urinary tract infection, irrespective of the number of episodes, and nocturia were not found to be significantly associated with enuresis.

This study has some limitations. For example, the subjective nature of the symptoms may have led to interpretation errors. Moreover, the severity of enuresis was assessed based on the responses provided by parents and children rather than by analyzing the number of dry nights recorded on a chart. However, to the best of our knowledge, although the association of OAB in patients with NE has been studied extensively, the association of NE in patients with

OAB has not. The results of the present study may shed more light on the actual rate of enuresis in children with OAB and on the profile of patients who are more prone to enuresis, thus opening perspectives for new studies. The impact of enuresis on both the patients with OAB and their caregivers remains to be evaluated. Nevertheless, understanding this impact is relevant since more than half of the patients present with this symptom. Furthermore, those patients with OAB who would benefit from a simultaneous treatment for enuresis should be clearly identified.

CONCLUSION

NE and OAB are commonly associated, with NE being present in 70.5% of children with OAB. In this study on children with overactive bladder, daytime urinary symptoms and non-monosymptomatic enuresis were both more common in girls. No reduction in enuresis was found with increasing age. Therefore, as long as overactive bladder and, consequently, daytime symptoms remain untreated, there will be no improvement in nocturnal symptoms. Of the OAB symptoms, only holding maneuvers were found to be associated with enuresis as an independent predictive factor. This suggests that when these daytime symptoms are present, OAB and NE probably share the same genesis.

ABBREVIATIONS

LUTS = lower urinary tract symptoms
Non-MSE = non-monosymptomatic enuresis
OAB = overactive bladder
NE = nocturnal enuresis
LUTD = lower urinary tract dysfunction

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 803-809, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0538

Do retractile testes have anatomical anomalies?

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ABSTRACT

Objectives: To assess the incidence of anatomical anomalies in patients with retractile testis.
Materials and Methods: We studied prospectively 20 patients (28 testes) with truly retractile testis and compared them with 25 human fetuses (50 testes) with testis in scrotal position. We analyzed the relations among the testis, epididymis and patency of the processus vaginalis (PV). To analyze the relations between the testis and epididymis, we used a previous classification according to epididymis attachment to the testis and the presence of epididymis atresia. To analyze the structure of the PV, we considered two situations: obliteration of the PV and patency of the PV. We used the Chi-square test for contingency analysis of the populations under study ($p < 0.05$).
Results: The fetuses ranged in age from 26 to 35 weeks post-conception (WPC) and the 20 patients with retractile testis ranged in ages from 1 to 12 years (average of 5.8). Of the 50 fetal testes, we observed complete patency of the PV in 2 cases (4%) and epididymal anomalies (EAs) in 1 testis (2%). Of the 28 retractile testes, we observed patency of the PV in 6 cases (21.4%) and EA in 4 (14.28%). When we compared the incidence of EAs and PV patency we observed a significantly higher prevalence of these anomalies in retractile testes ($p=0.0116$).
Conclusions: Retractile testis is not a normal variant with a significant risk of patent processus vaginalis and epididymal anomalies.

ARTICLE INFO

Keywords:
Testis; Epididymis; Cryptorchidism; Retractile testicle, Anatomic

Int Braz J Urol. 2016; 42: 803-9

Submitted for publication:
September 23, 2015

Accepted after revision:
January 03, 2016

INTRODUCTION

A retractile testis is defined as a supra-scrotal testis that can be manipulated easily into the scrotum and remain there without traction until the cremasteric reflex is induced (1). Recent studies generally urge observation of the evolution testicular position in cases of retractile testes (2, 3), because over 70% of patients with this condition show favorable evolution without the need for surgery (1). However, ascended testis or acquired undescended testis can occur in about 30% of cases (4).

Structural and ultrastructural studies have demonstrated morphological alterations in retractile testicle cases (5, 6), and one study of young adults who had been treated for retractile testis during the prepubertal period showed that only 28.5% had normal spermiograms (7).

Anomalies of the tunica vaginalis and the epididymis are associated with testicular torsion (8) and are very frequent in patients with cryptorchidism (9), but the anatomy of the processus vaginalis and mainly the relations between testis and epididymis in patients with retractile testis are unknown.

The objective of the present study was to assess the incidence of anatomical anomalies in patients with retractile testes.

MATERIALS AND METHODS

This study was approved and was carried out in accordance with the ethical standards of

the hospital's institutional committee on human experimentation.

We studied 62 patients prospectively with truly retractile testis during the period from January 2010 through January 2015. The retractile testis in this sample was defined based on physical examination findings. We included only patients with testis that can be brought down into the scrotum without tension and, after gentle massaging of the cord stay there upon release for a while.

We submitted to surgery 20 (32.25%) of the 62 patients. In eight cases of operated patients the retractile testis was bilateral. The surgery was performed because of parent anxiety and/or the impossibility for the periodic follow-up. We compared the anatomical findings of 28 retractile testes with 25 human fetuses (50 testes) with the testes in the scrotal position.

During the surgery, after the induction of anesthesia all patients had the testis in scrotal position and we used the trans-scrotal approach with a little midline scrotal incision with dissection of the cremaster muscle and fixation of the testis in dartos tunica in all cases.

The 25 fetuses were macroscopically well preserved. Their gestational age was determined in WPC, according to the foot-length criterion, which is currently considered the most acceptable parameter to calculate gestational age (10-12). The fetuses were also evaluated regarding crown-rump length (CRL) and body weight immediately before dissection. The same observer conducted the measurements.

After measurement, the fetuses were carefully dissected with the aid of a stereoscopic lens with 16/25X magnification. The abdomen and pelvis were opened to identify and expose the urogenital organs and inguinal canal and to show the testicular position. We observed patency of the processus vaginalis and the relationship between the testis and epididymis in fetuses and the patients.

To analyze the relations between the testis and epididymis in surgical patients and fetuses, we used a previous classification (13, 14): Type I - epididymis attached to the testis at the head and tail; Type II - epididymis totally attached to the testis; Type III - epididymis attached to the testis only at the head; Type IV - epididymis attached to the testis only at the tail; Type V - no visible connection between the testis and epididymis; and Type VI - epididymal atresia. Type I and II relationships are considered normal; while the other types are considered to be epididymal anomalies (EAs). To analyze the structure of the PV, we considered two situations: (a) complete obliteration of the PV between the internal inguinal ring and the upper pole of the testis; and (b) complete patency of the PV.

We used the Chi-square test for contingency analysis of the populations under study ($p < 0.05$), calculated by the Graph Pad Prism software.

RESULTS

The patients ranged in ages from 1 to 12 years old (average of 5.8). Table-1 reports the age of the patients, testicular position, PV patency and the presence of epididymal anomalies. The fetuses presented gestational ages between 25 to 35 WPC, weighed between 741 and 2600g, and had crown--rump length between 23 and 34cm. Of the 50 fetal testes, we observed complete patency of the PV in 2 cases (4%) and EAs in only 1 testis (2%). Table-2 reports the fetal parameters and the testis position. We observed two fetuses with patency of PV in the left testis and only one fetus had an epididymal anomaly (tail disjunction - Type III) on the right side.

Of the 28 retractile testes, we observed patency of the PV in 6 cases (21.4%) and EAs in 4 cases (14.28%). Of the 6 cases of PV patency, 4 (66.6%) were on the right side and 2 (33.3%) on the left side. Of the 4 cases of epididymal anomalies, 2 (50%) were on the right side and 2 (50%) on the left side. The majority of epididymal anomalies (3 - 75%) were tail disjunction (Type III – Figure-1) and only in one case (25%) did we observe total disjunction of the epididymis (Type IV). One of the patients had bilateral retractile testes with bilateral processus vaginalis patency and epididymal anomaly in the left testis.

When we compared the incidence of EAs and PV patency in the retractile testes with the fetuses, we observed a significantly higher prevalence of these anomalies in retractile testes ($p=0.0116$).

Table 1 - The table shows the age, the testicular position and the presence of patency of the processus vaginalis (PV) and epididymal anomalies. The patient number 10 had bilateral retractile testis with bilateral patency of processus vaginalis and epididymal anomaly in the left testis.

Patient	AGE	RT	LT	PV	Epididymis
1	1	Retractile	Retractile	Obliterated	Normal
2	2	Retractile	Scrotum	Obliterated	Normal
3	2	Scrotum	Retractile	Obliterated	Normal
4	3	Scrotum	Retractile	Obliterated	Normal
5	3	Scrotum	Retractile	Obliterated	Normal
6	3	Retractile	Scrotum	Patency (RT)	Anomaly in RT
7	3	Retractile	Scrotum	Obliterated	Normal
8	4	Scrotum	Retractile	Obliterated	Normal
9	5	Retractile	Scrotum	Obliterated	Normal
10	6	Retractile	Retractile	Patency Bil	Anomaly in LT
11	6	Retractile	Retractile	Obliterated	Normal
12	7	Retractile	Retractile	Obliterated	Normal
13	7	Retractile	Scrotum	Obliterated	Normal
14	8	Retractile	Retractile	Obliterated	Normal
15	8	Retractile	Retractile	Obliterated	Normal
16	9	Retractile	Retractile	Obliterated	Normal
17	9	Retractile	Scrotum	Patency (RT)	Anomaly in RT
18	11	Scrotum	Retractile	Patency (LT)	Normal
19	11	Retractile	Scrotum	Patency (RT)	Anomaly in RT
20	12	Retractile	Retractile	Obliterated	Normal

Bil = bilateral; **RT** = right testis and **LT** = left testis.

DISCUSSION

Retractile testis has traditionally been considered a variant of normal testis because it usually descends into the scrotum during adolescence (15). In general, patients with retractile testis are periodically reviewed until the end of adolescence or until the testis has completely descended into the scrotum. According to the guidelines of the European Association of Urology, cases of retractile testis do not warrant medication or surgical intervention, and instead should only be monitored periodically until adolescence (16). Nevertheless, this condition can cause discomfort and also worry parents, sometimes prompting the choice for surgery to bring the affected testis into the scrotum.

Although the question is controversial, some authors have reported histological changes and spermiogram abnormalities in follow-up of adult patients with retractile testis (7, 17). Previous studies suggest surgical correction is necessary in some cases to prevent histological alterations in the germinative epithelium of patients with retractile testis (6, 18). Some previous studies conducted with boys with retractile testis reported that 18 to 32% of patients required surgical correction due to the development of ascending testes or decreases in testicular volume (1, 4), although in a retrospective study with 274

Table 2 - The table shows the fetal age in weeks post conception (WPC) and the presence of epdidymal anomalies and patency of processus vaginalis (PV) in 25 fetus studied. The fetuses ranged in age between 25 to 35 WPC, weighted between 741 and 2600g, and had crown-rump length between 23 and 34 cm. The fetus number 2 and 3 had a PV patency in the left testis and only the fetus 10 had a epididymal anomaly (EA) a tail disjunction on the right side. RT = right testis and LT = left testis.

Fetus	Age (WPC)	RT	LT
1	25	Normal	Normal
2	26	Normal	**PV patente**
3	27	Normal	**PV patente**
4	27	Normal	Normal
5	27	Normal	Normal
6	27	Normal	Normal
7	28	Normal	Normal
8	28	Normal	Normal
9	28	Normal	Normal
10	28	**Tail disjunction**	Normal
11	28	Normal	Normal
12	28	Normal	Normal
13	28	Normal	Normal
14	28	Normal	Normal
15	28	Normal	Normal
16	29	Normal	Normal
17	29	Normal	Normal
18	30	Normal	Normal
19	30	Normal	Normal
20	31	Normal	Normal
21	31	Normal	Normal
22	32	Normal	Normal
23	33	Normal	Normal
24	35	Normal	Normal
25	35	Normal	Normal

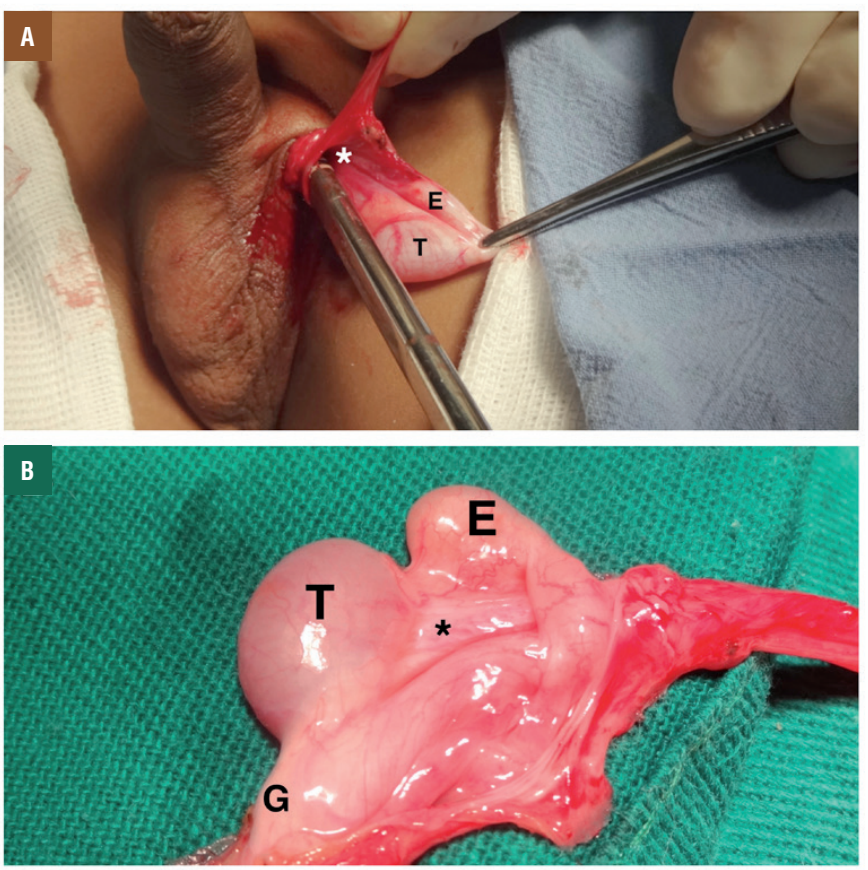
retractile testis only 6.9% of the patients needed surgical intervention; showing that the incidence of ascending testis is not always as high as has been reported in other studies (19).

In an interesting study with 3433 boys the authors observed that the prevalence of undescended testis in 6-year, 9-year and 13-year olds had a variation from 1.2% to 2.2% and after the age of 5 years, only acquired UDT was observed (20).

Studies applying ultrasound confirm that retractile testes show reduced volume in relation to normal testes (21). One recent retrospective study of 43 boys who had been diagnosed as having retractile testis noted that surgical intervention had been found necessary in 16.3% of the cases and the probability of surgery was higher in cases that had been diagnosed at younger ages (22).

Agarwal (4), in an important study, analyzed 204 retractile testicles and observed a risk of ascending testis in more than 30% of the cases. Of the patients in this study, surgery was performed on 61 testes and in 13% of the cases

Figure 1 - Anatomic anomalies in retractile testis. A) Patient with 3 years-old with retractile testis presents complete patency of processus vaginalis (*). We can observe the surgical instrument inside the processus vaginalis. T=Testis and E=Epididymis. B) Patient with 9 years-old with retractile testis presents the epididymis attached to the testis only at the head. T = Testis; E = Epididymis; G = Gubernaculum and *Mesorquium.



the processus vaginalis was found to be patent, while in the other cases of surgical intervention there was only observation of fibrous vestige of the processus vaginalis (4). The authors concluded that retractile testis can not be considered a normal variant because of the high risk of ascension and patency of the processus vaginalis.

In our sample, in which surgery was performed on 28 retractile testes, we found processus vaginalis patency in 21.4% of the cases. These findings confirm that the chance of patients with retractile testis presenting patent processus vaginalis is not negligible. In the control group composed of fetuses in which the testes had completed their migration, patency was only observed in 4% of the cases, a much lower rate than in the patients with retractile testis.

Cryptorchidism can be associated with various anatomical anomalies, but epididymal anomalies and patency of the processus vaginalis are among the most frequent. Epididymal anomalies are associated with cryptorchidism in over one-third of these cases (23, 24). Another study showed that individuals without cryptorchidism have a very low incidence of epididymal anomalies (13). Furthermore, human fetuses without apparent anomalies present epididymal anomalies in less than 3% of the cases, regardless of the testicular position (14). Epididymal anomalies can be classified as disjunction or atresia (13) and can be associated with infertility.

Patients with disjunction anomalies (head, tail or total disjunction) can present a longer distance between the testis and epididymis, the region

called the mesorchium (8, 13, 14). Testicular torsion can be intravaginal or extravaginal. Intravaginal testicular torsion can occur because of an anomaly in the implantation of the tunica vaginalis (bell-clapper deformity) or due to the presence of an elongated mesorchium because of disjunction anomalies of the epididymis (8). Therefore, patients suffering from epididymal anomalies face a higher risk of developing intravaginal testicular torsion (8).

The rate of epididymal anomalies in patients with retractile testis is not well defined in the literature. In our sample, we observed that 14% of the patients with retractile testis submitted to orchiopexy presented epididymal anomalies. In three cases we observed tail disjunction, an anomaly where the mesorchium is elongated, and in one case there was total disjunction between the testis and epididymis, a situation associated with infertility and also increased size of the mesorchium.

This article presents the first description in the literature of the presence of epididymal anomalies associated with retractile testes. Despite the small sample, these findings can be significant. Future studies with larger samples will be necessary to confirm this association between epididymal anomalies and retractile testes, to provide further evidence that retractile testis is not a normal variant and does need treatment.

The main limitation of this work is the small sample of patients with retractile testis, but because of the controversy over treatment, surveys with large samples of patients having this condition who underwent surgery are not common in the literature. Another limitation is the control group. The ideal control group would be boys without inguinal-scrotal anomalies having the same average age as the group with such anomalies. However, ethical considerations regarding use of living subjects and the extreme rarity of cadavers to study requires the use of human fetuses with testicles located in the scrotum as the control group.

CONCLUSIONS

Retractile testis is not a normal variant with a significant risk of patent processus vaginalis and epididymal anomalies.

ACNOWLEDGMENTS

This study was supported by grants from the National Council for Scientific and Technological Development (CNPq – Brazil) and the Rio de Janeiro State Research Foundation (FAPERJ).

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 810-816, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2016.0049

The combination of urinary IL – 6 and renal biometry as useful diagnostic tools to differentiate acute pyelonephritis from lower urinary tract infection

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ABSTRACT

Objective: To evaluate the role of renal ultrasound (RUS) and urinary IL-6 in the differentiation between acute pyelonephritis (APN) and lower urinary tract infection (LUTI).
Patients and methods: This prospective study was carried out at the Pediatric and urology outpatient and inpatient departments of Cairo University Children's Hospital as well as October 6 University Hospital and it included 155 children between one month and fourteen years old with positive culture UTI. Patients were categorized into APN and LUTI based on their clinical features and laboratory parameters. Thirty healthy children, age and sex matched constituted the control group. Children with positive urine cultures were treated with appropriate antibiotics. Before treatment, urinary IL-6 was measured by enzyme immunoassay technique (ELISA), and renal ultrasound (RUS) was done. CRP (C-reactive protein), IL-6 and RUS were repeated on the 14th day of antibiotic treatment to evaluate the changes in their levels in response to treatment.
Results: UIL-6 levels were more significantly higher in patients with APN than in patients with LUTI (24.3±19.3pg/mL for APN vs. 7.3±2.7pg/mL in LUTI (95% CI: 2.6-27.4; p<0.01). Similarly, serum CRP was more significantly higher in patients with APN than in children with LUTI (19.7±9.1µg/mL vs. 5.5±2.3µg/mL (p<0.01). IL-6 levels >20pg/mL and serum CRP >20µg/mL were highly reliable markers of APN. Mean renal volume and mean volume difference between the two kidneys in the APN group were more than that of the LUTI and control groups (P<0.001). Renal volume between 120-130% of normal was the best for differentiating APN from LUTI.
Conclusions: RUS and urinary IL-6 levels have a highly dependable role in the differentiation between APN and LUTI especially in places where other investigations are not available and/ or affordable.

ARTICLE INFO

Keywords:
Ultrasonography; Lower Urinary Tract Symptoms; Interleukin-6; Pyelonephritis

Int Braz J Urol. 2016; 42: 810-6

Submitted for publication:
January 22, 2016

Accepted after revision:
March 13, 2016

INTRODUCTION

Urinary tract infections (UTIs) remain one of the most common bacterial infections in infants and children (1). They are important in view of their acute morbidity and long term risk of renal scaring. In UTIs differentiation between acute pyelonephritis (APN) and lower urinary tract infection (LUTI) is recommended because of their therapeutic and prognostic consequences (2).

Traditionally accepted methods for the diagnosis and follow-up of pediatric UTIs need to be periodically assessed and should be discarded if they can be substituted by other methods that are

less invasive and more effective. In recent years, the clinical value of routine renal ultrasound (RUS) for young children in whom a first UTI is diagnosed has been questioned because of its limited effect of findings on clinical management (3). However, several investigators documented a significant volume increase with acute infection in one or both kidney(s) of those children having APN (4).

Defense against mucosal infections relies on chemokines that engage inflammatory cells to the mucosa (5). Pro-inflammatory cytokines, particularly interleukin-6 (IL-6), determined in urine (uIL-6) or serum (sIL-6), have been shown to be useful as parametric biological indicators of renal envolvement in UTI (6, 7). IL-6 is secreted by uroepithelial cells in response to bacterial invasion, particularly P-fimbriated Escherichia coli (8). In healthy children, IL-6 is found in only small quantities; however, these levels show a significant increase in patients with renal disease (9-11).

The present study included children with urinary tract infection (UTI), to evaluate the usefulness of measuring uIL-6 levels and RUS in distinguishing APN from LUTI.

PATIENTS AND METHODS

This prospective study was carried out at the Pediatric and Urology outpatient and inpatient departments of Cairo University Children's Hospital as well as October 6 University Hospital. The study population included children between one month and fourteen years old who were diagnosed with symptomatic culture positive first episode of UTI between March 2009 and March 2012. Children who had been treated with antibacterial agents within seven days before the admission were excluded.

Diagnosis of UTI was performed on the basis of suggestive clinical symptoms and at least one positive urine culture (colony counts >100.000 bacteria/mL). Patients were classified into APN and LUTI based on their clinical features and laboratory parameters. Diagnostic parameters for APN included the presence of all of the following criteria: loin pain, body temperature >38.5°C, total leucocyte count (TLC) ≥12000mm3, erythrocyte sedimentation rate ≥20mm/hour, and leukocyte casts in urinalysis (2). Patients were judged for lower UTI by fulfilling the clinical criteria including pain, frequency, urgency and dysuria, which was mentioned as crying during urination in infants. The laboratory data was suggestive of lower urinary tract infection when TLC was < 12000/mm3 and erythrocyte sedimentation rate <20mm/hour.

Urine analysis, culture and sensitivity were done by collecting morning midstream samples and by suprapubic aspiration in young infants. Finally, one hundred and fifty five children out of two hundred satisfied the study criteria and were enrolled in the study. The control group comprised thirty healthy children, with age and sex matched.

Serum CRP (C-reactive protein) was measured by quantitative enzyme linked immunosorbent assay.

Urinary IL-6 was measured by quantitative sandwich enzyme immunoassay technique (Quantakine ELISA catalog number D6050).

Renal ultrasound (RUS) was done using Siemens Elegra ultrasound machine. Measurement of the kidney was made in the maximum longitudinal and transverse planes, both of which were identified visually. The renal long axis is usually seen opened caudally to the median body plane at an angle of 10°. The transverse section was defined in the kidney hilar region at a right angle to the longitudinal renal axis. The planes were frozen at the screen and the major and minor kidney axes - the bipolar kidney length, width and depths were measured. The absolute volume of the kidney was calculated and compared with the average kidney volumes. The average absolute kidney volume of a normal person of distinct body weight is defined as 100%. Difference between this average volume and the volume of a patient's single kidney were expressed as percentage of the absolute kidney volume.

The mathematical formula used to calculate the absolute kidney volume was:

LXW (D1+D2)/2 X 0.523cm^3, where L=maximum bipolar length of the kidney, W=maximum width in kidney hilar region, D1=depth in the longitudinal plane, D2=depth in the transverse plane (12).

Children with positive urine cultures were treated with appropriate antibiotics. CRP, IL-6 and RUS were repeated on the 14th day of the antibiotic treatment, to note the changes in these parameters in response to treatment.

Statistical analysis

Data were statistically described in terms of mean±standard deviation (SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using Student t test. For comparing categorical data, Chi square ($\chi 2$) test was performed. Correlation between various variables was done using Spearman rank correlation equation. p values less than 0.05 were considered statistically significant. The Receiver Operating Characteristic (ROC) Curve was constructed to obtain the most sensitive and specific cutoff for each technique. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

RESULTS

Of the total 155 cases with UTI, 70 (45%) were labeled as APN and 85 (55%) as LUTI. The majority of the patients (72%) presented between 4-14 years of age; 80% were females, with female to male ratio 4:1. On urine culture, E. coli was the commonest grown organism: (110 cases: 71%), 70 cases (63%) in LUTI, and 40 cases (37%) in LUTI. Other organisms isolated were Klebsiella in 20 cases (13%), Proteus in 16 cases (10%), Staph. aureus in 7 cases (5%) and others in the remaining 2 cases (1%).

In the current study, uIL-6 levels at diagnosis were significantly higher in patients with APN than in patients with LUTI (24.3±19.3pg/mL for APN vs. 7.3±2.7pg/mL in LUTI (95% CI: 2.6-27.4; p<0.01). Similarly, sCRP was significantly higher in patients with APN than in children with LUTI: 19.7±9.1µg/mL vs. 5.5±2.3µg/mL respectively (p<0.01) (Table-1). Follow-up measurement of sCRP and uIL-6 after 14 days of the antibiotic therapy revealed undetectable levels in both groups of patients. The difference between uIL-6 and sCRP levels at diagnosis and recovery was statistically significant (p<0.05).

Table-1 shows comparison of the laboratory parameters in the study and control group.

Using Receiver Operator Characteristic (ROC) Curve, we found that the area below the ROC curves was 0.86 (95% CI: 0.73-0.98), and 0.67 (95% CI: 0.53-0.8) for sCRP, and uIL-6, respectively. Table-2 shows sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for uIL-6) in the diagnosis of APN.

Table 1 - Laboratory data of the study and control groups.

	APN (n = 70)	LUTI (n = 85)	Control (n = 30)	p value*
CRP(µg/mL)	19.7±9.1	5.5±2.3	0.09±0.1	<0.001
uIL-6 (pg/mL)	24.3±19.3	7.3±2.7	3.1±1.2	<0.001
Hemoglobin (gm %)	9.82±2.2	10.12±2.2	11.93±1.4	<0.05
TLC (per mm3)	24600±3200	11284±1160	6020±512	<0.001
ESR (mm/1st hour)	38±2.1	15±2.3	8.4±4.9	<0.001
Urinalysis Albuminuria: n (%)	56 (80%)	17 (20%)	0	<0.001
Pyuria: n (%)	70 (100%)	77 (89%)	0	<0.05
RBC: n (%)	42 (60%)	17 (20%)	0	<0.05
White cell cast: n (%)	70 (100%)	No (0%)	0	<0.001

Table 2 - Sensitivity, specificity and predictive value of urinary interleukin-6 (uIL-6) in the diagnosis of acute pyelonephritis (APN).

	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	Predictive value (%) (95% CI)	
			Positive	Negative
uIL-6>2pg/mL	79.9 (76.9-82.7)	57.2 (51.8-62.9)	65.8 (62.3-70.1)	72.4 (65.8-72.1)
uIL-6>20pg/mL	39.9 (34.9-42.9)	95.1 (92.1-96.2)	88.2 (79.1-90.8)	60.3 (55.3-60.2)

CI = Confidence interval

Mean renal volume and mean volume difference between the two kidneys in the APN group was more than the LUTI and control groups (P<0.001) (Table-3). Increase in renal volume was caused by parenchymal thickening and not by an enlarged central echo complex (Figure-1). No focal lesions were detected on US. Renal parenchymal cortical-medullar differentiation was lost in most cases of APN.

Table-3 shows the mean renal volume and the mean volume difference between the two kidneys in the study cases.

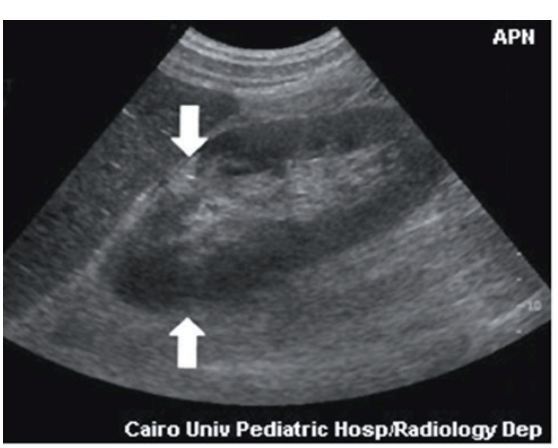
Table-4 shows sensitivity, specificity, PPV and NPV of renal biometry in the diagnosis of APN.

Kidney asymmetry was diagnosed if the difference in the volume of a kidney pair was more than 20%. In APN, asymmetry was present in 30%; volume difference of more than 40% occurred in 21% of these patients. Mean volume difference was 30.2%. Follow-up assessment of renal volume was done in 20 patients of APN, and showed an average of 60% reduction in volume of the affected kidney (from the first recorded value in the study) after 2 weeks of successful antibiotic therapy.

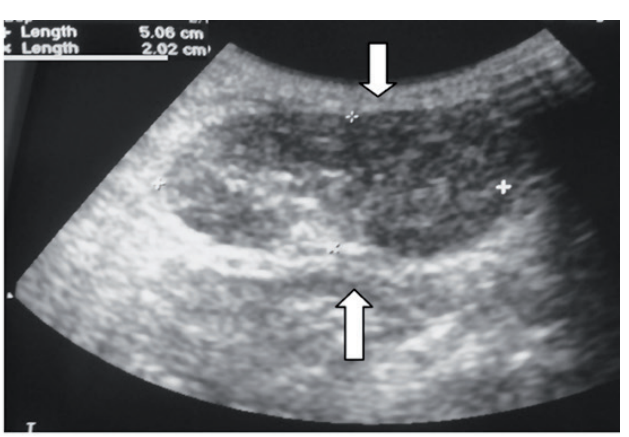
Table 3 - Renal volume assessment by ultrasound in patients with APN and LUTI.

	APN (n: 70)	LUTI (n: 85)	Control (n: 30)	P value
Mean volume of large kidney (%)	188.5±65.6	99.6±12.5	100±20	<0.001
Mean of difference in volume (%)	48.1±9.1	9.9±3.5	8.9±2	<0.001

Figure 1 - Ultrasound findings in the study cases.



Ultrasound findings in APN



Ultrasound findings in LUTI: Normal Ultrasound

Table 4 - Sensitivity, specificity and predictive values of renal biometry in the diagnosis of APN.

Volume of larger kidney	Sensitivity ratio	Specificity ratio	Predictive value (%)	
			Positive test	Negative test
>120%	62/70 (89)	76/85 (89)	62/69 (90)	76/85 (89)
>130%	59/70 (84)	82/85 (96)	59/62 (95)	82/93 (88)
>140%	55/70 (79)	85/85 (100)	52/52 (100)	85/102 (83)

Sensitivity = probability of a positive finding in a patient with acute pyelonephritis; **Specificity** = probability of a negative finding in a patient without acute pyelonephritis, that is, with acute lower UTI; **Predictive value of positive test** = percentage of patients with positive test results who have acute pyelonephritis; **Predictive value of negative test** = percentage of patients with negative test results who have acute lower UTI

DISCUSSION

Our study confirms the usefulness of determining urinary IL-6 to differentiate between APN and LUTI in children and also indicates that the process of recovery from the infection results in normalization of urinary IL-6 levels. This is in agreement with the results of Miguel et al. (13) and Sheu et al. (14). Serum and urinary levels of IL-6 increase during UTI, and its measurement have been suggested to be of value in differentiating between APN and lower UTI (7, 15, 16). However, measurement of urinary IL-6 is less aggressive than determination of serum levels and therefore more acceptable for patients and health professionals.

Moreover, our results show that, based on the specificity and sensitivity of the measurement, in the presence of clinical manifestations indicative of UTI, IL-6 levels >20pg/mL is a highly reliable marker of APN. Comparable findings were observed by Miguel et al. (13) who suggested a level >15pg/mL is an excellent marker of APN and concluded that a value of urinary IL-6 greater than 15pg/mL is 6.33 times more likely to be found in patients with APN than in those with lower UTI.

The efficiency of measuring urinary IL-6 in the diagnosis of UTI was assessed using two cutoff points, one standardized as positive or negative by the reference laboratory, and the other with utmost competence for differentiating APN from lower UTI obtained by creating ROC curves (17).

Although the current study was not designed to investigate the value of uIL-6 as a marker of therapeutic response, our results obviously showed that clinical remission is associated with normalization of uIL-6 levels. Moreover, Tullus et al. (11) in a former study demonstrated that persistent renal scarring, a year after APN, was evident only in children with increased urinary levels of IL-6. We concluded that the follow-up of uIL-6 levels in patients with APN can help us judge the proper duration of antibiotic treatment during the acute phase, and it also might be used as an indicator for the risk of persistent renal damage.

CRP is an acute phase reactant produced in the liver. Data from different studies support that elevated sCRP levels are useful for the discrimination between APN and LUTI in patients with distinct clinical signs of APN (18, 19). In the present study, the mean sCRP level in the APN group was significantly higher than that in LUTI as well as the control groups. The cutoff point for maximum diagnostic efficiency of sCRP in patients with APN was 65mg/L. On the other hand, Miguel et al. (14) suggested a sCRP level of 70mg/L as the most competent level for diagnosis of APN. Our results also confirm the observation of Dinkel et al. (2) who noted that CRP value <20µg/mL was suggestive of LUTI (2). Nevertheless, other studies have noted values of up to 30µg/mL in LUTI (20, 21).

In the current study, we could demonstrate that ultrasound also allows a reasonable level of differentiation between APN and lower UTI. In our study, patients with LUTI showed mean volume of the larger kidney to be 99.6±11.4% of normal; mean volume difference between the two kidneys was 9.9±3.59%. Comparable values were reported by Dinkel et al. (2) who reported 99.7% and 12.3% respectively and Khan et al. (19) who suggested a mean volume of 95.2±15.4% and mean volume difference of 9.0±4.7% in patients with LUTI.

These observations confirm that there is no significant alteration in the mean renal volume and mean volume difference in patients with LUTI.

Among patients with APN a significant increase in mean kidney size (188.5±65.6) and mean volume difference (48.1±9.14%) was noted (P<0.001). Nearly 80% of patients with APN had a renal volume exceeding 140% of normal. Similar figures of 175.8% and 30.2% mean renal volume and mean volume difference respectively have been reported by Dinkel et al. (2); 76% of the cases in their study had renal volume exceeding 140%. On the basis of these observations it is evident that the increase in renal size and unilateral renal enlargement are two important features of APN. The sensitivity, specificity and predictive value of renal biometry in the differentiation of acute UUTI from LUTI varied in our population according to whether a volume increase in larger kidney of 120%, 130% or 140% were chosen as the critical values (Table-4). We observed that kidney volume between 120-130% of normal is best for differentiating APN from LUTI, because of the higher sensitivity of this cut-off range compared to those with a value >140% this is in agreement with results of Khan et al. (19). Moreover, in the current study, follow-up of 20 patients with APN, revealed nearly a 60% reduction in the renal volume within 14 days. Similarly, Khan et al. (19) documented nearly a 43.6% reduction in the renal volume within the same follow-up period, and Dinkel et al. (2) demonstrated a 20-45% reduction in the renal volume within 6 days and 60% within 2 weeks of treatment.

Renal ultrasound as an investigation in children with first UTI has been recommended by several studies (22, 23). However, most workers emphasize that US although has high specificity in detecting APN and obstructive uropathy, its sensitivity is only modest especially while detecting vesicoureteral reflux and renal scarring (24). Therefore, it has been recommended that children under 5 years of age with recurrent UTI should be further subjected to micturating cystourethrogram (MCU) and renal dimercaptosuccinate acid (DMSA) scan if their US is normal. In a comparative study of US and DMSA scan in the same patients, it was found that US failed to detect half of the kidneys with scars (25). However, getting a DMSA scan in all patients with UTI is practically not feasible because this test, besides being more costly, it is not available in most centers.

CONCLUSIONS

Renal US and urinary IL-6 levels have a very important role in the differentiation between APN and LUTI especially in those who were either not clearly diagnosed with acute pyelonephritis or lower urinary tract infection by clinical criteria and routine laboratory investigations and in places where other investigations are not available and / or affordable. Urinary IL-6 level >20pg/mL along with increased renal volume should be taken as highly suggestive indicators of APN. Moreover, serial estimation of these parameters may have prognostic significance as well as an aid in monitoring response to therapy.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 817-824, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0409

A modified method by differential adhesion for enrichment of bladder cancer stem cells

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ABSTRACT

Purpose: In a previous study the vaccine was effective against bladder cancer in a mouse model. However, a small portion of tumors regrew because the vaccine could not eliminate bladder cancer stem cells (CSCs). In this study, we showed a modified method for the isolation of bladder CSCs using a combination of differential adhesion method and serum-free culture medium (SFM) method.

Materials and Methods: Trypsin-resistant cells and trypsin-sensitive cells were isolated from MB49, EJ and 5637 cells by a combination of differential adhesion method and SFM method. The CSCs characterizations of trypsin-resistant cells were verified by the flow cytometry, the western blotting, the quantitative polymerase chain reaction, the resistance to chemotherapy assay, the transwell assay, and the tumor xenograft formation assay.

Results: Trypsin-resistant cells were isolated and identified in CSCs characters, with high expression of CSCs markers, higher resistance to chemotherapy, greater migration in vitro, and stronger tumorigenicity in vivo.

Conclusion: Trypsin-resistant cells displayed specific CSCs properties. Our study showed trypsin-resistant cells were isolated successfully with a modified method using a combination of differential adhesion method and SFM method.

ARTICLE INFO

Keywords:
Urinary Bladder Neoplasms; Neoplastic Stem Cells; Trypsin

Int Braz J Urol. 2016; 42: 817-24

Submitted for publication:
July 24, 2015

Accepted after revision:
October 15, 2015

INTRODUCTION

The human interleukin-2 surface modified MB49 bladder cancer cells vaccine induced specific antitumor immunity and was effective against metastatic bladder cancer in our previous study (1). However, a small portion of the mouse bladder tumors underwent regression and regrew after a period of time because the cancer stem cells (CSCs) were not eliminated. Recurrence of solid tumors may be due to the inability of traditional chemotherapy and radiotherapy to eliminate CSCs (2, 3). The vaccine used in our previous study was not the CSCs vaccine and thus could not induce specific immunity directed against CSCs.

It has been found that repeated cycles of differential adhesion could enrich for breast CSCs by 20-fold, and the relation between stem cell properties and adhesiveness has been noted previously in other cancer cells (4). The serum-free culture medium (SFM) method had been used to isolate CSCs from cancer cells, but it was limited due to the deficiency of purity in the CSCs (5). As we known, the combination of the differential adhesion method and SFM method has not been used to enrich the CSCs, which could gain the

purity of cell sorting. The enrichment of bladder cancer stem cells would promote development of our vaccine research. Thus, we provide a modified method here by combining the differential adhesion and SFM methods to enrich bladder CSCs.

MATERIALS AND METHODS

Cell lines

The murine bladder cancer cell line, MB49, was a gift from Dr. I. C. Summerhayes (1). The human bladder cancer cell lines, EJ and 5637, were provided and preserved in Pathology Lab, Southern Medical University. These cells were cultured in RPMI1640 that contained 10% fetal bovine serum (FBS, Thermo Scientific HyClone, Logan, Utah) at 37°C in a 5%CO_2 humidified incubator.

The differential adhesion method

Cells were cultured to confluency in a 6-well plate, washed with phosphate buffered saline (PBS), and digested with trypsin solution (eBioscience, San Diego, California) at 37°C. After several minutes, cells were divided and collected by washing with PBS. Trypsin was added in the attached cells and the digested and collected process repeated several times with the same times. Cells collected after different times were cultured in a 6-well plate for 3 days. Then the trypsin--sensitive cells and trypsin-resistant cells were digested with trypsin again, divided and collected as former, separately. Such step was repeated for 3 cycles. Finally, the trypsin-resistant cells were cultured with SFM in a 6-well plate. By the 15th day, these cells had grown to spheres and were considered to be CSCs.

The constitutes of SFM were RPMI1640, fibroblast growth factor basic (20ng/mL), epidermal growth factor (20ng/mL), B-27 serum-free supplement (20μL/mL), leukemia inhibitory factor (20ng/mL) and bovine serum albumin (4μg/mL).

Flow cytometry (FCM)

The MB49, EJ and 5637 cells and their relevant CSCs were harvested respectively. They were dissociated in autoMACS running buffer (Miltenyi Biotec, Bergisch Gladbach, Germany), labeled with FITC antiCD44 (Miltenyi Biotec) and PE anti-prominin-1 (Miltenyi Biotec), incubated at 4°C for 20 minutes, and washed twice with PBS. The FITC rat IgG2bκ isotype control (eBioscience) and the PE rat IgG1κ isotype control (eBioscience) were used as a control. The portion of $CD133^+CD44^+$ cells was calculated using a BD FACSAria cell sorter (Becton-Dickinson, San Jose, California).

Quantitative polymerase chain reaction (qPCR)

Total RNA was isolated using Arcturus PicoPure RNA isolation kit (Arcturus, Life Technologies, CA, USA). The RNA quality was verified using Bioanalyzer RNA Pico Chip (Agilent Technologies, CA, USA). cDNAs were synthesized by reverse transcription using the Superscript III reverse transcriptase (Invitrogen, CA, USA). cDNAs were amplified using SYBR green PCR master mix (Bio-Rad, California) on a 7500 real time PCR system (AB Applied Biosystems, Singapore). The sequences of the primers used are listed in Table-1. GAPDH was used as a control. Normalization and fold changes were calculated using the $\Delta\Delta C_t$ method (6).

Western blotting (WB)

The protein extracts were separated by electrophoresis and transferred to polyvinylidene difluoride membranes (Millipore, MA, USA). Membranes were blocked and incubated using the primary antibody anti-CD133 (Abcam, MA, USA), anti-CD44 (Abcam) and anti-β-actin antibody (Abcam). Then membranes were incubated with anti-mouse secondary antibodies (Abcam) (7). Finally, protein bands were detected using Fluor Chem FC2 (Alpha Innotech, CA, USA) and their intensity was analyzed using the Image Lab software.

Chemotherapy-resistance ability

The cells were seeded onto a 96-well plate at a density of 1×10^4 per well. The chemotherapeutic agents paclitaxel (Sigma, MO, USA) and cisplatin (Sigma) were added at different concentrations. After 4 days, CCK-8 was added and the absorbance value was recorded. Cell viability was calculated as the percentage points of the absorbance values in treated wells relative to untreated control wells (6).

Table 1 - Primers of selected genes.

Gene name	Primers (forward/reverse)	Base pairs of product
CD133	F: 5'-CGGGATCCGAAAAACTGATCTGT-3'	615bp
	R: 5'-CCGCTCGAGTTACCTAGTTACTCTCTCC-3'	
CD44	F: 5'-CCCTGCTACCAGAGACCAAGAC-3'	401bp
	R; 5'-GCAGGTTCCTTGTCTCATCAGC-3'	
GAPDH	F: 5'-CCATGGAGAAGGCTGGGG-3'	198bp
	R: 5'-CAAAGTTGTCATCCATGACC-3'	

Migration abilities in vitro

Cells were seeded, in pure RPMI1640 (1×10^4 cells/0.25mL/well), onto the upper well, and a 6.5-mm pore-size polycarbonate membrane chamber was inserted into the transwell apparatus (Costar, MA, USA). RPMI1640 containing 10% FBS was added into the lower well. Cells were incubated and migrated to the bottom surface after 24 hours, fixed, stained, rinsed and examined by inverted microscopy.

Tumorigenic abilities in vivo

All animal experiments performed were approved by the Ethics Committee of Southern Medical University under Contract 1116904. The MB49, EJ and 5637 cells and their relevant CSCs were injected subcutaneously into 4-week-old nude mice (Guangzhou, China). The volume of the tumor xenograft was observed every week, removed at week 8 and measured. The volume of tumors was measured by using the formula $d^2\times D/2$, where d and D were the shortest and the longest diameters respectively (8).

Statistical analysis

All analyses were performed by the SPSS19.0 software, setting significance at $P<0.05$. All of the data was expressed as the mean±standard deviation and analyzed using one-way ANOVA.

RESULTS

Trypsin-resistant cells separable by differential adhesion method

The differential adhesion method showed that the digested time of MB49, EJ and 5637 cells was different, average time was 2, 3 and 5 mins, respectively (Figure-1A). It is found that cells detached by fewer time of trypsinization retained original shaped morphologies. On the other hand, cells detached by more time exhibited round shaped morphologies, and cells detached by middle time had mixed morphologies (Figure-1B).

Characterizations of CSCs

Compared with the trypsin-sensitive cells, trypsin-resistant cells could enrich for CSCs. And these cells cultured with SFM method could gain the purity of CSCs sorting. To confirm this conclusion, it is necessary to identify trypsin-resistant cells in CSCs characters with high expression of CSCs markers, higher resistance to chemotherapy, greater migration in vitro, and stronger tumorigenicity in vivo.

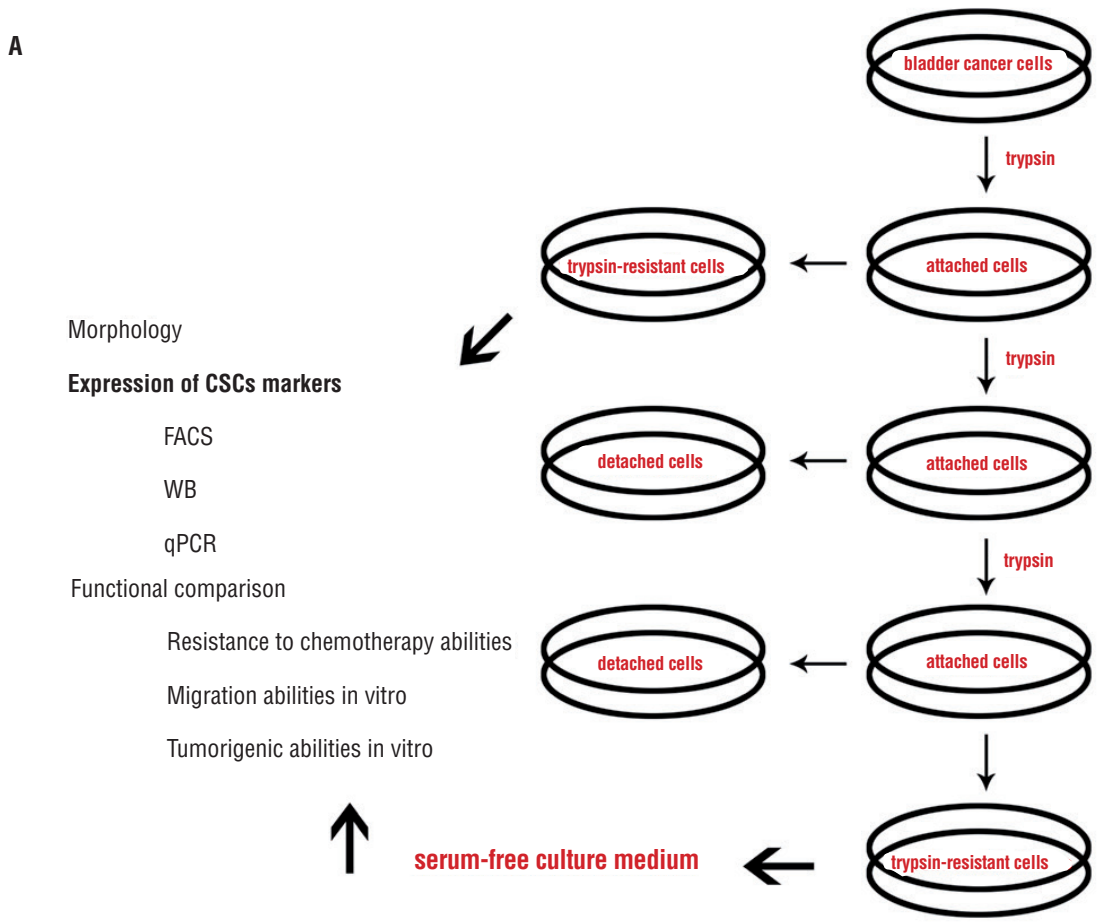
Expression of CSCs markers

The FCM analysis revealed that the fraction of $CD44^+CD133^+$ cells in trypsin-resistant cells was more than in trypsin-sensitive cells of MB49, EJ and 5637 cells (Figure-2A). The WB analysis indicated that the CD133 and CD44 proteins were abundantly expressed in trypsin-resistant cells, but much less in trypsin-sensitive cells (Figure--2B). The qPCR analysis showed that the relative levels of CD133 and CD44 mRNAs in trypsin-resistant cells were higher than those observed in trypsin-sensitive cells (Figure-2C).

Functional comparison

Compared to trypsin-sensitive cells, trypsin-resistant cells displayed higher cell viabilities after being exposed to different concentrations of doxorubicin, which suggested that trypsin-re-

Figure 1 - Isolation of cells by differential adhesion method and serum-free culture medium (SFM) method. (A) Diagram illustration to the proposed model for isolation of CSCs by differential adhesion method and SFM method. (B) Morphology of trypsin-resistant cells (T-R) and trypsin-sensitive cells (T-S) in MB49, EJ and 5637 cells.



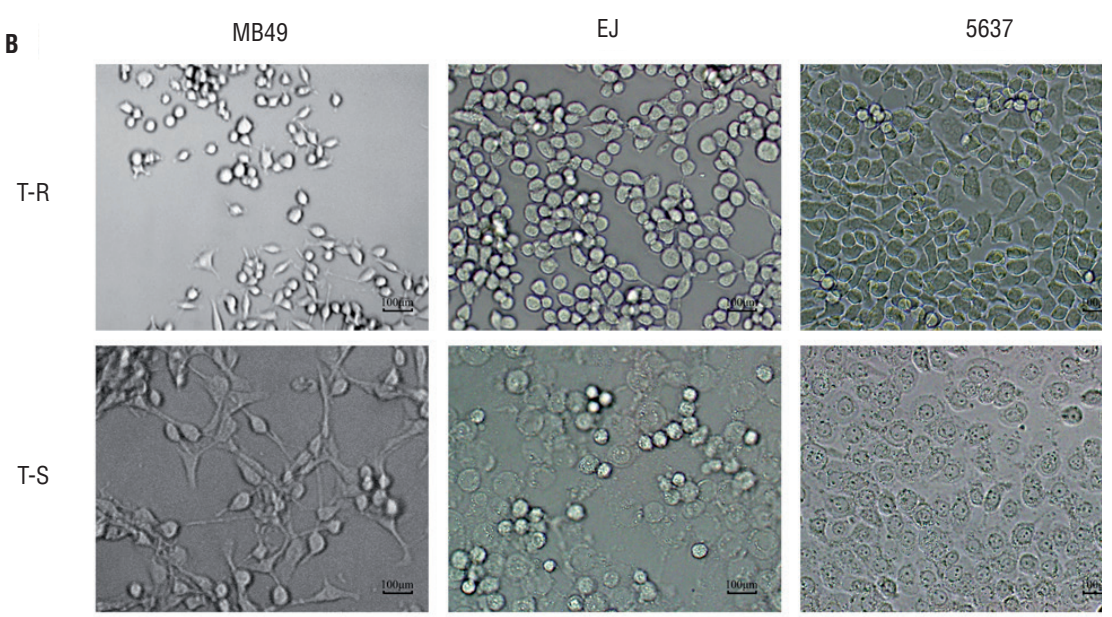
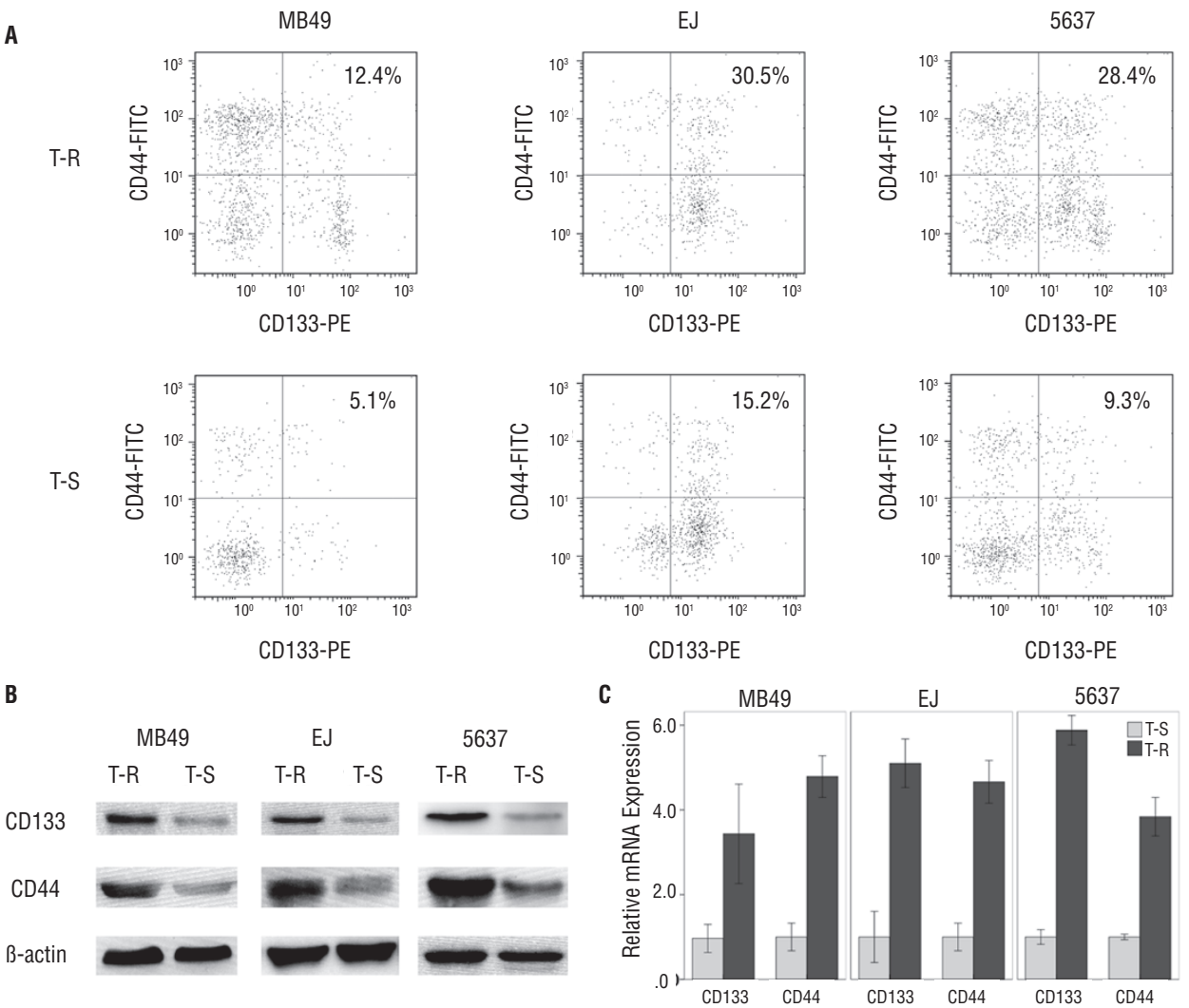


Figure 2 - Comparison of specific markers in trypsin -resistant cells (T-R) and trypsin-sensitive cells (T-S) of MB49, EJ and 5637 cells. (A) The FCM analysis revealed that the fraction of $CD44^{+}CD133^{+}$ cells in trypsin-resistant cells was more than in trypsin-sensitive cells. (B) The WB analysis indicated that the CD133 and CD44 proteins were abundantly expressed in trypsin-resistant cells, but much less in trypsin-sensitive cells. (C) The qPCR analysis showed that the relative levels of CD133 and CD44 mRNAs in trypsin-resistant cells were higher than those observed in trypsin-sensitive cells.

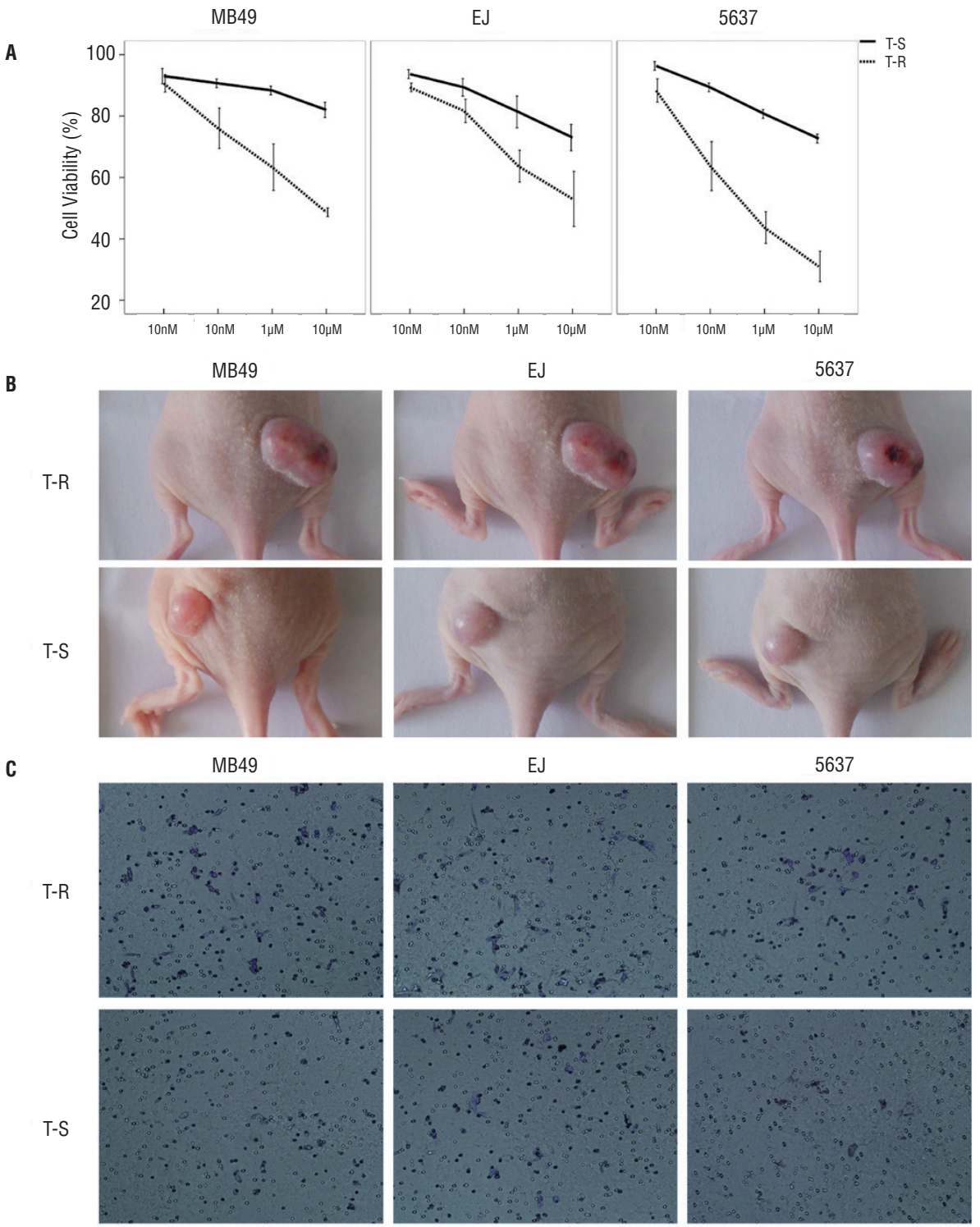


sistant cells had lower susceptibility to traditional anticancer agents (Figure-3A). The results of the transwell migration assay indicated that more trypsin-resistant cells invaded the bottom chamber when compared to trypsin-sensitive cells under the same incubation conditions, which suggested that trypsin-resistant cells had higher invasion ability than trypsin-sensitive cells (Figure-3B). Regarding xenograft formation, trypsin-resistant cells produced tumors with larger volumes than trypsin-sensitive cells did with the same number of injections (Figure-3C).

DISCUSSION

Enrichment of CSCs was an absolute necessity when using CSCs in vaccine applications. Three methods were mostly used to isolate CSCs from can-

Figure 3 - Functional characteristics comparison in trypsin-resistant cells (T-R) and trypsin-sensitive cells (T-S). (A) Comparison of resistance to chemotherapy using CCK-8. Compared to trypsin-sensitive cells, trypsin-resistant cells show higher cell viabilities after treatment with various concentrations of anti-cancer drugs doxorubicin. (B) In the transwell migration assay, the number of invaded trypsin-resistant was higher than that of trypsin-sensitive cells. (C) In xenograft formation experiments, trypsin-resistant produced larger tumor volumes than trypsin-sensitive cells did.



cers: specific CSCs surface markers, side population cells, and SFM. The shortcoming of these methods was the lack of purity and the purity was not enough for CSCs (5). Repeated cycles of differential trypsinization could gather CSCs by 20-fold in breast cancer cells, keratinocytes and human mammary epithelial cells. So the differential adhesion method was able to isolate CSCs from bladder cancer cells. Considering that the serum caused irreversible differentiation of stem cells, SFM selection might be useful for CSCs expansion and would allow for maintenance of an undifferentiated stem cell status (9). To our knowledge, this is the first report about the isolation and expansion of CSCs via a combination of differential adhesion method and SFM method, which is modified to improve the purity of CSCs.

The CD133 and CD44 markers were used to ascertain CSCs in most tumor tissues (10, 11). Additionally, our study found elevated expression levels of $CD133^+$ and $CD44^+$ in trypsin-resistant cells. Targeting $CD44^+$ and $CD133^+$ cancer cells involving a $CD133^+CD44^+$ cell subpopulation might be a way for colorectal cancer therapy (12). Thus $CD133^+CD44^+$ cells may be the concentrated CSC subpopulation in bladder cancer cell populations. Only cells expressing $CD133^+$ and $CD44^+$ were considered as CSCs by FCM analysis (13). In addition, the expression of both markers was found elevated in trypsin-resistant cells not only at the mRNA expression (qPCR) level, but also at the protein expression (WB) level.

We functionally characterized the trypsin-resistant cells populations by different techniques (14, 15). Specifically, trypsin-resistant cells had a greater ability to penetrate wells. Moreover, although chemotherapy killed most tumor cancer cells, it could not kill CSCs. Additionally, trypsin-resistant cells exhibited a lower sensitivity to doxorubicin, which meet the theory of resistance to chemotherapy (16, 17). Tumorigenicity in nude mice was the standard experiment used to evaluate the tumorigenic ability of CSCs (18). Trypsin-resistant cells had a greater ability to form subcutaneous tumors in nude mice. Taken these above results together, trypsin-resistant cells showed specific CSC properties.

Taken together, this study showed that cultured trypsin-resistant bladder cancer cells displayed specific CSC properties.

CONCLUSIONS

In conclusion, bladder CSCs were isolated successfully with a modified method using a combination of differential adhesion method and SFM method. Trypsin-resistant cells contained characteristics resembling CSCs such as chemotherapy resistance and in vivo tumorigenic capacity. Trypsin--resistant cells may provide an ideal model for the development of bladder cancer vaccine research.

ACKNOWLEDGEMENT

Yong-tong Zhu, Shi-yu Pang and Yang Luo contributed equally to this work.

This study was supported by the Science and Technology Innovation Project of Education Department in Guangdong Province (No. 2013KJCX0039) and the Scientific Initiative Research Foundation of Southern Medical University (No.PY2014N031).

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Vol. 42 (4): 825-837, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0606

Improvement of erectile dysfunction by the active pepide from *Urechis unicinctus* by high temperature/pressure and ultra – wave assisted lysis in Streptozotocin Induced Diabetic Rats

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ABSTRACT

Introduction: We investigate the effect of active peptide from Urechis unicinctus (UU) by high temperature/pressure and ultra-wave assisted lysis on erectile dysfunction in streptozotocin-induced diabetic rats.

Materials and Methods: Forty 12-week-old Sprague-Dawley rats were used in this study. Diabetes was induced by a one-time intraperitoneal injection of streptozotocin (50mg/kg). One week later, the diabetic rats were randomly divided into four groups: normal control, untreated diabetes control, and groups treated with 100 or 500mg/kg/d UU peptide. Rats were fed with UU peptide by intragastric administration for 8 weeks. After 8 weeks, penile hemodynamic function was evaluated in all groups by measuring the intracavernosal pressure after electrostimulating the cavernous nerve. Nitric oxide (NO) and cyclic guanosine monophosphate (cGMP) activities were measured and endothelial nitric oxide synthase (eNOS) and neuronal NOS (nNOS) protein expression was determined by Western blot.

Results: Maximum intracavernosal pressure in diabetic control rats decreased significantly compared to normal control rats, and was increased significantly compared to untreated diabetic rats after UU peptide supplementation. Treatment with the higher dose of UU peptide significantly increased the NO and cGMP levels compared with the diabetic control group. Decreased activity and expression eNOS and nNOS were found in the diabetic rats compared with the normal control group. Decreased eNOS and nNOS in diabetic rats were improved by UU peptide administration.

Conclusions: Active peptide from UU ameliorates erectile function in a streptozotocin induced diabetic rat model of erectile dysfunction.

ARTICLE INFO

Keywords:
Erectile Dysfunction; Streptozocin; UFEII protein, Urechis unicinctus [Supplementary Concept]

Int Braz J Urol. 2016; 42: 825-37

Submitted for publication:
October 23, 2015

Accepted after revision:
December 22, 2015

INTRODUCTION

Erectile dysfunction (ED) is defined as the consistent or recurrent inability to attain and/or maintain a penile erection sufficient for satisfactory sexual performance (1). About 52% of men between the age of 40 and 70 years suffer from ED. ED is closely associated with an increasing

number of systemic diseases including cardiovascular disease, hypertension, diabetes mellitus (DM), hypercholesterolemia, and depression, as well as behavioral disorders including alcoholism, smoking, and drug abuse (2, 3).

DM is a metabolic disease characterized by hyperglycemic condition resulting from damages in insulin secretion and/or insulin resistance, and disturbance of carbohydrate metabolism. DM is a major risk factor of ED and the prevalence of ED in men with DM is significantly higher than in those without DM (4). The pathophysiologic mechanism of ED induced by DM may result from neurovascular dysfunction (5, 6). Endothelial nitric oxide (NO) synthase (eNOS) produces a physiological level of NO in endothelial cells under the normal circumstance. Rats in whom DM has been induced by chemical diabetogenesis show significant reductions in penile eNOS and neuronal NO synthase (nNOS), followed by markedly decreased NO production (5). Dysfunction occurring in penile endothelial cells induces ED. Therefore, DM has the potential to have an impact on all the components of ED.

Multiple treatment strategies have been established to treat ED induced by DM. These include DM control, psychosexual counseling, and medication with inhibitors of type-5 phosphodiesterase (PDE5) (7). Although therapy with PDE5 is effective for ED, treatment efficacy in patients with DM is significantly lower (8). Therefore, new therapeutic strategies are needed for patients with ED and DM.

Urechis unicinctus (UU) (Figure-1) is a member of the Echiuroidea, Xenopneusta, Urechidae and cyclindrical or oval shaped marine inverterbrates. They inhabit marine intertidal and subtidal zones of North China, Korea and Japan. UU contains amino acids, such as glycine, glutamic acid, and aspartic acid, and a component that is a new potential source of fibrinolytic agents, which has antithrombotic effects in an animal model of thrombosis (9). Glycosaminoglycan from UU has a hypoglycemic effect in diabetic mice (10) and an isolated peptide from UU may enhance erectile function in vitro by increasing the levels of NO and cyclic guanosine monophosphate (cGMP) (11). UU is considered a natural tonic in Asian countries and is considered to have positive effects on erectile function. However, detailed studies have not been conducted to explore the active mechanisms of UU peptide in vivo.

The purpose of this study was to determine whether UU peptide improves ED induced by DM via the NO/cGMP pathway and recovers the function of endothelium in the corpus cavernosum. The effect of UU peptide on corpus cavernosal smooth muscle tissues in rat with ED associated DM also was investigated.

Figure 1 - The picture of Urechis unicinctus.

MATERIALS AND METHODS

Preparation of Urechis unicinctus peptide

UU was generously obtained from a local aquatic market (Jagalchi) in Busan, Republic of Korea. UU was washed and homogenated with the addition of water. Salt water was removed and UU was cut into 0.8-l. 0cm sized portions, which were pressurized and autoclaved at a pressure of 1kgf/cm^2 at a temperature of 121°C for 20 minutes. The preparation was ultrasonicated at a frequency of 40KHz for 60 minutes, vacuum filtered and freeze-dried. The resulting UU peptide was used for the experiments.

Animals experiments and diet

Forty 12-week-old adult male Sprague--Dawley rats weighing 250-300g were obtained from Orientbio Inc. (Seongnam, Korea). The study was designed and conducted in accordance with the Public Health Service Policy on Human Care and Use of Laboratory Animals (NIH Office of Laboratory Animal Welfare, revised 2002). Rats were handled according to the rules and regulations of the Institutional Animal Care and Use Committee in School of Medicine, The Catholic University of Korea. Animals were housed two per cage and maintained on a 12-h light-dark cycle with ad libitum access to water and food. After one week acclimatization, the rats were randomly divided into four groups of four rats each: untreated (normal control), streptozotocin (STZ) induced diabetes control (DM control), STZ induced diabetic rats administered with 100mg/kg of UU peptide (UU 100) and STZ induced diabetic rats administered with 500mg/kg of UU peptide (UU 500). All rats in the DM and DM+UU groups received a single intraperitoneal injection of STZ (50mg/kg). Glucose in blood drawn from the tail vein and body weight was checked weekly and significant diabetes (serum glucose >250mg/dL) was confirmed in all rats within 1 week. This diabetic serum glucose level was maintained throughout the experiment period. One week after the induction of diabetes, rats in the UU group were treated with daily oral UU peptide (100mg/kg or 500mg/kg) dissolved in 10mL distilled water and administered orally through an 8F oral zonde needle once a day for 8 weeks. After 8 weeks, intracavernosal pressure (ICP) and mean arterial pressure (MAP) measurements were performed in all 40 rats. After the measurements were completed, the penis of each rat was excised at the level of the crus and blood samples were collected. The excised penis was cut and divided into two portions. One portion was used for measurement of NO/cGMP. The other portion was used for histologic examination and Western blotting. The separated penile tissues were stored in-70°C liquid nitrogen until needed.

Assessment of ICP and MAP

Erectile function was evaluated by tracing the ICP under cavernous nerve electrical stimulation under anesthesia at 8 weeks after inducing DM and administrating UU peptide. Rats were anesthetized with Tiletamine (50mg/kg, Zoletil®; Virbac, Carros, France) intraperitoneally and anesthesia was retained with supplemental Tiletamine as needed. The major pelvic ganglion and cavernous nerves lateral to the right prostate were revealed and identified using a lower abdominal midline incision with the rat in the supine position. The shaft of the penis was removed of skin and fascia, and the corpus cavernosum and crus of the penis were exposed. The left corpus cavernosum of the proximal portion of the penis was cannulated by insertion of a 250IU/mL heparinized 23-gauge butterfly needle connected to a pressure transducer to assess ICP. The right carotid artery via a midline neck incision was cannulated with a PE-50 catheter filled with 250IU/mL heparinized saline to measure MAP. A hook-shaped bipolar silver electrical stimulator was placed on the pelvic ganglion to stimulate the cavernous nerve at 10V for 50s and 2.4mA with a pulse width of 0.5ms. Cavernous nerve stimulation was performed at least three times and the interval between stimulations was maintained for over 10 minutes. The peak ICP during nerve electrostimulation was calculated by an isometric force transducer and recorded on a computer using a Power Lab® data acquisition system (AD Instruments Pty Ltd., Oxford, UK). ICP and MAP ratios were analyzed using Chart 5 software (AD Instruments Pty Ltd.). After completion of functional analysis, the corpus cavernosum was removed and divided into two portions.

NO measurement

Blood samples obtained from the inferior vena cava were centrifuged at 3.000rpm for 10-15 minutes to separate the serum. An equivalent volume of methanol was added to the plasma and mixed well to remove serum proteins, and centrifuged at 15.000rpm for 10-15 minutes. The concentration of NO in the supernatant was measured with a model ENO-20NO analyzer using high-performance liquid chromatography (Eicom, Kyoto, Japan).

Measurement of cGMP in the corpus cavernosum

After assessment of ICP and MAP, corpus cavernosum tissue was immediately removed and frozen at-70°C in liquid nitrogen. A commercial cGMP direct immunoassay kit (K372-100; BioVision, Milpitas, CA, USA) was used to measure the cGMP level as detailed by the manufacturer.

Determination of eNOS and nNOS protein expression by Western blot analysis

The corpus cavernosum was collected from all rats and homogenized individually in a buffer solution of 32mM sucrose, 20mM HEPES, (pH 7.4), 1mM EDTA, 1mM dithiothreitol, 10μg/mL leupeptin, 2μg/mL aprotinin, 10μg/mL trypsin inhibitor, 1μg/mL pepstatin and 1mM phenylmethylsulfonyl fluoride. The homogenized buffer solution was stored on ice for 15 min and centrifuged at 4°C for 13.000rpm for 15 minutes. The supernatant solution was dissociated and amount determined to contain 30μg protein was boiled at 95°C for 5 minutes and proteins resolved by 12% discontinuous sodium dodecyl sulfate polyacrylamide electrophoresis (SDS-PAGE). The proteins were transferred into a 0.2μm polyvinylidene fluoride membrane (Amersham Bioscience, Piscataway, NJ, USA) for 150 minutes at 25V. Each membrane was reacted with blocking buffer (5% skim milk in Tris buffered saline-Tween 20, TBST) for 30 minutes at room temperature. eNOS or nNOS (BD Biosciences, San Jose, CA, USA) antibody, or beta--actin (1:10000; Santa Cruz Biotechnology, Santa Cruz, CA, USA) were added for 2 hours and the membrane was washed three times using full term for TBST at intervals of 10 min. The secondary antibody, either anti-mouse IgG or anti-goat IgG conjugated to horseradish peroxidase (1:2000; Zymed Laboratories, South San Francisco, CA, USA) were added at room temperature for 1 hour. Each membrane was washed six times using TBST with an interval of 5 minutes between each washing. Enhanced chemiluminescence was conducted using ECL Western blotting detection reagents. Densitometric analysis of band intensity was carried out using the Luminescent Image Analysis System (LAS-3000; FUJI Film, Tokyo, Japan) equipped with Multi Gauge 3.0 software. The intensity of the bands was measured and the expression of proteins including the differences between the control and experimental groups were analyzed.

Masson's trichrome staining of corpus cavernosum

The skin-free middle portions of the penile shafts were fixed overnight in 10% formalin and washed and stored in 70% alcohol at 40°C until processed for paraffin-embedded tissue sectioning. After the fixed cavernosal tissue was embedded in paraffin wax, 5-μm cross-sections of the cavernosal tissue was obtained for Masson trichrome staining to evaluate muscle fibrosis. For quantitative image analysis, stained sections were photographed using a model BX50 microscope (Olympus, Tokyo, Japan). Saved images were analyzed using Photoshop CS6 (Adobe Systems Incorporated, San Jose, CA, USA). Red and blue pixel numbers of the corpus cavernosum were distinguished and analyzed for smooth muscle (stained in red) and collagen (stained in blue) and the cavernous smooth muscle-to-collagen fiber ratio was calculated using Panoramic viewer 1.14 software (3DHISTECH Ltd., Budapest, Hungary). The ratio was evaluated three to four times for each specimen, and is presented as the mean±standard deviation (SD).

Statistical analysis

All data are presented as the mean±SD. For comparison of the four groups, analysis of variance test was used. If the results of the analysis of variance test were significant, Bonferroni multiple comparison's test was used. All calculations were performed using SPSS statistical software (SPSS,

Chicago, IL, USA). Differences of P <0.05 were considered statistically significant.

RESULTS

Measurements of body weight and blood glucose level

Body weight and blood glucose level of the rats at the beginning of administration of UU peptide and during the course of administration are shown in Table-1. At 8 weeks, body weight increase in all DM groups was significantly lower than that of the control group (P <0.05). Furthermore, all DM+UU groups had significant higher weight gain than that of the DM group (P <0.05). Eight weeks after UU peptide administration, the blood glucose levels in DM+UU 500 group were significantly lower than in that of the DM group (P <0.05). The increasing blood glucose level in all DM+UU groups were significantly lower than in that of the DM group at 8 weeks of the experiment.

Erectile function assessment

To assess erectile function, ICP and ICP/MAP ratio in response to cavernous nerve electrostimulation were measured after 8 weeks administration of UU peptide. Figure-2 graphically depicts the ICP/MAP ratios. No significant differences in MAP were observed between the groups. The ICP/MAP ratio in the control group (0.79±0.16) was significantly higher compared with the DM and DM+UU100 groups (P <0.05). The DM control group had a significantly decreased ICP/MAP ratio (0.23±0.09) compared with the other groups. The ICP/MAP ratio of the DM+UU 100 (0.47±0.08) and DM+UU 500 (0.71±0.1) group was both significantly higher compared with the DM group (P <0.05). Moreover, there were no statistically significant differences in the ICP/MAP ratio between the control group and the DM+UU 500 group (P=0.453).

NO level

NO concentrations in serum are summarized in Figure-3. Compared with the control group, the DM group had significantly decreased NO level (26.4±2.1 versus 18.4±1.2, P <0.05). At the same time, the DM+UU500 group had significantly increased NO level compared with the DM control group (25.1±1.6 versus 18.4±1.2, P <0.05). However, DM+UU100 group did not show significant difference of NO compared with the DM group. Furthermore, there is no significant difference between control group and DM+UU500 group (P=0.573).

Table 1 - Changes in Body Weight and Serum Glucose Levels in the Experimental Groups

	Pre-DM	4 weeks after DM	8 weeks after DM
Body weight (g)			
Control (n = 10)	314 ± 8	370 ± 9	552 ± 20
DM control (n = 10)	328 ± 11	353 ± 20	424 ± 20
DM+UU100 (n = 10)	314 ± 5	351 ± 22	471 ± 14*,#
DM+UU 500 (n = 10)	318 ± 9	349 ± 20	477 ± 13*,#
Serum glucose (mg/dL)			
Control (n = 10)	123.8 ± 3.3	120.8 ± 1.5	121.3 ± 2.9
DM control (n = 10)	120.8 ± 11.8	395 ± 8	497.5 ± 12.1
DM+UU100 (n = 10)	126.5 ± 1.3	381 ± 16.4*	457 ± 21.9*,#
DM+UU 500 (n = 10)	124.1 ± 6.2	324 ± 1.2*,#	386.4 ± 159.8*,#

DM, diabetes group; DM + UU, diabetes group treated with UU.
*Significant difference (P < 0.05) compared with the control group.
#Significant difference (P <0.05) compared with the DM group.

Figure 2 - (A) Measurement of ICP under cavernous nerve stimulation at 10V after 8 weeks administration of UU peptide. The black line represents electrical stimulation interval of 50s. (B) The ratio of ICP/MAP during electrical stimulation were calculated for each group *p <0.05.

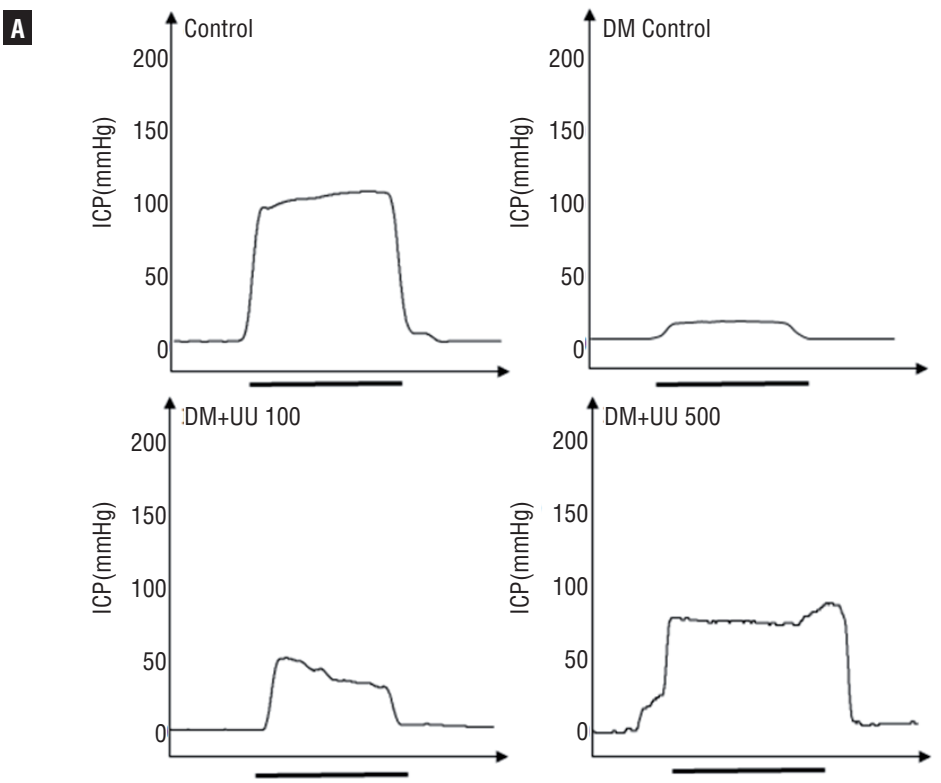
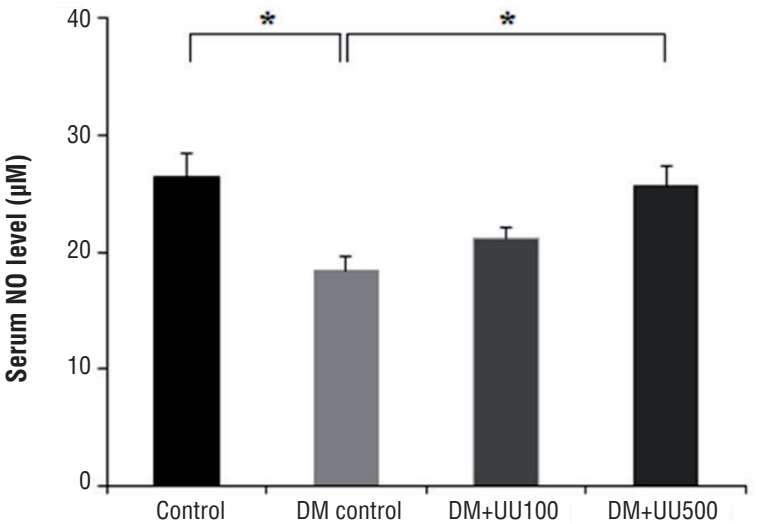


Figure 3 - Serum concentration of NO at 8 weeks after administration of UU peptide *P <0.05.



Level of cGMP in the corpus cavernosum

The corpus cavernosum concentration of cGMP (pmoL/g) in the control, DM control, DM+UU100 and DM+UU500 was 41.0±2.1, 24.9±1.2, 33.5±1.0 and 38.5±1.6, respectively (Figure-4). The concentration of cGMP in the corpus cavernosum was significantly increased in the DM+UU500 group compared with DM control group (P <0.05). However, there was no significant difference between the control and DM+UU500 group (P=0.421).

eNOS and nNOS protein expression

Densitometric analysis quantified the expression of eNOS and nNOS (Figure-5). Decreased expressions of eNOS and nNOS were observed in the DM control group compared to the control group (P <0.05). Increased expression of the eNOS and nNOS were evident in the DM+UU100 and DM+UU500 groups compared with DM control group (P <0.05). However, the densitometric results of rats administered with 100mg did not reach the level of the control group.

Smooth muscle – to - collagen ratio in the corpus cavernosum tissue

The content of collagen tissue and smooth muscle in the penile corpus cavernosum tissue was observed by Masson's trichrome staining (Figure-6). In the DM control group, cavernous tissue revealed a much higher density of collagen tissue compared with the control group. These results suggested that DM induces the deposition of collagen in corpus cavernosum with smooth muscle atrophy. The smooth muscle-to-collagen ratio in the DM+UU500 group was higher than in the DM group (14.8±0.5 versus 6.5±1.0, P <0.05). However, there was no significant difference in the ratios between the DM control group and DM+UU100 group. Additionally, the ratio in the DM+UU500 group was lower than in the control group (P <0.05).

DISCUSSION

The main findings of this present study demonstrate that the oral administration of UU peptide by high temperature/pressure and ultra-wave assisted lysis improves erectile responses in STZ-induced diabetic rats through the elevation of the NO/cGMP signaling activity and increased expression and activity of cavernosal eNOS and nNOS in penile tissues. Improvement of erectile function was also demonstrated by functional and histological approaches after oral administration of UU peptide. To our knowledge, this is the first

Figure 4 - Cyclic guanosine monophosphate (cGMP) concentration in the corpus cavernosum at 8 weeks after administration of UU peptide *P <0.05.

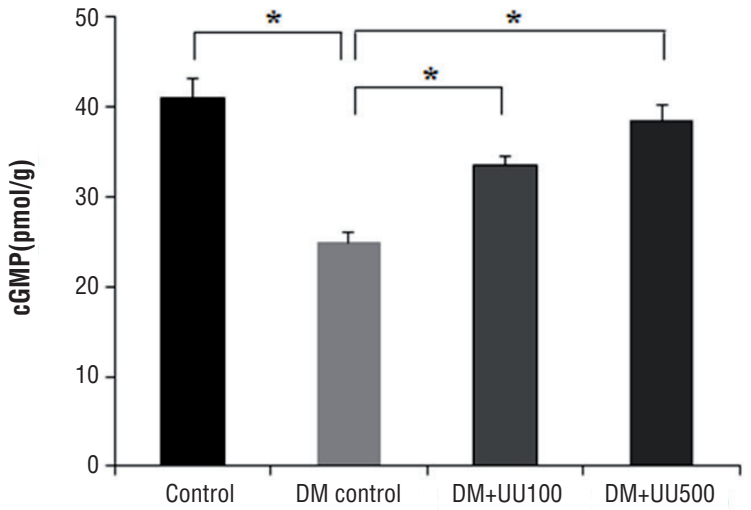


Figure 5 - Western blot analysis of eNOS and nNOS in corpus carvernosum at 8 weeks-control, DM control, UU+100, UU+500 (A), Densinometric analysis to β-actin of eNOS and nNOS (B) *P <0.05.

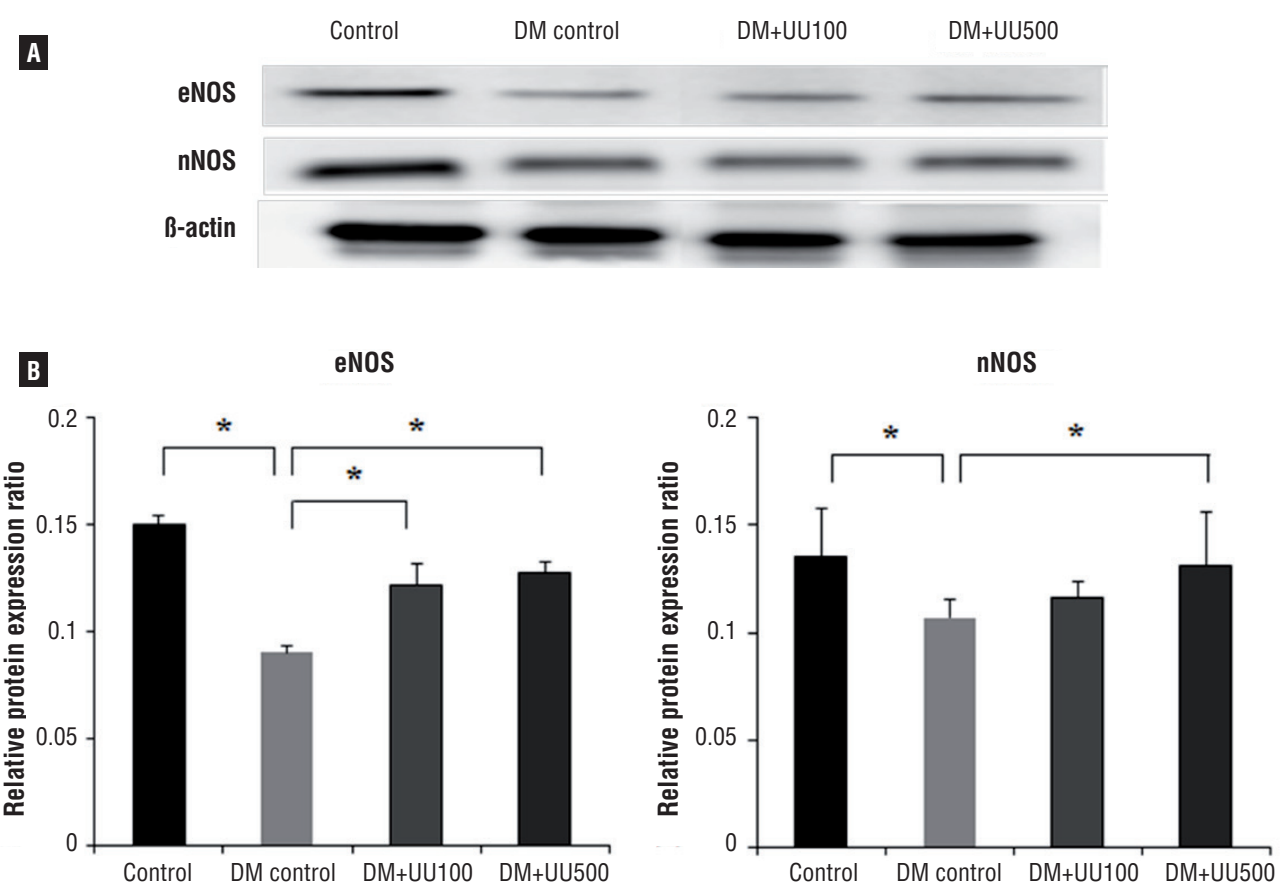
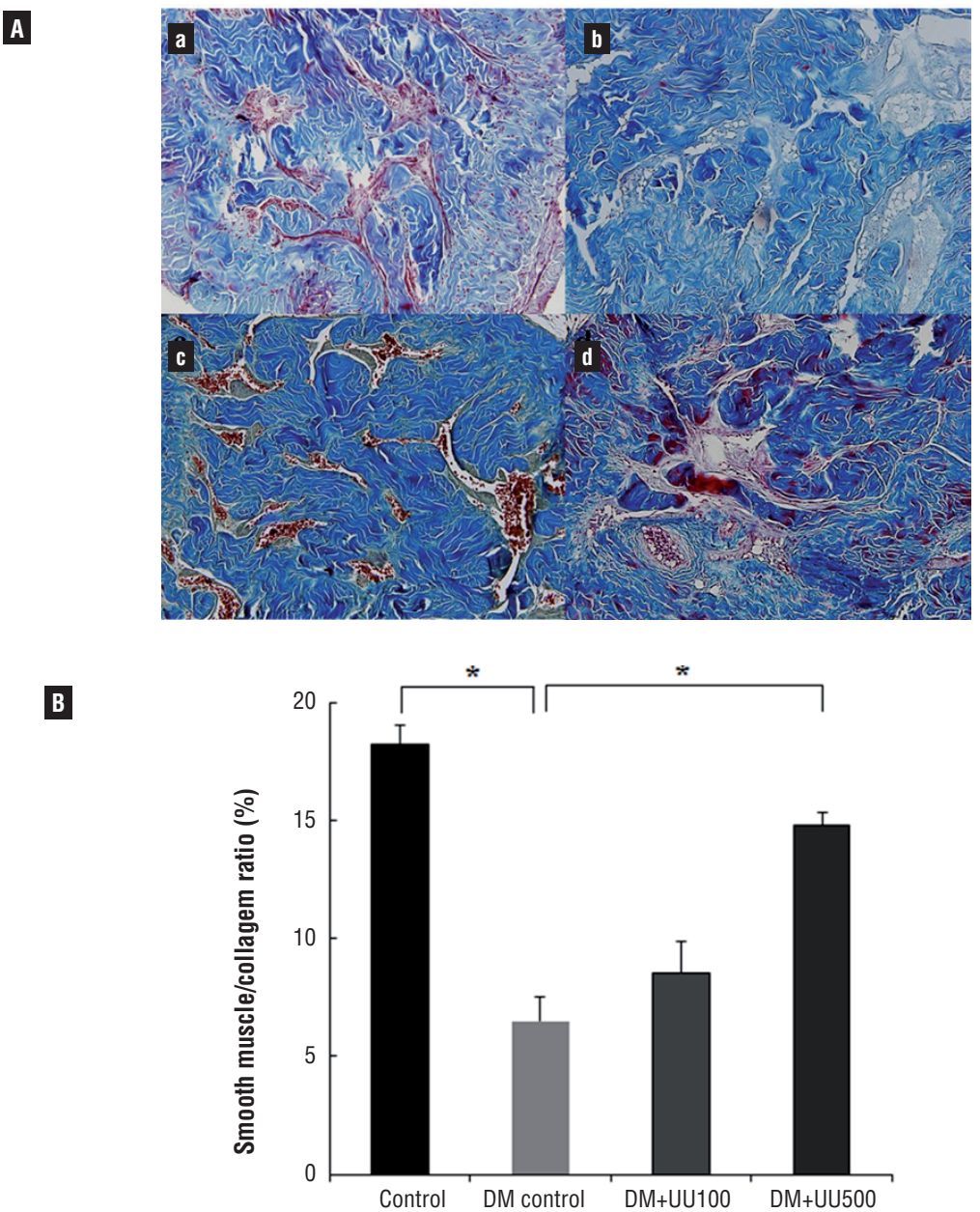


Figure 6 - (A) The Masson's trichrome staining of corpus cavernosum in control (a), DM control (b), DM+UU100 (c) and DM+UU500 (d) groups after 8 weeks. Smooth muscle was stained red color and collagen fibers were stained purple-blue color. (B) Quantitative analysis results of smooth muscle/collagen ratio in each group *P <0.05.



demonstration that oral administration of UU peptide can enhance erectile ability in vivo.

Normal penile erection is a hemodynamic event that is dependent on penile smooth muscle relaxation mediated by NO/cGMP signaling, parasympathetic neurotransmission and other regulatory factors (12). Corpus cavernosum smooth muscle relaxation begins and is retained by an increased NO production through the activation of eNOS and nNOS by sexual stimulation (13, 14). NO stimulates soluble guanylate cyclase, subsequently increasing cGMP levels in smooth muscle (15). Relaxation of smooth muscle, increased penile arterial blood flow and restricted venous

outflow generate penile erection. Dysfunction of the NO/cGMP pathway is widely regarded as one of the causes of erectile dysfunction (16). DM may lead to ED by a number of pathophysiological events including neuropathy, endothelial dysfunction, hormonal change and cavernosum smooth muscle structural/functional changes (17, 18).

Although the exact mechanisms of endothelial dysfunction in the penis are not fully understood, hyperglycemia is recognized as the primary cause in the pathogenesis of the endothelial dysfunction of the vasculature in DM (19). Therefore, it is important to control hyperglycemia to prevent and treat ED associated with DM. Romeo et al. (20) reported that glycemic control is an independent factor in the ED; a severe glycemic control group displayed a significant lower incidence of ED compared with a conventional treatment group. However, retaining a slightly higher glucose level than the normal glucose level is recommended according to the guidelines of the DM treatment (21, 22). Glycemic control with an additional therapy is a more ideal therapeutic strategy for the management of ED associated DM. Presently, UU showed a significant hypoglycemic effect in STZ-induced hyperglycemic rats. This result may be caused by glycosaminoglycan, which possesses hypoglycemic activity associated with improved antioxidant ability of DM mice, increasing superoxide dismutase activity and decreasing malondialdehyde, recovering liver and pancreatic tissue, enhancing capacity of the glucose tolerance and insulin sensitivity (10). In our study, we also confirmed that serum glucose level in the DM+UU groups were significantly lower than in that of the DM group (Table-1). Although serum glucose level in diabetic rats receiving UU peptide groups was lower than in that of the DM group, the higher glucose level compared with normal group should be managed by another treatment modality. In addition, Cho et al. (23) reported that well-controlled glucose level of diabetic rats affects recovery from ED associated with DM, and that strict glucose control can influence recovery from ED to almost normal status. Therefore, oral administration of UU peptide added to standard glycemic control treatment may be beneficial for treating ED associated with DM patients.

In the current study, ICP/MAP ratios were checked in response to electrostimulation to examine erectile function. ICP and ICP/MAP ratios were significantly increased in the DM+UU groups, suggesting that UU peptide likely recovers the erectile response in the ED associated DM rats. Furthermore, 500mg UU peptide administration represented more effective than 100mg UU peptide administration in the recovery of ICP.

In a recent in vitro study of UU peptide related to the erectile function (11), high temperature (125.86^{o}C) and pressure (1.13kgf/cm^{2}) UU lysate treated endothelial cells displayed up to 1.5-fold increased NO activity. Furthermore, smooth muscle cells treated with UU lysis after ultrasonic assisted breakdown of high temperature/pressure displayed increased cGMP activity and decreased Ca^{2+}activity. To confirm the bioactive peptide related the erectile function properties from UU lysate, chromatographic methods were used and the amino acid sequence associated with potent activity confirmed. In vitro, amino acid treated cells displayed a dose-dependent increase in NO and cGMP, and dose-dependent decrease in activities associated with Ca^{2+}. The authors concluded that acquired active peptide from high temperature/pressure and ultrasonication assisted UU peptide improves erectile function as a response to the observed increased and decreased activities. With this in vitro background, we prepared UU peptide to confirm the improvement of erectile dysfunction in vivo. Oral UU peptide supplementation increased the NO levels in the serum in a dose-dependent manner (Figure-3). Furthermore, cGMP levels in the corpus cavernosum revealed similar results (Figure-4). It has been reported that systemic NO level correlated with NO levels in the corpus cavernosum (24). Therefore, the positive effect of erectile function by oral UU peptide supplementation may be due to relaxation mediated by NO and cGMP production in the corpus cavernosum.

The different isoforms and subtypes of NOS include neuronal (nNOS), inducible (iNOS) and endothelial (eNOS) (25, 26). NO release in the penile vascular and non-adrenergic non-cholinergic system is regulated by eNOS and nNOS (25). eNOS is mainly found in the endothelium of the vessels of

the penis and is also present in cavernosum smooth muscle (3, 27). nNOS has been proposed to be important, compared with the other NOS isoforms, in promoting relaxation of the corpus cavernosum and inducing increased blood flow, which facilitates penile erection (28). eNOS and nNOS mediated cavernosum smooth muscle relaxation is impaired in a rat model of diabetes (29). Presently, diminished penile expression and activity of eNOS and nNOS in corpus cavernosum tissues were markedly increased after administration of UU peptide to diabetic ED rats, with NO production being increased (Figure-5). The mechanism of positive effects is unclear, but is likely due to the function of the another specific peptide from UU. These findings might mean that UU can modulate the activity or the expression of enzymes like nNOS and eNOS that are abundant in penile tissues.

We examined penile cavernosal structure by Masson's trichrome staining. Smooth muscle of the corpus cavernosum plays an important role in the erection and relaxation of the penis. Fibrosis and loss of corpus cavernosum smooth muscle have been observed in patients with ED and the percentage of corpus cavernosum smooth muscle declines with age (30, 31). The mean weight of cavernosal tissue strips harvested from diabetic rats is reportedly less than that from control rats (6). This finding is associated with the loss of corporal SM. Presently, the DM control group showed a decreased smooth muscle-to-collagen ratio compared with normal control group. Oral UU peptide supplementation restored the ratio in the ED induced by DM rats. Since UU peptide increasing NO production (11) and NO enhances angiogenesis and promotes release of other angiogenic growth factors (32), the increased NO level after oral UU peptide supplementation might lead to the development of angiogenesis in corpus cavernosum tissue. This might be the mechanism of the improved smooth muscle-to-collagen ratio of the corpus cavernosum.

The main limitation of this study is the focus on the effect of UU peptide in endothelial dysfunction. Other mechanisms involved in ED associated with DM, such as diabetic neuropathy, were not examined. Finally, the STZ-induced diabetic rat model mimics type 1DM. Further studies should investigate the role of UU peptide administration in type 2DM, which is the predominant form of DM.

Our results suggest that UU peptide leads to a significant reduction in serum glucose levels in diabetic rats and the mechanism underlying the therapeutic effects of UU peptide involves the NO/cGMP signaling pathways. UU peptide may be potentially valuable in the natural rejuvenation of diminished erectile function. While future clinical trials are needed to determine the efficacy and safety of UU peptide for clinical use, our results suggest that UU peptide is a viable adjuvant therapeutic option to current treatment for ED.

CONCLUSIONS

The study is the first to suggest that the peptide extracted from Urechis unicinctus, may have a potency to improve the erectile function in streptozotocin-induced diabetic rat erectile dysfunction model. Treatment with UU peptide improves maximal intracavernosal pressure by increasing NO and cGMP activity. Furthermore, treatment with UU peptide benefited eNOS and nNOS expression and smooth muscle distribution in the corpus cavernosum. Further studies are necessary to identify the active component in the UU peptide for ED.

ABBREVIATIONS

ED = erectile dysfunction
DM = diabetes mellitus
NO = nitric oxide
eNOS = endothelial nitric oxide synthase
nNOS = neuronal nitric oxide synthase
PDE5 = type-5 phosphodiesterase
UU = Urechis unicinctus
cGMP = cyclic guanosine monophosphate
ICP = intravavernosal pressure
MAP = mean arterial pressure
SD = standard deviation

ACKNOWLEDGMENTS

This research was supported by a grant from Marine Bioprocess Research Center of the

Marine Biotechnology Program funded by the Ministry of Oceans and Fisheries, R&D/2004-6002.

CONFLICT OF INTEREST

None declared.

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CHALLENGING CLINICAL CASES

Vol. 42 (4): 838-841, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0347

Metaplastic Conditions in The Bladder in Patient With Epidermolysis Bullosa

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ABSTRACT

Epidermolysis bullosa is a rare inherited muco-cutaneous disorder that sometimes presents with genitourinary involvement. Herein we report the case of an 11-year-old girl with a history of junctional epidermolysis bullosa who was admitted with urological symptoms. On cystoscopy, suspected bullous bladder lesions were observed. Mesonephroid, intestinal and squamous metaplasia is reported here for the first time.

ARTICLE INFO

Key words:
Urinary Bladder; Epidermolysis Bullosa; Metaplasia

Int Braz J Urol. 2016; 42: 838-41

Submitted for publication:
August 15, 2015

Accepted after revision:
April 24, 2016

INTRODUCTION

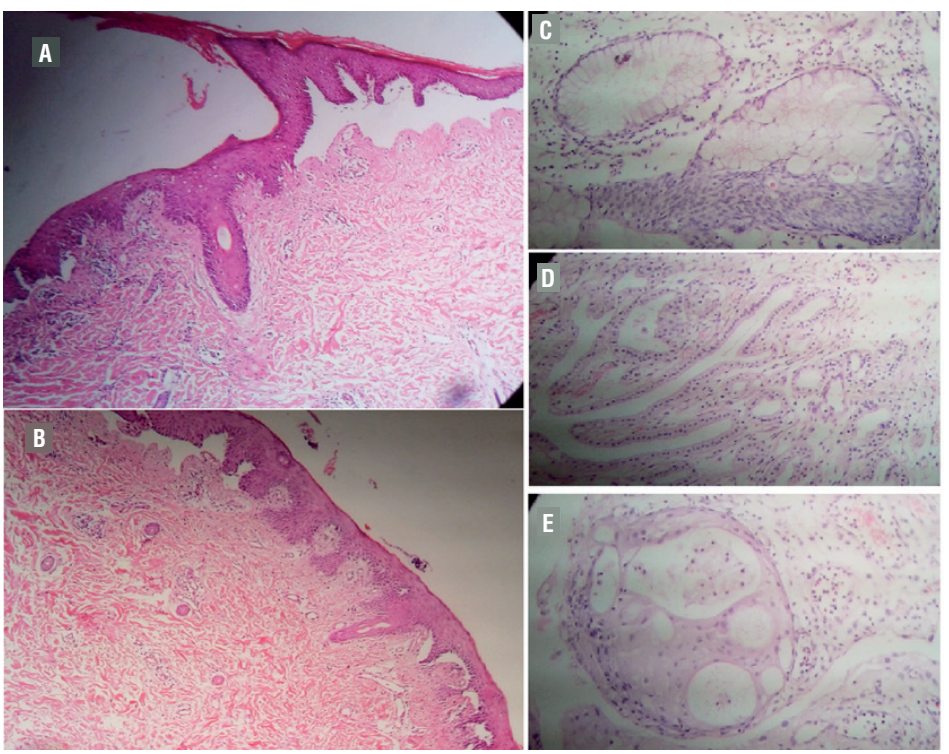
Epidermolysis bullosa (EB) is a rare heterogeneous dermatological disorder. In spite of the increasing rates of recent publications of patients presenting with urological complications EB has rarely been reported in the literature (1).

We were unable to find any reports of accompanying mesonephroid, intestinal or squamous metaplasia of the bladder in junctional EB in the English literature. Here we report the first case of an 11-year-old girl with the diagnosis of junctional EB with accompanying mesonephroid, intestinal and squamous metaplasia in the bladder.

CASE REPORT

An 11-year-old female patient, who was first diagnosed with junctional EB at 18 months of age, was admitted to our institution with hematuria and irritative voiding symptoms. She was under the care of dermatology clinic. Her physical examination revealed that her skin lesions were in remission. Her skin biyopsy image is shown in Figures 1A and B. However, in her urological examination, distal urethral stenosis was detected. There was microscopic hematuria. Urinary culture was sterile. Blood cell count and creatinine levels were within the normal ranges. In uroflowmetric examination there was normal outflow rate and

Figure 1 - Epidermolysis bullosa patient's skin biopsy (A, B) and Epidermolysis bullosa patient's bladder biopsy. The bladder epithelium exhibits marked metaplastic changes (C, D, and E). (A, B) There are marked subepidermal blisters of noninflammatory type.
The epidermis shows focal spongiosis. Mild dermal fibrosis and sparse inflammatory infiltrate in the dermis is observed. Hematoxylin and eosin stain, original magnification x100; (C) Intestinal metaplasia of the urinary bladder. A complex glandular structure lined by mucin-producing columnar cells. Hematoxylin and eosin stain, original magnification x 400; (D) Mesonephroid metaplasia of the urinary bladder. A complex clustering of microcystic and tubular formations lined by cuboidal to flattened cells in edematous stroma. Hematoxylin and eosin stain, original magnification x 400; (E) Squamous metaplasia of the urinary bladder. Note characteristics of squamous nests. Hematoxylin and eosin stain, original magnification x 400.



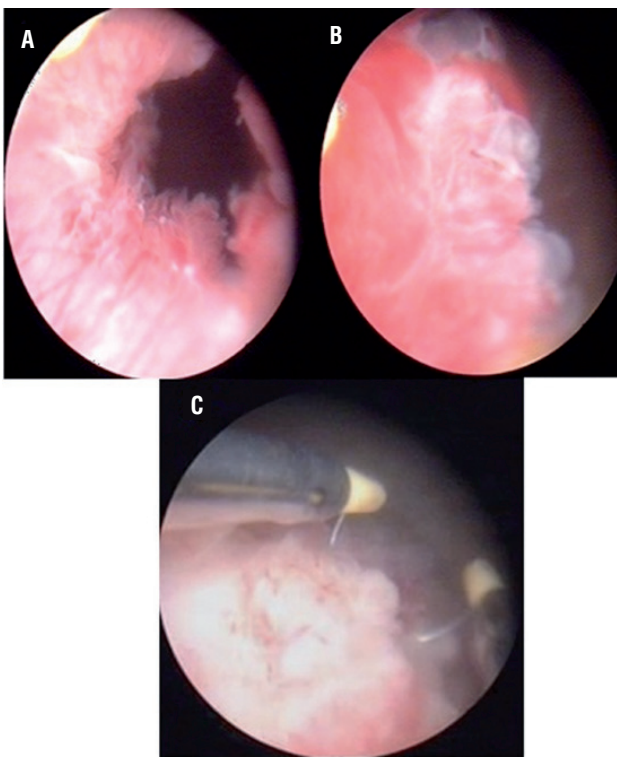
no post voiding residue. Bladder wall thickness was shown to be increased (7mm) on ultrasound examination. Van Buren dilatation was performed for female distal urethra. Cystoscopic evaluation showed several suspicious lesions (such as papilla--bullosa) around the bladder neck and right bladder wall. A complete transurethral resection was performed, as shown in Figure-2.

Histopathological examination reported mesonephroid, intestinal and squamous metaplasia in the bladder, as shown in Figures 1 C, D, and E. After the operation, the patient's complaints were resolved. Patient was followed-up for 2 years because of the bladder lesions by cystoscopy. After 2 years, cystoscopy follow-up ended and patient is still under follow-up using ultrasound and urine analysis. She didn't have any urinary complains up to present. No recurrent lesions were detected as metaplasia.

DISCUSSION

Epidermolysis Bullosa is a rare and severe disorder characterized by blistering lesions of the skin after trauma. There are four major type of inherited epidermolysis bullosa: EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB) and Kindler syndrome. The level of separation occurs within the epidermis in Epidermolysis bullosa simplex (EBS), in the lamina lucida in junctional EB (JEB) and under the lamina densa in dystrophic EB (DEB). The cleavage plane in Kindler Syndrome (KS) can occur within the basal keratinocytes, at the level of the lamina lucida or below the lamina densa (2). Kindler syndrome (KS) is an autosomal recessive skin disorder characterized by traumatic acral blister formation in infancy and early childhood, progressive poikiloderma, cutaneous atrophy and increased

Figure 2 - Cystoscopic images of lesions at bladder neck and right bladder wall.



photosensitivity. This rare genodermatosis represents combination of clinic features of hereditary epidermolysis bullosa and poikiloderma congenitale (3). The first case report of genitourinary tract involvement in EB was published in 1973 by Kretkowski (4).

Our patient, who had JEB (generalized intermediate) was diagnosed based on the clinical and histopathological (with immunofluorescence) findings. After the first year of life, her non-inflammatory blistering skin lesions in areas of the body exposed to mechanical trauma went into remission for several years. However, many years later she was admitted to our clinic with dysuria and hematuria. After examination, distal urethral stenosis and a thickened bladder wall were detected by ultrasound. The clinical spectrum in the literature varies from meatal stenosis leading to upper urinary tract dilatation to serious stenosis due to bullous lesions and scarring at the ureterovesical junction requiring permanent urinary diversion (1). In our case Van Buren dilatation was preferred for meatal stenosis due to female genitalia.

Mesonephroid metaplasia is an unusual lesion confined to the lamina propria of the lower urinary tract. It is defined by a characteristic histologic picture of tubular structures, formed by a single layer of cuboidal cells, surrounded by a thick basement membrane. In large published series of cases of mesonephroid metaplasia, the lesions were in most cases associated with chronic infection, stone disease or repeat surgical intervention in the genitourinary tract. Characteristically, the epithelial cells of nephrogenic adenomas show clear cell cytoplasm with vacuoles and uniform nuclei without mitoses in the benign form. The malignant form is characterized by mitotic figures and/or invasions into the muscle (5).

Intestinal metaplasia usually occurs with long standing inflammation/irritation, such as from indwelling catheters, calculi, neurogenic bladder and bladder exstrophy and it may be focal or diffuse, but it is usually only seen microscopically. Intestinal metaplasia often co-exists with adenocarcinoma of the bladder, and some authors have proposed that intestinal metaplasia may be a precursor lesion (6).

Squamous metaplasia is clinically significant and may be associated with the development of bladder cancer, bladder contracture or obstructive uropathy. According to different studies, the risk of developing squamous cell carcinoma in patients with keratinizing squamous metaplasia is estimated to be 21 to 42% (7).

In our case there was a predisposing factor, namely chronic blistering. In our opinion mesonephroid, intestinal and squamous metaplasia were the result of inflammation in the lamina lucida in junctional EB. In addition to JEB, urological complications have also been reported such as recessive DEB, Kindler Syndrome and EBS with muscular dystrophy (1).

Optimal patient management requires a multidisciplinary approach, and revolves around the protection of susceptible tissues against trauma, use of sophisticated wound care dressings, aggressive nutritional support, and early medical or surgical interventions to correct whenever possible the extracutaneous complications. Prognosis varies considerably and is based on both EB subtype and the overall health of the patient (1). It is

already well known that patients affected by JEB have a susceptibility to urogenital involvement and if not treated they are prone to cancer development (2). However, we were unable to find any report of accompanying mesonephroid, intestinal and squamous metaplasia of the bladder in junctional EB in the English literature. This is the first report in a patient with junctional EB with these lesions. These patients should be followed regularly due to possible devastating complications. In these patients the risk of malignant transformation of bladder lesions should be kept in mind.

CONFLICT OF INTEREST

None declared.

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Vol. 42 (4): 842-844, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0549

Retrocaval ureter and contra lateral renal agenesis – a case report and review of literature

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ABSTRACT

Associated congenital anomalies are seen in 21% of retrocaval ureter patients; among them, associated contralateral renal agenesis is a very rare entity. We report one such case of right circumcaval ureter with left renal agenesis, diagnosed after febrile UTI. Surgical correction with uretero-ureterostomy was successful. In literature very few such cases are reported and only one case with renal failure was reported. Unilateral renal agenesis cases complicated by associated such anomalies need definitive management and lifelong clinical monitoring to diagnose and prevent chronic kidney disease.

ARTICLE INFO

Key words:
Retrocaval Ureter; Hereditary renal agenesis [Supplementary Concept]

Int Braz J Urol. 2016; 42: 842-4

Submitted for publication:
September 26, 2015

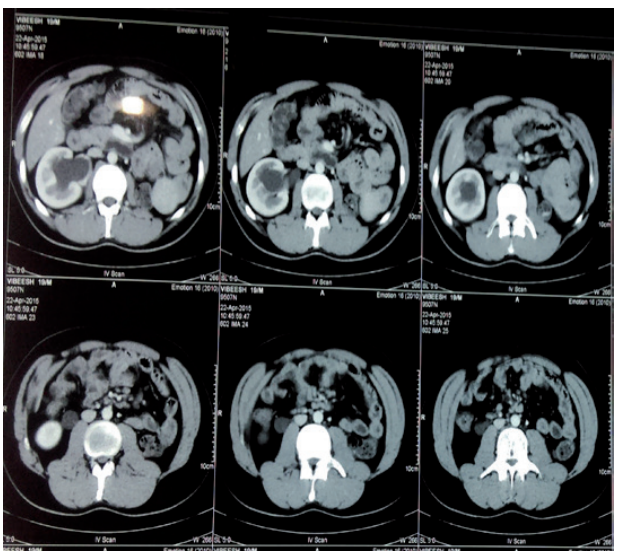
Accepted after revision:
April 05, 2016

INTRODUCTION

Retrocaval ureter, a misnomer, correct denomination circumcaval ureter, was first reported by Hochstetter in 1893 (1). Even though its incidence is about 1 in 1100 according to autopsy series, around 200 cases are reported in the literature. Circumcaval ureter associated with contralateral renal agenesis is a very rare presentation, very few cases reported in the literature. These cases need surgical correction and close clinical follow-up.

Case HTistory: 19 year-old male patient presented with fever with chills for 1 day. Patient had an unremarkable examination except for right renal angle tenderness. Urinalysis showed 8-10 piuria cells and urine culture was negative for any bacteria. His renal function test was normal (Blood urea-18 and serum creatinine-0.9). Ultrasonography revealed non visualised left kidney in renal fossa with normal sized right kidney with hydronephrosis with antero-posterior diameter at pelvis of 20mm, with internal echoes and proximal hydroureter for about 6cm from PUJ. Computed tomography shown absent left kidney and normal sized right kidney with hydronephrosis and dilated ureter up to L3 vertebra where the ureter was seen passing behind the inferior vena cava with features of pyelonephritis such as striated nephrogram (Figure-1). Intravenous urography showed Fish hook or 'S'

Figure 1 - CT scan image, shows absent left kidney and right hydronephrosis and hydroureter up to L3 vertebra at which level it passes behind IVC.



shaped deformity (Figure-2). Patient was diagnosed as right solitary functional kidney with retrocaval ureter with pyelonephritis. Patient was treated for pyelonephritis and he underwent right uretero-ureterostomy over 6Fr/26cm double J stent; retrocaval portion of the ureter was atretic and was excised (Figure-3). Patient had an uneventful recovery. On follow-up patient is doing well.

Figure 2 - IVP 50 min post void image, shows Fish hook or 'S' shaped deformity of right ureter with absent uptake/excretion of dye on left side.

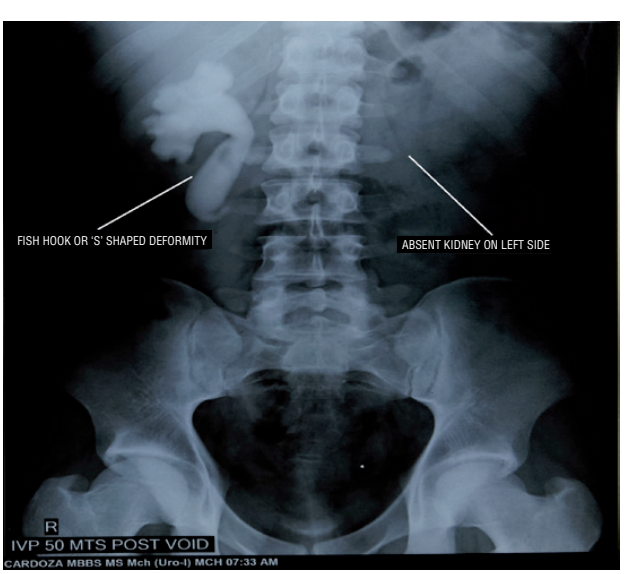
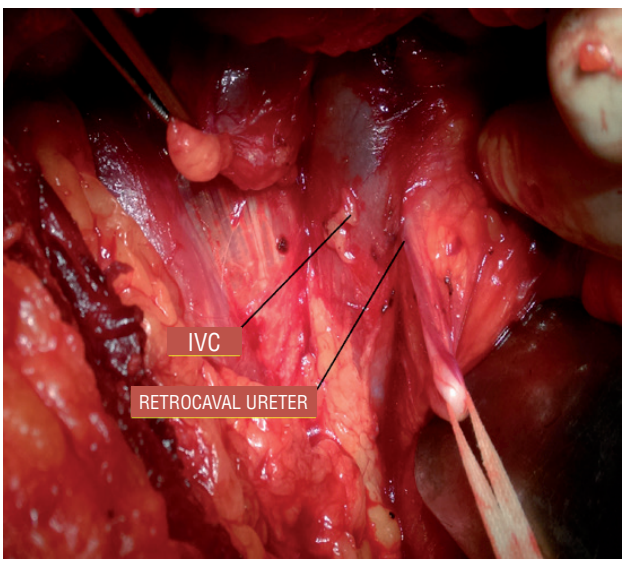


Figure 3 - Intra operative picture showing circumcaval ureter.



DISCUSSION

Retrocaval ureter is a rare congenital anomaly, which results from abnormality in the development of the inferior vena cava (IVC). Normally the fetal veins such as the vitelline vein, subcardinal vein and sacrocardinal vein undergo sequential development, anastomosis and regression to form IVC. Vitelline vein develops into pre renal segment of IVC, subcardinal vein forms renal segment of IVC and sacrocardinal vein forms post renal segment of IVC. Pre ureteral vena cava or retrocaval ureter develops when the renal segment of IVC develops from the abnormal persistence of right posterior cardinal vein (which fails to atrophy during development), which lies ventral to ureter.

These patients usually present in their third or fourth decade of life (2). They may be asymptomatic or may present with urinary tract infection, hematuria, flank pain, calculus disease or renal failure. This anomaly is diagnosed on IVU and confirmed by CT scan or MRI scan.

According to Bateson and Atkinson classification, retrocaval ureter is classified into two types. Type I or low loop type, accounts for 90% of the cases: here ureter crosses behind the IVC at the level of L3 vertebra, and has a 'S' or Fish

hook shaped deformity of the ureter on IVP, has marked hydronephrosis in up to 50% of the patients. In type II or high loop type, less common, accounts for 10% of the cases. Here renal pelvis and upper ureter lies horizontally, the retrocaval segment of the ureter is at the same level of the renal pelvis. On retrograde pyelogram the involved ureter looks like 'Sickle' shaped, and patient may have mild hydronephrosis. Main causes for hydronephrosis in these cases are because of stenosis, adhesion of the retrocaval segment and torsion (3).

Associated congenital anomalies are seen in 21% of retrocaval ureter patients which include horseshoe kidney, ectopic or malrotated opposite kidney, contra lateral renal agenesis, hypospadias, ureteropelvic junction obstruction (UPJO), congenital lack of vas deferens, agenesis of uterus and vagina, yolk sac tumour, myelomeningocele, variations of inferior vena cava, oesophageal atresia, cardiovascular anomalies such as situs inversus, brachial arch syndrome, Turner syndrome, and imperforate anus (4). Other disorders that have been reported to be associated with retrocaval ureter are renovascular hypertension, retroperitoneal fibrosis and carcinoma of the ureter. These patients usually need surgical correction such as ureteropyelostomy or uretero-ureterostomy if symptomatic.

In our case, patient presented with right pyelonephritis, he had right retrocaval ureter with contra lateral renal agenesis. Based on the investigation findings, he had type I retrocaval ureter. Patient underwent right uretero-ureterostomy over DJ stent after excising the atresic retrocaval segment. Patient had uneventful recovery.

There are two such cases reported in the literature, one with renal failure, the other with associated agenesis of uterus and vagina and imperforate anus. 10-20% of patients with URA (unilateral renal agenesis) may need dialysis by the age of 30 years if they are associated with other genitourinary anomalies such as PUV (posterior urethral valve), UPJO, retrocaval ureter etc. (5). If a patient with URA has associated retrocaval ureter, then the patient is even more prone for renal failure from contributing complications such as obstruction, pyelonephritis etc.

CONCLUSIONS

Patients with retrocaval ureter are looked for other associated congenital genitourinary and other anomalies carefully. Whenever associated contralateral renal agenesis is noted, they need a prompt surgical correction for retrocaval ureter and lifelong clinical monitoring and follow-up to prevent and early diagnose acute or chronic renal failure.

CONFLICT OF INTEREST

None declared.

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RADIOLOGY PAGE

Vol. 42 (4): 845-847, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0017

Rupture of ectopic renal arterial pseudoaneurysm after percutaneous nephrolithotomy

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ABSTRACT

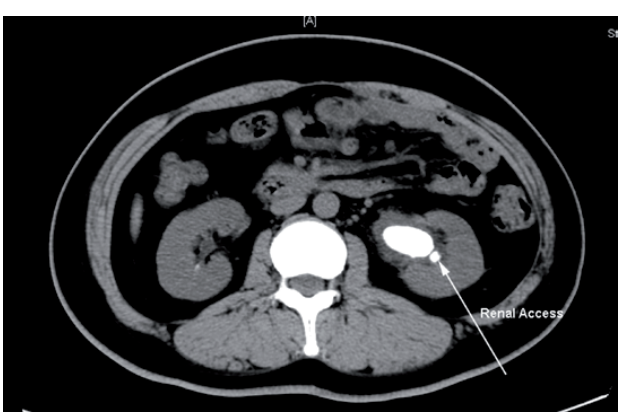
A 35-year-old female patient presented with swelling pain at left waist for 1 month. Left renal pelvis stones were found and standard percutaneous nephrolithotomy was successfully performed. Two weeks later, the patient suddenly suffered massive bleeding presented with gross hematuria. Rupture of ectopic renal artery pseudoaneurysm was identified by computed tomography and angiography of the renal artery. Emergency selective angioembolization of one branch of the artery was performed. To our knowledge, this is the first report of ruptured ectopic renal arterial pseudoaneurysm.

DESCRIPTION OF CASE

A 35-year-old female patient presented with back pain for 1 month. Plain computed tomography (CT) scan showed a stone measuring 3.2*1.6cm and a smaller one located in the left renal pelvis (Figure-1).

One experienced surgeon performed standard percutaneous nephrolithotomy. After general anesthesia, percutaneous renal access was obtained under ultrasound with an 18-gauge needle. Tract dilatation was accomplished using balloon dilator of 24F. The stone was fragmented utilizing an ultrasonic lithotripter through a rigid 24F nephroscope. A 20F nephrostomy tube was inserted after the successful completion of the procedure. The nephrostomy tube and urinary catheter were removed 1 week postoperatively. Unfortunately, 2 weeks after operation, the patient suddenly suffered massive bleeding presented with gross hematuria. Her blood hemoglobin decreased to 7.2g/L. CT angiography identified an ectopic renal artery leading to a pseudoaneurysm which appeared to be in the pathway of the access tract (Figure-2). Emergency selective angioembolization of this branch was performed in conjunction with the angiogram confirming rupture and pseudoaneurysm of the ectopic branch artery (Figure-3).

Figure 1 - Left renal stone, measuring 3.2*1.6cm.



Arterial pseudoaneurisms have occurred as consequence of extracorporeal shock wave lithotripsy (1). Gavant et al. firstly described rupture of renal pseudoaneurysm as a complication of percutaneous nephrostomy (2). It was repor-

Figure 2 - One ectopic renal artery was found in CT angiography of the left renal artery, and a branch of this artery was near the renal access.

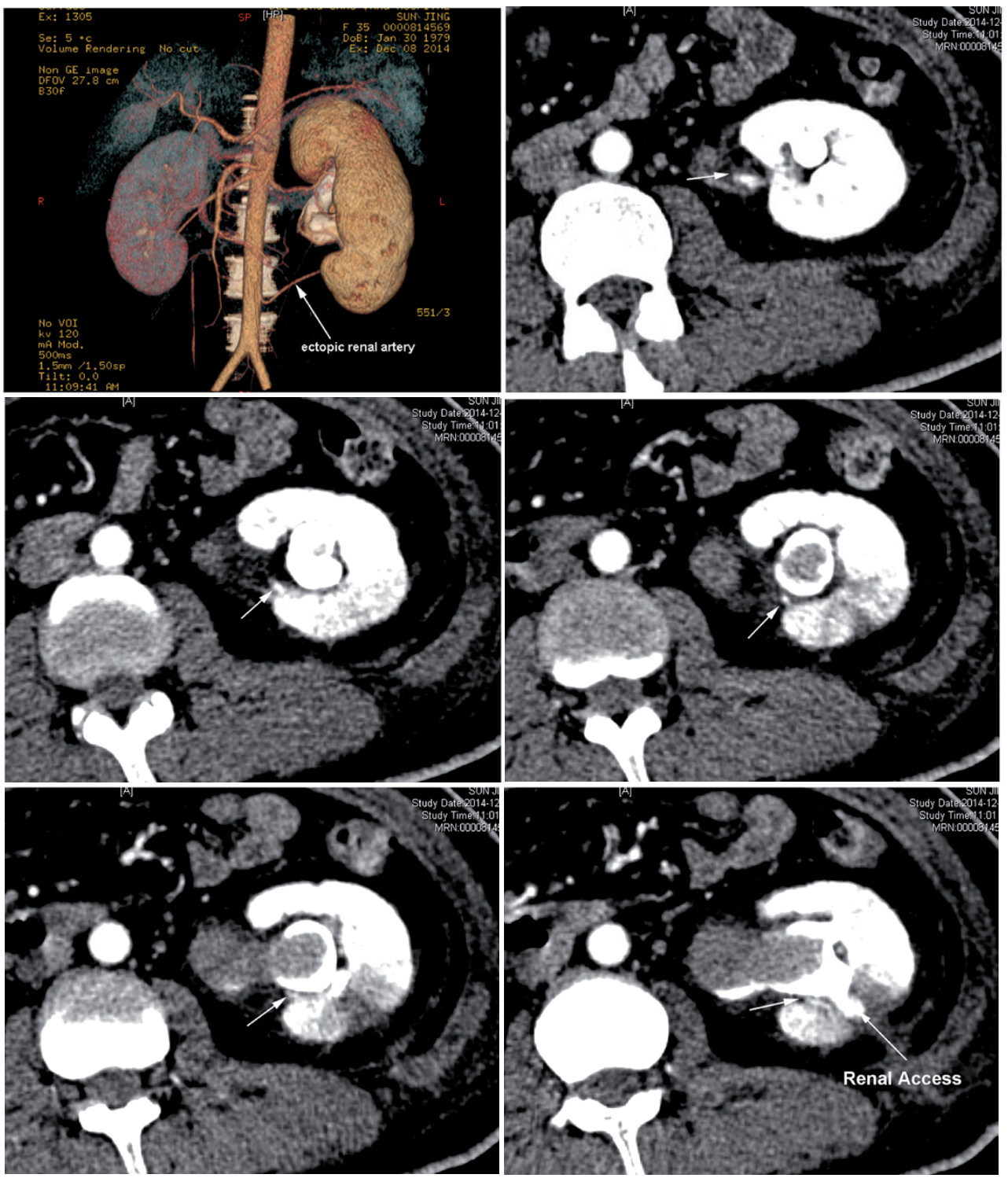
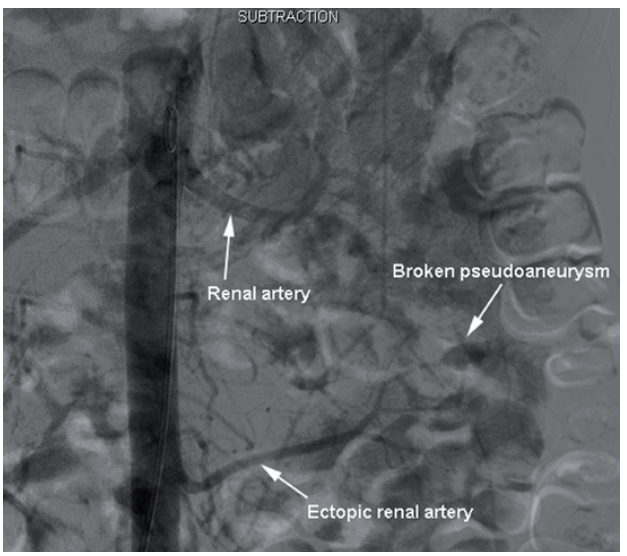


Figure 3 - Rupture of one branch of the ectopic renal artery angiography.



ted that pseudoaneurysm after percutaneous renal surgery was the most common angiographic finding (3). The access route to the stone has a major impact on the incidence of the complication, causing pseudo-aneurisms or arterio--venous fistulae. Because of the trajectory of the access-tract between arterial and venous channels in the upper and mid-pole arterial-venous fistula-formation may occur. This trajectory is different for a subcostal and intercostal approach, hence a different rate of attendant complications (4). However, rupture of ectopic renal arterial pseudoaneurysm is very rare, so much care should be taken for this kind of patient.

CONFLICT OF INTEREST

None declared.

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ARTICLE INFO

Int Braz J Urol. 2016; 42: 845-7

Submitted for publication:
January 11, 2015

Accepted after revision:
February 22, 2016

RADIOLOGY PAGE

Vol. 42 (4): 848-849, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0354

Hydronephrosis caused by a giant ovarian cyst

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CASE

A 52-year-old woman presented with abdominal distension. The laboratory data were as follows: white blood cell count, 7.100/mm^3; hemoglobin, 12.2g/dL; platelet count, 206.000/mm^3; blood urea nitrogen, 16.8mg/dL; serum creatinine, 1.6mg/dL; sodium, 146mEq/L; potassium, 3.2mEq/L; chloride, 94mEq/L; glucose, 110mg/dL; total protein, 8.6g/dL; and albumin, 4.9g/dL. Random urine protein concentration was 100mg/dL. Contrast-enhanced abdominopelvic computed tomography (CT) revealed a 36x21x30cm-sized cystic mass in the abdominopelvic cavity. The mass lesion had displaced adjacent visceral organs. Both kidneys were also displaced by this lesion. Bilateral hydronephrosis was observed, of which degree was more prominent in the right kidney (Figure-1). The serum level of carcinoembryonic antigen was 1.26ng/mL (reference range, 0-4.7ng/mL). The cancer antigen 125 concentration (CA-125) was 109.5IU/mL (reference range, 0-35IU/mL). An exploratory laparotomy revealed a large cystic mass originating from right ovary. The cyst contained approximately 10L of brownish fluid. Cytology of the fluid showed no evidence of malignancy. A pathological examination of the mass demonstrated a benign cystic lesion with hemorrhage and extensive thrombus formation. After surgical excision of the mass, contrast-enhanced abdominal CT urography showed partial the improvement of hydronephrosis (Figure-2).

Hydronephrosis may result from multiple diseases such as urinary tract stones, uroepithelial malignancies, anatomical abnormalities, and external compression. In woman, gynecologic diseases are important causes of hydronephrosis (1). Ovarian cysts are considered large when they are more than 5cm, and giant when they are more than 15cm (2). Giant ovarian cysts are very rare, however, when they do occur they require surgical resection because of not only the mass effect--associated morbidity and mortality but also the malignancy risk (2, 3). Furthermore, only a few cases of hydronephrosis caused by a giant ovarian cyst have been documented (2, 4). In the present case, the serum concentration of CA-125 was increased although the pathologic findings of ovarian cystic lesion and cytology of the cystic fluid were benign. The serum level of CA-125 may be increased in gynecologic malignancies. However, benign conditions also cause the increase of serum CA-125 including benign ovarian neoplasms, functional ovarian cysts, pelvic inflammatory diseases, pregnancy, menstruation (5).

In conclusion, we present a rare instructive case of hydronephrosis caused by a giant ovarian cyst. Clinicians should consider that hydronephrosis could be associated with various clinical conditions.

Figure 1 - The axial (A) and sagittal scan (B) of contrast-enhanced abdominopelvic computed tomography show the hydronephrosis caused by a large cystic mass in the abdominopelvic cavity.

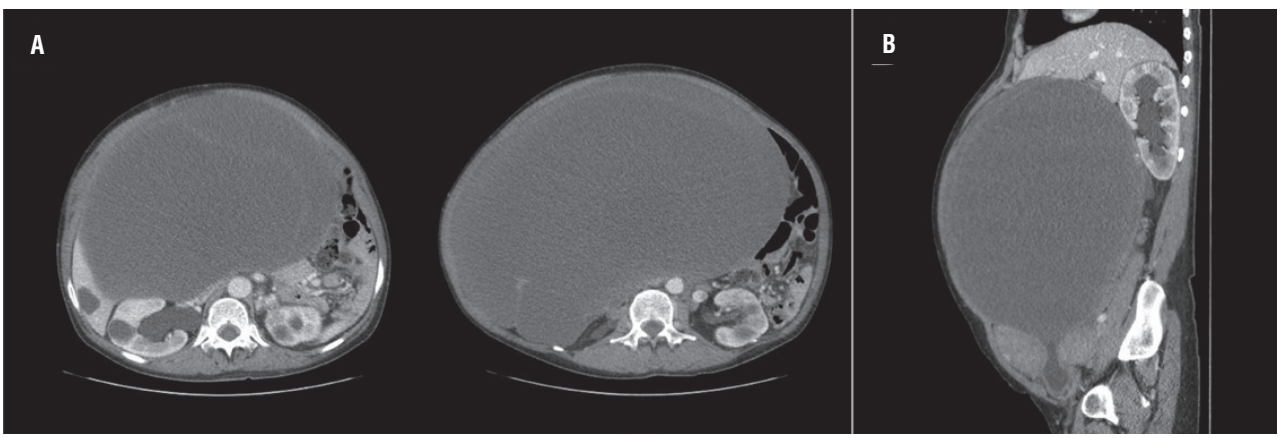
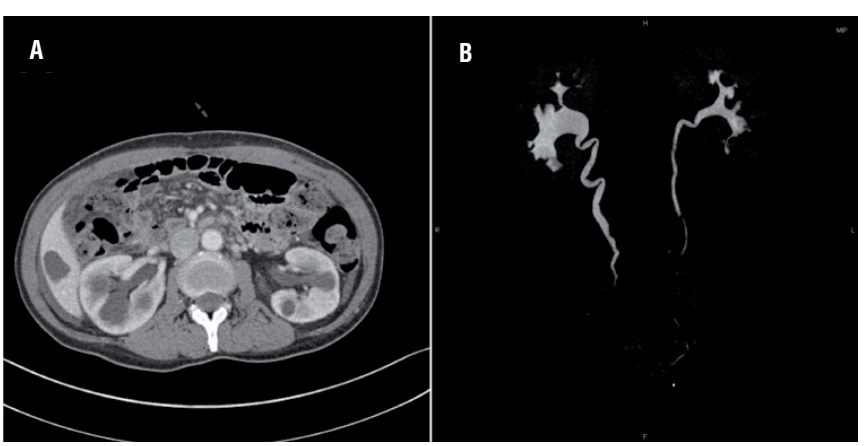


Figure 2 - Post-operative contrast-enhanced abdominal computed tomography scan shows the partial improvement of hydronephrosis in the axial scan (A) and the coronal scan of urography (B).



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ARTICLE INFO

Int Braz J Urol. 2016; 42: 848-9

Submitted for publication:
July 03, 2015

Accepted after revision:
January 20, 2016

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VIDEO SECTION

Vol. 42 (4): 850-851, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2014.0638

Two-part silicone mold. A new tool for flexible ureteroscopy surgical training

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ABSTRACT

Introduction and objectives: Flexible ureteroscopy is a common procedure nowadays. Most of the training programs use virtual reality simulators. The aim of this study was to standardize the building of a three-dimensional silicone mold (cavity) of the collecting system, on the basis of polyester resin endocasts, which can be used in surgical training programs.
Materials and Methods: A yellow polyester resin was injected into the ureter to fill the collecting system of 24 cadaveric fresh human kidneys. After setting off the resin, the kidneys were immersed in hydrochloric acid until total corrosion of the organic matter was achieved and the collecting system endocasts obtained. The endocasts were used to prepare white color two-part silicone molds, which after endocasts withdrawn, enabled a ureteroscope insertion into the collecting system molds (cavities). Also, the minor calices were painted with different colors in order to map the access to the different caliceal groups. The cost of the materials used in the molds is $30.00 and two days are needed to build them.
Results: Flexible ureteroscope could be inserted into all molds and the entire collecting system could be examined. Since some anatomical features, as infundular length, acute angle, and perpendicular minor calices may difficult the access to some minor calices, especially in the lower caliceal group, surgical training in models leads to better surgical results.
Conclusions: The two-part silicone mold is feasible, cheap and allows its use for flexible ureteroscopy surgical training.

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CONFLICT OF INTEREST

None declared.

ARTICLE INFO

Available at: www.intbrazjurol.com.br/video-section/marroig_850_851/

Int Braz J Urol. 2016; 42 (Video #6): 850-1

Submitted for publication:
December 10, 2014

Accepted after revision:
March 19, 2015

EDITORIAL COMMENT

Vol. 42 (4): 852-852, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2014.0638.1

EDITORIAL COMMENT: TWO-PART SILICONE MOLD. A NEW TOOL FOR FLEXIBLE URETEROSCOPY SURGICAL TRAINING

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The traditional surgical training model relies on an apprentice style learning where junior doctors are gradually turned into independent surgeons through a process of observation, assisted operating, supervised operating and finally independent operating (1). All of this takes place in the operating room, with real patients and requires a senior 'supervisor'. Limits on working hours and various other clinical and academic requirements limit operating time for junior staff. Availability of senior clinicians as teachers is also under threat as senior staff face increased patient loads and pressure by health systems to move towards consultant led care. This has led to considerable interest by surgeons in 'model' based learning over the past 20 years, especially as technology has progressed and minimally invasive techniques have become more numerous (2, 3). The main question is does surgical simulation transfer to skill in the operating room (3)? In urology this indeed appears to be true (4). This 2 part silicone mold presented in this video by Marroig et al. (5) appears to be a cheap, cost effective, efficient and ethical way for junior staff to familiarise themselves with flexible ureteroscopy. This model would offer a cheaper alternative to current 'high fidelity' ureteroscopy simulation trainers. More cost effective benchtop models have been shown to be just as useful as more expensive models (6), however the benefit of realistic model based trainers compared with cheaper computer based trainers has been questioned by some (4). The benefit of using simulation of any kind however is threefold; to the junior doctor who is able to have multiple attempts and opportunity for trial and error learning, to the hospital/senior clinician who has more efficient operating time and finally to patients whose operating time and complications may be reduced (3, 4).

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VIDEO SECTION

Vol. 42 (4): 853-854, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2014.0588

Laparoscopic – assisted transpyelic rigid nephroscopy – simple alternative when flexible ureteroscopy is not available

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ABSTRACT

Introduction: In special situations such as malrotated or ectopic kidneys and UPJ stenosis treatment of renal lithiasis can be challenging. In these rare cases laparoscopy can be indicated.
Objective: Describe the Laparoscopic-assisted rigid nephroscopy performed via transpyelic approach and report the feasibility.
Patients and methods: We present two cases of caliceal lithiasis. The first is a patient that ESWL and previous percutaneous lithotripsy have failed, with pelvic kidney where laparoscopic dissection of renal pelvis was carried out followed by nephroscopy utilizing the 30 Fr rigid nephroscope to remove the calculus. Ideal angle between the major axis of renal pelvis and the rigid nephroscope to allow success with this technique was 60-90 grades. In the second case, the kidney had a dilated infundibulum.
Results: The operative time was 180 minutes for both procedures. No significant blood loss or perioperative complications occurred. The bladder catheter was removed in the postoperative day 1 and Penrose drain on day 2 when patients were discharged. The convalescence was completed after 3 weeks. Patients were stone free without symptons in one year of follow-up.
Conclusions: Laparoscopic-assisted rigid nephroscopy performed via tranpyelic approach can be done safely with proper patient selection and adherence to standard laparoscopic surgical principles. This approach is an alternative in cases where flexible endoscope is not available and when standard procedure is unlikely to produce a stone-free status.

ARTICLE INFO

Available at: www.intbrazjurol.com.br/video-section/tobias-machado_853_854/

Int Braz J Urol. 2016; 42 (Video #7): 853-4

CONFLICT OF INTEREST

None declared.

Submitted for publication:
November 14, 2014

Accepted after revision:
October 28, 2015

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EDITORIAL COMMENT

Vol. 42 (4): 855-855, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2014.0588.1

EDITORIAL COMMENT: LAPAROSCOPIC - ASSISTED TRANSPYELIC RIGID NEPHROSCOPY - SIMPLE ALTERNATIVE WHEN FLEXIBLE URETEROSCOPY IS NOT AVAILABLE

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Percutaneous nephrolithotomy is generally considered the first choice for the treatment of large upper urinary tract stones. However, laparoscopic stone surgery with or without robotic assistance is a viable alternative especially in cases with aberrant anatomy such as ectopic or malrotated kidneys (1-3). A recent meta-analysis found several advantages of the laparoscopic approach, especially reduced blood loss, higher stone free rate and fewer secondary procedures (3).

Tobias-Machado et al (4) present a video on laparoscopic assisted rigid nephroscopy performed via a transpyelic approach for removal of stones in 2 cases with difficult anatomy. The authors are to be commended for their excellent surgical technique and description. However, using a rigid nephroscope would very rarely be necessary in most urologic centers in the US where flexible cystoscopes and ureteroscopes are nearly always available and preferred to avoid limitations due to angulation. When I have performed robotic pyelolithotomy (typically at concominant robotic pyeloplasty), my preference has been to use a flexible cystoscope.

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VIDEO SECTION

Vol. 42 (4): 856-857, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0080

Laparoscopic radical nephrectomy with inferior vena cava thrombectomy: highlight of key surgical steps

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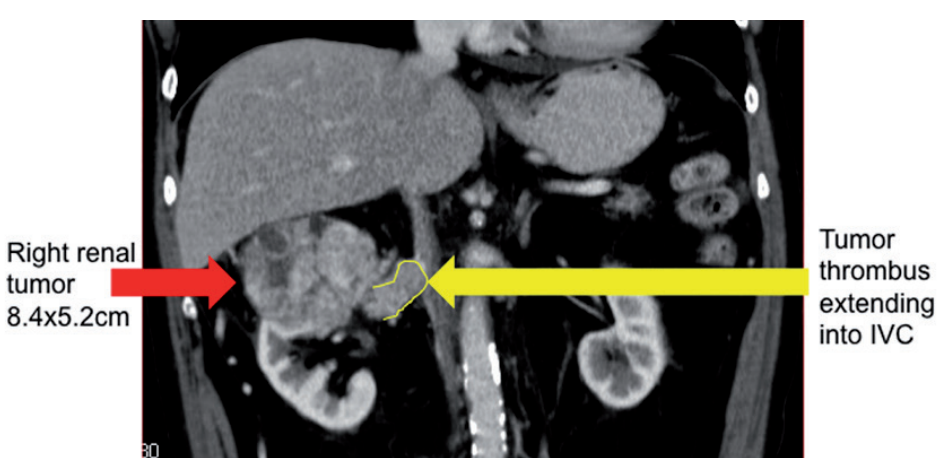
ABSTRACT

Objective: Vascular involvement in the form of renal vein (RV) or inferior vena cava (IVC) thrombus can be seen in 4-10% of patients presented with RCC. In patients without presence of metastasis, surgical treatment in the form of radical nephrectomy remains the treatment of choice with 5-year survival rates of 45-70%. Open surgery is still the first treatment option of choice at the moment for RCC patients with IVC thrombus.
Materials and Methods: In our study, we are reporting a case of patient with RCC and level I IVC thrombus treated with laparoscopy. Our patient is a 72 years old man with underlying co-morbidity of hypertension and chronic kidney disease (CKD) presented with right-sided RCC. The CT scan done showed a large right renal upper pole tumor measuring 8.4x5.2cm with level I IVC thrombus (Figure-1). There were no regional lymphadenopathy and the staging scans were negative.
Results: The operative time was 124 minutes and blood loss was minimal. The patient was progressed to diet on POD 1 with bowel movement on POD 2. There was no significant change in the pre and post-operative glomerular filtration rate (GFR). The surgical drain was removed on POD2. The patient was discharged well on POD 5. There were no perioperative complications. The pathology was pT3bN0M0 Fuhrman grade II clear cell RCC.
Conclusions: As a conclusion, laparoscopic radical nephrectomy and IVC thrombectomy is a complex and technically demanding surgery. With advancement of surgical skills as well as technology, more cases of minimally invasive laparoscopic radical nephrectomy and IVC thrombectomy can performed to improve the perioperative outcomes of carefully selected patients in a high volume center.

Figure 1 - Picture showing pre-operative CT scan showing right renal tumor with thrombus extending into IVC at the level of renal vein.



ARTICLE INFO

Available at: www.intbrazjurol.com.br/video-section/sim_856_857/

Int Braz J Urol. 2016; 42 (Video #8): 856-7

Submitted for publication:
February 21, 2015

Accepted after revision:
October 01, 2015

CONFLICT OF INTEREST

None declared.

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EDITORIAL
COMMENT

Vol. 42 (4): 858-858, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2015.0080.1

EDITORIAL COMMENT: LAPAROSCOPIC RADICAL NEPHRECTOMY WITH INFERIOR VENA CAVA THROMBECTOMY: HIGHLIGHT OF KEY SURGICAL STEPS

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In this video by Sim et al. (1), the authors nicely depict how laparoscopic surgery can be employed to tackle locally advanced renal tumors with venous vascular extension. The authors are to be congratulated on their elegant approach to such a case resulting in minimal blood loss, enhanced perioperative recovery, and most importantly strictly adhering to the essential principles of surgical oncology with complete tumor eradication. This being said, I would like to emphasize the last statement made by the authors in the their abstract which is that such an approach should be conducted in only highly selected cases at centers of excellence. I think low level IVC tumor thrombi (Mayo classification level 1 and 2) maybe appropriate to address in this manner in specific instances but tumor thrombi exhibiting intrahepatic or intracardiac extension (level 3 and 4, respectively) should be empirically approached using an open approach although some recent reports have raised the potential of robotic minimally invasive surgery in very highly selected cases. One can never forget the inherent morbidity associated with such high level IVC tumor thrombi cases, where the margin for error is infinitely small. Rapidly evolving technology will continually push the envelope as to how we perform surgery but the onus lies upon us as treating surgeons to always place the safety and wellbeing of our patients as the unwavering Hypocratic oath we will always adhere to.

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LETTER TO THE EDITOR

Vol. 42 (4): 859-860, July - August, 2016
doi: 10.1590/S1677-5538.IBJU.2016.0066

RE: Evaluation of sexual function in patients submitted to ureteroscopic procedures

Eryildirim B, Tuncer M, Sahin C, Yucetas U, Sarica K
Int Braz J Urol. 2015;41: 791–5

Mustafa Kadihasanoglu [1], Emin Özbek [1]

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Int Braz J Urol. 2015; 41: 791-5

Dear Editor,

We have read the article by Eryildirim et al. (1) which was interesting study evaluating the possible effects of ureteroscopy on the male and female sexual function. In this study they tried to evaluate the male and female sexual function before and after ureteroscopic procedure. They showed that the pre-and postoperative International Index of Erectile Function scores and Female Sexual Function Index scores were not influenced by ureteroscopy.

Multifactorial nature of sexuality should be considered during the evaluation of the sexual function of men and women. The factors affecting female sexual function include genetics, mental health status, symptoms of depression and anxiety, quality of relationships, menopause, hormonal imbalance, hysterectomy, ovariectomy, sexual abuse, negative sexual attitude, negative body image, drug and alcohol abuse, sexual orientation, childbirth and its outcomes, mode of delivery, number of childbirths, breastfeeding, and fears of pregnancy or sexually transmitted diseases (2). Similarly, male sexual dysfunction can result from physiological causes including depression, anxiety, stress, other mental health problems and physical causes including diabetes, obesity, metabolic syndrome, cardiovascular diseases, hypertension, treatments for prostate cancer, benign prostate hyperplasia, neurological diseases, hypogonadism, smoking, and pelvic surgeries (3). In addition to all well-known factors, urolithiasis and erectile dysfunction are defined as systemic diseases which are associated hormonal and metabolic disorders such as insulin resistance, obesity and metabolic syndrome (3, 4).

Thus, we consider that these factors for male and female sexual dysfunction, as mentioned above, are limitations of this study, because the authors did not exclude the patients with these factors and they aimed to reach a conclusion that ureteroscopy can adverse effect on male sexual function. Moreover, they did not suggest any pathophysiological mechanism resulted from ureteroscopy for sexual dysfunction. If the authors considered that the anxiety and pain may be a cause of sexual dysfunction, they should be evaluated with valid scales and evaluation forms. In addition, the authors did not report that the patient use any medical treatment including hormones, and phosphodiesterase inhibitors before and after treatment, because these medications can affect the sexual function. Furthermore, the interval for the postoperative evaluation of sexual dysfunction was only 4 weeks. Sofer et al suggested that complete recovery of sexual function is found at the 3 month

follow-up of all men who had normal of slightly impaired sexual function before going an endourological procedure (5). As a result, we claim that these factors should be indicated as a limitation to strengthen the outcomes of the study.

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Papers published in periodicals:

▪ Paterson RF, Lifshitz DA, Kuo RL, Siqueira Jr TM, Lingeman JE: Shock wave lithotripsy monotherapy for renal calculi. Int Braz J Urol. 2002; 28:291-301.
▪ Holm NR, Horn T, Smedts F, Nordling J, de la Rossete J: Does ultrastructural morphology of human detrusor smooth muscle cell characterize acute urinary retention? J Urol. 2002; 167:1705-9.

Books:
▪ Sabiston DC: Textbook of Surgery. Philadelphia, WB Saunders. 1986; vol. 1, p. 25.

Chapters in Books:
▪ Penn I: Neoplasias in the Allograft Recipient. In: Milford EL (ed.), Renal Transplantation. New York, Churchill Livingstone. 1989; pp. 181-95.

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