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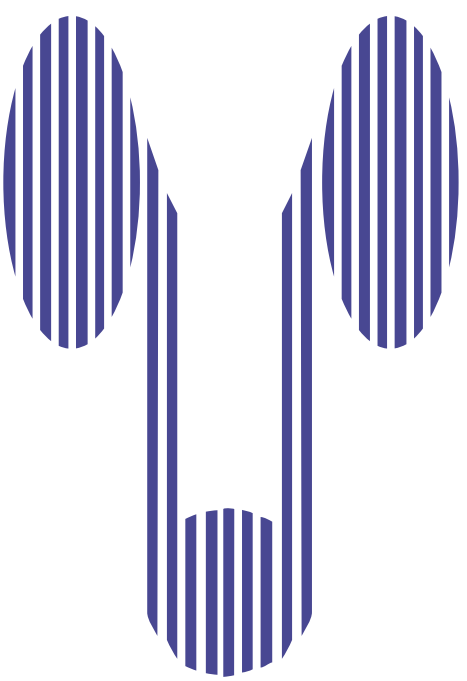

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International Braz J Urol

EDITOR'S COMMENT

The May – June 2006 issue of the International Braz J Urol presents interesting contributions from different countries, and as usual, the Editor's Comment highlights some important papers.

Doctor Daneshgari, from the Cleveland Clinic Foundation, Cleveland, Ohio, USA, recognized expert in the field, presents on page 262 a thorough review on current applications of neuromodulation of the lower urinary tract in female urology. Currently neuromodulation consist of the use of sacral nerve stimulation (SNS) and injectable therapies. In this review, the author discuss the background and development of SNS, its current indications, methods of patient selection and review the results of the recent published literature on SNS. The author also discusses some of the newer developments in SNS such as Bion device and the future direction in integration of SNS in female urology.

Doctor Camargo and colleagues, from University of California San Francisco, California, USA, discuss on page 273 the effect of kidney morcellation on operative time, incision complications, and postoperative analgesia after laparoscopic nephrectomy. After comparing the outcomes between kidney morcellation and 2 types of open specimen extraction incisions in 153 consecutive patients who underwent laparoscopic nephrectomy. A hundred and seven patients underwent specimen morcellation and 46 underwent intact specimen removal. Operative time, postoperative analgesia requirements, and incisional complications were evaluated. The authors concluded that morcellation does not extend operative time, and is associated with significantly less postoperative pain compared to intact specimen retrieval overall, although this is not statistically significant if a remote, muscle-splitting incision is made. Also, the authors found that morcellation markedly reduces the risk of incisional-related complications.

Doctor Kupeli and co-workers, from Gazi University School of Medicine, Ankara, Turkey, analyzed on page 287 the impact of pelvicaliceal anatomical variation between the stone- bearing and normal contralateral kidney on stone formation in adult patients with lower caliceal stones. The authors concluded that pelvicaliceal volume but not lower caliceal properties seem to be a risk factor for stone formation in lower calyx. Dr. Yair Lotan, from University of Texas Southwestern Medical Center, Dallas, Texas, USA, Dr. Edmund Chiong, National University Hospital, Singapore, and Dr. Monish Aron, All India Institute of Medical Sciences, New Delhi, India, provided excellent editorial comments on this paper.

Doctor Castillo and colleagues, in a study involving 3 South American centers, presented their experience on complications in laparoscopic radical cystectomy after 59 cases (page 300). The

authors experienced 18 (30%) postoperative complications (not counting mortalities), including 3 urinary tract infections, 1 pneumonia, 1 wound infection, 5 ileus, 2 persistent chylous drainage, 3 urinary fistulas, and 3 (5%) postoperative complications that required surgical intervention (2 hernias – one in the port site and one in the extraction incision, and 1 bowel obstruction). Two mortalities (3.3%) occurred in this series, one early mortality due to uncontrolled upper gastrointestinal bleeding and one late mortality following massive pulmonary embolism.

Doctor Tobias-Machado and associates, from ABC Medical School, Sao Paulo, Brazil, describe on page 316 a new minimally invasive approach for the radical resection of inguinal lymph nodes, called video endoscopic inguinal lymphadenectomy (VEIL. After 7 operated cases, the authors found that the VEIL technique is feasible and allows the radical removal of inguinal lymph nodes in the same limits of conventional surgery dissection. The main anatomic repairs of open surgery can be identified by the endoscopic view, confirming the complete removal of the lymphatic tissue within the pre-established limits. Preliminary results presented suggest that this technique can potentially reduce surgical morbidity.

Doctor Carvalho and collaborators, from the Kidney Stone Program, Division of Biological Sciences and the Pritzker School of Medicine, University of Chicago, Illinois, USA, world recognized experts in the field, present on page 342 an experimental study on defective urinary crystallization inhibition and urinary stone formation. The study included healthy Beagles, known to be non-stone forming dogs, and Mini-Schnauzers, known to be calcium oxalate stone formers. Nephrocalcin (NC), which is a glycoprotein produced in the kidney and that inhibits calcium oxalate crystal formation, was analyzed. The studied demonstrated that NC of these 2 species of dogs differently affects calcium oxalate crystallization and might have a role in determining ulterior urinary stone formation.

Dr. Francisco J.B. Sampaio
Editor-in-Chief

Review Article
International Braz J Urol Vol. 32 (3): 262-272, May - June, 2006

Applications of Neuromodulation of the Lower Urinary Tract in Female Urology

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ABSTRACT

Neuromodulation is becoming part of clinical armamentarium for treatment of a variety of lower urinary tract conditions in female urology. Its increased usage stems from need of patients who have exhausted all other therapeutic options for their complex and poorly understood lower urinary tract disorders. Currently neuromodulation may consist of the use of sacral nerve stimulation (SNS) and injectable therapies. Herein, we will discuss the background and development of SNS, its current indications, methods of patient selection and will review the results of the recent published literature on SNS. In addition, we will discuss some of the newer developments in SNS such as Bion device and the future direction in integration of SNS in female urology.

Key words*: bladder; urination disorders; female; neuromodulation; sacral plexus; electric stimulation*
Int Braz J Urol. 2006; 32: 262-72

INTRODUCTION

The first attempt at electrical stimulation of the lower urinary tract (LUT) may date back to 1878, when the Danish surgeon Saxtorph treated patients with urinary retention by intravesical stimulation (1), in which he inserted a special catheter with a metal electrode transurethrally.

After experimentations with various methods of simulating the bladder through the transurethral approach, direct detrusor stimulation (2), pelvic nerve stimulation (3) pelvic floor stimulation (4), spinal cord stimulation (5), with pioneering work of Tanagho and later Schmidt (6-9), it was demonstrated that the stimulation of sacral root S3 generally induces detrusor and sphincter action (10). Following 2 decades of experimentation with various approaches to sacral root stimulation, finally in October of 1997, sacral neuromodulation for treatment of refractory urge incontinence was approved by the Food and Drug Administration in the United States. Since then and at the time of this writing, more than 20,000 of Interstim (Medtronic Inc., Minnesota, Minneapolis, USA) have been implanted for 3 approved indications of the sacral nerve stimulation (SNS) of the lower urinary tract.

Herein, we will review the various aspects of the electrical stimulation of the bladder and its application in management of the LUT dysfunctions.

MECHANISMS OF ACTION

Neuromodulation of lower urinary tract function can be explained by relatively simple spinal circuits mediating somato-visceral interactions within the sacral spinal cord. It is proposed that SNS activates or “resets” the somatic afferent inputs that play a

pivotal role in the modulation of sensory processing and micturition reflex pathways in the spinal cord (11). Urinary retention and dysfunctional voiding can be resolved by inhibition of the guarding reflexes. Detrusor hyperreflexia and the overactive bladder syndrome can be suppressed by one or more pathways, i.e. direct inhibition of bladder preganglionic neurons, as well as inhibition of interneuronal transmission in the afferent limb of the micturition reflex.

PATIENT SELECTION

The selection of patient for SNS begins with a careful history, physical examination, routine tests such as urinalysis and urine culture, and most importantly use of bladder diaries to objectively record voiding variables.

The important elements of history focuses on the primary voiding variables such as the frequency and severity of urge incontinent episodes and the number of pads used per 24-hour period. For patients with refractory urgency frequency, the number of voids, the voided volumes and the degree of urgency are assessed, and in patients who experience inefficient voiding or urinary retention, the amount voided versus catheterized volumes per 24 hours and the patient's sense of completeness of evacuation are gathered. A voiding diary is invaluable in order to objectively document the patient's voiding habits and complaints. Urodynamic examination is commonly used to identify the patients with detrusor overactivity (DO) with or without urinary leakage or urinary retention. Some reports suggest the utility of the urodynamic studies (UDS) in identification of proper candidates to SNS (12).

ANATOMICAL LANDMARK AND SURGICAL TECHNIQUES OF SACRAL NEUROMODULATION

Sacral S3 foramen is the desired anatomical landmark for placement of lead of the sacral neuromodulation. The techniques for S3 localization have included manual or fluoroscopic methods. The manual approach includes the palpation of the sciatic notch, observation for least curved portion of the sacrum, and measurement of approximately 11 cm from the caudal tip of coccyx (Figure-1). The manual method is more difficult for obese patients or those without palpable landmarks. Chai & Mamo introduced the use of "cross-hair" fluoroscopic technique for S3 localization in 2001 (13). The intent of the fluoroscopy was not meant to see the S3 foramen, but rather help the surgeon to identify a specific region to start percutaneous access of S3 foramen (Figure-2). More importantly, the use of lateral imaging helped determine the depth required for implanting S3 lead (Figure-3). Use of fluoroscopy was familiar to surgeons such as urologists as they use of fluoroscopy in stone surgery and therefore, the application of fluoroscopy to sacral neuromodulation surgery was quickly accepted. The widespread use of fluoroscopic localization of S3 later allowed the introduction of tined S3 lead (14) and transformed the placement of a lead from an open procedure (15) to a completely percutaneous one. The widely adopted percutaneous use of tin lead approach abandoned the need for fixation of the lead by methods such as bone anchors.

Janknegt et al. (16) first described the staged implantation approach in which an implanted S3 lead, rather than the temporary lead, was used for initial testing. The staged technique bypassed the problems

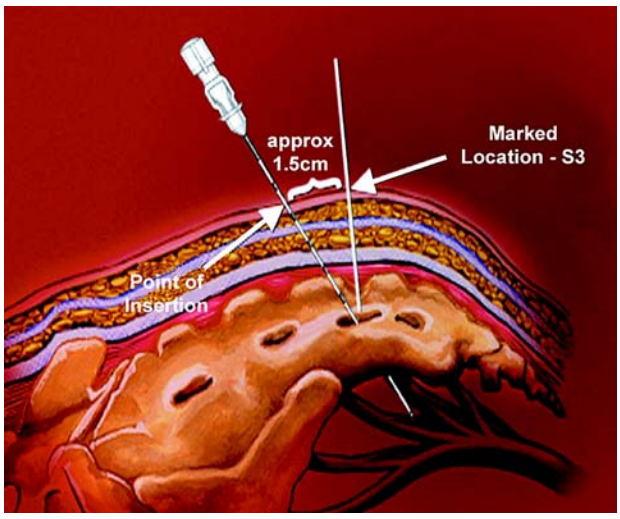

Figure 1 – *Localization of S3 foramen by anatomical landmark.*

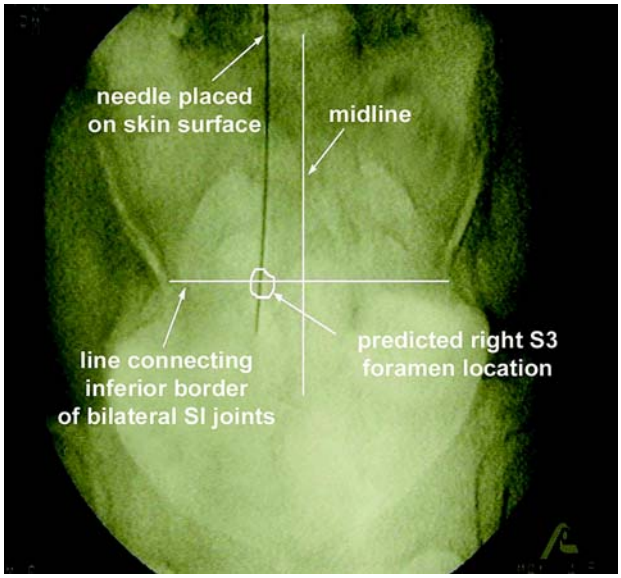

Figure 2 – *Localization of S3 Foramen by cross hair technique (from Chai TC, Mamo GJ: Modified techniques of S3 foramen localization and lead implantation in S3 neuromodulation. Urology. 2001; 58: 786-90, with permission).*

with percutaneous needle examination (PNE) which included a high risk of lead migration and the fact that the original response of the patient obtained by the temporary wire may have not been reproduced by the permanent lead. Several reports later confirmed a higher response rates and lesser rate of lead migration obtained by the staged approach.

After placement of the lead, the following sensory and motor responses related to stimulation of the specific sacral root may be observed:

S2 - Clamp movement or twisting and pinching of the anal sphincter (pulling down the coccyx).
- Plantar flexion of the entire foot, lateral rotation.

S3 - Bellows movement of the pelvic floor.
- Plantar flexion of the great toe(s).
- Parasthesia in the rectum, perineum, scrotum or vagina.

S4 - Bellows motion of the pelvic floor.
- No lower extremity activity.
- Sensing pulling in the rectum only.

The desired response and localization for electrical stimulation of LUT should include S3 responses.

Implantation of SNS consists of 2 steps. Stage I, or the trial stage, which involves the placement of a stimulation lead next to the dorsal root of S3 for a test period between 1-4 weeks (Figure-4). If the patient's symptoms under the existing list of indications for SNS improve more than 50% then the

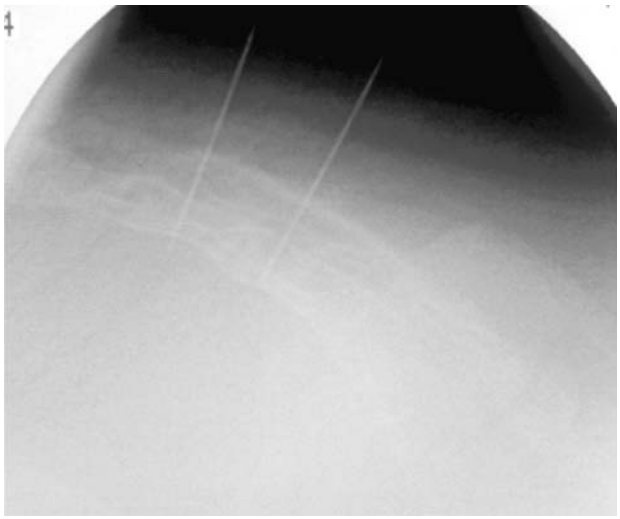

Figure 3 – *Site of percutaneous placement of needle stimulations and stage I lead.*

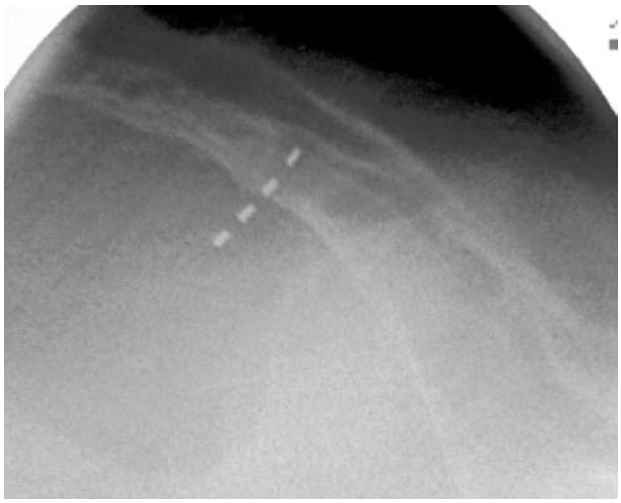

Figure 4 – *Tined lead is in proper position-2-3 contact plates of the quadripole lead are resting on the S-3 dorsal root nerve.*

patient is a candidate to undergo the stage II or permanent step in which the permanent implantable pulse generator (IPG) unit is implanted in the soft tissue of the buttock of the patient (Figures-5 to 7).

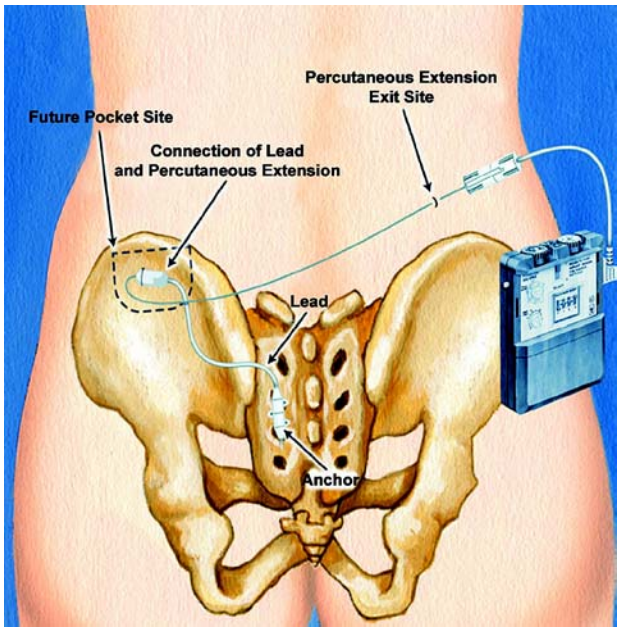

Figure 5 – *Stage I sacral neuromodulation - External stimulator connected to chronic lead for test period.*

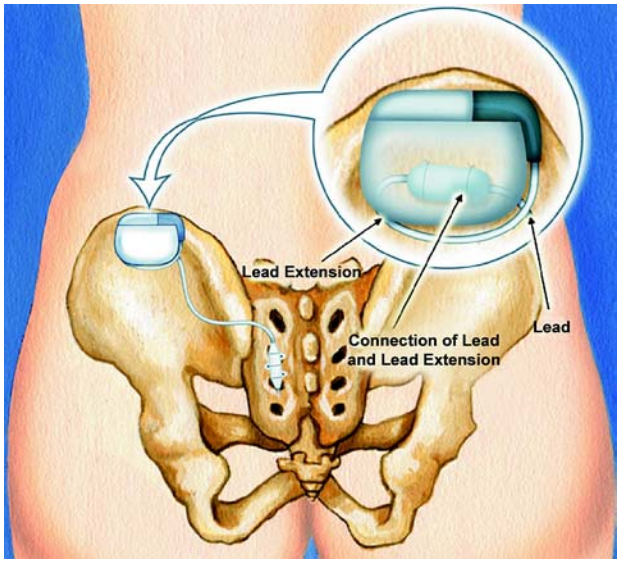

Figure 6 – *Stage II sacral neuromodulation- Implantable pulse generator (IPG) unit is placed in the subcutaneous pocket.*

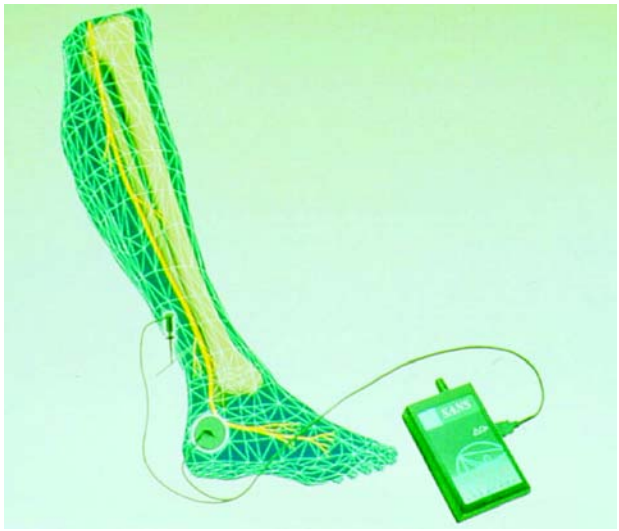

Figure 7 – *SANS device for percutaneous neurostimulation.*

There is no consensus as to whether 1 or 2 implanted S3 leads should be performed as in first stage. Bilateral implantation allows for testing for both the left and right S3 nerve roots. A time of the second stage, the side that is less efficacious can be removed or remain implanted for possible “backup” in case the other side fails. Currently, there is no evidence that bilateral simultaneous stimulation has any added benefits to unilateral stimulation. Furthermore, there is not the ability to stimulate both wires with one IPG in the USA because the IPG is not a dual channel stimulator. One would need to implant 2 IPGs for bilateral simultaneous stimulation. Nevertheless, bilateral implantation allows for a more complete evaluation and possibly offers the patient a higher chance of responding to sacral neurostimulation.

CLINICAL RESULTS

The reported outcomes of the SNS therefore includes the response of patients to the stage I (test stage) and to stage II (permanent implantation).

No discussion on the assessment of a treatment options could be complete without a discussion on the issue of level of evidence. The evidence required in the medical literature is limited to data reported in clinical trials, specifically

excluding expert opinion. This is similar to that required to determine the final judgment of a jury in a legal proceeding, which must be based upon the material evidence presented during the trial. The judgment (opinion) of the jury is not evidence. Evidence is factual information presented.

International Consultation on Incontinence has adopted the Oxford level of evidence as the following categories:

Level 1 - usually involves meta-analysis of trials, randomized clinical trials or a good quality randomized controlled trial (RCT) or "all or none" studies in which no treatment is not an option, for example, vesicovaginal fistula.

Level 2 - includes "low" quality RCT or meta-analysis of good quality prospective "cohort studies". These may include a single group when individuals who develop the condition are compared with others from within the original cohort group. There can be parallel cohorts, where those with the condition in the first group are compared with those in the second group.

Level 3 - evidence includes: A) Good quality retrospective "case-control studies" where a group of patients who have a condition are matched appropriately (e.g., for age, sex, etc.) with control individuals who do not have the condition, B) Good quality "case series" where a group of patients all, with the same condition, disease and therapeutic intervention, are described, without a comparison control group.

Level 4 - evidence includes expert opinion where the opinion is based not on evidence but on "first principles" (e.g., physiological or anatomical) bench research. The Delphi process can be used to give "expert opinion" or greater authority. In the Delphi process a series of questions are posed to a panel; the answers are collected into a series of "options"; the options are serially ranked; if a 75% agreement is reached then a Delphi consensus statement can be made.

Reports of Clinical Trials on Urge Incontinence, Urgency / Frequency and Non-Obstructive Urinary Retention

At this point in time, the SNS has been approved by the FDA for 3 indications: urge incontinence (UI), urgency frequency (U/F), and non-obstructive urinary retention (UR). However, SNS has also been reported to be used for other "off label" indications, such as neurogenic bladders in multiple sclerosis, interstitial cystitis, and chronic pelvic pain. Also, there are reports regarding the possible benefits of bilateral SNS. The majority of the reports on the non-formally indicated usages of SNS appear in the form of abstracts or case series.

The initial report on the efficacy of SNS on treatment of refractory urinary urgent incontinence was reported in 1999 (17) (level 2). This study reported the treatment of 76 patients with refractory urgent urinary incontinence from 16 contributing worldwide centers. The patients were randomized to immediate implantation and a control group with delayed implantation for a six-month period. At six months, the number of daily incontinence episodes, severity of episodes, and absorbent pads or diapers replaced daily due to incontinence was significantly reduced in the stimulation group compared to the delayed group. Of the 34 stimulation group patients, 16 (47%) were completely dry, and an additional 10 (29%) demonstrated a greater than 50% reduction in incontinence episodes. The interesting finding was that during the therapy evaluation, the group returned to the baseline level of incontinence when the stimulation was inactivated. Complications were site pain of the stimulator implantation in 16%, implants infection in 19%, and leak migration in 7%.

The use of SNS in urgency frequency was reported in 2000 by Hassouna et al. (18). Similar to the previous design, 51 patients from 12 centers were randomized into an immediate stimulation group and a control group (25 and 26 patients respectively) (level 2). Patients were followed for 1, 3 and 6 months, and afterwards at 6-month intervals up to 2 years. At the 6-month evaluation, the stimulation group showed improvement in the number of voiding dailies (16.9 ± 9.7 to 9.3 ± 5.1) volume per void (118 ± 74 to 226 ± 124 mL) and degree of urgency (the rank 2.2 ± 0.6 to 1.6 ± 0.9). In addition, significant improvement in quality of life was demonstrated, as measured by SF-36.

The report of use of SNS in urinary retention was published in 2001 by Jonas et al. (19), and in this

study, 177 patients with urinary retention refractory to conservative therapy were enrolled from 13 worldwide centers between 1993 and 1998 (level 2). Thirty-seven patients were assigned to treatment and 31 to the control group. The follow-up was done at 1, 3, 6, 12 and 18 months. The treatment group showed 69% elimination of catheterization at 6 months and an additional 14% with greater than 50% reduction in catheter volume per catheterization. Temporary inactivation of SNS therapy resulted in significant increase in residual volume, but the effectiveness of central nervous stimulation was sustained for 18 months after implantation.

In 2000, a follow-up report of some of the above series was published (20) (level 3). This report showed follow-up results after 3 years in all the approved indications. Fifty-nine percent of 41 patients had urinary urgent incontinence. Patients showed greater than 50% with 46% of patients being completely dry. After 2 years, 56% of the urgency frequency patients showed greater than 50% reduction in voids per day, and after 1-1/2 years, 70% of 42 retention patients showed greater than 50% reduction of catheter volume per catheterization.

The results of the use of SNS in the U.S. patient registry were published in 2002 (21) (level 3). The report included the use of SNS in 81 patients with all 3 indications: 27 for urgent continence, 10 with urgency frequency and 10 with urinary retention. In this report, 27 from 43 patients with urgent continence, 10 out of 19 with urgency frequency and 10 out of 19 with urinary retention showed improvement of more than 50%.

The results of an Italian registry were published in 2001 (22) (level 3). This report included the reports of 196 patients - 46 males and 150 females - for idiopathic urinary retention. Fifty percent of patients stopped catheterization and another 13% catheterized once a day at 1 year after implantation. At the 12-month follow-up, 50% of patients with hyperreflexia had less than 1 incontinence episode daily and the problem was completely solved in 66 patients. Of the patients with urgent continence, 39% were completely dry and 23% had less than 1 incontinence episode daily.

Results of use of SNS in Norway were published in 2002 (23) (level 3). The author reported the first 3 years of experience with 53 patients: 45 women and 8 men. This study showed similar results to previous reported series.

Table-1shown the published reports of use of SNS in various conditions of lower urinary tract dysfunction.

Other Indications

Use of SNS for other off-labeled applications has been reported for treatment of interstitial cystitis, chronic pelvic pain, pediatric voiding dysfunction, and neurogenic lower urinary dysfunction seen in multiple sclerosis. None of the reported case series (level 4) has led to new approved indications for SNS at the time of this writing.

COMPLICATIONS

A number of reports have published the complications of the SNS (17-19). The earlier reports describe the complications with PNE, which is no longer used in majority of the centers in the United States. Seigel et al. (20) summarized the complications in patients with refractory urge incontinence, urgency-frequency and urinary retention that were included in the original trials of SNS. The complications were divided into both percutaneous test stimulation related and post implant related problems. Of the 914 test stimulation procedures done on the 581 patients, 181 adverse events occurred in 166 of these procedures (18.2% of the 914 procedures). The vast majority of complications were related to lead migration (108 events, 11.8% of procedures). Technical problems and pain represented 2.6% and 2.1% of the adverse events. For the 219 patient who underwent implantation of the Interstim® system (lead and generator), pain at the neurostimulator site was the most commonly observed adverse effect at 12 month (15.3%). Surgical revisions of the implanted neurostimulator or lead system were performed in 33.3% of cases (73 of 219 patients) to resolve an adverse event. These included relocation of the neurostimulator because of pain at

Table 1 – *Published reports of use of SNS in various conditions of lower urinary tract dysfunction: urge incontinence (UI), urgency frequency (U/F), and non-obstructive urinary retention (UR).*

Study	**Total**	**Patients with UI**			**Patients with U/F**		**Patients with UR**		**Follow up**
		cured	> 50%	Improved	> 50%	Improved	> 50%	Improved	
US National Patient Register (21)	81		27/43		10/19		10/19		
Amundsen & Webster (28)	12		12/12	2/12					
Hedlund et al. (23)	14		13/14	8/14					
Bosch & Groen (30)	45		27/45	18/45					
Shaker & Hassouma (31)	18		12/18	8/18					
Siegel et al. (20)	112		21/41	19/41	16/29	5/29	29/42	24/42	
Schmidt et al. (17)	34	16/34	10/34	26/34			16/34		18m
Grunewald et al. (25)	39		13/18				18/21		18m
Jonas et al. (19)	29						20/29		12m
Hassouna et al. (18)	25				14/25				
Aboseif et al. (32)	32						18/20	2/20	24m

the subcutaneous pocket site and revision of the lead for suspected migration. Explant of the system was performed in 10.5% for lack of efficacy.

Everaert et al. (24) reported the complications related to SNS itself. Among the 53 patients who had undergone implantation of the quadripolar electrode (Medtronic Interstim, Model 3886 or 3080) and subcutaneous pulse generator in the abdominal site (Medtronic Interstim: Itrel 2, IPG) between 1994 and 1998, device related pain was the most frequent problem, occurred in 18 of the 53 patients (34%) and occurred equally in all implantation sites (sacral, flank or abdominal). Pain responded to physiotherapy in 8 patients and no explantation was done for pain reasons. Current related complications occurred in 11%. Fifteen revisions were performed in 12 patients. Revisions for prosthesis related pain (n = 3) and for late failures (n = 6) were not successful.

Grunewald et al. (25) reported their results after 4 years of use of SNS (Grunewald 1999). Complications requiring surgical revisions occurred in 11 of the 37 implanted patients (29.7%). They included infections in 3 cases (8.1%), lead migration in 2 cases (5.4%), pain at the site of the implanted pulse generator in 3 cases (8.1%) and a lead fracture, an electrode insulation defect and skin erosion at the

site of the impulse generator in 1 case (2.7%) respectively.

Hijaz & Vasavada (26) reported the complications of our group at the Cleveland Clinic Foundation. On hundred eighty stage I procedures were performed for indications of refractory overactive bladder, idiopathic and neurogenic urinary retention and interstitial cystitis. Among this cohort 130 (72.2%) proceeded to stage II implantation of the implantable pulse generator. In this group, 59 stage I leads were explanted (27.8%). The majority of lead explants were performed for unsatisfactory or poor clinical response (46/50; 92%). The rest of the explants were done for infection (4/50; 8%). Stage one revisions totaled 22 of the 180 stage one (12.2%). Revisions were done for marginal response (13/22), frayed subcutaneous extension wire (6/22), lead infection (3/22) and improper localization of stimulus (1/22). Eleven (50%) of the revisions proceeded for stage two generator implant. When the revision was done for a marginal response (13/22), the response was ultimately clinically satisfactory in 5/13 (38.5%) and they proceeded to generator implant. For stage II complications, explants was performed in 16/130 (12.3%) of the CCF group. Explants were done for infection and failure to maintain response in 56.3% and 43.7% respectively. Revisions were done for infection, mechanical (generator related), and response causes. The revision rate with stage II was 20% (26/130).

In summary, stage I complications can lead to either explants or revision of the tined lead. The reasons for either cause could be related to response of patient, mechanical failure or infection. Explants for response reasons should not truly be considered a complication as much as it is an integral part of the procedure. Stag II complications are also seen for decay of response, mechanical or infection reasons. Table-2 summarized the common complications of SNS reported in several series.

Hijaz & Vasavada (26) have also presented algorithms for trouble shooting of the SNS problems. When infection at the generator site is diagnosed, the best management would be explanation of the whole system. Despite attempts to salvage some of these patients, follow up revealed that the infection persisted in all and eventual explant was inevitable. Trouble shooting algorithm include search for causes of a) pocket (IPG site) discomfort; b) recurrent symptoms; c) stimulation occurring in the wrong area of pelvic; d) no stimulation; and e) intermittent stimulation.

THE BION DEVICE

In search for a smaller, lesser invasive and more selective electrical stimulation of the bladder, use of the Bion devise (Advanced Bionics Corporation, Valencia CA, USA) in 2 forms (radiofrequency activated bion or RF-bion; and rechargeable bion or bion-r) have been reported. The Bion device is a self-contained, battery-powered, telemetrically programmable, current-controlled mini-

Table 2 – *Summary of common complications of sacral nerve stimulation (SNS).*

	Siegel et al. (20)	**Everaert et al. (24)**	**Grunewald et al. (25)**	**Hijaz & Vasada (26)**
Number of patients	581		37	167
PNE- overall	18.02%	53	N/A	N/A
Stage I- overall	N/A	N/A		12.2%
Stage II- overall			29.7%	20%
Pain at neurostimulator site	15.3%	34%	8.1%	
Suspected lead migration	8.4%		5.4%	10.7%
Infection	6.1%		8.1%	20%
Revision of permanent SNS	33.3%	23%	29.7%	

PNE = percutaneous needle examination.

neurostimulator with an integrated electrode. It has a size of 27 x 3.3 mm and weighs only 0.7 g. It can be implanted adjacent to the pudendal nerve at Alcock's Canal (Figure-8), Bosch, 2005 (27). The results of the Bion pilot studies indicate that a considerable reduction in the degree of detrusor overactivity incontinence can be obtained in severely refractory cases, including women who had failed sacral nerve neuromodulation. The described technique is well tolerated by the patients. It is minimally invasive and relatively simple. Clinical trials of the Bion-r device involving larger numbers of patients are currently under way in the US and Europe.

Figure 8 – *Bion device (from Bosch JL: The bion device: a minimally invasive implantable ministimulator for pudendal nerve neuromodulation in patients with detrusor overactivity incontinence. Urol Clin North Am. 2005; 32: 109-12, with permission).*

FUTURE DIRECTIONS

The initial success of via SNS in treatment of some of the most bothersome conditions of the bladder has entered the electrical stimulation of the LUT into the therapeutic armamentarium of physicians dealing with those conditions. Subsequently, entry of this therapy has introduced new lines of research to enable us to answer many open and unresolved questions related to various issues of SNS in clinical practice. Daneshgari and Abrams compiled a list of the pertinent research questions that in the opinion of several experts in the area of SNS need to be addressed. Among those research questions were:

1. Clinical predictors of responders- it is highly desirable to predict, with a reasonable level of accuracy, the potential response of the patients to SNS, thus avoiding the test trial.
2. A comparison between effects of continuous versus intermittent stimulation with aim of improving the percent of patients benefiting from SNS.
3. Whether a unilateral versus bilateral stimulation in either categories of the current indications would lead to an improved and more durable response.
4. Comparing the effects of direct pudendal nerve stimulation versus SNS in patients with refractory OAB
5. Functional brain imaging of responders and failures after implant of SNS, to study possible differences in CNS effects of SNS in these 2 groups
6. Animal models to better delineate mechanisms of action for neuromodulation (i.e. neurotransmitters).
7. Longitudinal study to better understand the interaction between GU, GI and gynecologic complaints.

As in other areas in medicine, we are looking for those sparks of success that will lead to creative fires of expanding knowledge. But no shortcuts are acceptable. Further use of neuromodulation of the lower urinary tract will have to be examined though the time-tested tools such as properly designed clinical trials as we protect and explore the increasing territory of electrical stimulation of the lower urinary tract.

CONFLICT OF INTEREST

None declared.

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The Effect of Kidney Morcellation on Operative Time, Incision Complications, and Postoperative Analgesia after Laparoscopic Nephrectomy

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ABSTRACT

Introduction: Compare the outcomes between kidney morcellation and two types of open specimen extraction incisions, several covariates need to be taken into consideration that have not yet been studied.
Materials and Methods: We retrospectively reviewed 153 consecutive patients who underwent laparoscopic nephrectomy at our institution, 107 who underwent specimen morcellation and 46 with intact specimen removal, either those with connected port sites with a muscle-cutting incision and those with a remote, muscle-splitting incision. Operative time, postoperative analgesia requirements, and incisional complications were evaluated using univariate and multivariate analysis, comparing variables such as patient age, gender, body mass index (BMI), laterality, benign versus cancerous renal conditions, estimated blood loss, specimen weight, overall complications, and length of stay.
Results: There was no significant difference for operative time between the 2 treatment groups ($p = 0.65$). Incision related complications occurred in 2 patients (4.4%) from the intact specimen group but none in the morcellation group ($p = 0.03$). Overall narcotic requirement was lower in patients with morcellated (41 mg) compared to intact specimen retrieval (66 mg) on univariate ($p = 0.03$) and multivariate analysis ($p = 0.049$). Upon further stratification, however, there was no significant difference in mean narcotic requirement between the morcellation and muscle-splitting incision subgroup ($p = 0.14$).
Conclusion: Morcellation does not extend operative time, and is associated with significantly less postoperative pain compared to intact specimen retrieval overall, although this is not statistically significant if a remote, muscle-splitting incision is made. Morcellation markedly reduces the risk of incisional-related complications.

Key words*: nephrectomy; laparoscopy; pain*
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INTRODUCTION

Since its first report in 1991 (1), laparoscopic nephrectomy has progressively gained acceptance among urologists (2-5). Steps within this procedure are continuously being evaluated and modified to achieve better outcomes. Although a variety of techniques and devices have been developed for specimen entrapment and retrieval (6,7), no consensus on the best method has been established, but rather the choice is likely surgeon dependent or unproved factors. Specimen morcellation is associated with a smaller incision, better cosmesis, and fewer incision-related complications than open specimen extraction

incisions (8,9), but is associated with a longer operative time with a controversial benefit in regard to pain control. Morcellating a specimen containing tumor is felt to make accurate pathologic staging more difficult, but this has not yet been proved to be clinically detrimental due to the development of better clinical staging due to higher resolution imaging tests (10,11), and the application of nomograms and standardized protocols for pathologic evaluation of fragmented specimens (12). The potential increased risk of tumor spill and port-site metastasis after morcellation has yet to be proven clinically significant (13,14).

Previous studies evaluating the effects of tissue morcellation on morbidity and life quality have not shown a statistically significant difference regarding postoperative pain, hospital stay and recovery period when compared to intact specimen removal (15,16). Unfortunately, these studies did not take into consideration other variables that could potentially affect the relationship between morcellation and operative time and post-operative pain, such as age, sex, body mass index, benign versus malignant renal conditions and overall complications. Our objective was to more accurately assess and compare the operative time, analgesia requirements, incision related complications, and overall length of stay in patients with morcellated and intact specimen extraction by entering additional variables into the analysis.

MATERIALS AND METHODS

We retrospectively reviewed the charts of 153 consecutive patients who underwent transperitoneal, 4-port laparoscopic nephrectomy for benign or malignant disease at our institution from September 1999 through June 2004. Our technique for laparoscopic nephrectomy with the use of a blunt-tip, radial dilating trocar (Step®, US Surgical, Norwalk, CT) for all ports was published previously (17). We routinely infiltrated the peritoneum under the laparoscopic port site with 3 mL of 0.25% bupivacaine and the extraction incision (when used) with 10 mL of 0.25% bupivacaine. Patients who underwent hand-assisted nephrectomy, nephroureterectomy, donor nephrectomy, and cases requiring open conversion were excluded from the study. All specimens were placed within a medium or large size LapSac (Cook Urological, Spencer, IN) prior to specimen retrieval. All specimens could be placed within a medium or large LapSac.

In 107 patients the kidney specimen was morcellated, while 46 patients underwent intact specimen removal, either through a muscle-cutting incision connecting two port sites (n = 16) or through a remote, muscle-splitting incision, either midline infra-umbilical or Pfannestiel incision (n = 30). For morcellated specimens, the mouth of the LapSac was pulled up through a port site that previously had a 12-mm port, and ring forceps were used to extract pieces of the tissue until all was removed. For the open extractions, after making the incision into the peritoneum, the LapSac was grasped and removed with the specimen intact. The choice to morcellate or not and the type of incision chosen was made by the primary surgeon either at the time of surgery or in discussion with the patient preoperatively, and generally was based upon prior incisions and personal cosmetic concerns and not necessarily based upon kidney size or underlying pathology.

Operative times, analgesia requirements (morphine equivalents administered during the postoperative period), length of hospital stay, and postoperative complications (incision and non-incision related) were evaluated and compared to a number of variables, including age, gender, body mass index, type of renal pathology (malignant versus benign), estimated blood loss and specimen weight. The dosage of narcotics required during the postoperative hospital stay was converted to morphine sulfate equivalents using of an equianalgesic table (18). Univariate analysis and multivariate regression were performed for statistical evaluation and significance was defined as a p value ≤ 0.05.

RESULTS

Patient demographics are presented in Table-1. There was no significant difference in patient age,

sex, and laterality. There was a significant difference in the type of renal pathology, as 28 of 107 (26%) patients who underwent kidney morcellation had a benign pathology compared to only 3 of 46 (6.5%) within the intact specimen group (p = 0.01). The benign pathology consisted of patients with xanthogranulomatous pyelonephritis, chronic pyelonephritis, ureteropelvic junction obstruction, severe renal artery stenosis, and kidney tuberculosis. Patients undergoing radical nephrectomy whose final pathology were oncocytoma or angiomyolipoma were considered pre-operatively to have a potentially malignant disease and were therefore included in the cancer group.

The results of the univariate analysis are shown in Table-2. There was no significant difference between the mean operative time of the morcellation group (255 min) and the intact specimen group (247 min) (p = 0.65). No additional variables were significantly correlated to operative time, and thus a multivariate model was unnecessary. The postoperative length of stay was similar between the two groups: 2.1 and 2.3 days in the morcellated and non-morcellated groups respectively (p = 0.53).

The complications are listed in Table-3. The purpose of the list of complications is to determine the potential effect of a surgical complication on operative time, length of stay, and analgesia requirement. There were 18 complications in the morcellated group and 4 in the intact group. Detailed analysis revealed that the complications were completely unrelated to the incision in all cases except for 2 (4.4%) In contrast, there were no complications related to the specimen retrieval site in the morcellated group (0%; p = 0.03).

Univariate analysis indicated the mean narcotic requirement differed between the treatment groups (41 and 66 mg in the morcellated and non-morcellated patients, respectively, p = 0.03). Regression revealed that age and length of stay were

Table 1 – *Patient demographics.*

Variables	Morcellation (n = 107)	Intact Specimen (n = 46)	p Value
Mean age (years)	60 (range 42 - 79)	57 (range 37 - 81)	0.22
Body mass index	28	29	0.62
Sex (male/female)	65/42	24/22	0.32
Laterality (right/left)	49/58	21/25	0.99
Type of renal pathology (benign/malignant)	28/79	3/43	0.01
Specimen weight (grams)	397 (range 312 - 604)	510 (range 298 - 680)	0.10

Table 2 – *Univariate analysis of the morcellated and intact specimen retrieval groups.*

Variables	Morcellation (n = 107)	Intact Specimen (n = 46)	p Value
Operative time (minutes)	255 (range 128 - 310)	247 (range 134 - 304)	0.65
Incision related complications	0 (0%)	2 (4%)	0.03
Mean morphine equivalents required (mg)	41	66	0.03
Length of stay (days)	2.1 (range 1.2 - 5.0)	2.3 (range 1.2 - 5.2)	0.53

Table 3 – *Intraoperative and postoperative complications in the morcellated and intact specimen retrieval groups.*

Morcellation (n = 107)	**Intact Specimen Retrieval (n = 46)**
Intraoperative	**Intraoperative**
Retroperitoneal bleeding (3 cases)	Bladder injury during specimen retrieval (1 case)
Diaphragmatic injury (1 case)	
Liver injury during Veress needle (1 case)	
Small bleeding renal artery stump (1 case)	
Airway trauma during intubation (1 case)	
Groin hematoma (1 case)	
Postoperative	**Postoperative**
Right upper pulmonary lobe collapse (1 case)	Acute renal failure (1 case)
Pulmonary embolism (1 case)	Incisional hernia/small bowel obstruction (1 case)
Pulmonary edema (2 cases)	Dehiscence (1 case)
Respiratory failure (1 case)	
Myocardial Infarction (1 case)	
Arrhythmia (1 case)	
Superficial vein thrombosis (1 case)	
Prolonged ileus (1 case)	
Abdominal wall hematoma* (1 case)	

**The abdominal wall hematoma was unrelated to the morcellated specimen retrieval site.*

correlated with postoperative analgesia, with a higher average narcotic requirement associated with younger patients and a longer hospital stay. Multivariate analysis demonstrated that the effect of morcellation on postoperative analgesia remained significant between the treatment groups while controlling for significant covariates ($p = 0.049$). After stratification of the intact specimen group, no significant difference in the average narcotic requirement was found between the muscle cutting (79 mg) and muscle-splitting incision (61 mg) subgroups ($p = 0.60$). The two subgroups were individually compared with the morcellated specimen group. Analysis revealed a difference in postoperative analgesia between the morcellated group and the muscle cutting subgroup ($p = 0.046$ and $p = 0.05$ for univariate and multivariate, respectively), however, no significant difference was found between morcellation and the muscle splitting patients ($p = 0.06$ and $p = 0.14$ for univariate and multivariate analysis, respectively).

DISCUSSION

The introduction of laparoscopic nephrectomy and kidney morcellation in 1991 (1) was responsible for a substantial reduction in postoperative pain, hospital stay, and for a shorter recovery period compared to standard nephrectomy (5,6). Although the advantages of laparoscopic nephrectomy are widely recognized, the ideal method for specimen removal is ill defined. It remains controversial as to the true effect that specimen morcellation has on operative time, postoperative pain, and the accuracy of malignancy staging through pathologic evaluation (15,16).

It has been argued that morcellation should not be undertaken in cases of nephrectomy for cancer as this inhibits accurate tumor staging. While traditional staging can clearly not be performed in a morcellated specimen, the clinical effect of this is unknown. An in vitro study on pathological validity

of morcellated kidneys affected by renal tumors, including cases of perinephric fat invasion, revealed identical histology, grade, and stage when intact specimen evaluations were compared to a second analysis of the same specimens after morcellation (19). Additionally, advances in abdominal imaging tests (10,11), and mathematical models developed to guide pathologic sampling and analysis of morcellated specimens (12) can substantially increase the reliability of diagnosis and staging of renal malignancies.

In regards to operative time, as shown by previous studies and confirmed by our analysis (15,16), morcellation following laparoscopic nephrectomy is not associated with longer operative times when compared to intact specimen retrieval. While morcellation may be a time consuming procedure, especially in patients with history of recurrent urinary tract infections, xanthogranulomatous pyelonephritis, and/or renal scarring, this is clearly offset by the time required to open and close an additional incision. Additionally, conditions such as obesity and inadvertent injury of subcutaneous vessels during an incision may account for even longer operative times. In addition, many of the patients in the morcellated group underwent nephrectomy for xanthogranulomatous pyelonephritis, chronic pyelonephritis, tuberculosis, and other end-stage kidney disorders, which caused the kidneys to have a severe scar around them, making surgery much more difficult and time consuming.

While the overall length of hospital stay was not statistically significantly different between the two groups, this was true despite the higher number of complications in the morcellated group that certainly led to longer hospital stays. This difference in complication rate in this review probably has a number of explanations including random chance. Certainly, the complex nature of many of the kidneys removed for non-cancerous causes, which compromised 36% of the morcellated group, could have contributed to the difference in complication rate. The only two incision-related complications were in the intact group.

Recent publications failed to prove the benefits of morcellation regarding postoperative pain intensity (15,16). However, these studies did not consider the possible effects of other variables on postoperative pain. In our study, patient age and length of stay were strongly correlated to postoperative pain. To generate a nonbiased assessment of the effect of morcellation on narcotic requirement, we used a multivariate regression model. Analysis revealed that older patients required lower dosages of morphine for postoperative pain control. This fact is consistent with a number of studies that demonstrated an increased pain threshold in the elderly patients that is felt to be due to a variety of physiologic changes (20).

For further analysis, we divided the intact specimen retrieval group into those who underwent a muscle cutting (i.e. connecting two ports) compared to muscle splitting (i.e. Pfannenstiel, low midline, or Gibson-type) incision. When comparing the two subgroups of intact incisions, there was no significant difference between the narcotic requirements. When comparing the narcotic requirements of each subgroup separately to that of the morcellated group, while there was a statistically significant difference between the muscle cutting group and the morcellated group, this was not significantly different in the muscle splitting group. It seems likely therefore that postoperative pain following laparoscopic nephrectomy may not be influenced by a single variable but more likely by a combination of retrieval incision location and length.

A potential weakness of the study is the retrospective nature of the review. Therefore, certain information that could further give insight to better outcomes, such as the change in surgical and laparoscopic experience over time, an actual accurate measurement of incision length, true analog pain scale results, and accurate time to return to daily activities could not be entirely assessed and for this reason were not included. A prospective randomized trial with multivariate statistical analysis is mandatory to help even better define these conclusions.

CONCLUSIONS

Kidney morcellation after laparoscopic nephrectomy does not extend operative time and is

associated with a lower rate of incision-related complications. Patients who underwent kidney morcellation had a significantly lower postoperative narcotic requirement when compared to those in the intact specimen retrieval group. However, the difference in the mean analgesia requirement was not statistically significant between the morcellated group and those with a remote, muscle-splitting incision. Postoperative analgesia is likely influenced by a combination of factors.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The present study approaches the fairly controversial area of specimen morcellation after laparoscopic nephrectomy, especially in malignant disease. Reviews of scientific literature reveal the many advantages of morcellation over intact removal, such as reduction of incision length with consequent reduced usage of postoperative analgesia, and shorter hospital stays (1); however, care must be taken with this technique in order to avoid sac perforation and possible subsequent dissemination of tumor cells within the abdominal cavity, as well as trocar site implantation (2-5) and inadvertent lesion of intra-abdominal structures (6). Intact removal increases the size of the incision by 5-7 cm in those procedures considered minimally invasive, thus altering the aesthetic result and increasing postoperative pain (7). However, intact removal of the surgical specimen falls within the principles of oncologic surgery, thus reducing the risk of metastatic implants and aiding anatomical and pathological staging of the specimen (8). Another relatively controversial aspect found in scientific reviews regards the amount of time necessary in morcellation of renal specimens, which some authors have reported as an average of 18 minutes (with durations varying from 6 to 34 minutes) (1); others claim an average time of 33 minutes (ranging from 18-115 minutes) (9).

The authors of the study in question have presented an excellent casuistry (153 laparoscopic nephrectomies) and have approached the main controversial aspects of morcellation, analyzing those variables, which may be related to operative time, postoperative analgesia, length of hospital stay, and complications associated with the incision.

It is a well-delineated retrospective study, which utilized a uniform methodology for the groups examined, with adequate statistical analysis of all variables involved (sex, age, body mass index, laterality, type of renal pathology, and weight of operative specimen). On the other hand, when the

authors report the routine use of 0.25% bupivacaine for infiltration in incision and trocar sites, the amount of anesthetic used is not specified, and this may cause some alteration in the analysis of postoperative pain, as greater incisions will require a larger infiltration of local anesthetic.

The subject approached is controversial and sheds new perspectives in the field of specimen removal subsequent to laparoscopic nephrectomy, clarifying several myths about the prolonged time necessary for morcellation, as well as those regarding the risks inherent to the method.

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Ultrasound Guided Percutaneous Nephrostomy for Obstructive Uropathy in Benign and Malignant Diseases

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ABSTRACT

Objective: Analyze the success rate, complications and overall benefit of ultrasound guided percutaneous nephrostomy (PCN) for the relief of obstructive uropathy in benign and malignant diseases.
Materials and Methods: PCN was performed in 50 kidneys of 32 patients. It was performed in emergency rooms totally under ultrasound guidance by general surgeons. Seldinger technique was used in all cases. Changes in renal function after the procedure were analyzed using paired t-test.
Results: The procedure was successfully completed in 42 out of 50 kidneys (84%). There has been no major complication and 28% minor complications. The renal function improved significantly when PCN was performed for benign conditions (mean creatinine 3.52 mg/dL before and 2.18 mg/dL after PCN), however in malignancy there has been no significant improvement in renal function (before PCN mean creatinine 6.39 mg/dL and after PCN 5.41 mg/dL).
Conclusion: We conclude that PCN can be effectively performed under ultrasound guidance and should be the initial procedure in acutely obstructed kidneys with pyonephrosis and poor renal function. In malignant cases, however, improvement in renal function is possible only if the procedure is carried out at an early stage.

***Key words**: hydronephrosis; ureteral obstruction; percutaneous nephrostomy; ultrasound*
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INTRODUCTION

Obstructive uropathy is a condition occurring due to blockage of urine flow, resulting in increased pressure within the collecting system and kidney injury. Interruption of urinary flow results in pain, infection, sepsis, and loss of renal function. It is a potentially life threatening condition and immediate measures are required to decompress the kidneys. The various modalities available are retrograde stenting, open drainage of kidneys and percutaneous nephrostomy.

Percutaneous nephrostomy (PCN) has come a long way from the times of William Goodwin, who inadvertently punctured the renal pelvis attempting a translumbar aortogram (1). Although percutaneous nephrostomy was developed using fluoroscopic guidance, ultrasound guided procedures are now safe, easy and effective (2-5).

We performed PCN in patients, with both benign and malignant conditions solely under ultrasound guidance with the help of radiologists and evaluated the success rate of the procedure, related complications and outcome in patients with benign and malignant renal diseases.

MATERIALS AND METHODS

A prospective study was carried out in 50 kidneys of 32 patients suffering from obstructive uropathy. It included 18 males and 14 females with both benign and malignant causes of obstructive uropathy. The mean age in this study group was 41.4 years, ranging from 10 to 63 years. In males the average age was 41.5 years ranging from 10 to 63 years and in females it was 42 years ranging from 19 years to 63 years.

The percutaneous nephrostomy was performed entirely under ultrasound guidance as soon as it was possible in emergency. The procedure was thoroughly explained to the patient and relatives. Informed consent was obtained.

All patients were subjected to routine investigations and the following patients were excluded from the study: untreated bleeding disorders, untreated urinary tract infection, hemoglobin less than 10 mg/dL. In patients failing to meet these criteria all parameters were corrected before proceeding with PCN.

The patients were placed on the ultrasound table in prone position and a pillow placed under the abdomen on the side to be operated to correct lumbar lordosis and support the kidney. Ultrasound scanning was performed using a 7.5 MHz transducer to obtain a median longitudinal scan through the kidney. As soon as the initial puncture site was chosen it was cleaned and draped. Local anesthesia was injected at the puncture site and around it using 3-5 mL of 1% lignocaine. Sterile betadine jelly was applied to the transducer and localization of the puncture site was carried out again.

We performed the Seldinger technique in all patients. The skin and fascia were incised with a #11 blade and then the scanning head was shifted over the incision to measure the distance between the skin and the calyx. An 18G-sheathed needle was inserted blindly through the incision and aimed at the direction previously determined by the ultrasound. The sonographic view as well as urine confirmed that the needle was at the desired site. The needle was removed leaving a small catheter in place and a curved J tip 0.038 guide wire was inserted into the collecting system through the puncture needle. Once the guide wire was in position, the fascial dilators were inserted with rotating movements during advancement. The tract was dilated 2F over the desired catheter to be placed, after tract dilation a polyethylene pigtail catheter was introduced over the guide wire. The pigtail catheter was firmly sutured to the skin using silk 1-0 and adhesive strapping was performed.

RESULTS

Percutaneous nephrostomies were performed for various indications in obstructive uropathy due to benign and malignant tumors. Twenty one (42%) nephrostomies were done for benign indications and 29 (58%) for malignant conditions (Table-1).

PCN was successfully completed in 42 kidneys (84%) cases. The 8 cases in which the procedure was not completed included both benign and malignant conditions (Table-2).

Failure was seen mostly in the early part of study and was attributed to the learning curve and difficult renal anatomy. Open nephrostomy was carried out in failed procedures.

The average time taken for completing the procedure was 48 minutes ranging from 20 minutes to 120 minutes. There were no major procedure related complications or deaths. Tube displacement was seen in 6 cases (12%). Transient hematuria was seen in 7 cases (14%). No blood transfusions were required and hematuria settled on its own in 1-3 days. Post procedure urine leak was present in one patient (2%).

There were no procedure related complications in patients in whom the procedure failed. The complication rate between benign and malignant diseases was not significant p value = 0.0945.

The serum creatinine was compared after the procedure with those of previous values using the paired t test (Tables-3 and 4).

Of the 32 patients who were subjected to PCN for various conditions, 20 were subjected to open definitive surgeries. There were 4 deaths in the study group; 3 of these were in the malignancy group and 1

Table 1 – *Distribution of indications for percutaneous nephrostomy (PCN).*

Indication	Number of PCN	Definitive Surgery Performed
Benign		
Calculus diseases	8 (16%)	Pyelolithotomy/ureterolithotomy
UPJ obstruction	7 (14%)	Pyeloplasty
Pyonephrosis	4 (8%)	Pyelolithotomy
Chyluria	2 (4%)	Resolved conservatively
Malignant		
Ca urinary bladder	10 (20%)	TURBT
Ca uterine cervix	6 (12%)	None
Ca endometrium	4 (8%)	None
Ca rectum	5 (10%)	APR
Ovarian tumors	2 (4%)	None
Renal cell carcinoma	2 (4%)	None

UPJ = ureteropelvic junction; Ca = cancer; TURBT = transurethral resection of bladder tumor; APR = abdominoperineal resection.

Table 2 – *Distribution of cases in which percutaneous nephrostomy failed.*

Indication	Number
Malignant	2 (4%)
Renal cell carcinoma	2 (4%)
Ca Endometrium	1 (2%)
Ovarian tumors	1 (2%)
Ca uterine cervix	
Benign	
Calculus disease	1 (2%)
UPJ obstruction	1 (2%)

UPJ = ureteropelvic junction.

Table 3 – *Comparison of percutaneous nephrostomy complications in benign and malignant cases.*

	Complication	No Complication	Total
Benign	9	12	21
Malignant	5	24	29
Total	14	36	50

$\chi^2 = 2.8$; $p = 0.0945$ (not significant).

Table 4 – *Comparison of serum creatinine (mg/dL) before and after percutaneous nephrostomy in all 50 cases.*

	Mean	SD	SE
Before	5.22	3.73	0.528
After	4.40	3.71	0.525
Difference	0.82	2.31	0.327

Difference between means = 0.82; confidence interval (95%) = 0.16 – 1.48; t = 2.5; 2-tailed p = 0.0158 (significant).

in the benign group, however, none of these were procedure related.

In the benign group out of 17 patients, 15 improved, 1 died and 1 was referred to a higher centre.

In the malignant group of 15 patients, 6 patients showed improvement, 6 patients did not show any improvement, 3 patients died and no patient was referred.

COMMENTS

Most of the studies have shown a success rate of more than 90% under various types of guidance modalities (2,3,6). PCN has traditionally been done

under fluoroscopic guidance by radiologists and a success rate of more than 95% is common (2). It is in only the last decade that more and more procedures have been performed under other guidance modalities such as ultrasound and CT scan (7,8).

Percutaneous nephrostomy can be performed under ultrasound guidance with a success rate ranging from 83.1% to 92% (3,6).

Traditionally diversion has been accomplished by cystoscopy with retrograde passage of ureteric catheter and only in the event of obstruction to catheter passage, nephrostomy is performed but in our setup where cystoscopy is not always readily available nephrostomy is an attractive alternative.

Pederson was the first to use only sonographic guidance for Percutaneous nephrostomy, and reported a success rate of 70 % (4). Since then a large number of studies have been carried out under sole ultrasound guidance describing success rate up to 92%. This is because of the advent of high resolution ultrasound machines with better view of the pelvicaliceal system allowing a success rate comparable to fluoroscopic guidance with practically no radiation hazard.

In our study the success rate was 84%, which was consistent with the above mentioned studies.

Azotemia due to bilateral obstructed kidneys has been the most frequent indication of nephrostomy. PCN is often the simplest method for the initial management of obstructive renal failure due to hazards of surgery in uremic patients.

PCN is sometimes described as a temporizing measure prior to corrective surgery (5,6). We observed similar pattern in our series too as in 10 out of 17 benign cases (58%) surgery was carried out. PCN was definitive in 5 patients (29%). In the malignant group definitive surgery was planned according to the origin and grading of malignancy.

PCN was performed for both benign and malignant diseases. In 17 benign cases it was done to relieve obstruction and salvage the kidneys, which was significantly achieved. (Tables-4 and 5). Subsequent surgery followed in 10 cases. PCN proved to be definitive by itself in one patient with chyluria. Patient improved markedly and no further intervention was required. There was one death in the study, 7 days after the procedure; the cause of death being rheumatic heart disease with mitral regurgitation, mitral stenosis and tricuspid regurgitation. One child was referred because of procedure failure.

The most consistent and gratifying results were seen in patients who presented pyonephrosis. PCN was successfully completed in all 4 cases and kidneys were salvaged in all cases with the least morbidity. The co-existence of azotemia and pyonephrosis increases the urgency as well as value of percutaneous Nephrostomy. Camunez et al. also observed that following PCN in pyonephrosis clinical symptoms disappeared in 24 - 48 h after the procedure and once the acute phase was over definitive surgery could be carried out (9).

Table 5 – *Comparison in serum creatinine (mg/dL) in benign (n = 21) and malignant (n = 29) cases before and after percutaneous nephrostomy (PCN).*

	Benign Cases			**Malignant Cases**		
Creatinine	**Mean**	**SD**	**SE**	**Mean**	**SD**	**SE**
Before PCN	3.52	3.21	0.702	6.39	3.51	0.651
After PCN	2.18	2.18	0.475	5.41	3.21	0.596
Difference	1.34	2.27	0.494	0.98	3.20	0.595

Benign cases: difference between means = 1.34; confidence interval (95%) = 0.31 – 2.37; t = 2.72; 2-tailed p = 0.0133 (significant). Malignant cases: difference between means = 0.98; confidence interval (95%) = 0.24 – 2.20, t = 1.65; 2-tailed p = 0.1098 (not significant).

In the malignant group there was no significant recovery of the renal functions (Table-5). Definitive surgery was carried out in only 4 out of 15 patients. In 2 patients open nephrostomy had to be performed due to failure or catheter dislodgement. 3 patients succumbed to their illness in the hospital only, the cause of death being grossly deranged renal functions with dyselectrolytemia. Only 6 patients showed definite improvement.

The usefulness of percutaneous nephrostomy as an adjunct in many pelvic organ malignancies has been reviewed in many series. Samarsinghe et al. did not find any renal function improvement in patients with chronic obstruction and terminal malignancy (10).

When hydronephrosis occur from advanced pelvic malignant disease, percutaneous nephrostomy can effectively improve renal function. However, since these patients have an overall poor prognosis, several authors earlier used to question the appropriateness of interventional uroradiological procedures (11,12). Hoe & Tung observed an overall survival median of 5 months after PCN and 68% of people achieving a useful life (13). They concluded that PCN should be performed only in cases where there is no evidence of carcinomatous spread and few or no medical problems.

Various other studies have disputed this claim; Markovich et al. concluded that PCN was beneficial for malignant obstructive uropathy associated with fewer complications as compared to open nephrostomy and increased percentage of time spent at home. The average post-nephrostomy survival time in this study was 7 months (14).

Our study showed definite improvement in 6 out of 15 patients with terminal malignancy, 6 patients did not show any improvement and there were 3 deaths due to an underlying disease. Our results in malignant group were consistent with all previously mentioned studies; renal function could not be recovered in patients who presented late unsalvageable kidneys. However, patients who were seen at an earlier stage benefited from PCN.

PCN is usually performed when a retrograde stenting is not possible. It may be due to difficult anatomy or lack of technical expertise. Comparative studies have been carried out between percutaneous nephrostomy and retrograde ureteric stenting. Pearle et al. found no difference in clinical efficacy, or patient preference between the two procedures and concluded that the choice of procedure may be based on particular circumstance of the patient and availability of facilities to carry it out (15).

A similar study however found PCN to be superior to retrograde stenting, their results demonstrated that percutaneous nephrostomy is tolerated better by patients and has a lower influence on the quality of life than ureteral stents. The effectiveness of percutaneous nephrostomy should be given preference over ureteral stents in case initial signs of infected hydronephrosis are detected (16).

We observed a complication rate of 28%. There was no major complication throughout the study and in 14% of the cases hematuria settled by itself. Tube displacement was other minor complication (12%) for which 3 open nephrostomies had to be performed. Post procedure urine leak was seen in 1 patient which also subsided by itself.

Procedure-related complications continue to be widely reported regardless of the type of imaging employed (17). Rates vary from 25 - 60% though this includes late (more than 24 hours after insertion) minor complications such as those related to tube malfunction, leakage, dislodgment and incrustations. Picus et al. summarized early complications inherent with fluoroscopy-guided PCN, being the most common acute bleeding requiring transfusion (< 5%), failed access (< 5%), adjacent organ injury: bowel, spleen, lung (< 1%), and septicemia (< 1) (17).

In most of the studies significant hemorrhage requiring transfusion or surgical control ranks first among the complications (5.3%) and is equally distributed among ultrasound guided and fluoroscopic guided groups (17). Significant bleeding occurs in patients with associated stones, although this is usually manageable by means of transfusions, open control remains an option and in such instance stone surgery may then be performed. Minor bleeding is common but usually resolves spontaneously with observation and occasional flushing of the catheter.

Adjacent organ injury is another complication, the colon and pleura may be

inadvertently injured; the former had the need of a colostomy, the latter, a tube thoracostomy. Pleural tear has been deemed more common in instances wherein the nephrostomy tract is placed more superiorly, particularly when subsequent stone manipulation is contemplated (17).

These aforementioned complications being present equally in both ultrasound and fluoroscopy-guided PCN may simply indicate no distinction between the two as far as patient safeties is concerned. Overall patient status, skill of the operator, technique and instrumentation would probably play a more significant role.

All findings confirm that PCN is quite effective in improving renal functions provided it is preformed at an earlier stage. Intervention in malignant ureteric obstruction should not necessarily be viewed with as much pessimism as in the past. Ultimately the decision to place a nephrostomy tube lies in the doctor, the family and above all the patient.

CONFLICT OF INTEREST

None declared.

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The Impact of Pelvicaliceal Anatomical Variation between the Stone-Bearing and Normal Contralateral Kidney on Stone Formation in Adult Patients with Lower Caliceal Stones

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ABSTRACT

Objective: We aimed to investigate the effect of pelvicaliceal anatomical differences on the etiology of lower caliceal stones.
Materials and Methods: Records of adult patients between January 1996 and December 2005 with solitary lower caliceal stone were reviewed. After exclusion of patients with hydronephrosis, major renal anatomic anomalies, non-calcium stones, history of recurrent stone disease and previous renal surgery, 78 patients were enrolled into the study. Lower pole infundibulopelvic angle (IPA), infundibulovertebral angle (IVA), infundibular length (IL), width (IW), number of minor calices and cortical thickness of the lower pole together with other caliceal variables obtained from the whole pelvicaliceal anatomy of both stone-bearing and contralateral normal kidneys were measured from intravenous pyelogram of the patients. Total pelvicaliceal volume was also calculated by a previously described formula for both kidneys.
Results: There were statistically significant difference between two kidneys in terms of IW ($p < 0.001$) and IL ($p = 0.002$) of the upper calyx, IW ($p = 0.001$) and IVA ($p < 0.001$) of the lower calyx), pelvicaliceal volume ($p < 0.001$), IPA of middle calyx ($p = 0.006$) and cortical thickness over the lower pole ($p < 0.001$). However there was no difference between stone-bearing and contralateral normal kidneys in terms of lower pole IPA ($p = 0.864$) and IL ($p = 0.568$).
Conclusion: Pelvicaliceal volume but not lower caliceal properties seem to be a risk factor for stone formation in lower calyx.

Key words*: kidney calculi; etiology; kidney pelvis; kidney calices; anatomy*
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INTRODUCTION

Urinary stone disease has afflicted humankind since antiquity. Epidemiological data show an increase in prevalence and incidence rates. The prevalence of this disease has been estimated to be at 13% for adult men and 7% for adult women in the United States (1). The impact of epidemiologic intrinsic (genetics, age and sex) and extrinsic (geography, climatic and seasonal factors, water intake, occupation, diet and stress) factors, urine physical chemistry and inhibitors which play a role on crystal formation, growth and aggregation on the etiology of stone formation have been evaluated extensively in the literature, however the exact mechanism of stone formation remains unclear (2,3).

Pelvicaliceal anatomical variations in stone-bearing kidneys may also play a role in the etiology,

however studies, which investigate pelvicaliceal anatomical differences, are generally interested on stone clearance of lower caliceal stones after shock wave lithotripsy (SWL) rather than its etiologic role. In these studies, several anatomical factors, such as infundibular length, width and infundibulopelvic angle were measured and lower pole ratio was calculated from pretreatment intravenous urogram and most studies concluded that caliceal anatomy was an important risk factor for lower pole stone clearance after SWL (4-6). On the other hand, the effects of pelvicaliceal anatomy on stone formation was not well evaluated up to date. If we consider that the all risk factors for stone formation are similar for both kidneys on a patient, it is very difficult to explain why a calculus is primarily formed in a single calyx but not in another calyx of both kidneys only by metabolic factors. From this point of view, it is very logical to consider that different pelvicaliceal properties among normal and stone-bearing kidneys are the key factors for the lateralization of the stone and also constitute a risk factor for their etiology. In the light of the aforementioned points, our aim in this study was to investigate the probable effect of pelvicaliceal anatomical differences between lower caliceal stone-bearing and normal contralateral kidney on the etiology of stone formation.

MATERIALS AND METHODS

The records of adult patients with solitary lower caliceal stone between January 1996 and December 2005 were reviewed for this retrospective study. After exclusion of patients with hydronephrosis, major renal anatomic anomalies (horseshoe, pelvic and malrotated kidney, bifid pelvis, bifid ureters, ectopic pelvic fusion anomaly), non-calcium stones, history of recurrent stone disease and previous renal surgery, 78 patients were enrolled into the study.

The mean age was 44.5 (range: 21 - 65) years. All the patients had intravenous pyelogram (IVP) available for review. The lower pole infundibulopelvic angle (IPA), infundibular length (IL) and width (IW) of both the stone-bearing and contralateral normal kidneys were measured from IVP of the patients, as described by Elbahnasy et al. (6). These variables were also calculated for upper and middle calices with modification of the same method to these caliceal structures. In addition, infundibulovertebral angle (IVA) as described by Srivastava et al. (7), cortical thickness over the lower pole and the number of minor calices were determined for both stone-bearing and contralateral kidneys. Surface area of the renal collecting system was measured from IVP of the patients using a 1 mm^2 grid, on which the borders and diameters of the pelvicaliceal system were marked. Thus, the surface area of the renal collecting system was calculated by counting the enclosed grid squares. Surface area estimates obtained by three of the study members showed less than 5 percent variability for the same areas. Also, a formula defined as 0.6 $(area)^{1.27}$ was used to calculate the total pelvicaliceal volume of both kidneys (8). Mann-Whitney U and chi-square tests were used for the statistical evaluation of both kidneys' pelvicaliceal parameters.

RESULTS

There were 35 patients with stones on left side and 43 patients on right side. Comparison of the anatomical variables between the stone-bearing and normal kidneys were shown in Table-1. The lower caliceal IPA of the stone-bearing kidney when compared to the normal contralateral kidney was more acute, equal and wider in 53.7%, 2.5% and 43.8% of the patients, respectively. The pelvicaliceal volume of the stone-bearing side ranged from 752 to 6264,2 mm^3 (mean 2569,85) and the difference of the pelvicaliceal volumes of both sides was statistically significant ($p < 0.001$). There was a statistically significant difference in IW and IL of the upper calyx between stone-bearing and contralateral normal kidneys ($p < 0.001$) ($p = 0.002$). The difference in terms of the middle calyx IPA of the stone-bearing and non-stone-bearing contralateral side was also statistically significant ($p = 0.006$). Again, lower pole IVA, IW and cortical thickness of the lower pole were significantly different ($p < 0.001$) ($p = 0.001$) ($p < 0.001$). However, no difference was found in terms of IPA and IW of lower calyx.

Table 1 – *Comparison of pelvicaliceal anatomical variables between the stone-bearing and normal contralateral kidney.*

Variable	Stone-bearing Kidney (Range)	Contralateral Normal Kidney (Range)	p Value
Lower IPA	56.62 (0-144)	56.84 (4- 180)	0.864
Middle IPA	101.28 (20-145)	110.57 (40-155)	0.006
Upper IPA	165 (0-214)	171.19 (16-220)	0.36
Lower IL (mm)	8.88 (1-20)	9.6 (1-25)	0.568
Middle IL (mm)	7.51 (2-18)	7.67 (1-17)	0.725
Upper IL (mm)	9.82 (2-24)	12.28 (2-30)	0.002
Lower IW (mm)	5.62 (1-15)	3.92 (1-12)	0.001
Middle IW (mm)	3.05 (1-10)	2.71 (1-10)	0.208
Upper IW (mm)	4.19 (1-14)	3.01 (1-10)	< 0.001
Lower IVA	33.11 (9-78)	40.66 (10-86)	< 0.001
Number of minor calices	2.12 (1-4)	2.02 (1-3)	0.275
Lower pole cortical thickness (mm)	23.82 (14-36)	27.23 (16-37)	< 0.001
Pelvicaliceal Volume (mm^3)	2569,85 (752-6264,2)	1824,94 (423,4-3997,3)	< 0.001

IPA = infundibulo pelvic angle; IL = infundibular length; IW = infundibular width; IVA = infundibulumvertebral angle.

DISCUSSION

Studies investigating the pathophysiology of urinary stone disease in anatomically normal kidneys generally focus on metabolic risk factors. However, metabolic factors alone are not sufficient to explain both unilateral stone disease and lower caliceal dominance. Some non-metabolic causes like sleep posture have been investigated to explain unilateral urolithiasis (9), but this hypothesis is also unsatisfactory for lower caliceal stones. Also, recurrent stone formation occurs usually in the same calyx and this finding based on our experiences supports our thought that some caliceal properties could play a critical role on stone formation.

The investigations of the relationship between pelvicaliceal anatomical features and urolithiasis started with the pioneering study of Sampaio & Aragão (4). After that, several studies analyzed the pelvicaliceal factors although these studies were generally interested in stone clearance of lower caliceal stones after SWL rather than in its etiologic role (5,6,10). In these studies, several anatomical factors, such as infundibular length, width and infundibulopelvic angle were measured and lower pole ratio was calculated on pretreatment intravenous urogram. Sampaio & Aragão concluded that an angle of less than 90-degrees between lower pole infundibulum and pelvis, multiple calyces and a caliceal width < 4 mm might lead to retention of residual stones in lower caliceal group after lithotripsy (4). Similarly most studies agreed that the caliceal anatomy was an important risk factor for lower pole stone clearance after SWL (5,6), however opposite opinions also exist (10).

In this study, our aim was to determine the probable effect of intrarenal anatomic variations on the etiology of lower caliceal stones and we evaluated the whole pelvicaliceal specifications of the stone-bearing and normal contralateral kidneys of 78 adult patients with unilateral lower caliceal stones. However, our results were somewhat confusing. Although there was a statistically significant difference in middle caliceal IPA ($p = 0.023$), upper caliceal IL and IW ($p = 0.025$) ($p = 0.029$) and lower caliceal IW ($p = 0.001$) between normal and stone-bearing kidneys, there were no difference in lower caliceal IL and IPA. Although gravitational factor might be more effective than the effect of the upper or middle caliceal variations on stone formation, these findings are also inadequate to explain the lateralization of the stone unless the stone exists in

this defective upper or middle calyx. On the hand, there are only few studies, which focus on the etiologic role of these intrarenal anatomical factors (11,12). Gökalp et al. compared 119 lower caliceal stone-forming kidneys with 40 healthy controls and they concluded that lower pole IPA was not an important factor for stone formation in lower calyx similar to our study (11).

They found statistical significant difference in terms of lower infundibulum diameter and lower caliceal length. But their study group was different from our study group in that they compared the intrarenal anatomical parameters of the stone forming kidney with the normal kidney of healthy controls. The important paradox on this comparison was that the two kidneys were not under the similar metabolic conditions, while in our study the stone-bearing and control kidneys were under same metabolic load. In another study, Nabi et al. evaluated 100 consecutive patients with lower caliceal stones and they found that lower pole IPA was more acute in 74% of cases in stone-forming side than the normal contralateral kidney (12). They concluded that IPA was a significant risk factor for lower caliceal stones. However, they did not evaluate the factors other than IPA and IW of lower calyx. Also, they did not mention the age distribution of their patient group since pediatric and adult patients could have different intrarenal anatomies. When we consider the stone clearance after SWL in lower caliceal stones, we demonstrated different stone-free rates in pediatric and adult patients according to their different pelvicaliceal features (13) and this difference might also have a role on stone formation.

Interpretation of pelvicaliceal anatomy from two-dimensional IVP is very difficult. A large series of three-dimensional endocasts of the kidney collecting system showed that the superior pole was drained by a single caliceal infundibulum in 98% of cases where as the inferior pole was drained by paired calices arranged in two rows in 58% of cases and by a single caliceal infundibulum in only 42% of cases (14,15). Moreover, some kidneys may have even more complex anatomy with atypical minor caliceal structures although we did not find any significant difference between the number of minor calices at lower pole. However, main lower caliceal infundibulum still seems to be the major factor for lower caliceal drainage. Our results showed statistical difference in lower caliceal IW but not in IL. These factors can change among patients and complicate to reach a final conclusion so all lower caliceal features should be accounted together. Because of this fact, studies that can be performed with 3 dimensional scanning could be more comprehensive. On the other hand, there were no baseline data to compare the pelvicaliceal variations and there would be a similar variation between 2 healthy kidneys. However, if there is an additional underlying metabolic factor, these anatomic differences might be a complementary factor on stone formation.

Another important point on interpretation of pelvicaliceal variations is the different measurement techniques and interobserver variations. Proper assessment of lower caliceal features seems to be a particular problem because several authors described different methods (6,16,17). A recent study showed that there were high interobserver variations among different techniques (18). We performed our measurements with the method described by Elbahnasy et al. (6) and the mean of the measurements by three different members of the study was accepted as the study data to eliminate the effect of intraobserver variations, which can also affect the results. Again, the imaging quality should be taken into account to achieve the best reliable data.

On the other hand, crystals must remain some time in pelvicaliceal system to form urinary stones and Schulz found that patients with urolithiasis are characterized by larger areas of renal pelvis or calyx on urogram (19). He hypothesized that larger pelvicaliceal system dimensions and higher ramification was the etiology of stone formation assuming that both healthy people and urolithiasis patients excrete similar volumes of urine. In addition, in the above study, it was estimated that the duration of stay for the urine might be up to 20 times longer in urolithiasis patients when compared to normal people. The stagnation and retention of crystals is at least as important as the formation of the crystals. In our study, the mean pelvicaliceal volume of the stone-forming and the normal kidneys were 2569,85 (752-6264,2)

and 1824,94 (423,4-3997,3) mm^3, respectively ($p < 0.001$). The difference between these two groups in our study is a finding that parallels with the aforementioned hypothesis. We excluded all patients with hydronephrotic systems or any kind of caliceal dilations from the study so the large pelvicaliceal volumes are not related with obstruction but seem to be an anatomic specification of the affected kidney. Some reasons for large unilateral pelvicaliceal volume such as prior undetermined silent stone episode, complex renal anatomy with multiple calices or factors that affected the kidney at the evolution phase during childhood can be speculated. No matter what the reason was, the larger pelvicaliceal volumes of the stone-bearing kidney might be the evidence of urine stagnation although this should be confirmed with diuretic renograms to exclude any obstruction. Even if the longer stay of urine in the renal collecting system is not the sole factor, longer stay of crystals in a supersaturated media may cause calculi when a nidus exists. Although some lithogenesis can begin within the tubules, static condition of the lower calyx may be a complementary factor for lower caliceal stone etiology.

Concluding, our result shows that the etiology of stone formation does not depend solely on the lower pole pelvicaliceal anatomy in patients with lower caliceal stones but rather confirm the multifactorial etiology responsible for stone formation in the urinary tract. Larger pelvicaliceal volumes may result in impairment of drainage of the lower caliceal system and play a subtle role during the beginning of the nucleation process. The statistical significance of lower IW could not though be very important alone without statistical significance of lower IL and IPA, it can rather be a variant of larger pelvicaliceal system. Although we found significant differences in middle IPA, upper IL and IW between the stone bearing and normal contralateral kidneys, etiologic role of these middle and/or upper caliceal anatomical variations were uncertain. From this point of view, we can conclude that pelvicaliceal volume and lower caliceal IW seem to be risk factors for stone formation in lower calyx, however, all caliceal features should be accounted together to individualize the situation in each case.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The high prevalence of nephrolithiasis has lead to significant interest in determining risk factors for stone formation. Most studies have focused on metabolic causes to identify risk factors for stone formation. This study by Kupeli et al. evaluates the relationship of pelvicaliceal anatomy and risk for lower caliceal stone formation. They found the stone-bearing kidney had a higher pelvicaliceal volume than the contralateral "normal" kidney controlling for obstruction, but no clear association was found with regard to IPA, IL, IW or IVA. The authors should be commended for attempting to identify anatomic risk factors for stone formation. However, there are several potential limitations of their study that may impact their conclusions.

First, the authors excluded patients with recurrent stones. If an anatomic variation is associated with an increased the risk of stone formation then the impact of this factor should be most evident in patients with recurrent and not first time stone-formers. It has

been suggested that some anatomic abnormalities associated with stasis may contribute to an increased risk of stone-formation such as noted by the authors (hydronephrosis, UPJ obstruction, horseshoe kidney, etc) and does point to the importance of imaging such as intravenous pyelogram in the evaluation of stone-formers.

Although anatomic factors may contribute to the likelihood of forming a stone, the actual clinical usefulness of identifying these abnormalities is questionable. Unless one plans to screen the population to identify those harboring an anatomic abnormality that places them at increased risk of stone formation and then treatment them prophylactically without them having a stone, this information may be of limited value. The importance of the work of Sampaio and others in evaluating anatomic variations was to help guide treatment in patients with stones.

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EDITORIAL COMMENT

Since the pioneering work of Sampaio & Aragao (1), who introduced the concept of inferior pole collecting system anatomy, impacting the results of shock wave lithotripsy (SWL) for lower pole renal calculi, many clinical series have been published on this topic. The debate on the role of various anatomical features, on stone clearance after SWL, is still on going and far from being resolved.

Subsequently, there have been only a handful of articles looking at renal collecting system anatomy, especially lower pole caliceal anatomy, and its probable etiological role in lower caliceal stone formation. The most commonly sited significant anatomical features in these studies remain to be that of acute infundibulo-pelvic angle (IPA), greater infundibular length (IL) and smaller infundibular width (IW). The authors in this study compared the normal kidney to the contralateral stone forming side, and with this design, they were able to control for known confounding patient factors such as urine output and metabolic load. It is also commendable that they have taken much effort to minimize inter-observer variability in their measurement techniques. Interestingly, in contrast to the other studies, even with one of similar design, this study found that a larger mean pelvicaliceal volume and IW, rather than the other common lower caliceal anatomical features, appear to be the possible risk factors for lower caliceal stone formation. As hypothesized by Schulz (2), reduced flow rates and urine stagnation associated with larger pelvicaliceal dimensions could play a part in urinary calculi formation, seemingly providing a basis for the authors' current postulations, in this study.

However, it must be borne in mind that measurements of anatomical factors in many studies so far, have been made on a 2-dimensional radiograph, which may not accurately reflect the true 3-dimensional anatomical structure of the renal collecting system, and fraud with high observer variability. Furthermore, the fact that the renal collecting system is one of dynamic rather than a static geometric structure, and that mainly static imaging techniques are used to assess these anatomical factors, introduces a significant confounding factor in studies of this kind. Unless novel use of dynamic imaging studies are made to determine actual urinary drainage, and until a clearer consensus appears in literature, it

can only be said that significant renal anatomical factors that predispose to lower caliceal stone formation are yet to be determined, and further investigation in this area should be carried out.

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EDITORIAL COMMENT

It is becoming increasingly evident that urolithiasis is a group of disorders rather than a single disease. Despite extensive study, we still do not have clear answers about the etiology of urinary stone disease. Anatomical factors could play a role in causation, although, their exact place within the context of a unified hypothesis remains unclear.

This study compared anatomical variables of collecting system volume, and individual caliceal group morphology between stone-bearing and normal contralateral kidney in 78 patients. The data showed that in the stone bearing kidney the overall collecting system volume is significantly greater, the lower pole cortex is thinner, the lower infundibulovertebral angle is smaller and the lower infundibular width is greater compared to the normal contralateral kidney. They also found that stone bearing kidneys had a smaller middle infundibulopelvic angle, as well as a shorter and wider upper infundibulum. The authors conclude that pelvicaliceal volume and lower infundibular width are risk factors for stone formation in the lower pole calices, while the significance of other findings is uncertain.

Although the paper does provoke thought, solid evidence for stagnation of urine in the stone-bearing kidney is lacking. A larger pelvicaliceal system volume does not necessarily translate into urine stagnation in the collecting system without functional evidence of delayed drainage. The role of a wider lower pole infundibulum in the causation of lower pole calculi also remains unclear. The thinner lower pole cortex could be an interesting observation and could be a cause or an effect of the stone. A scarred pyelonephritic group of calices may be associated with stone formation.

The collecting system of the kidney is a dynamic rather than a static geometrical structure and that fact will remain a confounding factor in studies of this nature, unless some kind of novel scintigraphic study can be used to determine actual drainage from individual components of the collecting system. In addition, the intrarenal caliceal anatomy is more complex than is evident from a two-dimensional IVP film, in terms of how minor calices drain into the major caliceal group or even into the renal pelvis.

Clearly, more work is needed to study the complex anatomical and functional features of stone bearing kidneys and calices for a better understanding of the interplay between anatomical and metabolic factors in the etiopathogenesis of urinary calculi.

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Ureteroscopic Pneumatic Lithotripsy of Impacted Ureteral Calculi

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ABSTRACT

Introduction: This work evaluates the results of ureteroscopic treatment of impacted ureteral stones with a pneumatic lithotripter.
Materials and Methods: From March 1997 to May 2002, 42 patients with impacted ureteral stones were treated by retrograde ureteroscopic pneumatic lithotripsy. Twenty-eight patients were female and 14 were male. The stone size ranged from 5 to 20 mm. The ureteral sites of the stones were distal in 21, middle in 12 and proximal in 9.
Results: Considering stones with distal location in the ureter, 1 patient had ureteral perforation and developed a stricture in the follow-up (4.7%). As for stones in the middle ureter, 2 perforations and 1 stricture were observed (8.3%) and regarding stones located in the proximal ureter, 5 perforations and 4 strictures occurred (44%). In the mid ureter, 1 ureteral avulsion was verified. In 34 patients without ureteral perforation, only 1 developed a stricture (2.9%). Of 8 patients who had perforation, 6 developed strictures. The overall incidence of stricture following treatment of impacted ureteral calculi was 14.2%.
Conclusions: Ureteroscopy for impacted ureteral calculi is associated with a higher incidence of ureteral perforation and stricture. Ureteroscopy of proximal ureteral calculi is associated with a high risk of perforation, when compared to mid or distal ureteral calculi. Ureteral perforation at the site of the stone seems to be the primary risk factor for stricture formation in these cases.

Key words*: ureteroscopy; ureteral calculi; lithotripsy; injury; stenosis*
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INTRODUCTION

Impacted ureteral stone is commonly considered as a condition where a stone remains at the same site for more than 2 months (1). Impacted ureteral stone are the most difficult to treat, because there is a severe ureteral inflammation. This fact results in an increased risk of ureteral injury by instruments during endoscopic procedure (2). Extracorporeal shockwave lithotripsy (SWL) is widely used for treatment of ureteral stones as well as ureteroscopic techniques with a high rate of success (3,4). However, poor results have been obtained with the treatment of impacted ureteral stones by SWL (5,6). On the other hand, ureteroscopic approach is not so easy and has a high rate of complications (2). Although new ureteroscopes and lithotripters have been developed, the best treatment for impacted ureteral stones remains controversial. Ureteral stricture formation is a well recognized complication of impacted stone disease with rates as high as 5% after any treatment modality employed in early series (7).

Harmon et al. reported the rate of stricture formation after ureteroscopy to be 0.5% in 1992 compared to 1.5% 10 years earlier (8). In the present study, we assessed prospectively the effectiveness of ureteroscopic pneumatic lithotripsy for treatment of impacted ureteral stones.

MATERIALS AND METHODS

From March 1997 to May 2002, 42 patients with impacted ureteral stones were treated by ureteroscopic pneumatic lithotripsy. Twenty-eight patients were female and 14 were male. The age ranged from 23 to 72 years old. The stone size ranged between 5 and 20 mm. One patient had a 5 mm calculus, 11 had calculi between 6 and 10 mm, 18 had calculi between 11 and 15 mm and 12 patients had calculi between 16 and 20 mm. Stones were located in the distal ureter in 21 patients, in the mid ureter in 12 and in the proximal ureter in 9.

The access to the calculi was retrograde in all patients. The procedures were carried out with the patients in the lithotomy position under lumbar anesthesia. Ureteral orifice dilatation was necessary in 3 patients.

A retrograde ureteropyelogram was performed in all cases to study the ureteral anatomy and a guide wire (Teflon or hydrophilic) was inserted prior to the introduction of the ureteroscope. The hydrophilic guide wire was used in the cases where it was impossible to pass the Teflon guide wire.

Ureteroscopy was performed with 8.5F semi rigid ureteroscope (Wolf Medical Instruments, Vernon Hills, Illinois, USA). The ureteroscope was introduced just under the stone and confirmation of its attachment to the edematous and hyperemic ureteral mucosa was obtained. The fragmentation of the stones was done with a pneumatic lithotripter (Electro Medical Systems, Kaufering, Germany). The fragments were removed with a grasping forceps or a Dormia basket. At the end of the procedure, a retrograde ureteropyelogram was performed to verify whether there was perforation and a double-J catheter was introduced in all the patients and left in place for 3 weeks (Figure-1). All the procedures were performed

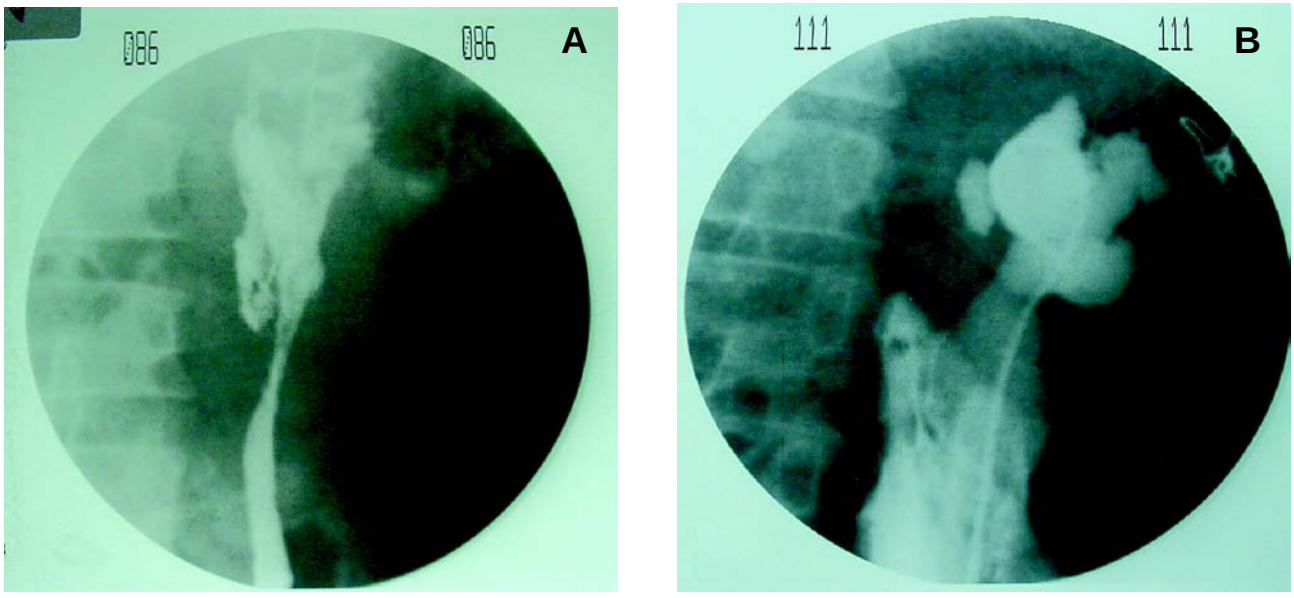

Figure 1 *– Intraoperative proximal ureteral perforation (A) treated with double-J stenting (B).*

Table 1 – *Stone size and incidence (percentage) of ureteral perforation.*

Stone Size	Distal Ureter	Mid Ureter	Proximal Ureter
< 5 mm	Patients = 1 Perforation = 0	Patients = 0 Perforation = 0	Patients = 0 Perforation = 0
6 - 10 mm	Patients = 8 Perforation = 0	Patients = 2 Avulsion = 1 (50%)	Patients = 1 Perforation = 0
11 - 15 mm	Patients = 4 Perforation = 0	Patients = 6 Perforation = 0	Patients = 8 Perforation = 5 (62.5%)
16 - 20 mm	Patients = 9 Perforation = 1 (11.1%)	Patients = 3 Perforation = 2 (66.6%)	Patients = 0 Perforation = 0

under fluoroscopic and visual guidance. All patients were submitted to an intravenous pyelogram after 2 months to verify ureteral patency.

RESULTS

No complication was observed for stone smaller than 5 mm. For the 11 stones between 6 and 10 mm, there was 1 ureteral avulsion with the Dormia basket. This complication was treated by ureteral reimplantation with a Boari bladder flap. Postoperative evaluation at 6 months, by intravenous pyelogram, showed a good result. For the 18 calculi between 11 and 15 mm there were 5 ureteral perforations and for the 12 calculi between 16 and 20 mm, there were 3 cases of ureteral perforation (Table-1).

The relation of the calculi site and perforation showed that in 21 distal calculi there were only 1 perforation and 1 stricture (4.7%). In the 12 mid ureteral calculi, there were 1 ureteral avulsion, 2 perforations and 1 stricture (8.3%), and in the 9 proximal ureteral calculi, there were 5 perforations and 4 strictures (44%). In 3 of these 4 patients that developed strictures, it was not possible to withdraw all fragments, because during the procedure there has been a mild hemorrhage and it was stopped (Table-2).

The overall incidence of strictures was 14.2%. For the treatment of ureteral strictures, the renal function was also available in 4 patients that presented large pelvicaliceal dilation. In these patients, a nephrostomy tube was placed and a renal scintigraphy was done. In 3 patients, renal scintigraphy shows a renal function lower than 20%, being indicated nephrectomy for these cases and in 1 patient the renal function was higher than 20% being indicated incision of the stenosis with the Acucise® catheter (Applied Urology, Rancho Santa Margarita,

Table 2 – *Complications of impacted ureteral calculus.*

Calculus Site		Distal Ureter	Mid Ureter	Proximal Ureter
Patients		21	12	9
Complications	Perforation	1 (4.7%)	2 (16.6%)	5 (55.5%)
	Avulsion	0	1 (11.1%)	0
Stricture		1 (4.7%)	1 (8.3%)	4 (44%)

California, USA). Three patients had ureteral stenosis with good renal function and an incision of the stenosis with the Acucise® catheter was indicated. Evaluation by intravenous pyelogram, at 6 months, of the 4 patients in that was did incision with Acucise® catheter, showed good results in all.

Analysis of all cases of ureteral stricture showed that in 34 patients without ureteral perforation only one presented late stricture (2.9%), while in 8 patients that had perforation, 6 presented strictures (75%).

The overall stone free rate was 92.9%.

DISCUSSION

SWL can be a modality treatment for most upper urinary tract stones, because of its simplicity, noninvasiveness and minimal morbidity. However, some stones are difficult to fragment by SWL or the fragments may remain in the urinary tract even after successful fragmentation of the stone. Since residual stones can cause hydronephrosis followed by a decrease in renal function or urinary tract infection, residual fragments should be removed even if they are less than 4 mm in diameter (9). Impacted ureteral calculi are more difficult to fragment with SWL than stones lying in the renal pelvis, because of the lack of natural expansion space for stones in ureter (10,11). In the aforementioned situations, ureterolithotripsy is the best treatment option (12).

Four sources of energy for intracorporeal lithotripsy are now available, that is, electrohydraulic, ultrasound, pneumatic and Holmium laser. With electrohydraulic and ultrasonic energy, there is more risk of complication, as for example ureteral perforation. The pneumatic energy is strong enough for fragmenting all types of stones and is cheaper than Holmium laser. However, with the pneumatic lithotripter, there is more retrograde migration of the ureteral stone during its fragmentation.

Impacted ureteral stone, is considered a condition where a stone remains at the same site for more than 2 months (1). All cases in our series fulfilled this criterion and were treated by ureteroscopic pneumatic lithotripsy.

Migration of stone fragments to the kidney is an unfavorable aspect that may occur during pneumatic lithotripsy requiring special care during stone fragmentation (13). Removal of all the stone fragments is important to prevent additional chronic mucosal inflammation leading to stricture formation (14,15).

Ureteral stricture formation is a recognized complication of ureteral instrumentation and stone removal. The mechanism of stricture formation has not yet been completely elucidated and it is likely to be multi-factorial. However, direct mechanical trauma (perforation or avulsion), relative ischemia from the use of large diameter ureteral instruments and thermal injury have been implicated as contributing factors in stricture formation (1).

Patients with chronically impacted stones, show inflammation and edema of the ureteral wall, and these changes may spread to the surrounding tissues. Histological studies have revealed chronic inflammation, interstitial fibrosis and urothelial hypertrophy at the site of impacted stones. Ureteral edema and fibrosis may arise from ischemia secondary to chronic pressure or from an immunological reaction to the stone material (2,15).

Dretler & Young identified residual stones as an etiological factor of ureteral stricture. They found foreign body reaction around calcium oxalate crystals, at the site of the stricture, in patients who underwent stone fragmentation before extraction. This finding suggests that fragments of calculi embedded in the ureteral mucosa may stimulate inflammation that may result in stricture formation (15).

After this study, we believe that large impacted ureteral stones, in the proximal ureter, should be treated by retroperitoneoscopy or flexible ureteroscope with Holmium laser stone-fragmentation and not with semi rigid ureteroscopic. In this study, we work only with semi rigid ureteroscopic and stone fragmentation with pneumatic lithotripter because we did not have flexible ureteroscope and Holmium laser by that time.

Our experience showed that when there was ureteral perforation during the extraction of impacted calculi, there was a higher risk of ureteral stricture formation. Although ureteral perforation can be

avoided with meticulous technique, the luminal pathological changes increase odds of the injury and stricture formation.

CONCLUSIONS

Ureteroscopic pneumatic lithotripsy is a useful treatment modality of impacted ureteral calculi, but it is associated with a higher incidence of strictures. The treatment of proximal ureteral calculi has an increased risk of perforation, when compared to distal ureteral calculi, and ureteral perforation increases the risk of stricture formation.

CONFLICT OF INTEREST

None declared.

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Complications in Laparoscopic Radical Cystectomy. The South American Experience with 59 Cases

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ABSTRACT

Objective: In this study, we have gathered the second largest series yet published on laparoscopic radical cystectomy in order to evaluate the incidence and cause of intra and postoperative complication, conversion to open surgery, and patient mortality.
Materials and Methods: From 1997 to 2005, 59 laparoscopic radical cystectomies were performed for the management of bladder cancer at 3 institutions in South America. Twenty nine patients received continent urinary diversion, including 25 orthotopic ileal neobladders and 4 Indiana pouches. Only one case of continent urinary diversion was performed completely intracorporeally.
Results: Mean operative time was 337 minutes (150-600). Estimated intraoperative blood loss was 488 mL (50-1500) and 12 patients (20%) required blood transfusion. All 7 (12%) intraoperative complications were vascular in nature, that is, 1 epigastric vessel injury, 2 injuries to the iliac vessels (1 artery and 1 vein), and 4 bleedings that occurred during the bladder pedicles control. Eighteen (30%) postoperative complications (not counting mortalities) occurred, including 3 urinary tract infections, 1 pneumonia, 1 wound infection, 5 ileus, 2 persistent chylous drainage, 3 urinary fistulas, and 3 (5%) postoperative complications that required surgical intervention (2 hernias – one in the port site and one in the extraction incision, and 1 bowel obstruction). One case (1.7%) was electively converted to open surgery due to a larger tumor that precluded proper posterior dissection. Two mortalities (3.3%) occurred in this series, one early mortality due to uncontrolled upper gastrointestinal bleeding and one late mortality following massive pulmonary embolism.
Conclusions: Laparoscopic radical cystectomy is a safe operation with morbidity and mortality rates comparable to the open surgery.

***Key words**: laparoscopy; bladder neoplasms; cystectomy; intraoperative complications*
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INTRODUCTION

Open radical cystectomy remains the gold standard for the treatment of muscle invasive bladder cancer. Over the last decade, this complex and time consuming operation has been refined and standardized into a safe procedure with a 1-3% operative mortality in most modern series (1). Nonetheless, the overall complication rate after open radical cystectomy and urinary diversion could be as high as 25% to 35% (1). Recently, there has been an increased interest in the laparoscopic approach for radical cystectomy, which could potentially have a positive impact on the morbidity of this operation (2). In this

study, we have gathered the second largest series yet published on laparoscopic radical cystectomy in order to evaluate the incidence and cause of intra and postoperative complications, conversion to open surgery, and patient mortality.

MATERIALS AND METHODS

From 1997 to 2005, 59 laparoscopic radical cystectomies were performed for the management of bladder cancer at 3 institutions in South America (Figure-1), including 51 cases of muscle invasive cancer, 4 cases of recurrent carcinoma in situ (CIS) and 4 cases of salvage operation after chemotherapy failure. All patients had negative metastatic work-out based on chest x-ray and abdominal computed tomography (CT). A 5-port transperitoneal approach was employed in all operations as described in details elsewhere (3,4). Nonetheless, more recently, in all institutions involved in this study, the camera port has been re-positioned 2 fingerbreadths above the umbilicus, thus facilitating the complete resection of the uracus. Pelvic lymphadenectomy was performed after radical cystectomy using the following boundaries; the pubic bone distally to the bifurcation of the common iliac artery proximally and from the genitofemoral nerve laterally and the obturator nerve inferiorly. All surgical specimens were extracted intact within an impermeable bag either through a 5-6 cm midline incision (46 cases), a 5-12 cm Pfannenstiel incision (6 cases), a perineal incision (1 case of radical cystectomy and concomitant uretrectomy in a male), extension of the stomal incision (1 case), and through the open vaginal vault (5 cases). Out of 13 cases of laparoscopic radical cystectomy in female patients, anterior pelvic exenteration was performed in 8 with concomitant uretrectomy in 5 cases. In 4 cases, the uterus and vagina were spared and in 1 case the patient had a prior hysterectomy. Twenty nine patients received continent urinary diversion, including 25 orthotopic ileal neobladders and 4 Indiana pouches. Only one case of continent urinary diversion was performed completely intracorporeally (Y-shaped ileal neobladder constructed with non-absorbable titanium staples) (5), the others were performed by open surgery through either an infra-umbilical midline incision or a Pfannenstiel incision in a hybrid laparoscopic assisted approach (6). The uretero-intestinal anastomosis were also performed using conventional open surgical techniques except in 2 cases of ileal neobladder, 1 totally intra-corporeally constructed and 1 in which the ureters did not reach the Pfannenstiel incision and had to be anastomosed to neobladder using free hand laparoscopic suturing. The uretero-intestinal anastomosis was performed open surgically in only one (through an extended 12 cm Pfannenstiel incision) case as described by Basillote (7). In the other cases, the recently fashioned reservoir was re-introduced into the abdominal cavity, pneumoperitoneum was restored and the urethra-intestinal anastomosis was preformed laparoscopically. Non-continent urinary diversion was used in 30 patients, including: ileal conduit and cutaneous ureterostomy (3 cases after salvage operation). All procedures were performed by the same primary surgeon at each institution. Data were collected prospectively and analyzed regarding morbidity, mortality and conversion to open surgery.

RESULTS

Mean operative time was 337 minutes (150-600). Estimated intraoperative blood loss was 488 mL (50-1500) and 12 patients (20%) required blood transfusion. All 7 (12%) intraoperative complications were vascular in nature, that is, 1 epigastric vessel injury, 2 injuries to the iliac vessels (1 artery and 1 vein), and 4 bleedings that occurred during the bladder pedicles control. All intraoperative hemorrhages (except the epigastric vessels injury) were managed laparoscopically either by free hand laparoscopic suturing or by the use of the Endo-GIA stapler device. Eighteen (30%) postoperative complications (not counting mortalities) occurred, including 3 urinary tract infections, 1 pneumonia, 1 wound infection, 5 paralytic ileus, 2 persistent chylous drainage, 3 urinary fistulas, and 3 (5%) postoperative complications that required surgical intervention (2 hernias – one in the port site and one in the extraction incision, and 1 bowel obstruction). Overall, the complication rate was

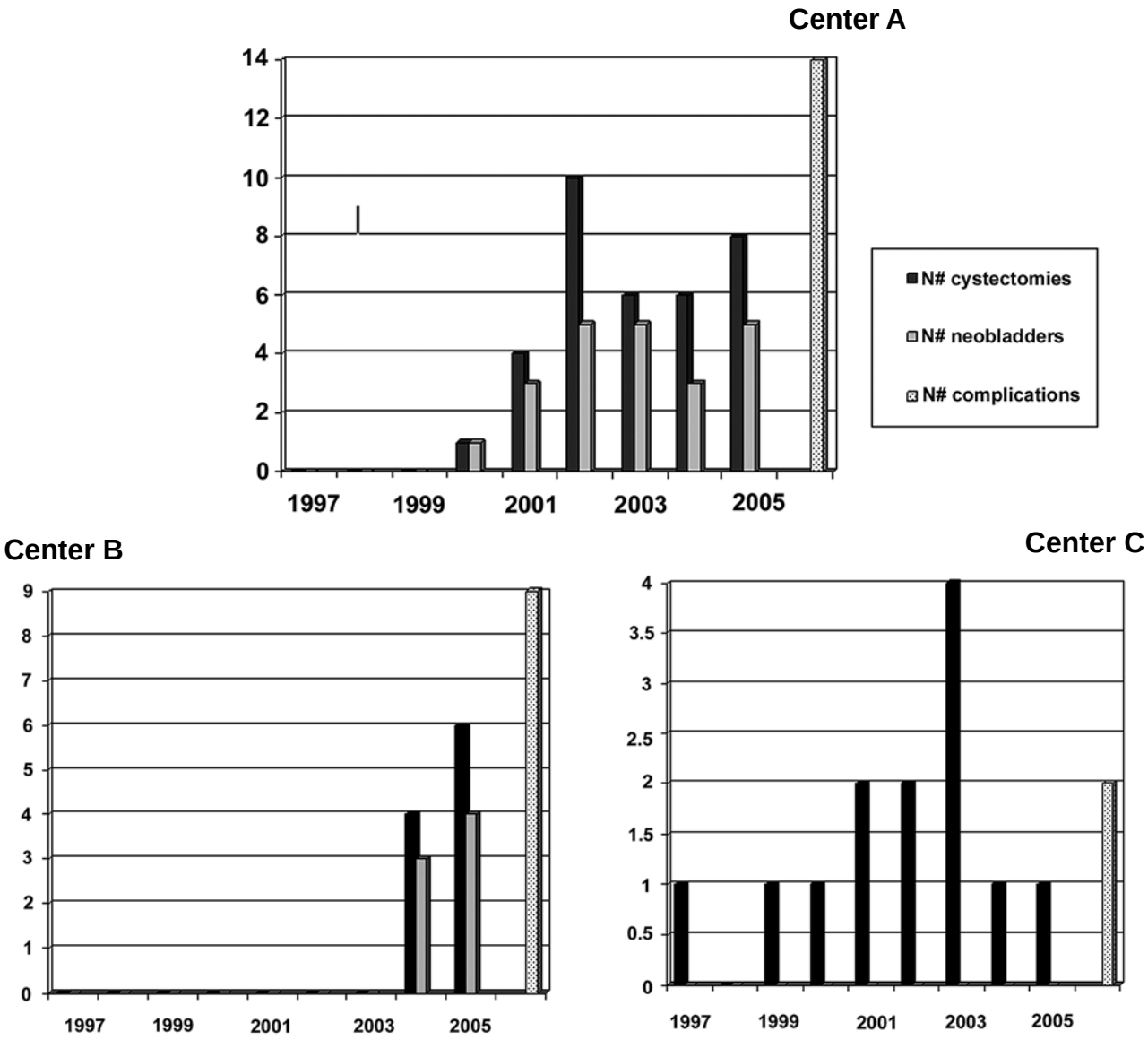

Figure 1 – *Year based distribution (from 1997 to 2005) of 59 cases of laparoscopic radical cystectomy, with the number of continent urinary diversions and also the overall complication rate from each center.*

42% (25 cases). One case (1.7%) was electively converted to open surgery. Two mortalities (3.3%) occurred in this series, one early mortality due to uncontrolled upper gastrointestinal bleeding and one late mortality following massive pulmonary embolism. Final pathology revealed 30 cases (50.8%) of pT2, 11 cases (18.6%) of pT3, 2 cases of pT4 (3.4%) and 8 cases with positive nodes (N+ = 13.5%).

DISCUSSION

Laparoscopic radical cystectomy seems to be a safe minimally invasive approach to bladder cancer. In our series, the overall incidence of complications was 42%, being 7 intraoperative (12%) and 18 postoperative (30%), which is comparable to the 30.5% of complications (only postoperative complica-

tions) that were found after studying 2,538 subjects that underwent open radical cystectomy, with ileus in 9.7%, urinary tract infection in 7.8%, dehiscence in 5.5%, wound infection in 5.2%, and postoperative hemorrhage in 1.8%, requiring transfusion greater than 4 units within 72 hours postoperatively (8). In fact, in a review of 152 laparoscopic radical cystectomies performed at 5 centers, the mean operative time was 398 minutes and the mean blood loss was 605 mL (7, 9-12). Twenty eight complications occurred (18.5%), including 1 dehydration, 1 obturator nerve paresis, 1 pelvic infection, 4 urinary tract infection, 1 injury to the external iliac vein, 1 subcutaneous emphysema in one patient with hypercarbia, 2 pulmonary embolism, 5 urinary fistulas (1 case of neobladder to vagina fistula), 3 hematomas, 1 ureteral obstruction secondary to misplaced ureteral catheter, 1 bladder neck contracture, 1 epididymal abscess, 1 wound dehiscence, 1 internal hernia requiring laparotomy 19 days postoperatively, 2 small rectal tears and 2 partial small bowel obstruction. Conversion to open surgery was required in 3 cases; one patient with a markedly enlarged size bladder tumor that prohibited the posterior dissection between the prostate and rectum safely. The other patient who previously had undergone left nephroureterectomy had to undergo conversion to open surgery after difficult dissection was encountered around the left lateral aspect of the bladder. The third one is also the single case of mortality in this series. This patient presented subcutaneous emphysema leading to hypercarbia, needing conversion to open surgery. Four weeks after surgery this patient died of multiple organ failure.

A few complications in our series are worth to be highlighted. Out of 7 intraoperative complications that occurred, 4 of them happened during control of the vascular pedicles. This may be related to the fact that we have mainly used clips (metallic or Hem-o-lock) or harmonic shears to control the vesical vascular pedicles in our cases, attempting to decrease the intraoperative costs related to the use of disposables such as the Endo-GIA stapler (up to 10 vascular loads could be used in one operation), which represents a great obstacle for laparoscopic radical cystectomy to gain acceptance, specially in developing countries (3,13). In one case, despite an uneventful operation, the patient developed chylous fistula (drain fluid analysis with a high concentration of triglycerides 1015 ng/dL and cholesterol 238 ng/dL). The patient was successfully treated with conservative dietary measures (high protein, low fat, medium chain triglyceride diet and salt restriction) for 3 weeks (3). In order to avoid this problem, we have subsequently carefully clip-ligated any larger lymphatic channel prior to its transaction (14). Overall, 3 patients developed urinary fistulas, one case in which the patient did not follow the recommendations in order to properly empty the neobladder, thus resulting in a significant post-void volume and consequently in a cutaneous urinary fistula formation. Fortunately, this fistula was managed conservatively and healed spontaneously with 14 days of indwelling catheterization. In the 2 remaining cases, a fistula developed due to leakage at the ureterointestinal anastomosis. In both cases we have experienced difficulties to exteriorize the ureters through the Pfannenstiel extraction incision. In the first case, the uretero-intestinal anastomosis had to be performed intracorporeally using free hand laparoscopically suturing exclusively, which may had contribute to the fistula formation. In the second case, although we managed to perform the anastomosis open surgically, we have probably applied excessive tension and traction to the ureters to pull them up through the incision, perhaps leading to distal ureteral ischemia, focal necroses, and urinary extravasation. Based on these 2 cases, we only recommend the use of the Pfannenstiel incision to perform the urinary diversion in selected patients. In fact, if one anticipates any difficulty to perform bowel mobilization and uretero-intestinal anastomosis through a low Pfannenstiel incision, an infraumbilical midline incision would certainly be a better option.

Only one case in our series required electively open surgical conversion due to lack of progression in a patient with a high-volume, larger tumor, which precluded proper exposure and dissection of the seminal vesicles and bladder pedicles. This is in line with what have been previously reported by Basillote et al. that had to convert a laparoscopic procedure due

to the markedly enlarged size (10 cm) of the bladder tumor arising in posterior bladder wall that preclude the posterior dissection between the prostate and rectum safely (7). Based on this experience, we believe that the tumor size (high-volume tumors) is an important criteria for proper patient selection and may represent relative or even a formal contraindication for the laparoscopic approach.

In a review of 1,054 patients that underwent open radical cystectomy, Stein et al. reported a 2.5% (27 patients) perioperative mortality rate (15). In our series, 2 patients died of clinical related causes; one patient with pelvic ankyloses and limited ambulation capacity underwent an uneventful operation and presented deep venous thrombus and massive pulmonary embolism on postoperative day 21. The other patient with past history of peptic ulcer presented uncontrolled upper gastrointestinal tract bleeding on postoperative day 5. Nevertheless, gathering our series (2 deaths in 59 cases) with the series from the 5 centers (1 death in 152 cases) previously described we will have a 1.4% mortality rate (3 deaths in 211 procedures) following laparoscopic radical cystectomy that favorably compare to the modern series of the open surgery.

Finally, we would like to point out that although this series represents the South America's initial experience with laparoscopic radical cystectomy with encouraging results, all groups involved in this study have familiarity with major laparoscopic surgery, having already successfully performed more than 800 laparoscopic radical prostatectomies in the past years. Based on this, we can also suppose that the complication rate of each institution may be more related to the complexity of the operations performed (number of continent urinary diversions) rather than to the prior experience of each group, see Figure-1.

CONCLUSIONS

Laparoscopic radical cystectomy is a safe procedure with an acceptable morbidity and mortality rates. Although feasible and safe, long term oncological data are mandatory to evaluate its efficacy for the treatment of invasive bladder cancer.

CONFLICT OF INTEREST

None declared.

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Case Report
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Bilateral Metastatic Renal Hemangiopericytoma Ten Years after Primary Intracranial Lesion

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ABSTRACT

We report a case of bilateral metastatic renal hemangiopericytoma. A 37-year-old Caucasian male presented in 1993 with intracranial hemangiopericytoma. Subsequent metastatic disease noted years later include bilateral renal hemangiopericytoma 10 years after initial presentation. To our knowledge, this is only the second reported case of bilateral metastatic renal hemangiopericytoma.

Key words*: intracranial neoplasms; hemangiopericytoma; kidney; metastases; bilateral*
Int Braz J Urol. 2006; 32: 306-7

INTRODUCTION

Since Black & Heinemann are credited as first described a renal hemangiopericytoma in 1955, 34 other cases have been reported. Only one report described bilateral renal involvement. This rarity occurred in 1991 when Heppe et al. described a male patient with bilateral metastases 12 years after an initial intracranial lesion (1). To our knowledge, this is only the second reported case of bilateral metastatic renal hemangiopericytoma.

CASE REPORT

A 37-year-old white male presented in 1993 with headaches and dizziness, vomiting, and personality changes. A large dural-based middle fossa intracranial mass was discovered and excised after a subdural hematoma developed following embolization. Cellular morphology was consistent with hemangiopericytoma. Subsequently, 2 episodes of recurrence within the middle fossa were noted on follow-up imaging. The patient's intracranial lesions responded favorably to gamma knife irradiation and further imaging studies were done to detect metastatic lesions. Abdominal imaging demonstrated 2 large enhancing lesions in the right hepatic lobe. After resection, examination of the specimen revealed 2 large foci (13.5 cm and 10.5 cm) of metastatic disease. Immunoperoxidase staining for cytokeratin, EMA, actin, and CD-34 markers showed only CD-34 stain uptake in the prominent vascularity of the lesions.

These radiographic studies also revealed a 1.5 x 1.3 cm isodense mass arising from the lower pole of the left kidney. Growth occurred over time. A new 4 mm mass of unknown significance also developed during this interval in the mid to lower pole of the right kidney. Plans were made to remove the left kidney after no further evidence of metastasis was

noted on PET scan. In December 2003, a left hand-assisted laparoscopic radical nephrectomy was performed. Pathologic examination confirmed a 2.4 x 2.3 x 2.3 cm hemangiopericytoma with focal areas of hemorrhage. A smaller focus of tumor with similar characteristics was also found in the specimen. Both metastases were confined within the boundaries of the renal capsule.

In May 2004, many lesions appeared in the lateral segment of the left hepatic lobe and pancreatic body. Interval enlargement was also noted in the right renal mass, which had increased in size to 2.7 x 1.1 cm. The aggressive nature already demonstrated by this malignancy, presence of multiple metastases, and similar progression of the contralateral renal mass are evidence to conclude bilateral renal involvement.

COMMENT

Grossly, these tumors do not share a characteristic appearance but do tend to grow rapidly within the confinements of a capsule or pseudocapsule, but calcifications are seldom evident unless tumors have been present for long durations. Histological confirmation also is difficult because of microscopic similarities that exist between these lesions and other soft tissue tumors, namely synovial sarcomas, fibrous histiocytomas, and solitary fibrous tumors. It should be noted that while most hemangiopericytomas express CD-34 as illustrated by our case, the sensitivity of this marker is suboptimal in some cases, often limited to endothelial cells (2).

Despite reports of hemangiopericytomas in all age ranges, 2 distinct clinical types with separate prognoses have emerged. An infantile form exists only during the first year of life, while over 90% occur during adulthood with a peak incidence in the fifth and sixth decades. Efforts to correlate such long-term outcomes with factors such as tumor size, degree of tumor necrosis, and presence of mitotic figures have only achieved limited success. The single prognostic indicator after primary diagnosis remains the presence or absence of metastasis. Studies have shown the most important factor in reducing tumor spread to be complete excision of the primary lesion (3).

CONFLICT OF INTEREST

None declared.

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Case Report
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Repeat Knot Formation in a Patient with an Indwelling Ureteral Stent

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ABSTRACT

A patient treated for nephrolithiasis formed knots in 2 occasions, in 2 separate indwelling ureteral stents. This rare complication may make stent removal difficult. To our knowledge, this is the first case report of repeat knot formation in a single patient.

***Key words**: ureter; stent; complications; lithiasis*
Int Braz J Urol. 2006; 32: 308-9

INTRODUCTION

A rare complication of indwelling ureteral stents is knot-formation within the body or coiled portion of the ureteral stent. Several techniques for removal have been described, including simple traction, removal with guide wire assistance, ureteroscopy, and percutaneous removal (1-3). We report a case in which a patient formed knots in 2 separate stents.

CASE REPORT

An 82-year-old critically ill female with multiple medical problems, including multiple sclerosis requiring tracheostomy, was treated for an 11x8 mm left renal stone with a Cook Kwart Retro-Inject stent (6F x 22-32 cm) in August, 2002. She was lost to follow up until July 2003 when she developed Escherichia coli urosepsis. The stent was thickly encrusted requiring 2 shock wave lithotripsies and a ureteroscopy with laser lithotripsy to facilitate removal. Examination revealed a knot in the proximal coiled portion. Due to extensive manipulation during the procedure, a new Kwart stent was placed with the plan to remove it within a short period of time.

An attempt to remove the stent using an externalized string was unsuccessful in the clinic. Radiography revealed a knot in the proximal coiled portion of the stent (Figure-1). The patient was taken to the operating room for planned cystoscopy with possible ureteroscopy to perform complex stent removal. During attempted induction of anesthesia, difficulties with the patient's tracheostomy caused several forceful coughs, producing a Valsalva effect. Due to the difficulty of anesthesia and complexity of the patient, prior to instrumentation, the stent was easily removed by simple traction. The knot was no longer present.

COMMENTS

Knot formation is a rare complication of indwelling ureteral stents. We report a patient who

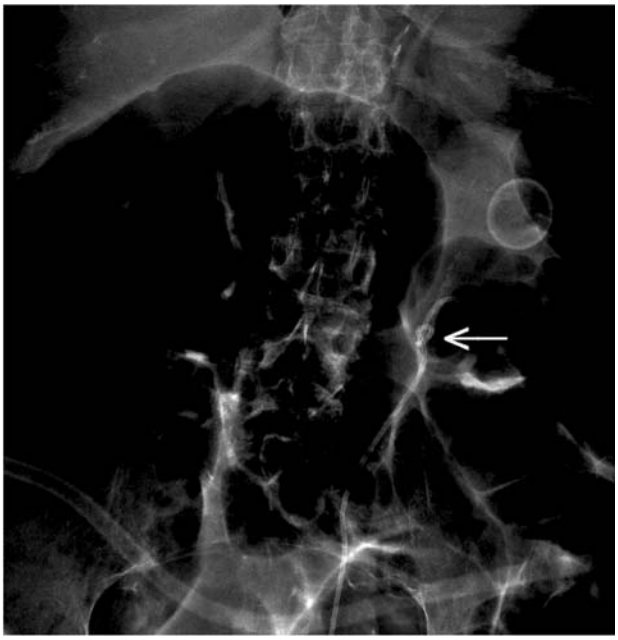

Figure 1 – *Knot formation seen on abdominal X-ray (arrow).*

formed knots in 2 indwelling stents. Previous authors have hypothesized that stent length, as well as coil configuration may be contributing factors to stent knot formation (3). We surmise that the anatomy of the patient's renal pelvis in conjunction with the use of a Cook Kwart Retro-Inject stent with multiple proximal coils increased the likelihood of knot formation.

Several authors have described novel methods to remove knotted stents (1-3). To our knowledge, this is the first report of repeat stent knot formation on a single patient. In our patient, the first stent required ureteroscopic treatment of encrusted stone fragments for removal. The second knotted stent was in place for a short period without evidence of encrustations. Repeated Valsalva (coughing) was the only interim event that could account for the knot uncoiling. We hypothesize that increase in intraabdominal pressure caused movements in the position of the kidney, ureter, and/or indwelling stent, causing the knot to come undone. Valsalva is an easy and relatively innocuous treatment that may aid in removal of knotted stents and avoidance of more invasive procedures.

CONFLICT OF INTEREST

None declared.

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Case Report
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Synchronous Presentation of Nasopharyngeal and Renal Cell Carcinomas

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ABSTRACT

We report a rare case of synchronous presentation of nasopharyngeal and renal cell carcinomas in a-50-year old male patient with long standing smoking history. The patient was initially presented with a diagnosis of nasopharyngeal carcinoma. During staging process, the abdominal computed tomography detected a right renal solid mass, 6.5 cm in diameter, originating from posterior portion of the right renal cortex. Right radical nephrectomy was performed and pathological examination revealed renal cell carcinoma. Smoking was thought to be a risk factor for both cancers. Systemic evaluation of kidney should not be discarded in patients diagnosed with nasopharyngeal carcinoma living in western countries with a smoking history.

Key words*: renal cell carcinoma; nasopharyngeal cancer; nephrectomy; chemotherapy; radiotherapy*
Int Braz J Urol. 2006; 32: 310-2

INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignancy with an unusual variable incidence rate across the world. NPC has 3 unique etiologic factors, including genetic susceptibility, chemical carcinogens such as tobacco carcinogens especially in western countries, and association with Epstein-Barr virus infection. Concurrent cisplatin and radiotherapy with or without adjuvant chemotherapy is standard of care for patients with locally advanced NPC (1). Renal cell carcinoma (RCC) accounts for 3% of all adult malignancies; with the increasing number of incidentally detected kidney tumors there has been migration to smaller, lower-stage tumors. Several risk factors have been described for RCC, including tobacco smoking (2). Radical nephrectomy is the gold standard of care for localized RCC.

CASE REPORT

A-50-year old male patient admitted to our hospital with a newly diagnosed NPC. He had a 70 packs/year cigarette smoking history. Magnetic resonance imaging of neck and nasopharynx revealed a nasopharyngeal mass invading the oropharynx with bilateral lymphadenopathy (the largest lymph node had 7 cm in diameter - T3N3M0, stage IV NPC). Reexamination of biopsy confirmed the diagnosis of undifferentiated carcinoma, WHO type III (Figure-

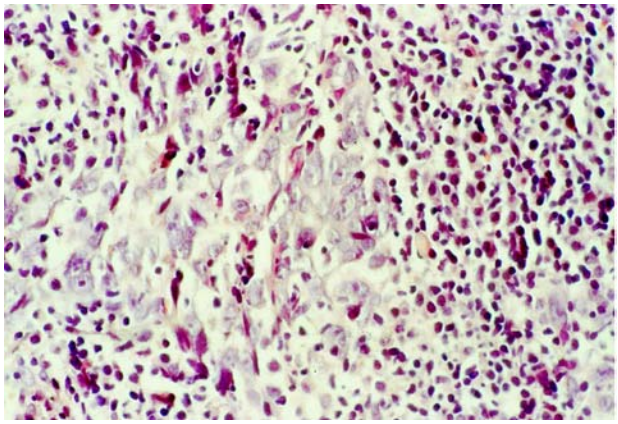

Figure 1 – *Undifferentiated nasopharyngeal carcinoma, WHO type III (HE, X10).*

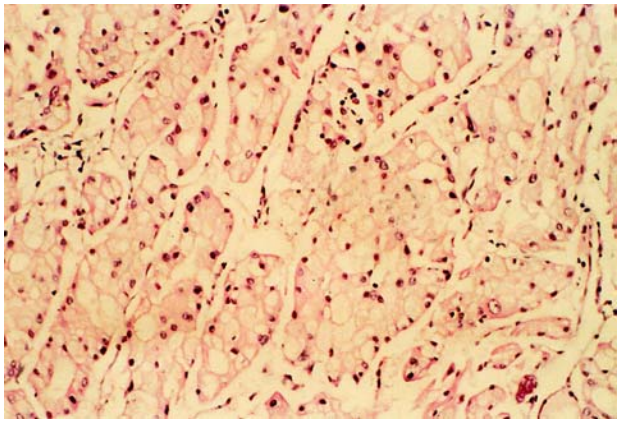

Figure 2 – *Renal cell carcinoma with a trabecular and alveolar pattern (HE, X10).*

1). During staging process, the abdominal computed tomography detected a right renal solid mass, 6.5 cm in diameter, originating from a posterior portion of the right renal cortex. Right radical nephrectomy was performed and pathological examination revealed multifocal tumoral growth surrounded by capillary network with trabecular and alveolar patterns, which were reported as a RCC of clear cell type, grade 1 (Figure-2). Tumor had a pT1bN0M0 stage with no invasion to renal artery, vein, ureter and perirenal adipose tissue. Concurrent cisplatin-radiotherapy and adjuvant 3 cycles of carbolatin and infusional 5-fluorouracil were planned for the treatment of NPC and no treatment was planned for RCC. Response evaluation showed complete remission after the completion of the treatment. The patient is now in complete remission for 2 years.

COMMENTS

Our patient had 2 distinct synchronous primary tumors, NPC and RCC. In English literature, there is only one similar case published by Nemoto et al. (3) that reported a primary hyperparathyroidism associated with synchronous presentation of triple carcinomas originating from kidney, nasopharynx, and thyroid. Smoking is known to be a risk factor for both NPC and RCC. In particular, meta-analysis of 24 studies including 19 case-control and 5 cohort studies performed to look at the relation between RCC and cigarette smoking clearly showed that inhaled tobacco smoke is implicated in the etiology of RCC, with a strong dose-dependent increase in risk associated with numbers of cigarettes smoked per day and a substantial reduction in risk for long-term former smokers (2). Having known the fact that smoking is simultaneous risk factor for all cancers susceptible to tobacco carcinogens both in aero-digestive tract, so called field cancerization effect and in distant sites such as pancreas, urinary bladder, and kidney, we may call it - as “distant” cancerization effect, systemic evaluation of kidney should not be discarded specifically, in patient diagnosed with NPC living in western countries with a smoking history.

CONFLICT OF INTEREST

None declared.

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Case Report
International Braz J Urol Vol. 32 (3): 313-315, May - June, 2006

Brucella Epididymo-Orchitis: A Consideration in Endemic Area

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ABSTRACT

Brucellosis is a zoonotic disease caused by Brucella sp. and may affect many parts of the body. Brucella epididymo-orchitis had been reported in up to 20% of patients with brucellosis. This is a case report of Brucella epididymo-orchitis in a Saudi male patient. He presented with a unilateral swelling of the left testicle. He had fever, arthralgia and night sweats. Ultrasound examination revealed enlarged left epididymis and testicle. Brucella serology was positive and the patient responded to treatment with doxycycline and gentamicin. Thus, brucella infection should be considered in the differential diagnosis of patients presenting with epididymo-orchitis from an endemic area.

Key words*: epididymitis; orchitis; Brucella; diagnosis; therapeutics*
Int Braz J Urol. 2006; 32: 313-5

INTRODUCTION

Epididymo-orchitis is usually caused by Neisseria gonorrhea and Chlamydia trachomatis in male patients younger than 35 years of age and by enterobacteriaceae in patients older than 35 years of age. Other causes of epididymo-orchitis include Brucella sp. in endemic areas. Genitourinary system involvement occurs in 2-20% of patients with brucellosis and includes prostatitis, epididymo-orchitis, cystitis, pyelonephritis, interstitial nephritis, exudative glomerulonephritis and renal abscess.

Here we describe a case of Brucella epididymo-orchitis and draw attention to this diagnosis in patients presenting with epididymo-orchitis from endemic areas.

CASE REPORT

A forty-one year old Saudi male presented with a 2-week history of fever, night sweats, and arthralgia. He had a 2-day history of left testicular swelling but no urinary symptom. He had a history of raw milk ingestion few weeks earlier. His temperature was 39° C and systemic examination was unremarkable. The left epididymis and left testicle were enlarged and tender. The white blood cell (WBC) count was 5400/mm^3. Blood cultures were negative. Urinalysis showed a WBC of 0-5/high power field (hpf) and red blood cell of 10-25/hpf. Testicular ultrasound revealed an enlarged left testicle measuring 3.4 x 3.8 x 4.9 cm with increased blood flow (Figure-1). The left epididymis was enlarged with increased back shadowing raising the possibility of early abscess formation (Figure-2). Brucella abortus antibodies were < 1:160 for IgG and > 1:2560 for IgM. The patient was treated with doxycycline (6 weeks) and gentamicin (2 weeks) with complete resolution of all signs and symptoms.

COMMENTS

Brucellosis is a zoonotic disease, which may be caused by 4 Brucella species: B. abortus, B.

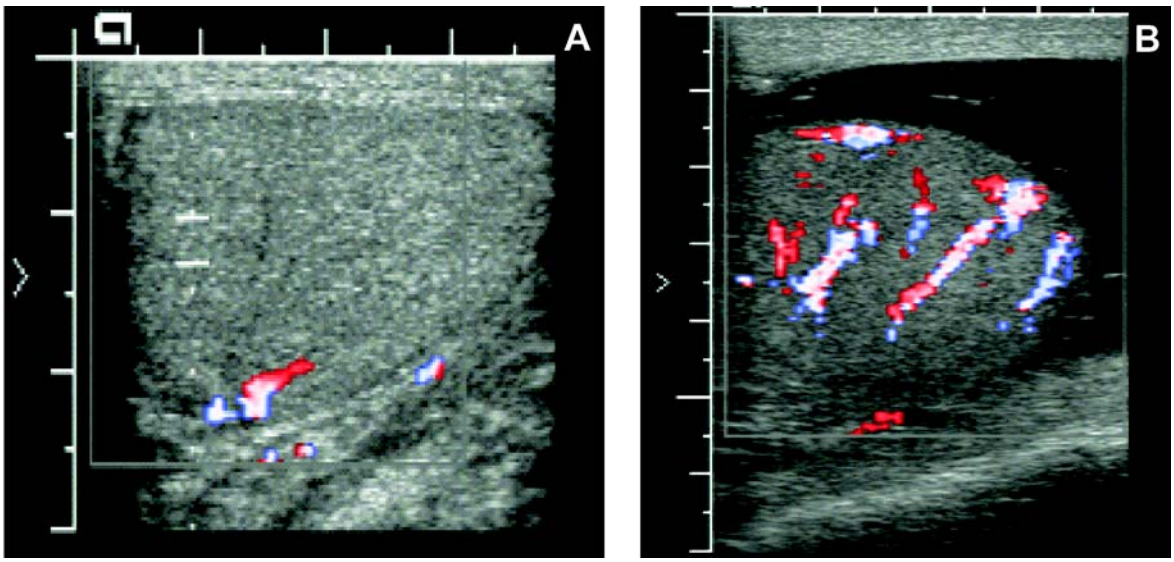

Figure 1 *– Testicular ultrasound showing a normal blood flow in the right testicle (A) and increased blood flow in the left testicle (B).*

melitensis, B. uis or B. canis. Brucellosis may cause granulomatous orchitis in up to 20% of affected patients (1). Patients usually present with acute symptoms of less than 2 weeks of duration (1). Although patients may have unilateral epididymo-orchitis or orchitis alone, bilateral epididymo-orchitis occurs in up to 59% of affected patients (1) and may occur in the absence of systemic symptoms in endemic areas (2).

Brucella epididymo-orchitis can be distinguished from nonspecific epididymo-orchitis by a history of contact with animals, consuming raw milk or cheese made from it, gradual onset, longer duration, typical undulant fever, relatively minimal local

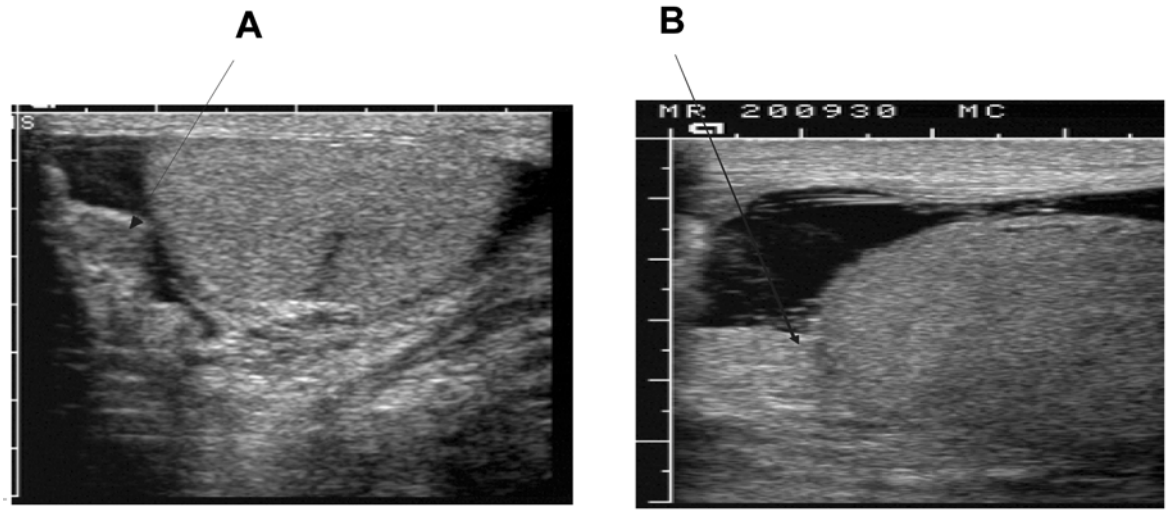

Figure 2 *– Testicular ultrasound showing a normal right epididymis (A) and an enlarged and thickened left epididymis (B).*

inflammation, and absence of lower urinary tract symptoms and no significant leukocytosis (1). The differentiation is important since the delay of specific treatment increases the risk of contralateral involvement, necrosis and systemic manifestations (3). Thus, in endemic areas, the suspicion is enough to initiate therapy for brucellosis while awaiting the confirmatory laboratory tests (1).

As in our case, normal urine analysis and culture is reported in the majority of patients with Brucella epididymo-orchitis (65%) (1). The majority of patients with Brucella epididymo-orchitis have initial agglutination titers of > 1:320, 53-69% of patients have positive blood cultures (1) and 6.7% have positive culture from epididymal aspirations. Doxycycline plus rifampicin for 6 weeks or doxycycline (6 weeks) plus gentamicin for 2-3 weeks is usually prescribed for treatment. Alternatively, streptomycin intramuscularly and tetracycline, with or without cotrimoxazole orally may be used in cases that do not respond to standard therapy. The complication rate is usually low with 5% of patients developing necrotizing orchitis requiring orchiectomy.

In conclusion, brucella epididymo-orchitis should be a consideration in the differential diagnosis of patients presenting with signs and symptoms of this entity in endemic areas of brucellosis. The condition usually has a favorable outcome with the standard treatment of brucellosis. Inappropriate management of Brucella epididymo-orchitis may result in serious complications such as testicular abscess, atrophy and male infertility.

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CONFLICT OF INTEREST

None declared.

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Surgical Technique
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Video Endoscopic Inguinal Lymphadenectomy (VEIL): Minimally Invasive Resection of Inguinal Lymph Nodes

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ABSTRACT

Objectives: Describe and illustrate a new minimally invasive approach for the radical resection of inguinal lymph nodes.
Surgical Technique: From the experience acquired in 7 operated cases, the video endoscopic inguinal lymphadenectomy (VEIL) technique was standardized in the following surgical steps: 1) Positioning of the inferior member extended in abduction, 2) Introduction of 3 work ports distal to the femoral triangle, 3) Expansion of the working space with gas, 4) Retrograde separation of the skin flap with a harmonic scalpel, 5) Identification and dissection of the long saphenous vein until the oval fossa, 6) Identification of the femoral artery, 7) Distal ligature of the lymph node block at the femoral triangle vertex, 8) Liberation of the lymph node tissue up to the great vessels above the femoral floor, 9) Distal ligature of the long saphenous vein, 10) Control of the saphenofemoral junction, 11) Final liberation of the surgical specimen and endoscopic view showing that all the tissue of the region was resected, 12) Removal of the surgical specimen through the initial orifice, 13) Vacuum drainage and synthesis of the incisions.
Comments: The VEIL technique is feasible and allows the radical removal of inguinal lymph nodes in the same limits of conventional surgery dissection. The main anatomic repairs of open surgery can be identified by the endoscopic view, confirming the complete removal of the lymphatic tissue within the pre-established limits. Preliminary results suggest that this technique can potentially reduce surgical morbidity. Oncologic follow-up is yet premature to demonstrate equivalence on the oncologic point of view.

Key words*: penile cancer; groin; lymphadenectomy; video-assisted surgery*
Int Braz J Urol. 2006; 32: 316-21

INTRODUCTION

Inguinal lymphadenectomy is indicated in patients presenting penile and urethral cancer, after local treatment, when there is a lymph node mass that does not disappear with antibiotic therapy, or when palpable lymph nodes appear in the postoperative follow-up or when there are risk factors for the development of inguinal metastasis (prophylactic lymphadenectomy). This operation is frequently performed through a bilateral inguinal incision from the iliac crest until the pubic tubercle. There is, however, a high morbidity regarding the dissected skin flap to access the inguinal lymph nodes, as well as skin necrosis and local infection, and depending on the extension of the lymphadenectomy, higher frequency of edema in inferior members, lymphocele, lymphedema and lymphorea (1).

Trying to reduce the morbidity of this radical operation the literature shows surgical alternatives

that aim at restricting the inguinal dissection area. However, all techniques present different local recurrence rates, probably due to false negative results (2).

Video-assisted surgery has been employed in the iliac and retroperitoneal lymph nodes approach, reducing postoperative discomfort, minimizing anatomic sequels and allowing a faster recuperation of patients, keeping the functional results of conventional surgery for the majority of indications.

We aimed at describing and illustrating the technical details of a minimally invasive procedure for inguinal lymphadenectomy recently described in the clinical scenario (3). This technique duplicates the principles of conventional technique, promoting a radical resection of inguinal lymph nodes, with encouraging preliminary results regarding the reduction of surgical morbidity.

SURGICAL TECHNIQUE

The technique described was developed in a prospective protocol that includes up to now 7 patients presenting penile spinocellular carcinoma, without palpable lymph nodes or that had a regression after a 6-week-antibiotic therapy. All patients had an indication of bilateral lymphadenectomy due to the presence of risk factors for lymph node dissemination such as: clinical stage > T1 or information regarding the initial biopsy such as histological grade > 1, lymphatic or vascular invasion.

After signature of the informed consent the patients were submitted to classic open surgery in one of the members (control group) and a video-assisted surgery, named video endoscopic inguinal lymphadenectomy (VEIL) in the other member (group of the technique to be assessed).

Control Member

For the open conventional surgery, we have used the superficial inguinal lymphadenectomy technique and deep in the Dressler triangle, medial to the femoral artery, without the preservation of the long saphenous vein through a large inguinotomy.

Video Endoscopic Inguinal Lymphadenectomy (VEIL)

1 – Positioning and preparation of the inferior member - The leg is folded over the thigh in a way to put in evidence the femoral triangle that is marked with ink over the skin. After the marking, the leg is extended and fixed to the table with abduction and light external rotation of the thigh. The video monitor is positioned at the contralateral side to the operated one at the patient's pelvic waist.

2 – Introduction of the ports - At 2 cm of the femoral triangle vertex in a distal sense an incision of 1.5 cm in the skin and in the subcutaneous tissue until the Scarpa's fascia is performed, being developed a subcutaneous plan with scissors and later with a digital maneuver in the largest possible extension. A second incision of 1 cm, at around 2 cm above and 6 cm medially to the first incision, to the introduction of a 10 mm port. It is possible to identify the trajectory of the saphenous vein through this access. A laterally symmetric position 5 mm port is introduced for graspers, dissection tweezers and scissors. At the initial access, a 10 mm Hasson trocar is preferably introduced. All the ports are fixed to the skin through a purse-string suture with cotton 0. At the initial port, we introduce a 0-degree optic, and at the medial port, we introduce the tweezers of the harmonic scalpel and the clipper. The surgeon and the camera operator are positioned laterally to the operated member.

3 – Expansion with gas of the working space – The creation of a working space is completed through the initial insufflation of CO2 with a 15-mmHg pressure, with its fast diffusion, being able to keep the pressure at 5-10 mmHg during the procedure (Figure-1). Transillumination allows a good orientation regarding the progression of the dissection area.

4 – Retrograde separation of the skin flap – This time is fundamental to the success of the procedure and is performed with a harmonic scalpel. Initially we perform the separation between the skin and the fibroareolar tissue that contains the superficial lymph nodes until the external oblique muscle fascia on the superior part (Figure-2). Afterwards we proceed to the dissection of the fundamental parameters, having as a limit the long adductor muscle and its

Figure 1 *– Trocar disposition for a right member lymphadenectomy. The work space was almost all filled up by the diffusion of gas.*

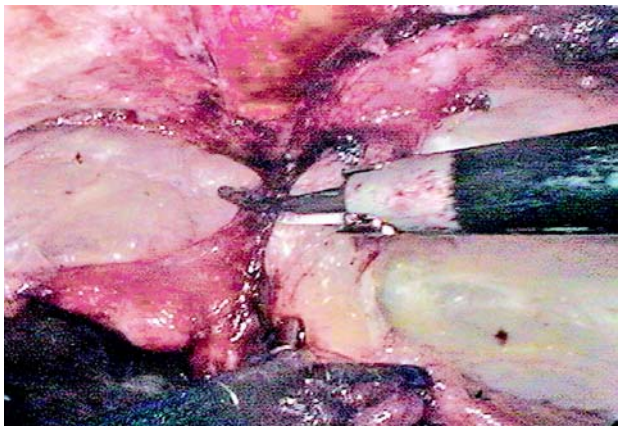

Figure 2 *– Separation of the skin and the fibroareolar tissue that contains the lymph nodes, with the aid of a harmonic scalpel.*

fascia medially, the sartorius muscle and its fascia laterally, and the inguinal ligament superiorly. It is possible to identify branches of the femoral nerve that should be preserved.

5 – Identification and cranial dissection of long saphenous vein until the oval fossa (Figure-3).

6 – Identification of the femoral artery – After the identification of the femoral artery and the opening of the femoral vein sheath we define the lateral limit of the dissection, allowing the access to the deep cervical lymph nodes (Figure-4). At this moment it can be necessary to control with 1 or 2 branch clips coming from the femoral artery that run anteriorly to the femoral vein.

7 – Distal ligature of the lymph node block at the femoral triangle vertex – the fibroareolar tissue is dissected with a harmonic scalpel and the control of the final section at the femoral triangle vertex is obtained with clips.

8 – Liberation of the lymph nodes until the great vessels above the femoral floor. During this operative time, the use of the harmonic scalpel and a careful manipulation of the specimen in areas near the veins are necessary to avoid vascular lesion. As in the conventional technique, the aim is to skeletonize the femoral veins, resecting all local lymphatic tissue (Figure-4).

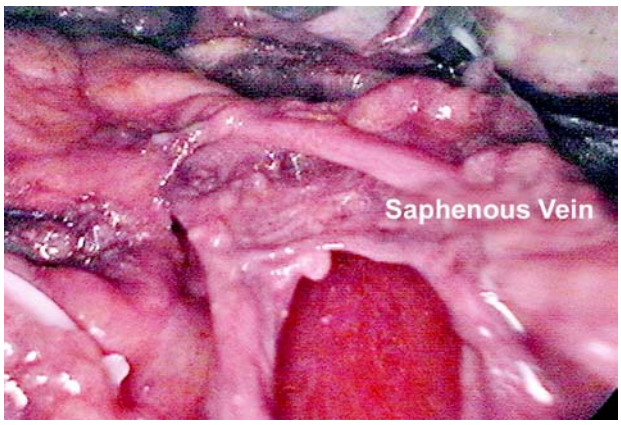

Figure 3 *– Dissection of the long saphenous vein in a cranial aspect.*

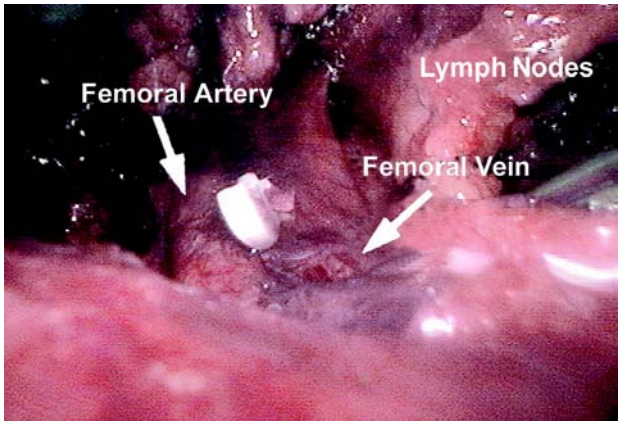

Figure 4 *– Exposition of femoral artery and vein after the control of 3 small branches of the femoral artery that course anteriorly to the femoral vein.*

9 – Distal ligature of the long saphenous vein with clips

10 – Control of the branches and the long saphenofemoral junction with a harmonic scalpel and metallic clips - most part of the branches of the long saphenous vein are controlled only by the harmonic scalpel. Branches larger than 4 mm need clips for the ligature. The entrance of the long saphenous vein in the femoral vein should be well dissected and controlled preferably with polymer clips (Figure-5).

11 – Final liberation of the specimen medially to the long saphenous vein, ligating the proximal portion of the lymph nodes at the deep region of the femoral channel with clips. After completing the liberation of the specimen, the endoscope view attests that all the tissue of the region was completely resected (Figure-6).

12 – Removal of the surgical specimen by the 15 mm incision. In case the specimen is of large dimensions, it can be put inside a bag and latter removed.

13 – Vacuum drainage through the 5 mm orifice and suture of the larger incisions (Figure-7).

COMMENTS

Approximately 30% of the patients with penile spinocellular carcinoma present lymph node metastasis at the time of the diagnosis. Bilateral inguinal lymphadenectomy is a procedure accepted as a prognostic and therapeutic value in cases of penile and urethral spinocellular carcinoma with high risk of developing metastasis (1). However, morbidity associated to this surgery is high, being questioned its need mainly when the intention is prophylactic. In the past, due to the data presented, some centers adopted a conservative conduct through a rigid clinic follow-up.

Contemporary works have demonstrated that prophylactic lymphadenectomy offers better survival

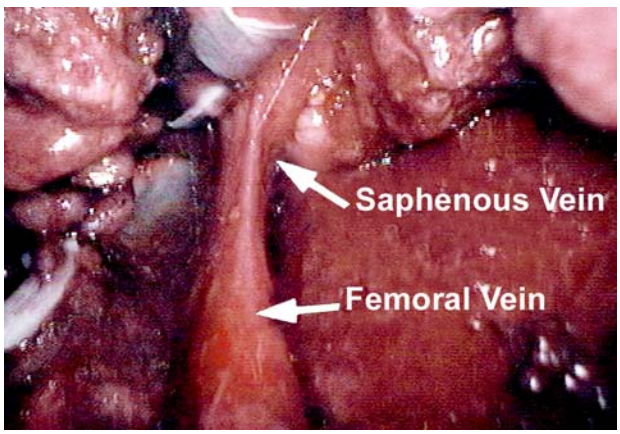

Figure 5 – *Aspect of the long saphenous vein in its entrance into the femoral vein.*

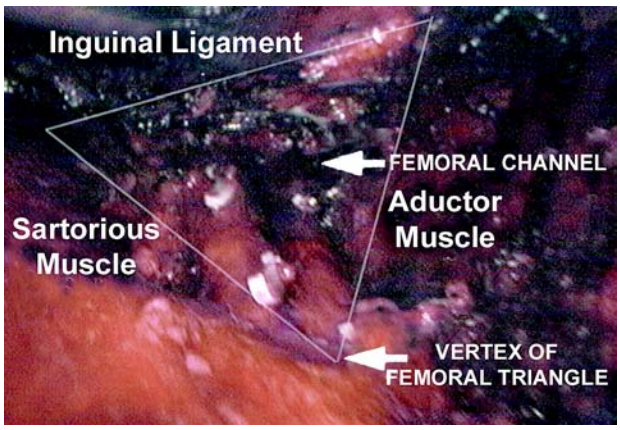

Figure 6 – *Endoscopic view at the end of the lymph node dissection. The limits of the lymphadenectomy are viewed and all the lymphatic tissue was removed.*

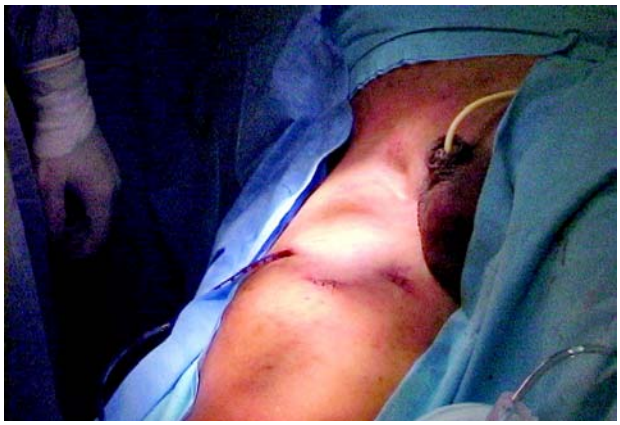

Figure 7 – *Final aspect of the incisions and vacuum drainage.*

results than salvage lymphadenectomy performed in those patients where we have initially opted for a rigorous observation. Besides that, they have also showed that the non-controlled lymph node disease was an important cause for morbidity and mortality in patients with penile cancer.

Before the dilemma of offering radical surgery with a significant morbidity to 70% of the patients in an unnecessary way or harm the survival of 30% of the patients submitted to the surveillance regimen, new alternatives were reported in literature. The techniques described in the last 20 years to reduce the morbidity are based on the reduction of inguinal dissection templates. Even though the evident reduction of operation complications described both with simplified lymphadenectomy and with the employment of sentinel lymph node with radioisotopes, some authors believe that its higher morbidity could be related to a rate of 15% of late recurrence of the disease with possible involvement of these individual's survival (2).

The present work was motivated by the attempt to reduce the complications of inguinal lymphadenectomy, based on the initial works of video-assisted saphenous vein resection, subcutaneous endoscopic procedures used in plastic surgery and video endoscopic resection of axillary lymph nodes. (4-6).

Recently, Bishoff et al. described the possibility of modified dissection of inguinal lymph nodes through endoscopic subcutaneous access performed in 2 human cadavers and in 1 patient with penile cancer stage T3N1M0. Dissection was possible on the human cadavers but it was however not possible in the patient due to the adherence of the enlarged lymph nodes to the femoral veins (7). After some technical changes we have performed, to this date, the surgery in a safe and efficient way in 7 patients with indication of prophylactic lymphadenectomy.

The idealized technique allows a complete excision of inguinal lymph nodes, the way it is done in conventional surgery, allowing an initial impression of benefit regarding the lower postoperative morbidity when compared to the conventional technique. The medium 120 minutes operative time is still superior to the open technique; however, we should consider the learning curve. Surprisingly enough, there were no skin complications. The presence of infraumbilical subcutaneous emphysema of spontaneous resolution is the rule, being uncommon the clinical manifestation. Hypercarbia can occur intraoperatively, being completely reversible with hyperventilation, without the need for conversion. In a subjective analysis, all patients preferred endoscopic surgery. Pathological exam of surgical specimens showed that the medium number of lymph nodes excised did not differ from that obtained with conventional surgery.

We attribute this preliminary result to the following technical principles: 1) Non use of electrical current and mechanical retraction with subcutaneous retractors. The retraction is performed atraumatically by the gas, minimizing cutaneous lesions, 2) Short incisions outside the area of the great vessels allow a shorter area of lesion of the separated flap and probably less chance of infection, besides making unnecessary the rotation of the sartorius muscle flap to recover femoral veins, 3) Control of the lymph nodes, visualized by magnification, with harmonic scalpel and clips. The proximal and distal ligature of major channels is fundamental to avoid important lymphoceles or lymphorea.

The presence of skin adherences or palpable mass of lymph nodes, predictive factors for technical difficulty, were excluded from this initial study which objectives were to assess the possibility and technical equivalence to classical lymph nodes resection.

CONCLUSIONS

The VEIL technique is feasible and allows the radical removal of inguinal lymph nodes at the same dissection template as conventional surgery. The main anatomic repairs of open surgery can be identified in an endoscopic view, confirming the complete removal of the lymphatic tissue within the pre-established limits.

Preliminary results with this new endoscopic approach for inguinal lymphadenectomy are promising, with potential to reduce morbidity. It seems not to change expected oncologic results with the conventional technique, but the follow-up is still short for definite conclusions.

Future studies and validation by other authors will determine the real role of this procedure in the staging and treatment of patients with penile and urethral spinocellular carcinoma.

CONFLICT OF INTEREST

None declared.

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Ballistic Ureteroscopic Lithotripsy in Prepubertal Patients: A Feasible Option for Ureteral Stones

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ABSTRACT

Objective: To evaluate the role of ballistic ureteroscopic lithotripsy in children with ureteral stones.
Materials and Methods: Children under 14 years with ureteral stones were treated with ureteroscopy in a 5-year period in our institution.
Results: Twenty-three procedures were performed in 20 children. Mean surgical time, age and stone size were 31 min. (15 - 120min.), 11 years. (4-13 years), 5.3 mm (3-10 mm) respectively. Three patients underwent two ballistic ureteroscopic lithotripsy each. There were 22 successful procedures (96%) and a 100% stone-free rate per patient. Complications (mucosal tear) occurred in 2 procedures (8%) without extravasation of contrast media on retrograde pyelogram and their follow-up was uneventful.
Conclusion: Ureteroscopic ballistic lithotripsy is a feasible option for ureteral stones in prepubertal patients, with high stone-free rate and few complications.

Key words*: ureteral calculi; child; ureteroscopy; complications*
Int Braz J Urol. 2006; 32: 322-9

INTRODUCTION

Ureteral stones in children have been traditionally managed by extracorporeal shock wave lithotripsy (SWL), stenting and open surgery, while the smaller dimensions of the pediatric genitourinary system limited endourology. SWL replaced open surgery achieving high stone-free rates (1). Besides the need to eliminate stone fragments, re-treatment is eventually required (2) and differently from adults, SWL in children may require general anesthesia.

Endourological progress in the last decades changed the treatment of ureteral stones. Equipment miniaturization, surgical experience and new technologies on video-surgery promoted such evolution, rendering high success rates and few complications in adults (3,4). Ureteroscopy has been applied to pediatric ureteral stones since 1988 (5,6), but success rates and long term safety are still being addressed (7-9). Issues related to ureteral dilation, stenting, lithotripsy energy source and postoperative reflux are also not well defined, however, immediate ureteral clearing, stone resolution in a 24-hour postoperative hospital stay and fast recovering are appealing features of this method (7).

Since there are controversies about the optimal treatment for ureteral stones in children, we studied ballistic ureteroscopic lithotripsy treatment of ureteral calculi in the pediatric population focusing on success rates and complications.

MATERIALS AND METHODS

Since 1999, all patients with ureteral stones who underwent ureteroscopy had a specific chart where preoperative, surgical and postoperative data were inserted in a computerized database. From July 1999 to June 2005, 1495 ureteroscopies for ureteral stones were included. Twenty-three (1.5%) procedures were performed in children under 14 years old. Stones were diagnosed by ultrasound (US) and KUB. Intravenous pyelogram (IVP) or CT (computerized tomography) were indicated when diagnosis or stone location was not evident.

Two endoscopes were used: MRO7 (Circon-ACMI: length: 42 cm, distal diameter: 7F) and 27400K (Karl-Storz: length 34 cm, distal diameter 7.5F) semi-rigid ureterorenoscopes. An electrohydraulic lithotripter (Circon-ACMI: AEH-2A, probe 3F, length 120 cm) and a pneumatic-ballistic lithotripter (Calculitus: maximal pressure 10 bar) were available, but all fragmentations were accomplished with the ballistic energy source with the aid of baskets (Cook: Helical stone extractor, size 3.2F, length 115 cm, 4 wire basket).

A description of our technique is summarized below: after general anesthesia induction and prophylactic antibiotic (hospital: cefalotin sodium 50 mg/kg/24h, home: cefalexin 7 days), children were placed in lithotomy position and the endoscope was inserted into the urethra and the bladder. We did not employ a pediatric urethrocystoscope. Ureteral meatus was approached with the aid of the tip of a guidewire (Cook Urological: PTFE - shaft size 0.035", length 145 cm, flexible tip 3 cm ; Bard: Hydro-Glide shaft size 0.035", length 145 cm) followed by endoscope insertion. Dilation (Cook: fascial dilator set 6-18F, length 60 cm) was not routinely used, unless severe edema prevented endoscopic access to the stone. The safety guidewire was advanced to renal pelvis only after the stone was visualized and when it could be advanced clearly between the stone and ureteral wall. Fragmentation was always tried when feasible while simple basketting was left for very small stones or its fragments. Retrograde pyelogram was routinely used at the end of the procedure to exclude ureteral perforations and false passages. Stents (Cook: double pigtail stent set 4.7F and 6F, length 26 cm) were used in the presence of complications (4 weeks.) or severe edema (1 week.). A variable length from the vesical extremity was cut to adapt to child's height and the tip was tied to a 4.0 mononylon, exteriorized and adhered to penile/perineal skin. We did not use mononylon exteriorization when stent stay exceeded one week. Such patients and patients whose mononylon was displaced into the bladder required cystoscopy and stent retrieval with baskets.

Any residual ureteral stone was considered a failure. All children with intraoperative complications underwent IVP 3 months after surgery regardless of symptoms. All patients underwent US on follow-up (3 months after surgery), but only symptomatic patients or persistent hydronephrosis had an IVP. Routine postoperative cystourethrography, urinalysis or urine cultures were not performed.

RESULTS

Twenty-three procedures were performed in 20 children. Most of the children were boys (85%) and two (10%) of them had previous SWL. Mean surgical time, age and stone size were 31 min. (15-120 min), 11 years (4-13 years) 5 mm. (3-10 mm) respectively (Table-1). There was one (4%) failed ureteroscopy and a 100% ureteral stone-free rate per patient. Fifteen (63%) procedures were stented. All patients were discharged home 24 hours after the procedure.

Three children underwent two procedures: patient #5: bilateral ureteral stones treated at the same time; patient #13: two episodes of impacted ureteral stones in the same year; patient #6: failure of the first procedure due to intense edema of the ureteral orifice (stone not visualized), stented and successfully reapproached after one week.

We found mucosal tearing without extravasation of contrast media after two (8%) procedures (#2 and #3): in procedure #2 we had much difficulty to reach the stone due to its location (iliac vessels) and the stone could not be pulled to a more distal and amenable location to be fragmented. Despite these difficulties, ureterolithotripsy was carried out success-

Table 1 – *Patients characteristics and results of stone treatment.*

Procedure	Patient	Gender	Age (years)	Previous Treatment	Stone Size (mm.)	Stone Location	Operative Time (min.)	Result	Stent	Complication	Follow up (m)
#1	#1	male	12	SWL	8	distal	30	success	yes	no	8
#2	#2	male	5	no	10	iliac vessels	120	success	yes	mucosal tear	47
#3	#3	male	13	no	5	distal	20	success	yes	mucosal tear	10
#4	#4	female	13	no	5	distal	30	success	yes	no	5
#5	#5	male	13	no	7	distal	40	success	no	no	-
#6	#5	male	13	no	7	distal		success	no	no	13
#7	#6	male	11	no	3	distal	50	failure	yes	no	-
#8	#6	male	11	no	3	distal	30	success	yes	no	18
#9	#7	male	7	SWL	6	distal	20	success	yes	no	13
#10	#8	male	13	no	5	distal	30	success	no	no	7
#11	#9	female	13	no	5	distal	30	success	no	no	18
#12	#10	female	12	no	4	distal	20	success	yes	no	26
#13	#11	male	10	no	6	distal	20	success	no	no	15
#14	#12	male	10	no	5	distal	40	success	yes	no	17
#15	#13	female	13	no	6	distal	30	success	no	no	-
#16	#13	female	13	no	5	distal	15	success	no	no	12
#17	#14	female	8	no	5	distal	15	success	yes	no	20
#18	#15	female	12	no	4	distal	20	success	yes	no	6
#19	#16	female	13	no	4	distal	30	success	no	no	18
#20	#17	male	11	no	4	distal	20	success	yes	no	14
#21	#18	male	11	no	5	proximal	30	success	yes	no	11
#22	#19	male	4	no	6	proximal	30	success	yes	no	4
#23	#20	male	13	no	5	distal	15	success	yes	no	9
Mean			11 (4-13)		5.3 (3-10)		31 (15-120)				
Frequency				8%				96%	63%	8%	14.5

SWL= extracorporeal shock wave lithotripsy; m = months.

fully in this location and retrograde pyelogram showed no extravasation. Stone in procedure #3 showed an intense ureteral edema and was fragmented and retrieved with basket. Before stenting this patient, we could see a mucosal tear along the lateral ureteral wall. Contrast media injection showed a submucosal false passage not reaching retroperitoneal space. Both patients were asymptomatic on follow-up and IVP was unremarkable.

Moderate hydronephrosis persisted on follow-up in patient #5, however his postoperative IVP did not show obstruction and he had symptoms for one year before ureteroscopy, suggesting sequela from long time obstruction. Patient #18 had flank pain and underwent IVP, but no obstruction was found. Urine culture was negative and pain resolved spontaneously.

COMMENTS

We performed our first ureteroscopy in an adult patient in 1995. At this time, SWL was not available in our hospital and patients with ureteral calculi were sent to another institution. Such limitation helped us to increase our endourological experience while failures and complications felt to a minimal rate (4). After 1998, we then expanded ureteroscopic ballistic lithotripsy to children and their results remained similar to adults. Though we now have SWL, no children with ureterolithiasis in our institution have been treated with SWL.

Most ureteral stones sized less than 5 mm will be spontaneously eliminated in adults. Surgery is limited to 2% of cases while conservative treatment remains the best option for ureterolithiasis in children as in adults (10). Savage et al. (11) studied patients under 18 years (mean = 12 years) who were treated for ureteral stones. Only 36% of 33 stones passed spontaneously and no stone greater than 3 mm was eliminated. Fifty five percent of stones sized less than 4 mm passed spontaneously. Thus, some children with ureteral stones will need active medical treatment.

SWL is the first line treatment for ureteral stones in children in some institutions. Muslumanoglu et al. achieved a 90.6% stone free rate for distal ureteral stones smaller than 10 mm and Landau et al. reported a 100% stone free rate for lower ureteral stones. On the other side, these results are associated to a re-treatment rate of 30% and 51%, respectively. Such inconvenience is avoidable with endoscopic treatment, as only 1 (4%) of our children required a repeated procedure.

As reported in other series (7,12,13), we could show that delicate handling of ureteroscopes and baskets allow stone treatment with few complications and high success rates in pediatric patients. Some aspects of our technique must be clarified as follows. The use of a pediatric urethrocystoscope is dispensable, as the ureteroscope also allows stone and stent retrieval. Inserting the guidewire into the ureter is a main step. We always try to advance it only when facing a space between the stone and the ureteral mucosa. This detail is paramount because we had adults whose ureteral submucosa was inadvertently penetrated at the level of the stone by the blinding advancement of the guidewire, which was only noticed after stone fragmentation. We do not advocate routine ureteral dilation and it was required in only one child (procedure #7). The tip of the endoscopes allows easy penetration into the ureter. Different energy sources have been applied to pediatric ureteroscopic lithotripsy (8,12,14). We applied electrohydraulic energy in a few adults, but it was replaced by the pneumatic-ballistic device. Our choice was due to its superior efficiency and precision to drive the impact to the exact point in the stone we want to fragment. Some authors also utilized ballistic energy in children with excellent results (8,14-16). We always fragmented the entirely stone into minimal fragments. Since we had an ureteral avulsion in an adult patient, we prefer to extract only small fragments with special attention to the edematous ureteral mucosa surrounding the stone. We routinely perform retrograde pyelogram in children and adults. Visual inspection of a manipulated and inflamed ureteral wall is not reliable. We had adults whose ureteral perforation was only diagnosed by pyelography. As other authors (7,9,16), we stented most of our patients and, maybe it was not necessary. However, the aspect of a pediatric manipulated ureter favored ureteral stenting.

Most pediatric ureteroscopy series also show a stone-free rate above 90%. We had one failure (procedure #7) in an 11-year-old boy. Safety guidewire was advanced above the stone, but intense ureteral edema distal to the stone prevented ureteroscopic access. We tried ureteral dilation but ureteral mucosa was upward directed with the dilators, what could complicate into avulsion. A stent was left and another ureteroscopy was scheduled to next week. At this time, the edema resolved and the stone could be easily treated, but a stent was left again. Such failure was not related to a specific pediatric limitation, as many adults in our experience have been managed in the same way when severe ureteral edema is present. Al Busaidy et al. (12) also reported a similar occurrence in their study, but their resolution required open surgery. Satar et al. (15) reported one failure secondary to a proximal stone push-up. Most of our children had stones located in the distal ureter and we did not have stone migration. We had no partial fragmentation, which was related by some authors as a cause of failure (9,12,17).

Even though perforations and ureteral lacerations have been described in children requiring open surgery (12), most complications may be managed endoscopically (13). We had two minor complications restricted to mucosal tear and managed with stent. No ureteral stenosis was detected on follow-up of these cases. Two cases underwent previous unsuccessful SWL in other institutions and managed with ureteroscopy. No complications or difficulties were observed. We did not perform cystourethrography in our patients because reflux rarely occurs, with minimal consequences (7,8) and it is associated to intraoperative ureteral dilation (12). Urinary tract infection (8,16-18) and hematuria with clots (16,18) were already described, but they rarely occur. In this manner, few complications were reported in pediatric ureteroscopy.

CONCLUSION

Ballistic ureteroscopic lithotripsy is a feasible option for ureteral stones in children, with high stone-free rate and few complications.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

In this study, Fuganti et al. report their experience on ureteroscopic lithotripsy in children by using ballistic and electrohydraulic energy sources with a high success rate. The authors correctly conclude that semirigid retrograde ureteroscopy is an effective and safe method for prepubertal children with ureteral stones. However, it is worth noting some points. Patient selection is controversial in ureteroscopic management of pediatric ureteral stones. In the literature, the ideal algorithm of ureteral stone management in children has not been reported with scientific analysis. Unfortunately, this study is failing to not answer this question. Nevertheless, it does let us know that the semirigid ureteroscopes and inflexible energy source probes that are used routinely in adults can be safely used in children. But, it is also very vital to point out that this series include only 4 children younger than 10 years of age and only 2 proximal ureter stones. Complication rate might be expected to go higher in younger age groups where flexible ureteroscopy is not available. Authors openheartedly admit their bias on ureteroscopy over shock wave lithotripsy for ureteral stones. We must emphasize that shockwave lithotripsy has been a very useful primary tool to fragment stones particulary in proximal ureter of even much younger kids. There are also some points need to be stressed in the technique of pediatric ureteroscopy. Although most steps are very similar to adult counterparts in ureteroscopy, the surgeon should be very aware of prominent psoas muscle and remarkable high incidence of anatomic variations due to either congenital anomalies or reconstructive surgeries. We generally start the ureteroscopy with a low pressure retrograde pyelography to check the ureteral anatomy since almost no intravenous urographies are ordered

in children now. Intramural ureter dilatation has been strongly suggested by many pediatric urologists but there have been no proof that it might permanently jeopardize the ureterovesical junction but we faced with some problems associated with ureteral baloon dilatations. We have observed that hydrodistention of intramural ureter with a pressure bag or an arthroscopy irrigation set is even possible. Fragmenting the stone can be sometimes very frustrating in small and inflamed ureters. If we are using an energy source other than Ho:YAG laser, stone size and stone composition in our opinion is important. Our threshold of leaving ureteral stent and schedule a relook procedure is very low in cases with any difficulty in advancing the ureteroscope or following the ureteral lumen. We believe that a "failed" ureteroscopy is a better outcome than a "complicated" one. We tend to stent children with office removal dangler on as authors described, but we no longer cut the excess coiling tip of the stent because of very high rate of bladder spasms and occasional severe hematuria. We either use the appropriate stent length or let it coil inside the bladder.

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EDITORIAL COMMENT

This is an interesting paper highlighting an ever-increasing use of ureteroscopy in the pediatric age group.

As worldwide experience increases in pediatric ureteroscopy and with technological advances and miniaturization of instruments, more urologists are using either rigid or flexible ureteroscopy as a first line treatment for ureteric stones.

The main alternative is extracorporeal shock wave lithotripsy (SWL) however; one of the major drawbacks for SWL is the rate of retreatments required and therefore for younger children usually under the age of 12 repeat general anesthetics. The authors group of patients have a mean age of 11 years with 12 out of the 23 being over 12 years old. Children over 12 years old generally can be considered for SWL without general anesthesia. All patients in this group however required general anesthesia with 3 patients requiring repeat procedures and therefore 2 anesthetics each.

The mean stone size was 5.3 mm. The authors used ballistic lithotripsy, which is infrequently used in children (more common electrohydraulic lithotripsy), and more recently Holmium lasertripsy becoming more popular. Bassiri et al. (1) used ballistic lithotripsy in 34/66 children although there overall stone free rate was 88% the stone free rate for ballistic lithotripsy on its own was not stated. In 4 patients, stones migrated into the kidney during ureterorenoscopy but once again, the report does not state what modality was being used in these cases. Previous reports in adults have described the risk of propulsion of stones back into the kidney with ballistic lithotripsy. This is one of the major drawbacks of this technology.

The authors state that fragmentation was always tried unless there was a small fragment, which could be removed with a basket. I feel that if the stone can be removed in one piece in a basket or with stone graspers without trauma to the ureter, this should be tried in preference to disintegration, as there is less

risk to the ureter from trauma and less chance of retreatment. Stone fragments 4 mm or less should be considered for removal intact if at all possible.

The authors used stents in the presence of severe edema or complications. Fifteen of the patients required stents, which in general were exteriorized for ease of subsequent removal. I do feel that the use of stents should be minimized as they can cause distress to child when exteriorized and also if indwelling require either a local anesthetic removal or general anesthetic depending on the child. We have used ureteric catheters overnight in children with ureteric edema without complication and these are easily removed the following day.

I do think that the use of ureteroscopy should be limited to those with significant expertise and only be undertaken as a primary treatment modality if SWL is not readily available. Ureteroscopy is generally safe but there is still a risk of vesicoureteric reflux, ureteric stricture and urethral stricture in boys secondary to instrumentation. Long term follow up of children treated with ureteroscopy is still lacking.

The age of the child, anatomy, stone size and location, available treatment modalities as well as local expertise should all be considered before deciding on whether ureteroscopy or SWL is a more appropriate primary treatment modality for the individual child.

The authors however have clearly demonstrated that ballistic lithotripsy has a good success rate in treating pediatric ureteric stones and is safe.

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The CAG Repeat within the Androgen Receptor Gene and Its Relationship to Cryptorchidism

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ABSTRACT

Purpose: We examined the significance of the CAG repeat polymorphism in the pathogenesis of cryptorchidism.
Materials and Methods: Genomic deoxyribonucleic acid (DNA) was extracted from blood samples from 42 cryptorchid boys and from 31 non-cryptorchid control subjects. In the cryptorchid group, 7 had bilateral cryptorchidism and 6 had patent processus vaginalis in the contralateral side. To determine the number of CAG repeats, the DNA was amplified by polymerase chain reaction and sequenced.
Results: The mean CAG repeat length in the AR gene was 22.5 (range 16 to 28) in patients and 21.5 (range 17 to 26) in controls (non-significant). Patients with bilateral cryptorchidism had a mean length of 24.3 (range 21 to 26) and patients with unilateral cryptorchidism and patent processus vaginalis in the contra lateral side had a mean of 25.2 (range 21 to 28), which was statistically different from controls ($p = 0.015$ and $p = 0.005$ respectively).
Conclusion: CAG repeat length of the AR gene does not seem to play a major role in patients with unilateral cryptorchidism. However, in patients with bilateral undescended testis, a less functional androgen receptor through a longer polyglutamine chain may have a role in its pathogenesis. In the same way, patients with unilateral cryptorchidism a contralateral patent processus vaginalis have longer CAG repeats that might be responsible for a slower testicular descent and incomplete closure of the processus vaginalis.

Key words*: cryptorchidism; androgens receptors; genetic polymorphisms*
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INTRODUCTION

Cryptorchidism is the most common congenital genital abnormality. Although it may be associated with a number of chromosomal and hereditary disorders, the majority of cases are isolated and the exact etiology remains to be defined. One of the several factors important in testicular descent is the presence of androgens and functional androgen receptor. The critical role of the androgen receptor (AR) in the development of the external genitalia is evident in the various forms of the androgen insensitivity syndrome (1). Hutson suggested that androgens are important mainly on the inguinal portion of the testicular descent, because mice with the testicular feminization (Tfm) mutation that confers a complete androgen resistance phenotype had uniformly descended testis to the level of the internal inguinal ring, but no further (2).

The AR gene is located on the X chromosome, so in normal 46 XY males, only one copy of the gene is present, and any alteration of the gene

may result in an abnormality of phenotypic development. The AR gene consists of 8 exons. Exon 1 is the largest and encodes the transactivation domain, which determines the transcriptional activity of the receptor. Exons 2 and 3 encode the receptor DNA binding domain, and exons 5 to 8 encode the portion of the receptor that binds to androgens. Mutations in the DNA and ligand binding domains have been reported in various androgen resistance phenotypes (3-5), however these mutations were not found in patients with isolated undescended testis (6).

Exon 1 codes a highly polymorphic glutamine (CAG) repetitive sequence. In vitro studies have shown that the longer the polyglutamine repeat the lesser the transcriptional activity of the receptor (7,8). There is evidence that this may be clinically important. Large expansions of the polyglutamine tract result in spinal bulbar atrophy, a fatal neuromuscular disease associated with low virilization and infertility, in these patients the severity of the disease is correlated with the repeat length (9). Also various studies showed an increased number of CAG repeats in patients with isolated infertility, and in XY males with undermasculinized genitalia (10-13). In the current study we analyzed the CAG repeat length in the AR gene in patients with cryptorchidism and no other genital abnormality.

MATERIALS AND METHODS

Forty-two patients were prospectively recruited for this study from the operative cases of 2 hospitals. The sole inclusion criterion was the presence of cryptorchidism with no other genital malformations. Patients with hernia and/or hydrocele were included, and patency of the processus vaginalis was accessed at surgery. They ranged in age from 3 to 77 years (mean 20.9). Seven had bilateral cryptorchidism, 6 had unilateral undescended testis with clinically evident patent processus vaginalis (PPV) in the contralateral side, 3 patients had unilateral ectopic testis in the superficial inguinal pouch and 2 had unilateral intrabdominal testis. Thirty-one volunteers with no personal or family history of genital abnormalities were recruited among the hospital staff to form a control group. They ranged in age from 22 to 69 years (mean 41.7). Informed consent was obtained from all subjects or from their parents under an approved protocol by the hospitals' Ethic Committees.

Genomic DNA was extracted from whole blood samples stored at -20ºC, using the automated instrument MagNA Pure LC (Roche, Germany), with the MagNA Pure LC DNA Isolation Kit I (Roche, Germany), and the DNA I – Whole Blood/High Performance extraction method.

The CAG repeat region was amplified by polymerase chain reaction (PCR), using previously described primers (14) - sense (5')-AGAGGCC GCGAGCGCAGCACCTC-(3'), and antisense (5')-GCTGTGAAGGTTGCTGTTCCTCAT-(3'). The PCR reactions were carried out with 100 ng DNA in a 50µL volume containing 5.0µL of 10x Mg2+- free buffer for DyNAzyme EXT DNA polymerase (Finnzymes, Finland), 1.0mM MgCl2, 0.2mM of each dNTP, 15 pmol of each primer, and 2.0 U of DyNAzyme EXT DNA polymerase. The samples were subjected to denaturation at 95ºC for 5 minutes, followed by 45 cycles of amplification consisting of denaturation at 95ºC for 1 minute, annealing for 1 minute at 65ºC, and extension for 1 minute at 70ºC. A final extension step at 70ºC for 5 minutes was also performed.

The amplified fragments were run on a 3.5% intermediate melting temperature agarose gel (MetaPhor agarose, BioWhittaker Molecular Applications, USA), in chilled 1x TBE for 7 hours and 30 minutes at 5.2V/cm. The agarose gels were subsequently stained with GelStar nucleic acid gel stain (FMC BioProducts, USA), and visualized on the Fluor-S MultImager analyzer (BioRad). PCR fragment length was determined by comparison with a 10bp molecular weight ladder (Invitrogen, UK), and results were accepted if concordant in at least three experiments. Afterwards, for each group of samples with differing CAG number, one sample was sequenced (DNA Sequencing Kit - BigDye Terminator Cycle Sequencing v3.1, Applied Biosystems) on a ABI PRISM 310 instrument (Applied Biosystems) and used as a DNA CAG-repeat size standard. These stan-

dards were compared to the non-sequenced samples by microchip electrophoresis (LabChip and DNA 500 Reagents, Agilent Technologies) on an Agilent 2100 Bioanalyzer (Agilent).

Data analysis was computer based using commercially available software. Because AR transcriptional activity decreases linearly across the entire CAG spectrum (7,8), we analyzed CAG repeats as a continuous variable. Normal data distribution was assessed using the Kolmogorov-Smirnov test. Differences in CAG repeat length were tested by the independent samples t test when data distribution was normal, and by Mann-Whitney test in the smaller subgroups with no normal distribution. Statistical significance was considered at $p < 0.05$.

RESULTS

The mean CAG repeat length was 22.5 (range 16 to 28) in patients and 21.5 (range 17 to 26) in controls (p = non-significant). Patients with bilateral cryptorchidism had a mean length of 24.3 (range 21 to 26) and patients with unilateral cryptorchidism and PPV in the contra lateral side had a mean of 25.2 (range 21 to 28). There was a statistically significant difference in the bilateral cryptorchid group and in the patent processus vaginalis group compared to controls ($p = 0.014$ and $p = 0.019$ respectively) (Table-1). Six patients had positive family history for cryptorchidism. These patients belonged to 2 families; in both families child, father and paternal grandfather were affected, and as expected there was no concordance in the number of CAG repeats between family members.

COMMENTS

Androgens clearly have a role in testicular descent (15), and a diminished androgenic stimulation may be responsible for a slower and incomplete testicular descent. Biologic and epidemiologic evidence suggests that moderate expansions of the CAG repeat, can influence androgen receptor activity and may be important in several clinical situations. Longer CAG repeats have been associated with several phenotypes of undermasculinized genitalia and idiopathic infertility. Lim et al. analyzing tissue samples from patients with abnormal male genital development, selected from the Cambridge intersex database found that patients with less severe malformations and unknown etiology tended to have longer CAG repeats compared to those with more severe malformations and known etiology (13). Suggesting that patients with less severe abnormalities have a multifactorial cause, and a small reduction of function of the AR could be important added to other "weak" causal factors in this group of patients. They also studied the CAG repeat length in groups of patients with different levels of testicular descent, and found no difference (13), however these groups were not compared to a population with no genital abnormality. Similarly Sasagawa et al. did not found a significant difference in the CAG repeat length between patients with cryptorchidism and controls in a Japanese population (16). Our data

Table 1 – *Number of CAG repeats in the AR gene in cryptorchid and non-cryptorchid subjects.*

	Mean Length ± SD (range)	**Median Length**	**p Value**[a]
Controls	21.5 ± 2.7 (16-26)	22	
All cryptorchid patients	22.4 ± 3.2 (15-29)	22.5	0.206 [b]
Unilateral cryptorchidism	22.1 ± 3.3 (15-29)	21	0.474 [b]
Bilateral cryptorchidism	24.7 ± 1.8 (21-26)	25.5	0.019 [c]
Unilateral cryptorchidism with contralateral patent processus vaginalis	25.2 ± 2.9 (20-29)	25	0.014 [c]

a = comparing to controls; b = student t test; c = Mann-Whitney test.

however, suggests that a difference may exist in a subset of patients. Comparing to our study the most striking difference was noted in the higher mean number of repeats in the control group of the Japanese patients. In fact the number of CAG repeats in Asians seems to be higher than in Caucasians (17,18), this could explain the higher incidence of Cryptorchidism in Asian populations (19) and perhaps in these populations the impact of this polymorphism in distinguishing patients from controls is minor.

A recent study (20) also showed that a combination of longer CAG repeats associated with longer GGC repeats in the AR gene, was more frequent in patients with bilateral cryptorchidism than on controls. In our series, patients with bilateral cryptorchidism and patients with unilateral cryptorchidism and contralateral PPV also had significant longer CAG repeats. Albeit the statically significance of the results, the short number of patients in these subgroups hinders definite conclusions. However is plausible that in these patients a less functional androgen receptor could be responsible for a slower testicular descent originating bilateral undescended testis or a unilateral undescended testis and a later testicular descent in the contralateral side resulting in an incomplete closure of the processus vaginalis.

Obliteration of the processus vaginalis normally occurs after testicular descent is complete (21), and spontaneous closure may occur in the first year of life, perhaps in response to the testosterone surge that occurs in the first months of postnatal life (22). Our data further supports a role for androgens in the closure of the processus vaginalis.

Androgen receptor gene alterations have been associated with partial or complete androgen insensitivity syndrome; a phenotype that often includes cryptorchidism, which is usually bilateral. Our data also shows that patients with bilateral undescended testes with no other genital abnormalities may also have a less functional androgen receptor through a longer polyglutamine chain. On the other hand unilateral cryptorchidism is often isolated, and not associated with AR gene mutations (6) or longer CAG repeats. This supports the idea that unilateral and bilateral cryptorchidism has different pathogenesis, and that bilateral cryptorchidism is more likely to have a genetic basis and an endocrine cause.

CONFLICT OF INTEREST AND FINANCIAL SUPPORT

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EDITORIAL COMMENT

A unilateral undescended testis is the most frequent form of cryptorchidism, There are, however, three different types of cryptorchidism: 1) primary, undescended testis(es) – UDT (common) since birth, 2) secondary, UDT descended at birth but subsequently ascends (in nearly 20% of all UDT) and, 3) UDT associated with a congenital syndrome (< 1% all UDT). Furthermore, a considerable number of unilateral UDT with a retractile contra lateral testis will eventually progress to bilateral UDT.

In the present paper, Silva-Ramos et al. examined a small number of patients with bilateral UDT. It is therefore possible that this group of patients was skewed towards the congenital syndrome type of cryptorchidism. Moreover, the importance of open processus vaginalis is still a contentious issue today. On one side of the argument, an open processus vaginalis is frequently observed during autopsies in adult males with normal genitalia. On the other hand, cryptorchid boys with open processus vaginalis and epididymo-testicular dissociation have the lowest germ cell number and the most pronounced form of hypogonadotropic hypogonadism (1). If there is a defect of androgen receptors in those with bilateral UDT, then prepubertal hypergonadotropic hypogonadism must follow. This however does not correlate with previously published findings (1). Nevertheless, this paper contributes towards a better understanding of the role of androgens in epididymo-testicular descent. Additional studies that include a larger number of patients with bilateral UDT are required in order to establish the necessity and the role of CAG-repeat for epididymo-testicular descent.

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Magnetic Resonance Imaging Urodynamics. Technique Development and Preliminary Results

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ABSTRACT

Objectives: In this preliminary study we report the development of the video urodynamic technique using magnetic resonance imaging (MRI).
Materials and Methods: We studied 6 women with genuine stress urinary incontinence, diagnosed by history and physical examination. Urodynamic examination was performed on multichannel equipment with the patient in the supine position. Coughing and Valsalva maneuvers were performed at volumes of 150, 250 and 350 mL. Simultaneously, MRI was carried out by using 1.5 T GE Signa CV/i high-speed scanner with real time fluoroscopic imaging possibilities. Fluoroscopic imaging was accomplished in the corresponding planes with T2-weighted single shot fast spin echo sequences at a speed of about 1 frame per second. Both studies were recorded and synchronized, resulting in a single video urodynamic examination.
Results: Dynamic MRI with cine-loop reconstruction of 1 image per second demonstrated the movement of all compartment of the relaxed pelvis during straining with the concomitant registration of abdominal and intravesical pressures. In 5 patients, urinary leakage was demonstrated during straining and the Valsalva leak point pressure (VLPP) was determined as the vesical pressure at leak subtracted from baseline bladder pressure. Mean VLPP was 72.6 cm H_2O (ranging from 43 to 122 cm H_2O).
Conclusions: The concept of MRI video urodynamics is feasible. In a clinical perspective, practical aspects represent a barrier to daily use and it should be recommended for research purposes.

Key words*: urinary incontinence, stress; urodynamics; magnetic resonance imaging*
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INTRODUCTION

Video urodynamics displaying simultaneous data with radiographic images of the bladder and urethra were originally described by Miller in 1971 (1). Pressure flow study combined with fluoroscopy or ultrasonography is generally referred as video urodynamics, which is currently the gold standard to diagnose and localize lower urinary tract dysfunction (2).

Magnetic resonance imaging (MRI) with its noninvasive, nonionizing, multi-planner imaging capabilities offers distinct advantages over computerized tomography/fluoroscopy and since it has greater accuracy over ultrasound in the detection of discrete structures, it has rapidly become a major diagnostic tool in the assessment of pelvic conditions.

Our attention was prompted by the possibility of using this new modality towards a better understanding of female stress urinary incontinence

(SUI). SUI is the observation of involuntary leakage of urine from the urethra synchronous with exertion/ effort, or sneezing, or coughing (3). Normally, anatomical support of the bladder neck and proximal urethra allows the transmission of increased intra-abdominal pressure to that area of continence, compensating the closure mechanism and maintaining continence. Leakage occurs as a result of pressure transmission failure, lack of intact intrinsic mechanism or both (4). However, these pathophysiological concepts are yet a matter of controversy.

To this date, there has been no satisfactory investigative method combining observations regarding bladder and urethra hypermobility, intrinsic sphincter insufficiency, and anatomical pelvic floor abnormalities in such patients. The fast MRI-systems available have a capability of functional examinations. Those have been explored and are currently used for evaluating other organ systems. The possibility of simultaneous evaluation of bladder and abdominal pressures, bladder and urethral mobility under effort, and pelvic floor muscles integrity and disposition, may have a potential role for better understanding SUI (5). Herein we report this preliminary and innovative effort to develop this technique.

MATERIALS AND METHODS

After our Institutional Review Board's approval and informed consent, we studied 6 women with genuine stress urinary incontinence, diagnosed by history and physical examination. Mean age was 53.1 years (range 28 to 70).

Urodynamic examination was performed on multichannel equipment with the patient in the supine position. Intravesical pressure was measured by a transurethral 7F double lumen catheter. Abdominal pressure was measured by a balloon catheter inflated with 5 to 10 mL saline. Detrusor pressure was indicated by electronically subtracting abdominal pressure from bladder pressure. Filling cystometry was performed at filling rate of 50 mL per minute with saline at room temperature. Coughing and Valsalva maneuvers were performed at volumes of 150, 250 and 350 mL.

Simultaneously, magnetic resonance imaging was performed by using 1.5 T (Magneton Sonata Maestro Class, Siemens, Erlangen, Germany) with a 6-channel belt type surface coil placed around the patient at the level of the symphysis pubis. Morphological T2 true FISP (true fast imaging with steady-state precession TR 4.5, TE 2.3) weighted images were taken in sagittal plane during 360 seconds at a speed of 1 frame per second.

Some devices were developed to accomplish the MRI urodynamics. An especially designed portable polygraph was coupled to a notebook, together with an adjustable infusion pump. Tube connections 5 meters long were adapted to the system, in order to maintain the electronic equipments out of the reach of the magnetic field.

Both studies were recorded and synchronized, resulting in a single video urodynamic examination (Figure-1).

RESULTS

This is the report of the last 6 patients when synchronization of both exams was achieved. Previously, 8 patients were submitted to the MRI video urodynamics with unsatisfactory results. Although both MRI and urodynamic data were properly obtained, they were not synchronous making impossible their evaluation as a single video urodynamic exam.

Mean age was 53.1 years (range 28 to 70). Table-1 shows patients characteristics.

Dynamic MRI with cine-loop reconstruction of 1 image per second produced images of striking vividness, which demonstrated the movement of all compartment of the relaxed pelvis during straining with the concomitant registration of abdominal and intravesical pressures (Figure-2). In 5 patients, urinary leakage was demonstrated during straining and the Valsalva leak point pressure (VLPP) was determined as the vesical pressure at leak subtracted from baseline bladder pressure. Mean VLPP was 72.6 cm H_2O (ranging from 43 to 122 cm H_2O) (Figure-2). The recording of leaking point pressure values simultaneous to the anatomic images of pelvic floor

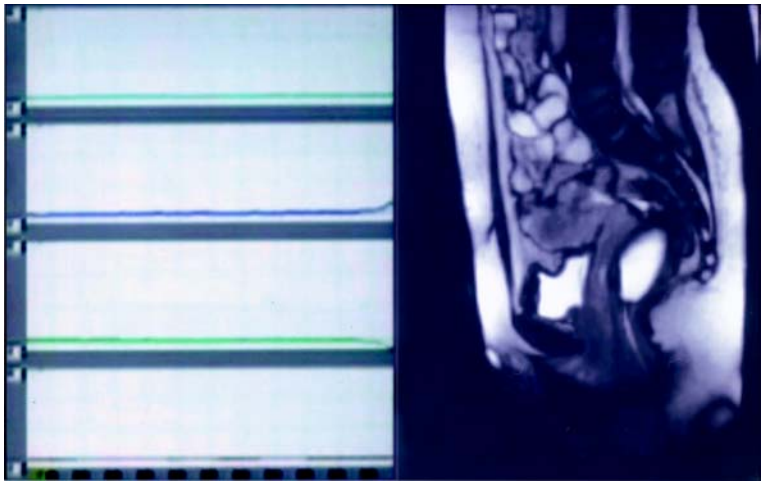

Figure 1 – *Magnetic resonance imaging video urodynamics. Synchronous display of urodynamic parameters and sagittal magnetic resonance image of the pelvis.*

Table 1 – *Patient's history and physical examination characteristics.*

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**	**Patient 6**
Age	50	51	28	70	70	50
Parity	none	4	3	3	5	4
Vaginal deliveries	none	none	2	3	4	none
Previous anti-incontinence surgery	none	none	none	none	none	none
Cystocele	I	I	I	absent	I	absent
Rectocele	absent	absent	absent	absent	absent	absent
Urethral hypermobility	present	present	present	absent	present	present

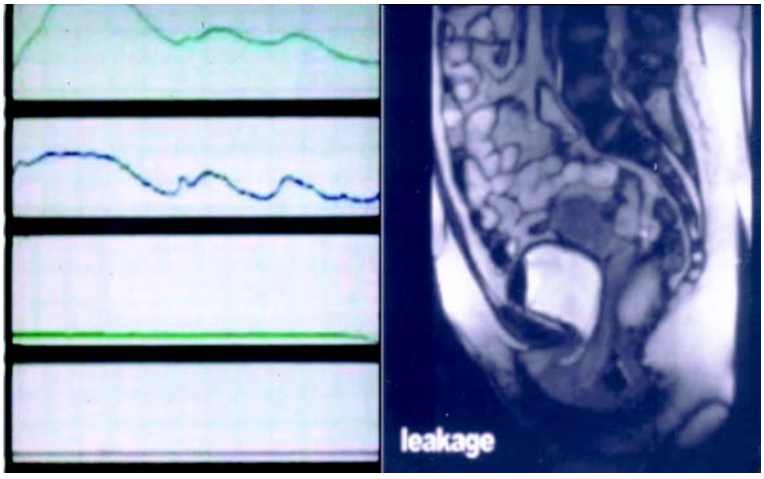

Figure 2 – *Magnetic resonance imaging video urodynamics. Urodynamic parameters during Valsalva maneuvers concomitant to magnetic resonance image of the pelvis showing descent of the bladder neck below the pucococcygeal line and the urethra fully opened, allowing loss of urine.*

muscles and bladder base descent under effort was achieved, providing a new visual dimension to understand SUI.

Urinary leakage was not demonstrated during MRI urodynamics in only one patient, despite previously demonstrated by physical examination. No pelvic organ prolapse was observed in this patient, neither by physical examination nor by MRI. We cannot doubtless state the reason for this disagreement, but possibly the patient's inability to satisfactorily increase intra-abdominal pressure during cough and Valsalva maneuvers. Patient age (70 years old), and the performance of the exam in the supine position inside the MRI tunnel with a belt type coil placed around the patient's body may have played a role as well.

The pubococcygeal reference line was employed for diagnosis of descent of the organs. Cystocele was seen in all patients (4 mild and 2 moderate) and rectocele in only one (moderate). No enterocele was noted. Pelvic organ prolapse evaluation by MRI correlated well with the physician examination, except in one patient. Table-2 shows the pelvic organ prolapse findings by the 2 methods.

Patients accepted well the procedure and experienced discomfort similar to standard urodynamic test. All patients said that they would agree to have a similar procedure in the future.

COMMENTS

Recent studies have changed our understanding of underlying multifactorial causes to incontinence. Our first understandings supposed that SUI was mainly a result of descent of the proximal urethra in relation to pelvic floor. Lately, our attention was focused to the fact that in many women with bladder dysfunction disorders including incontinence, other facts have to be considered as specific damage to pelvic muscle ligaments, integrity of soft connective tissue, peripheral nerves and segmental vessels.

Pelvic floor weakness strongly correlates with lower urinary tract dysfunction. Stress urinary incontinence often coexists with pelvic organ prolapse and vice versa. The fact that pelvic muscle exercises improve urinary control in many women confirms that muscle action can influence urinary control. The lack of universal success of such therapy emphasizes the importance of a better understanding of the relationship among pelvic muscles, pelvic floor fascial structures, bladder and urethra mobility, and how their damage can lead or contribute to SUI. Most women with SUI seem to have a combination of urethral dysfunction and loss of support, and scientific study of these issues awaits insight into the quantification of each of these parameters as independent variables (6,7).

In the last 10 years there has been a great increase in both availability and quality of MRI examinations. Its potential in the evaluation of pelvic floor disorders is well established. The advantages of MRI are well known and include the lack of radiation, and the ability to provide a high-resolution global assessment of the pelvis, its constituent organs, and the musculofascial support structures. Analysis of the levator plate complex can be made in the axial and mid-coronal images. Increased signal intensity

Table 2 – *Pelvic organ prolapse findings.*

	Physical Examination (grades I to IV)		**MRI** (mild, moderate, severe)	
	cistocele	rectocele	cistocele	rectocele
Patient 1	I	absent	mild	absent
Patient 2	I	absent	mild	absent
Patient 3	I	absent	mild	absent
Patient 4	absent	absent	mild	absent
Patient 5	I	absent	mild	absent
Patient 6	absent	absent	moderate	moderate

of the levator relative to the obturator internus muscle on proton density images, decreased length, thickness and muscle area can be used as parameters of levator complex lesion (8,9). Fascial defects cannot be appreciated on functional cine MRI alone (10). Endoluminal imaging has the potential to solve the problem regarding urethral support because a smaller field of view can be used, thereby providing images of higher spatial resolution. However, it would interfere with the synchronous realization of the urodynamics.

Functional MRI of the pelvic floor with depiction of organ movement was first introduced by Yang et al. and Kruyt et al. in 1991. (11,12). Nevertheless, MRI functional examinations are still limited in urological practice. The combination of function and morphology allows for an innovative view of the pelvic floor, and thus adds to our understanding of the various structure interactions. The intention of developing a MRI urodynamic examination is the possibility of gathering the objective functional test of bladder and urethra function provided by urodynamics with the best anatomical images of the pelvis offered by MRI. However, this was initially hampered by some practical problems. The magnetic fields prevent the use of other magnetic material close to the patient. We had to develop long connections to keep the polygraph outside the room. The long tunnel in which patients were placed was an obstacle to routine functional examinations, like having to perform micturition lying on the table within the MRI. Dynamic MRI has been performed previously during voiding only in an open MRI system (7). The problems with open systems are costs and availability, as well as poor spatial and time resolution compared with closed systems (13). For this reason, in this study, pressure/ flow studies were not performed.

Despite the fact that MRI is considered to be physically benign, it appears to be associated with psychological side effects. Patients may experience severe claustrophobia or panic attacks and others may report milder distress due to the necessity to lie in a very confined space for a long period. Although all patients in this study have undergone a MRI procedure for the first time, none of them experienced significant anxiety. Still, they have not been evaluated with pre and post-scan specific anxiety questionnaires.

To our knowledge, these preliminary results represent the first attempt where dynamic MRI has been used during urodynamic examination.

CONCLUSIONS

The concept of MRI video urodynamics is feasible and the basic technique was achieved after studying the 6 first patients. It is likely to believe that difficulties in some practical aspects represent a barrier to daily use, thus limiting routine clinical studies. However, it brings new possibilities for the study of SUI and bladder dysfunction and represents a useful tool for research purposes and further studies. Clinical research is needed to evaluate the possible diagnostic gains and possible additional use of MRI in urology.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The authors describe a merging of magnetic resonance imaging and urodynamic technologies. Though fluorourodynamics when initially described was potentially looked upon as an intellectual curiosity, it has since improved into a state-of-the-art method for evaluation of voiding dysfunction. Perhaps with this article we are also observing the emergence of a new marriage of technologies to aid the diagnosis and quantification of bladder dysfunction. Magnetic resonance imaging is already finding a place in the evaluation of pelvic floor prolapse. This extension of application to voiding dysfunction seems to be a reasonably logical step and in retrospect may even be thought of as the obvious natural sequence of diagnostic evolution. It will be unusual if other research groups choose not to examine this process and thus leave these authors known for their sui generis method of patient evaluation. The authors should be credited with their original thoughts and their desire to advance science.

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Defective Urinary Crystallization Inhibition and Urinary Stone Formation

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ABSTRACT

Introduction: Nephrocalcin (NC) is a glycoprotein produced in the kidney and inhibits calcium oxalate crystal formation. It has been separated into 4 isoforms (A, B, C, and D) and found that (A + B) are more abundant than (C + D) in urine of healthy subjects, but the reverse is seen in human urine of kidney stone patients. To further examine the role of this protein in inhibition of urinary crystallization, nephrocalcin isoforms were purified from 2 genetically pure dog species.
Materials and Methods: We studied healthy Beagles, known to be non-stone forming dogs, and Mini-Schnauzers, known to be calcium oxalate stone formers. NC was isolated and purified from each group. Urinary biochemistry and calcium oxalate crystal growth inhibition were measured.
Results: Specific crystal growth inhibition activity was significantly higher in non-stone forming dogs (9.79 ± 2.25 in Beagles vs. 2.75 ± 1.34 of Mini-Schnauzers, $p < 0.005$). Dissociation constants toward calcium oxalate monohydrate were 10-fold different, with Beagles' isoforms being 10 times stronger inhibitors compare to those of Mini-Schnauzers'. Isoforms C + D of NC were the main isoforms isolated in stone-forming dogs.
Conclusion: NC of these two species of dogs differently affects calcium oxalate crystallization and might have a role in determining ulterior urinary stone formation.

Key words*: kidney stone; calcium oxalate; crystallization; experiments; dogs*
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INTRODUCTION

Normal urine is supersaturated with respect to crystalline components, as a consequence of the essential homeostatic water conservation. This condition suggests the existence of physiological mechanisms that actively inhibit urinary crystallization of calcium salts (1). Various inhibitory macromolecules have been implicated in this process, e.g. osteopontin, crystal matrix protein, bikunin and nephrocalcin.

Nephrocalcin (NC) was isolated from human urine and kidney tissues (2), and later found in urine of 9 vertebrates' species (3). This glycoprotein is produced in proximal tubules in kidney (4) and its excretion is increased in renal carcinoma patients (5) and during pregnancy (6). NC has a mol. wt. of 14 kD, and can be separated into 4 isoforms with differ-

ent degrees of phosphorylation and amphiphilicities (7). Healthy subjects excrete more isoforms A and B that are less phosphorylated and have stronger hydrophobicity properties. In contrast, kidney stone forming patients excrete more isoforms -C and -D, which have higher degree of phosphorylation and weaker hydrophobicity. These isoforms of NC coat the surface of calcium oxalate crystals and control morphology, size and surface topography of crystals (8).

Evidence suggests that defective inhibitors can cause nephrolithiasis and NC accounts for a considerable portion of the inhibitory property of crystallization in urine (9). To examine this premise, we evaluated two species of pure-breed dogs with different incidences of kidney stones. We purified NC from urine samples from Beagles dogs, a non-stone forming species (10) and from Mini-Schnauzer dogs, known for frequent formation of calcium oxalate stones (11,12). In this report we compared chemical and physicochemical properties of NCs isolated from these species.

MATERIALS AND METHODS

Eleven healthy Beagles (3 neutered males and 8 neutered females, 4.0 ± 0.4 years old, body weight 9.28 ± 0.36 kg), and 7 Mini-Schnauzers (4 neutered males and 3 neutered females, 2.5 to 10.5 years old, body weight 6.6 ± 1.9 kg, who had at least one urinary stone) were selected. They were housed in individual cages under the conditions of controlled lighting and temperature, at the College of Veterinary Medicine, the University of Minnesota, according to the principles outlined in the National Institutes of Health "Guide for the Care and Use of Laboratory Animals".

At the beginning of collection period, the urine from the bladders of dogs was emptied by transurethral catheterization. They were then housed in metabolic cages to facilitate complete collection of voided urine. Water was accessible throughout the collection period. Urine was collected in plastic containers surrounded by ice and stored in capped plastic containers with thymol at 4° C. To ensure complete removal of urine, dogs were catheterized at the end of 24 h. To minimize catheter induced bacterial urinary tract infection, cefadroxil® was administered orally (20 mg/kg, q 12 h) during the 24 h period of urine collection (13). Refrigerated urine samples were warmed at room temperature. Urine pH was measured by using a Beckman pHmeter. Calcium, citrate, creatinine, oxalate, phosphate, and uric acid were determined by using a Beckman CX-5 autoanalyzer. Protein was determined in urine by micro-Lowry method using Folin-Ciocalteu Phenol reagent (14). Bovine serum albumin was used as a calibration standard with a concentration range between 10 to 50 μg.

NC was isolated and purified by the method previously described (15). Briefly, urine was diluted 3-fold by distilled water, pH adjusted to 7.3, and added 1/10 volume of DEAE-cellulose pre-equilibrated in 0.05 M Tris-HCl, pH 7.3, then stirred gently for 30 min at room temperature. The DEAE cellulose was separated by filtering through Whatman #1 filter paper with a Buchner funnel. The DEAE-cellulose cake was then washed with 1 L of 0.05 M Tris-HCl, pH 7.3 containing 0.1 M NaCl (Buffer-A). NC was eluted by 200 mL of 0.05 M Tris-HCl, pH 7.3 containing 0.5 M NaCl (Buffer-B) with gentle stirring for 30 min at room temperature. The filtrated NC fraction was dialyzed against 10 L of distilled water overnight with 1 change. The dialyzed fraction was further subjected to a DEAE-cellulose column (2 x 15 cm), and 4 NC isoforms (A,B,C, and D) were isolated by a linear NaCl gradient using 125 mL each of Buffer-A and Buffer-B. The salt gradient was monitored by a conductivity meter (Radiometer CDM210). The quantity of the individual isoform inhibition as measured under the curve was calculated and expressed as a relative ratio of inhibitory activity by percentage. Each of the four NC isoforms was further purified by a molecular sieve column of BioRad P-10 column (2 x 85 cm) using 50% formamide for separating urobilirubin from nephrocalcin, then followed by Sephacryl S-200 (1 x 90 cm) using Buffer-A. Purified NC concentration was determined by an alkaline hydrolysis followed by a ninhydrin reaction (7). Phosphoric acid content was determined by the method described by Ames (16). The color was developed by using Fiske-Subbarow reagent and 0.01 M KH_2PO_4 was used for preparing a

calibration standard ranging between 50 to 500 μ moles of phosphate concentration.

Surface tension at the air-water interface was measured by Lauda film balance (Brinkman Instruments Co., Westbury, NY) using 0.01 M Tris-HCl, pH 7.4, containing 0.1 M NaCl, and applied 100 μg of protein over the surface of the buffer solution. The protein film was compressed from the surface area of 327 cm^2 to 18 cm^2 in 30 min and the pressure changes were monitored and recorded through a computer.

Calcium oxalate crystal growth inhibition was measured by either ^{14}C-calcium oxalate incorporation method (15) or spectrophotometric method measuring decrease of oxalic acid (2). In brief, ^{14}C-calcium oxalate incorporation assay was done by mixing 500 μL of sodium acetate buffer (50 mM acetic acid, 5 mM barbituric acid, 0.15 M NaCl, pH 5.7 containing 0.05 μCi/mL of ^{14}C-oxalic acid), 500 μL of calcium chloride solution (50 mM acetic acid, 2 mM $CaCl_2.2\ H_2O$, 0.13 M NaCl, 5 mM barbituric acid, pH 5.7) and 25 μL of a sample solution. The crystallization is initiated by adding 100 μL of calcium oxalate monohydrate crystal slurry (1.8 mg/mL in sodium acetate buffer, pH 5.7). After 40 minutes of incubation, the mixture was centrifuged, and radioactivity was measured in the supernatant. Inhibitory activity is calculated as the following equation: $I = (C_{40} - C_{blank})/(C_0 - C_{40}).(C_{blank})$ radioactivity of buffer solution; Co: radioactivity counts at initial time, C_{40}: radioactivity count in the supernatant after 40 min incubation. Spectrophotometric assay was performed as following: 1 mL of sodium oxalate was added to acetate buffer (8.75 mM acetic acid and 90 mM NaCl, pH 5.7) and to a calcium chloride solution in a cuvette, with an aliquot of the sample solution. While this mixture was stirring, 10 μL of calcium oxalate monohydrate slurry in acetate buffer (0.8 mg calcium oxalate monohydrate/mL of acetate buffer) was collected to the spectrophotometric analysis. As oxalic acid consumed to forming calcium oxalate, absorbance at 214 nm decreases. The slope of the curve reflects the strength of crystal growth inhibitory activity of a sample, and also the dissociation constant of an isolated inhibitor can be calculated by plotting a Langmuir isotherm type plot. Amino acid composition was determined by a Beckman amino acid analyzer (Model 119CL, Beckman Instruments, Palo Alto, CA), after hydrolysis in an evacuated tube containing 6 N HCl for 24 hrs at 11º C. Neutral sugar analysis was carried out by phenol-H_2SO_4 method (17). Calibration curve was made by using 5 to 20 μg of glucose aqueous solution. Molecular weight was determined by HPLC with a molecular sieve column (TSK-2000SW, ToSoHaas, Montogomeryville, PA). Molecular weight standards used were BSA, soybean trypsin inhibitor, and cytochrome C. The solvent used was a Buffer-B, and running conditions were isocratic mode, flow rate 1.0 mL/min, and detection wavelength at 220 nm.

Results are expressed as means ± SD. Statistical analyses were performed using Minitab 11.0 software. Group differences were compared by unpaired t-test and the frequency of nephrocalcin isoforms by χ^2-statistical analysis. A value of $p < 0.05$ was considered significant.

RESULTS

Urine of individual dogs was analyzed and averaged values of pH, calcium, phosphate, uric acid, citrate, oxalate, and protein are summarized in Table-1. There were significant differences in calcium and uric acid excretion between Mini-Schnauzers and Beagles ($p < 0.005$).

Urinary protein concentration and crystal growth inhibition activities of both species were compared in Table-2. The specific inhibitory activity of non-stone forming dogs (Beagles) was approximately

Table 1 – *Urine biochemistry. Concentrations are expressed as mg/creatinine basis.*

	Mini-Schnauzers (n = 7)	**Beagles** (n = 11)
pH	6.53 ± 0.72	6.79 ± 0.32
Protein	0.03 ± 0.01	0.02 ± 0.02
Calcium*	0.07 ± 0.02	0.03 ± 0.02
Uric acid*	0.17 ± 0.05	0.07 ± 0.02
Phosphate	0.52 ± 0.48	0.95 ± 0.38
Oxalate	0.04 ± 0.06	0.05 ± 0.01
Citrate	0.28 ± 0.40	0.12 ± 0.10

******* *Mini-Schnauzers vs. Beagles; $p < 0.005$.*

Table 2 – *Comparisons of urinary protein concentration and calcium oxalate crystal inhibition activity.*

	Protein Concentration (mg/mL)	**Specific Crystal Growth Inhibition Rate**
Beagles	0.21 ± 0.05	9.79 ± 2.25
Mini-Schnauzers*	0.23 ± 0.11	2.75 ± 1.34

**Inhibition rate, Beagles vs. Mini-Schnauzers; p < 0.005.*

4 times higher than stone forming dogs (Mini-Schnauzers).

Elution patterns of NC isoforms A,B,C, and D are summarized in Table-3. Non-stone forming Beagles excreted in their urine 56% of isoforms (A + B), and 44% of (C + D) isoforms. Particularly, B isoform peaked in the isoforms isolated. The ratios of isoforms in the Mini-Schnauzers dogs were 43% of isoforms (A + B) and 57% of isoforms (C + D). In this group, C was the main isoform isolated.

Carbohydrate content was measured by phenol-sulfonic acid method and calculated by molar ratio per protein (Table-4). All isoforms contained 0.01 to 0.02 g per gram of protein. Dogs urinary NC showed high content of acidic amino acid residues and low content of aromatic and basic amino acid residues. However, both species showed almost identical amino acid compositions. On the other hand, phosphate content in Mini-Schnauzers' NC was significantly higher compared to Beagles (Table-4).

Figure-1 shows typical force area curves of these isoforms at the air-water interface measured by a Lauda film balance. Isoform A of the Beagles showed the highest collapsing pressure, 44.8 mN/m, and gradual decreases were seen in B,C and D. Mini-Schnauzers showed lower collapse pressure in isoforms A and higher collapse pressure in isoforms C and D when compared to the Beagles' group. Table-4 summarizes collapsing pressure and dissociation constants of 4 NC isoforms isolated from both species.

Table 3 – *Distribution ratios (%) of 4 nephrocalcin isoforms.*

	Isoform-A	**Isoform-B**	**Isoform-C**	**Isoform-D**
Beagles (n = 11)*	11.45 ± 4.25	44.42 ± 14.31	21.05 ± 6.74	21.90 ± 13.37
Mini-Schnauzers (n = 7)	17.80 ± 6.41	26.79 ± 11.36	32.91 ± 14.13	18.19 ± 6.95

**Beagles vs. Mini-Schnauzers IsoA + IsoB, p < 0.05*

Table 4 – *Chemical composition and physical properties of 4 NC-Isoforms.*

	Beagles				**Mini-Schnauzers**			
Isoform	**A**	**B**	**C**	**D**	**A**	**B**	**C**	**D**
Carbohydrate	0.01	0.02	0.02	0.02	0.02	0.01	0.01	0.02
Phosphate	0.52	1.30	1.72	3.24	1.72	2.48	4.42	12.96*
Collapse pressure	44.8**	40.8**	27.4	31.0	35.8	31.2	33.7	36.9
Dissociation Constant**	$x10^{-7}$ M				$x10^{-6}$ M			

**Mini-Schnauzers vs. Beagles p < 0.005; ** Mini-Schnauzers vs. Beagles p < 0.05. Carbohydrate and phosphate are expressed in molar ratio to protein. Collapse pressure (Nm/m) was measured by a Lauda film balance. Dissociation constant toward calcium oxalate monohydrate crystals was determined by a spectrophotometric method and calculated from Langmuir isotherm type plot.*

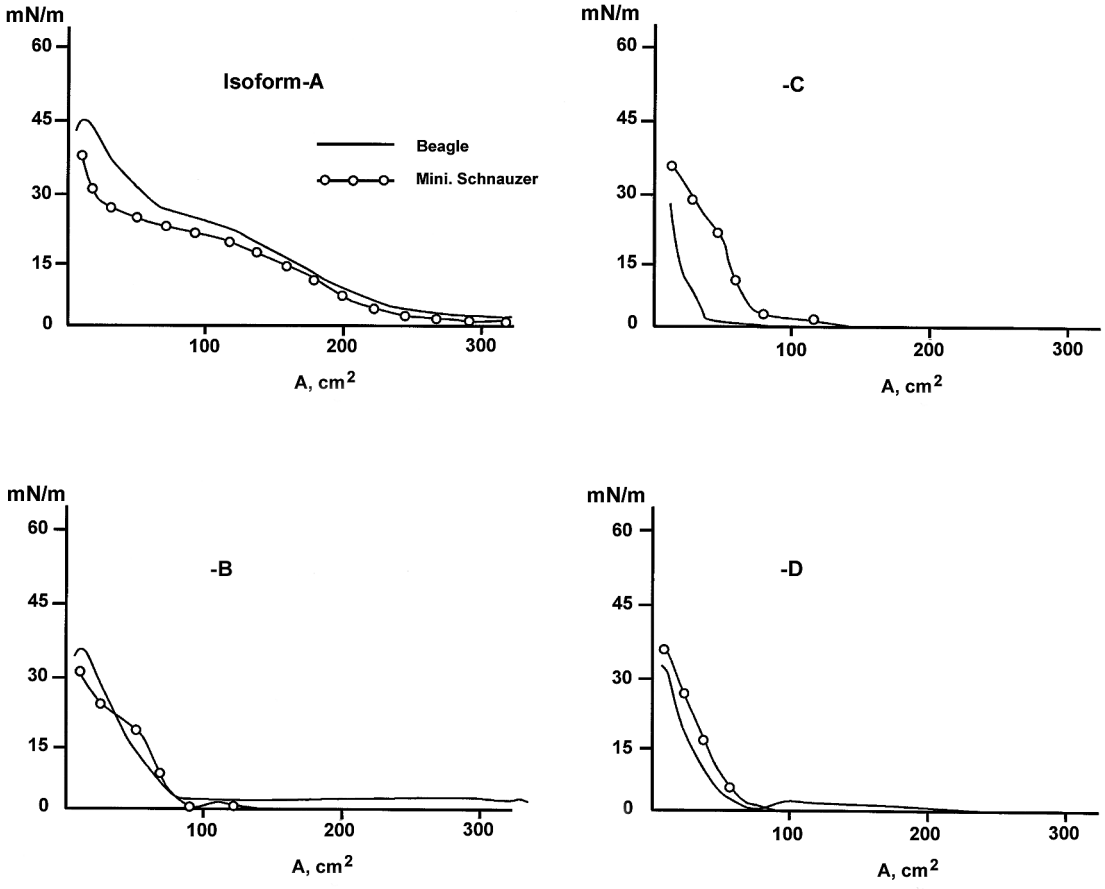

Figure 1 – *A force area curve of isolated isoforms at the air-water interface measured by Laud film balance. Experimental details are described in Materials and Methods section.*

COMMENTS

It has been accepted that stone formation is a crystallization process, taking place in supersaturated urine. However, despite nearly universal urine supersaturation, stones occur in a minority of people. Crystallization inhibitors, like citrate, proteins and glycosaminoglycans may account for this discrepancy (18). In this study, using two different species of dogs with distinct incidences of urinary stones several conclusions can be reached.

Mini-Schnauzers, a class of dogs with high formation of kidney stones, excreted more calcium and uric acid in their urine ($p < 0.005$) when compared to Beagle's group, a species that rarely presents with nephrolithiasis. These electrolytes combine to promote higher supersaturated urine, certainly predisposing these dogs to urinary stone formation.

However, we also found a remarkable difference in the qualitative excretion of urinary NC between these dogs' breeds. The NC isolated from the urine of Beagles showed strong inhibitory activity toward calcium oxalate crystals, but Mini-Schnauzers' urine has 4 times less inhibitory activity (Table-2). Previously we reported the same pattern of data in humans with or without urinary stones (7).

Non-stone forming Beagles' excreted in their urine more NC isoforms A and B than isoforms C and D when compared to Mini-Schnauzers ($p < 0.05$). NC isoforms are calcium-binding proteins, and binds

4 atoms of calcium ions per one molecule of NC. The Ca^{2+} binding mode is significantly different between isoform A or B and C or D: isoforms A-B binds Ca^{2+} directly through carboxyl groups of asp and/or glu residues. However, isoforms C-D requires at least two molecules of water between Ca^{2+} and carboxyl groups (19). Isoforms A and B changes its conformation and increase its hydrophobicity upon binding Ca^{2+}, but isoforms C or D do not. As a consequence isoforms C and D are more soluble in water and forms a less stable monolayer at the interface of air-water, and the collapsing pressure is lower. Less hydrophobicity of isoforms C and D might be related to a higher content of phosphate residues. In resume, we can say that in the current study we found the presence of a larger quantity of "good" inhibitors in Beagles' urine when compared to the group of Mini-Schnauzers dogs. Our classification of "good" inhibitors is based on different hydrophobicity, charge of the molecule and phosphate content. We can speculate at this moment that the isoforms that acts as strong (A-B) or weak (C-D) inhibitors of calcium oxalate crystallization are the same protein with different post-transcriptional modifications.

Finally, we found another indication of better inhibitory performance in the NC isolated from the urine of Beagles' group. When compared to the stone forming Mini-Schnauzer's dogs, dissociation constants toward CaOx monohydrate crystals for Beagles NC isoforms are 10-fold higher than those of stone forming dogs' isoforms. This means that they are at least 10-fold stronger in binding capacity to the CaOx crystal surface when compared to those of the Mini-Schnauzer NC.

We would like to point some limitations of our work. We did not study others inhibitors like glycosaminoglycans or Tamm-Horsfall protein, for example. However, we (20,21) have showed that almost 80% of inhibitory crystallization of calcium oxalate in urine is due to NC. Also, we made some inter-species analysis without using controls in each group. Nonetheless, this work can be considered as a pilot study and supported by these findings inter- and intra-species assessments will be the theme of a future analysis. Finally, our findings are not necessarily applicable to human nephrolithiasis. But in some cases animals' models of nephrolithiasis have close pathogenetic association to kidney stone formation in humans (22,23).

CONCLUSION

Nephrocalcin isolated from urine samples of Beagles dogs, a non-stone forming species, and from Mini-Schnauzer dogs, known for frequent formation of calcium oxalate stones, differently affected calcium oxalate crystallization and might have a role in determining urinary stone formation.

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EDITORIAL COMMENT

Nucleation, growth and aggregation are the principal crystallization mechanisms in stone development (1). Urine contains compounds that modulate such processes as well as the attachment of crystals to renal epithelial cells. While nucleation promotion activity is most likely sustained by membrane lipids, most of the inhibitory aggregation activity resides in macromolecules such as glycoproteins and glycosaminoglycans (2). Inhibitory proteins found in urine include nephrocalcin, Tamm-Horsfall glycoprotein (THG), prothrombin fragment 1, bikunin (uronic acid-rich protein), osteopontin, inter-α-trypsin inhibitor, among others. Most of the molecules are anionic, with many acidic amino acid residues, frequently contain post-translational modifications such as phosphorylation and glycosylation, and appear to exert their effects by binding to calcium oxalate surface (3). The specific structural motifs that favor crystal binding and inhibition are not yet known. A number of proteins are made by renal epithelial cells, whereas others gain access to the urine by glomerular filtration. In a number of cases, abnormalities of protein structure or function have been found in stone formers. It is not yet known what proportion of stone formers have an abnormality of inhibitor function (3).

Nephrocalcin, first described by Nakagawa et al. (4), has subsequently been shown in studies by the same group, to be deficient in gamma-carboxyglutamic acid in patients with calcium oxalate nephrolithiasis (5,6), hence reducing its ability to inhibit CaOx crystallization. According to Ryall (7), the fact that this protein has not been sequenced yet may raise some questions about it being possibly related to bikunin, a fragment of inter-α-trypsin inhibitor (8).

In this issue, Carvalho et al. compared biochemical and physicochemical properties of NC in 2 species of dogs that form (Mini-Schnauzers) or do not form (Beagles) calcium oxalate stones. They concluded that the specific crystal growth inhibition activity was significantly higher in the latter, which also possessed the isoforms usually not implicated in stone formation. Although these findings may not be applicable to human nephrolithiasis, it sheds further light into the understanding of how crystallization inhibitors may ultimately affect stone formation.

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Experimental Supratrigonal Cystectomy. Evaluation of Long-Term Complications

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ABSTRACT

Objective: The present study aims at assessing the occurrence of pyelonephritis and long-term complications in rats submitted to surgical reduction of bladder capacity.
Materials and Methods: Sprague-Dawley rats were submitted to supratrigonal cystectomy (29 animals) or sham operation (15 animals) and sacrificed 2, 4 and 6 months after the surgical procedure. The arterial blood pressure and serum creatinine levels were assessed before the surgery and at the time of the sacrifice. After the sacrifice a careful inspection of the urinary apparatus was performed to the characterization of the hydronephrosis and for the detection of the presence of calculi. With sterile technique, the urine was aspirated from the bladder and the kidneys removed and sent to a microbiologic study.
Results: Pyelonephritis was frequent in animals submitted to supratrigonal cystectomy. The most frequent and isolated microorganisms were Staphylococcus sp. and E. coli. The presence of urinary calculi was correlated significantly to the presence of urinary tract infection ($p < 0.003$). Arterial hypertension was frequent amongst animals submitted to supratrigonal cystectomy. Serum creatinine was high in 72.4% of the animals in the group submitted to supratrigonal cystectomy. The presence of calculi and pyelonephritis were frequent in rats presenting renal insufficiency and in hypertensive rats.
Conclusions: The long-term course of urinary infection in rats submitted to supratrigonal cystectomy was characterized by a high incidence of renal insufficiency and arterial hypertension that seem to be related to dysfunction and bladder obstruction induced by an extensive surgical procedure and the presence of urolithiasis and pyelonephritis.

Key words*: pyelonephritis; experiments; rats; cystectomy; lithiasis*
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INTRODUCTION

Urinary infection is one of the most frequently found bacterial infections in medical practice. Clinical forms are variable, ranging from asymptomatic bacteriuria to pyelonephritis and sepsis, depending on the degree of the disease (1,2). Both factors related to the virulence of the infecting agent and the factors of host defense (natural, immunologic and molecular), are determinant of the severity of the urinary infection (3-6).

The intact bladder has important mechanisms of protection against bacterial infections (7-9). It is widely known that bladder dysfunction related to structural alterations or to neurological diseases cause urinary tract functional obstruction, stasis and vesicoureteral reflux, increasing the incidence of urinary tract infections (7,10-12). The role of the bladder capacity as a protection/increase factor to the predisposition to urinary infection and pyelonephritis, is not completely understood. In previous experimental studies the increase of urinary infection and spon-

taneous pyelonephritis was observed in rats submitted to different types of cystectomies when studied in the first postoperative weeks (13).

The objective of the present study was to evaluate the occurrence of long-term urinary tract infection and other complications in rats submitted to surgical reduction of the bladder capacity.

MATERIALS AND METHODS

Sprague-Dawley rats approximately 2 months old were anesthetized with pentobarbital and submitted to supratrigonal cystectomy, leaving both ureters intact. A second group of rats were submitted to a sham surgery in which, though a suprapubic incision, the bladder was exposed and left intact. All surgical procedures were aseptic. During all study regular rat food and filtered water ad libitum were provided. Groups of animals were sacrificed 2, 4 and 6 months after the surgical procedure. Arterial blood pressure and serum creatinine level were measured before the surgical procedure and at the time of the sacrifice.

After the sacrifice a careful inspection of the urinary tract was performed to characterize hydronephrosis, defined by the presence of dilation of the renal pelvis and the ureters and to detect the presence of calculi. Afterwards, bladder urine was aspirated and sent to microbiologic analyses. The kidneys were then removed and sectioned. Half of the kidney was homogenized in a 5 mL sterile saline solution (TRI-instruments) and after successive dilutions (10^{-1},10^{3},10^{-5}) slides to determine the number of bacteria were made after the correction to the dilution factor. Microbiological standard techniques were used. The finding of $\geq 10^5$ units forming colonies - ufc/mL of urine indicated the presence of infection. We considered pyelonephritis the presence of $\geq 10^5$ ufc per gram or renal tissue (13,14). Animals with systolic arterial blood pressure persistently superior to 140 mmHg were considered hypertensive. Renal insufficiency was defined by serum creatinine superior to 1.0 mg/dL.

Data are presented as mean ± standard deviation. Student's t test was used to compare continuous variables among groups and the χ^2 test and Fisher exact test for categorical variables as appropriate. $P < 0.05$ was considered as statistically significant.

RESULTS

Eighty seven rats were submitted to supratrigonal cystectomy and 20 rats were submitted to sham surgery. The mean systolic arterial pressures measured at the animals' tails before the surgeries was 103.3 ± 11.6 mmHg (103.6 ± 12.7 mmHg for animals submitted to supratrigonal cystectomy and 102.0 ± 9.4 mmHg for the animals in the sham group, $p > 0.05$) and mean serum creatinine was 0.74 ± 0.24 mg/dL (0.77 ± 0.23 mg/dL and 0.66 ± 0.24 mg/dL respectively to the groups submitted to supratrigonal cystectomy and sham, $p > 0.05$). From the surviving animals submitted to supratrigonal cystectomy, 10 were studied 2 months after surgery, 9 were studied 4 months after surgery and 10 animals were studied 6 months after the surgical procedure. The incidence of pyelonephritis, the frequency of lithiasis and the number of animals with serum creatinine increase (renal insufficiency) and of the systolic pressure are shown in Table-1.

Pyelonephritis was frequent in animals submitted to supratrigonal cystectomy, present in 50% of the animals in the first 2 months follow-up, in 67% in the fourth month and in 60% in the sixth month. In every one of these animals urine culture was also positive for the same bacteria. From the total of 17 animals with pyelonephritis, Staphylococcus sp were isolated in 8 (47%), E. coli in 6 (35.3%). Proteus sp. in one. In one rat sacrificed 2 months after the cystectomy Staphylococcus sp. + E. coli + Klebsiella sp. were isolated (5.9%) and in another rat sacrificed 6 months after the surgical procedure Staphylococcus sp. + E. coli were isolated (5.9%).

The presence of vesical calculi (Table-1) was elevated (62%) and was significantly correlated to the presence of urinary tract infection ($p < 0.003$). Arterial hypertension was also frequent amongst animals submitted to supratrigonal cystectomy, opposite to what was observed in the sham group.

At the time of the sacrifice, mean serum creatinine was more elevated in the group of animals sub-

Table 1 – *Complications in rats submitted to supratrigonal cystectomy and sham surgery.*

	N	PN / UTI	Urinary Calculus	Renal Insufficiency	Arterial Hypertension
Cystectomy					
2 months	10	5	5	10	4
4 months	9	6	8	6	5
6 months	10	6	5	5	4
Sham					
2 months	6	0	0	0	0
4 month	4	0	0	1	0
6 months	5	0	0	0	0

PN = pyelonephritis; UTI = urinary tract infection.

mitted to supratrigonal cystectomy in relation to the group submitted to sham surgery (1.34 ± 0.64 versus 0.75 ± 0. 20, respectively, $p < 0.003$). Serum creatinine was at normal levels in all 15 rats submitted to sham surgery, however it was high in 21 (72.4%) of the 29 rats submitted to supratrigonal surgery ($p < 0.0006$).

There was a statistically significant association ($p < 0.001$) between the presence of calculi and pyelonephritis - 83% of the animals with urinary calculus had associated pyelonephritis (Table-2). The presence of renal insufficiency (72.2%) and of arterial hypertension (50%) were frequent in animals with urinary calculus as well as in rats with pyelonephritis (76.5% and 64.7%, respectively) even though not statistically significant. Similarly, the presence of urinary calculus and pyelonephritis were frequent in rats presenting renal insufficiency (61.9% each) and in hypertensive rats (69.2% and 84.5%, respectively).

COMMENTS

The long-term course of urinary tract infection in rats submitted to supratrigonal cystectomy was complicated by the high incidence of renal insufficiency and arterial hypertension. In a previous study in animals assessed 4 weeks after the same surgical procedure used in the present study, an increased frequency of pyelonephritis/urinary infection and calculi was demonstrated. We have concluded that the infection is spontaneous and related to an accentuated vesical dysfunction induced by the surgical procedure, with the section of muscle fibers and nerves, causing functional obstruction, urinary stasis and vesicoureteral reflux (13).

It is possible that the accentuated reduction of bladder capacity and consequent reduction of its complacency, increasing intraluminal pressure, leads to hydronephrosis urinary stasis, predisposing to urinary infection, pyelonephritis and renal parenchyma

Table 2 – *Association between renal insufficiency and arterial hypertension in rats with urinary calculus and pyelonephritis.*

	N	Urinary Calculus	PN / UTI	Arterial Hypertension	Renal Insufficiency
Urinary calculus	18		15	9	
Pyelonephritis / UTI	17	15		11	13
Hypertension	13	9	11		13
Renal insufficiency	21	13	13	9	9

PN = pyelonephritis; UTI = urinary tract infection.

lesion (7,10,15-17). Additionally, the association between the urinary infection and the formation of calculi suggests that the presence of urolithiasis keeps the infection and increases the possibility of vesicoureteral reflux and renal damage (11,17). The infecting flora in the present study, similarly to previous studies, called the attention to the frequency of gram-positive bacteria. The infection did not seem to be related to the contamination during the surgical act, since strict aseptic techniques were used, even though this possibility cannot be secluded.

The high frequency of arterial hypertension and/or renal insufficiency in the present investigation was not unexpected, even though they were not analyzed in shot-term studies (13). The trend of being kept constant during the period of the study suggest that they are complications installed precociously. However, the constancy observed can be due to a selection bias, since 41 of the 81 rats submitted to supratrigonal cystectomy died in the first 4 months follow-up suggesting that severely affected animals did not survive until the sacrifice period.

The presence of vesical calculus was documented in 62% of the rats submitted to supratrigonal cystectomy and was significantly correlated to the presence of urinary infection. Hydronephrosis was also frequently observed to sacrifice, even though the present study did not aim to study the incidence of obstructive uropathy. The association of lithiasis and pyelonephritis was high in animals with renal insufficiency (61.9%). Pyelonephritis associated to obstruction of the urinary tract is an important cause of renal parenchyma lesion and subsequent renal insufficiency and arterial hypertension (15,16,18,19). Additionally, 69.2% of hypertensive animals has, associated renal insufficiency, being arterial hypertension an important cause for and factor of progression of renal insufficiency (20).

CONCLUSIONS

The incidence of urinary infection/pyelonephritis and urolithiasis is high in rats submitted to supratrigonal cystectomy. The long-term course was characterized by an elevated incidence of renal insufficiency and arterial hypertension, which seem to be related to vesical dysfunction induced by the extensive surgical procedure and the presence of urolithiasis and pyelonephritis with extensive destruction of the renal parenchyma.

CONFLICT OF INTEREST

None declared.

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UROLOGICAL SURVEY

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STONE DISEASE

Diabetes Mellitus and Hypertension Associated With Shock Wave Lithotripsy of Renal and Proximal Ureteral Stones at 19 Years of Followup

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J Urol. 2006; 175: 1742-7

Purpose: SWL has revolutionized the management of nephrolithiasis and it is a preferred treatment for uncomplicated renal and proximal ureteral calculi. Since its introduction in 1982, conflicting reports of early adverse effects have been published. However, to our knowledge the long-term medical effects associated with SWL are unknown. We evaluated these adverse medical effects associated with SWL for renal and proximal ureteral stones.
Materials and Methods: Chart review identified 630 patients treated with SWL at our institution in 1985. Questionnaires were sent to 578 patients who were alive in 2004. The response rate was 58.9%. Respondents were matched by age, sex and year of presentation to a cohort of patients with nephrolithiasis who were treated nonsurgically.
Results: At 19 years of followup hypertension was more prevalent in the SWL group (OR 1.47, 95% CI 1.03, 2.10, $p = 0.034$). The development of hypertension was related to bilateral treatment ($p = 0.033$). In the SWL group diabetes mellitus developed in 16.8% of patients. Patients treated with SWL were more likely to have diabetes mellitus than controls (OR 3.23, 95% CI 1.73 to 6.02, $p < 0.001$). Multivariate analysis controlling for change in body mass index showed a persistent risk of diabetes mellitus in the SWL group (OR 3.75, 95% CI 1.56 to 9.02, $p = 0.003$). Diabetes mellitus was related to the number of administered shocks and treatment intensity ($p = 0.005$ and 0.007).
Conclusions: At 19 years of followup SWL for renal and proximal ureteral stones was associated with the development of hypertension and diabetes mellitus. The incidence of these conditions was significantly higher than in a cohort of conservatively treated patients with nephrolithiasis.

Editorial Comment

This provocative study underscores the need for long-term studies of the impact of our interventions, be they medical or surgical. Specifically, it raises concerns of the development of hypertension and diabetes mellitus following shockwave lithotripsy. The data related to the development of diabetes is particularly compelling, with a high odds ratio (3.75) that persists despite controlling for body mass index, and demonstrates a dose-dependency (correlation with number and intensity of shocks) that supports the hypothesis that a true biological effect exists. Deterioration in pancreatic endocrine function has been reported in up to 30% of patients undergoing SWL for pancreatic stones, though whether this reflects underlying pancreatic disease or the effects of the SW has not been determined. It is also unclear whether the effects noted in this study are peculiar to the shock path and focal area of the Dornier HM-3, or if similar effects may be anticipated with current lithotripter designs.

The data pertaining to hypertension is less compelling. Though more patients who underwent SWL developed hypertension, shockwave lithotripsy had no impact on the final prevalence of hypertension. In other words, the differences seen can be attributed to baseline differences in the rate of hypertension. It is plausible that other differences at baseline, in particular differences in stone size (those observed had smaller stones) reflect a bias that patients treated with SWL were further along in their disease process. Lastly, no dose-response correlation was noted with regards to number or intensity of shockwave and the development of hypertension, making it less likely that a true biological effect exists.

It is important to also note a few weaknesses in study design. The method of follow-up was not consistent in the study – patients treated with SWL were followed by questionnaire while the control group was followed by chart review, though the authors acknowledge that less than 20% of their patients return to their institution for follow-up. No information was gathered regarding subsequent SWL or other therapies for stone disease in either group during the 13 year follow that may confound the analyses conducted.

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Effect of Dietary Modification on Urinary Stone Risk Factors

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Kidney Int. 2005; 68: 2264-73

Background: This study was undertaken to ascertain the effect of dietary modification on urinary stone risks, and to determine whether the response depends on the prevailing urinary calcium.
Methods: A retrospective data analysis was conducted from our stone registry involving 951 patients with calcareous stones undergoing ambulatory evaluation, whereby 24-hour urine samples were collected during random diet and after dietary modification composed of restriction of calcium, oxalate, sodium, and meat products. Samples were analyzed for stone risk factors. Urinary calcium was also obtained after overnight fast and following a 1 g-calcium load. Changes produced by dietary modification from the random diet were evaluated in 356 patients with moderate-severe hypercalciuria (> 6.88 mmol/day, group I), 243 patients with mild hypercalciuria (5.00-6.88 mmol/day, group II), and 352 with normocalciuria (< 5.00 mmol/day, group III).
Results: Urinary calcium postcalcium load and the percentage of patients with absorptive hypercalciuria type I were highest in group I, intermediate in group II, and lowest in group III. During dietary modification, urinary calcium declined by 29% in group I, 19% in group II, and 10% in group III. Urinary oxalate did not change. Urinary saturation of calcium oxalate declined by only 12% in group I, 6% in group II, and nonsignificantly in group III, owing to various physicochemical changes in urinary biochemistry, which attenuated the effect of the decline in urinary calcium. Urinary saturation of brushite declined in all 3 groups due to the fall in urinary calcium, phosphorus, and pH. This reduction was more marked in the hypercalciuric groups than in the normocalciuric group. Urinary saturation of monosodium urate also decreased from a decline in urinary sodium and uric acid.
Conclusion: Secondary rise in urinary oxalate occurring from calcium restriction can be avoided by concurrent dietary oxalate restriction. Dietary modification (restriction of dietary calcium, oxalate, sodium, and meat products) is more useful in reducing urinary saturation of calcium oxalate among patients with hypercalciuria than among those with normocalciuria.

Editorial Comment

The pendulum swings once more. Dietary restriction of calcium may play a select role in recurrent stone management. This study suggests that those who stand to benefit most from calcium restriction are those with urinary CA > 275 mg/day and those with calcium phosphate supersaturation. The authors correctly note that the addition of potassium citrate supplementation to dietary restriction of calcium may be important to have a

significant impact on calcium oxalate saturation, as limiting dairy products alone will decrease the alkali load leading to lower pH and citrate levels. They also emphasize that calcium restriction should be part of a broad dietary intervention that also limits oxalate intake so as to avoid a compensatory increase in urinary oxalate due to increased bowel absorption. Though a diagnosis of absorptive hypercalcuria type I (AH1) was determined by a calcium load test, the authors did not stratify response to calcium restriction based on this diagnosis. However, almost 75% of patients with urinary CA > 275 mg/day were diagnosed with AH1. The authors propose that the use of a calcium-sparing diuretic and potassium citrate supplementation are additional important considerations to prevent a negative calcium balance with subsequent impact on bone density.

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ENDOUROLOGY & LAPAROSCOPY

Robot Assisted Laparoscopic Partial Nephrectomy: Initial Experience

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J Urol. 2006; 176: 36-39

Purpose: Advances in laparoscopy have made laparoscopic partial nephrectomy a technically feasible procedure but it remains challenging to even experienced laparoscopists. We hypothesized that robotic assisted laparoscopic partial nephrectomy may make this procedure more efficacious than the standard laparoscopic approach.
Materials and Methods: Ten patients with a mean age of 58 years and mean tumor size of 2.0 cm underwent robotic assisted laparoscopic partial nephrectomy and another 10 with a mean age of 61 years and mean tumor size of 2.18 cm underwent laparoscopic partial nephrectomy, as performed by a team of 2 surgeons (MS and ST) between May 2002 and January 2004. Demographic data, intraoperative parameters and postoperative data were compared between the 2 groups.
Results: There were no significant differences in patient demographics between the 2 groups. Intraoperative data and postoperative outcomes were statistically similar. In the 10 patients who underwent robotic assisted laparoscopic partial nephrectomy there were 2 intraoperative complications. There was 1 conversion in the laparoscopic partial nephrectomy group.
Conclusions: Robotic assisted laparoscopic partial nephrectomy is a safe and feasible procedure in patients with small exophytic masses. The robotic approach to laparoscopic partial nephrectomy does not offer any clinical advantage over conventional laparoscopic nephrectomy.

Editorial Comment
Advances in laparoscopy allowed surgeons to perform complex reconstructive and ablative surgical procedures. Laparoscopic partial nephrectomy is the best example to depict these innovations where accuracy, speed and surgeon's expertise must work in concert. Robotic surgery may bring some advantages to the novice laparoscopists when performing laparoscopic radical prostatectomies but for nephron-sparing nephrectomies does not appear to help. Although the authors acknowledge the need of randomization of larger number of patients for clinical

validation, this study is a pioneer comparing laparoscopic partial nephrectomy (LPN) versus robotic assisted laparoscopic partial nephrectomy (RALPN). Interestingly, the authors believe that the distance between the surgeon and the sterile surgical field may have decreased the threshold to convert the RALPN to a hand assisted or open procedure. Other potential disadvantages of the robotic system are cost, training, equipment malfunction and setup time. Additionally, while LPN can safely be performed with a primary surgeon and an assistant, RALPN is a procedure that must be done with 2 experienced surgeons. In conclusion, RALPN is not ready for primetime yet.

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Comparison of Laparoscopic Partial Nephrectomy and Laparoscopic Hand Pain During Hand Assisted Laparoscopic Nephrectomy - An Ischemic Event?

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J Urol. 2006; 176: 149-54

Purpose: The etiology of hand discomfort during hand assisted laparoscopic nephrectomy may be ischemic in nature. We determined if pneumoperitoneal pressure sustained to the hand during hand assisted laparoscopic nephrectomy poses an occupational risk, contributing to local hand hypoxia and resultant extremity pain.
Materials and Methods: A total of 442 measurements of hand oxygen saturation were made during hand assisted laparoscopic nephrectomy. A Nellcor(r) OxiMax(tm) Max-1(r) oxygen sensor was attached to the left index finger of each surgeon and hand assisted laparoscopic nephrectomy was performed using a LapDisc(r) at 15 mm Hg pneumoperitoneal pressures. Local hand oximetry readings and a numerical pain distress scale (range 0 to 10) were recorded every 2 minutes. To control for motion artifact oximetry readings were taken during hand motion and at rest. The Student t test was used to compare differences in local hand oxygen saturation and hand pain in and between study groups.
Results: A history of hand pain during hand assisted laparoscopic nephrectomy was significantly associated with local hypoxia during operative motion and at rest (p= 0.023 and 0.012, respectively), even with an adequate fascial incision and standard pneumoperitoneal pressures. During hand assisted laparoscopic nephrectomy hand pain was most significantly associated with local hypoxia after 24 minutes (p 0.0002), when local oxygen saturation was 56% to 88%.
Conclusions: A cohort of urologists is predisposed to ischemic hand pain during hand assisted laparoscopic nephrectomy. The etiology of this pain may be hypoxic in nature, attributable to pneumoperitoneal pressure decreasing perfusion and causing venous congestion or regional local ischemia. Circumferential antebrachial constriction from the LapDisc(r) does not seem to be a significant contributing factor in the presence of an adequate fascial incision. Hand pain secondary to ischemia is most significant after 24 minutes at 15 mm Hg. Future studies in more subjects are called for to validate these findings to elucidate which surgeons are predisposed to this potential occupational hazard and what perioperative measures can be taken to avoid hand pain during hand assisted laparoscopic nephrectomy.

Editorial Comment

Hand assisted procedures allowed less experienced laparoscopic surgeons to offer a less invasive approach to their patients with results comparable to purely laparoscopic surgery; i.e.; radical nephrectomy.

Unfortunately, the causes of hand numbness and/or pain have never been completely elucidated, i.e. fascial length and compression, pneumoperitoneum, etc.

Interestingly, this paper demonstrated that after 24 minutes of pneumoperitoneum (15 mm of Hg) the surgeon's hand would suffer hypoxia that may trigger symptoms of discomfort and pain. For surgeons that would occasionally perform this type of surgery may not suffer the effects of local hypoxia but for those who would routinely perform hand-assisted procedures that would last more than 24 minutes should be aware of this occupational risk and take precautions to prevent from chronic problems.

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IMAGING

Prophylaxis of Contrast Material-Induced Nephropathy in Patients in Intensive Care: Acetylcysteine, Theophylline, or Both? A Randomized Study

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Purpose: To prospectively compare the protective effect of acetylcysteine, theophylline, and both agents combined in patients who are admitted to the intensive care unit with at least one risk factor for contrast material-induced nephropathy and who receive at least 100 mL of iodinated contrast medium.

Materials and Methods: Institutional ethics review board approval and informed consent were obtained. A total of 91 patients (mean age, 58.5 years+/-14.8 [standard deviation]; 31 women, 60 men; 150 examinations) were admitted to the intensive care unit with at least one risk factor for contrast-induced nephropathy and received either (a) 200 mg theophylline 30 minutes before contrast medium administration (group T), (b) 600 mg acetylcysteine twice daily on the day of and (if possible) the day before the examination (group A), or (c) both agents combined (group AT). The primary endpoint for this study was the incidence of contrast-induced nephropathy (chi2 test).

Results: Groups T, A, and AT were comparable with regard to baseline creatinine levels and the amount of contrast medium administered. The incidence of contrast-induced nephropathy in groups T, A, and AT was 2%, 12%, and 4%, respectively, and was significantly lower in group T than in group A (P = 0.047). There was no significant difference in the incidence of contrast-induced nephropathy between groups A and AT (P = 0.148) or between groups T and AT (P = 0.53). For group A, serum creatinine did not change after 12, 24, or 48 hours compared with baseline. Creatinine levels in group T decreased 12 hours (1.19 mg/dL+/-0.58; P = 0.008) and 48 hours (1.16 mg/dL+/-0.55; P = 0.034) after contrast material injection compared with baseline (1.25 mg/

dL+/-0.61). In group AT, creatinine significantly decreased 24 hours (1.21 mg/dL+/-0.74; P = 0.003) and 48 hours (1.17 mg/dL+/-0.69; P < 0.001) after contrast material injection compared with baseline (1.28 mg/dL+/-0.74). Group A had significantly higher maximal increases in creatinine than groups T and AT (P = 0.014).
Conclusion: For prophylaxis of contrast-induced nephropathy in patients who are admitted to the intensive care unit and who receive 100 mL or more of contrast medium, theophylline is superior to acetylcysteine.

Editorial Comment
Although contrast-induced nephropathy is relatively rare in patients with no risk factors, it is considered an import clinical issue since is the third most frequent cause of acute renal failure. The frequency of contrast-induced nephropathy strongly depends on a number of risk factors: pre-existing renal dysfunction (nephropathies associated with diabetes and multiple myeloma), dehydration, congestive heart failure and use of concurrent nephrotoxic medication (including aminoglycosids and amphotericin B). For this reason, several strategies are currently proposed in order to prevent this complication, such as the use of non-contrast based imaging techniques, the reduction of the total amount of contrast material injected, the use of iso-osmolar or low-osmolar contrast agents and hyperhydration. Recently several preventive measures to avoid contrast-induced nephropathy have been proposed which include administration of N-acetylcysteine, theophylline, or fenoldopam, sodium bicarbonate infusion, and peri-procedure hemofiltration/hemodialysis. This is a very interesting and unique prospective randomized study showing that in 150 patients who were admitted to the intensive care unit and who received at least 100 mL of contrast medium, theophylline an “easy to handle” agent was superior to acetylcysteine with regard to prevention of contrast material–induced nephropathy.

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Comparison of 16-MDCT and MRI for Characterization of Kidney Lesions

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Objective: The objective of our study was to compare the diagnostic performance of 16-MDCT with that of MRI in the characterization of kidney lesions.
Subjects and Methods: Twenty-eight patients with kidney lesions detected with sonography and requiring further evaluation were examined. MDCT was performed in the unenhanced, arterial, and portal venous phases. MRI was performed at 1.5 T with T2- and T1-weighted and dynamic gadolinium-enhanced sequences. Consensus reading was done by two radiologists. Image quality was rated on a four-point scale. Classification of lesions as surgical or nonsurgical was done with five levels of confidence, and it was required that a definite diagnosis be assigned to each lesion. The 1997 TNM classification was used for staging. Statistical analysis was done by receiver operating characteristic analysis or paired Student’s t test. Histologic or follow-up findings at least 12 months after the primary diagnosis served as the standard of reference.
Results: The image quality of MDCT (mean grade, 2.79 on a 0-3 scale) was superior to that of MRI (1.93; p < 0.01). The area under the curve for differentiating surgical from nonsurgical lesions was 0.979 for MDCT and 0.957 for MRI with resulting sensitivity and specificity values of 92.3% and 96.3% for MDCT and 92.3% and

91.3% for MRI. Sensitivity and specificity for definite classification of the lesions were 93.8% and 68.4% for MDCT and 93.8% and 71.4% for MRI.
Conclusion: Both MDCT and MRI are excellent for differentiating surgical from nonsurgical kidney lesions. Both methods have low specificity for the differentiation of benign from malignant lesions.

Editorial Comment
In this interesting original study, the authors compared the performance of state of the art, 16 channel-MDCT and 1.5 T MRI in the characterization of renal lesions previously detected by ultrasound in the same patient group. Due the presence of artifacts on MR examinations, MDCT proved superior to MRI with regard to image quality. Both MDCT and MRI however proved excellent for differentiating surgical from nonsurgical kidney lesions (sensitivity and specificity of 92.3% and 96.3% for MDCT and 92.3% and 91.3% for MRI). It is also interesting to note that both MDCT and MRI correctly depicted 15 of 16 renal cell carcinomas (sensitivity, 93.3%) but both technique had similar limitation for depiction of benign lesions (specificity, 68.4% and 71.4% respectively). This occurred because both methods were unable to differentiate between oncocitoma and renal cell carcinoma. This study confirms the classic limitation of imaging methods regarding the criteria for identification of enlarged lymph node as metastatic disease from renal cancer. In this series the authors reports that both MDCT and MRI interpretation led to overstaging 3 and 4 lesions respectively, due to the presence of enlarged lymph node(> 15 mm), currently criteria for interpreting as malignant but with reactive changes at histological examination. In our experience, MDCT and fast MR imaging has similar specificity for the detection, characterization and staging of solid renal masses larger than 1.0 cm in diameter. Similarly to the authors´ experience, we consider MDCT superior for the detection of very small solid renal lesions (< 1.0 cm), but fast MRI and sometimes high-resolution ultrasound, are in some cases superior for the evaluation of complicated renal cystic masses. MRI and occasionally ultrasound better demonstrates internal septations, thickening of the cyst wall and/or septa. MRI better demonstrates areas of abnormal enhancement. In both situations, these additional findings will transform a nonsurgical into a surgical cystic mass (1).

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UROGENITAL TRAUMA

Predictors of the Need for Nephrectomy after Renal Trauma

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Background: Initial management of solid organ injuries in hemodynamically stable patients is nonoperative. Therefore, early identification of those injuries likely to require surgical intervention is key. We sought to identify factors predictive of the need for nephrectomy after trauma.
Methods: This is a retrospective review of renal injuries admitted over a 12-year period to a Level I trauma center.
Results: Ninety-seven patients (73% male) sustained a kidney injury (mean age, 27 +/- 16; mean Injury Severity Score, 13 +/- 10). Of the 72 blunt trauma patients, 5 patients (7%) underwent urgent nephrectomy, 3 (4%) had repair and/or stenting, and 89% were observed despite a 29% laparotomy rate for associated intraabdominal injuries in this group. Twenty-five patients with penetrating trauma underwent eight nephrectomies (31%), one partial nephrectomy, and two renal repairs. Regardless of the mechanism of injury, patients requiring nephrectomy were in shock, had a higher 24-hour transfusion requirement, and were more likely to have a high-grade renal laceration (all $p < 0.05$). Bluntly injured patients requiring nephrectomy had more concurrent intraabdominal injuries ($p < 0.0001$). Overall, patients after penetrating trauma were more severely injured, had higher 24-hour transfusion requirements, and a higher nephrectomy rate (all $p < 0.05$). Despite a higher injury severity in the penetrating group, however, mortality was higher in the bluntly injured group ($p < 0.0001$). Univariate predictors for nephrectomy included: revised trauma score, injury severity score, Glasgow Coma Scale score, shock on presentation, renal injury grade, and 24-hour transfusion requirement. No patient with a mild or moderate renal injury required nephrectomy, whereas 6 of 12 (50%) grade 4 injuries and 7 of 8 (88%) grade 5 injuries required nephrectomy. Multiple logistic regression analysis confirmed penetrating injury, renal injury grade, and Glasgow Coma Scale score as predictive of nephrectomy.
Conclusion: Overall, injury severity, severity of renal injury grade, hemodynamic instability, and transfusion requirements are predictive of nephrectomy after both blunt and penetrating trauma. Nephrectomy is more likely after penetrating injury.

Editorial Comment

This study confirms the well-established concept that most renal injuries are AAST grade 1-3, and can be safely managed non-operatively. Predictors for nephrectomy were shock, higher AAST grade of renal injury (4 - 5), ongoing transfusion requirement, and associated intraabdominal injuries. Grade 5 injuries, by definition are potentially life-threatening with avulsion of the renal hilum or a completely shattered kidney. That the nephrectomy rate in this study for Grade 5 kidney injuries approached 90% is not surprising. In unstable kidney trauma patients with ongoing blood loss, nephrectomy is part of a “damage control” approach to stabilize the patient, get them off the OR stable, and quickly into the ICU for resuscitation.

Clearly, opening up Gerota’s fascia and releasing the tamponade effect of the retroperitoneal hematoma may result in uncontrollable bleeding and subsequent nephrectomy. Thus, there are 2 main ways to avoid unnecessary nephrectomy: 1) For the stable trauma patient, image the abdomen with CT with delayed images in order to properly stage the kidney injury. With an accurate kidney injury stage and location of the retroperitoneal hematoma, patients can then be selected for surgery or expectant management. 2) Retroperitoneal hematomas that are not zone 1, stable, non-expanding, non-pulsatile, and contained do not demand exploration. Zone 1 hematomas, namely midline supramesocolic or midline inframesocolic, from a blunt or penetrating mechanism demand exploration. Zone 2, lateral perinephric hematomas should be selectively explored for penetrating trauma, and typically observed for blunt trauma (1).

In Davis et al, half of Grade 4 injuries ended up with nephrectomy. This is higher then prior reports, but again nephrectomy may have been performed as “damage control” in the face of instability and associated injuries. Prior reports, however, have demonstrated that most Grade 4 renal injuries can be managed expectantly, with the kidney being re-imaged by CT with intravenous contrast and delayed images (3 to 5 days after initial

injury) to assess for persistent urinary leakage. Worsened or unimproved leak warrants ureteral stent placement of urinoma drain placement.

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Damage Control Management of Experimental Grade 5 Renal Injuries: Further Evaluation of FloSeal Gelatin Matrix

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J Trauma. 2006; 60: 346-50

Background: We developed a porcine grade 5 renal laceration damage control model to evaluate the hemostatic efficacy of FloSeal gelatin matrix (Baxter Healthcare, Corp., Deerfield, Ill).
Methods: Ten commercial swine underwent celiotomy, contralateral nephrectomy, and cooling to 32 degrees C after a well-established hypothermia protocol to simulate a damage control scenario. Following prospective randomization, a complex grade 5 renal injury was uniformly produced on the remaining kidney. Control animals (group 1, n = 5) were treated with direct manual compression with a gelatin sponge. Experimental animals (group 2, n = 5) were treated by application of FloSeal gelatin matrix followed by direct compression with a gelatin sponge. Operative blood loss and efficacy of hemostasis were compared. Creatinine levels were obtained daily until postoperative day 7. Abdominal computed tomography was performed at 10 days.
Results: Use of FloSeal gelatin matrix hemostatic sealant resulted in significantly less mean blood loss than gelatin sponge bolster compression alone (202.4 mL vs. 540.4 mL, respectively, p = 0.016). Hemostasis was complete in 60% (three out of five) of experimental animals after 2 minutes, but was incomplete in all control animals. After an initial increase, serum creatinine approached baseline by postoperative day 7 in all animals. Axial imaging 10 days postoperatively revealed no evidence of significant delayed perirenal hemorrhage.
Conclusions: FloSeal gelatin matrix performed well as a rapidly deployable, effective hemostatic agent in a hypothermic grade 5 renal injury damage control model. The absence of delayed bleeding and nephrotoxicity suggests a possible increased role for FloSeal in the treatment of devastating renal injuries in damage control surgery.

Editorial Comment

This article illustrates nicely the concept of damage control and the use of a pig model. Damage control is the concept that an abdominal trauma surgery is abbreviated to control hemorrhage and fecal and urinary contamination, to not perform the definitive repair until a planned staged re-operation improves survival, and to resuscitate the patient in the ICU before any prolonged reconstructive surgery. Such a policy of staged, abbreviated operations, has clearly been shown to improve overall survival, and helps the avoid the lethal triad of cold (body temperature), coagulopathy and acidosis.

The use of fibrin sealants in urology has been particularly popular recently, due to its use in laparoscopic kidney surgery. With the expanding role of laparoscopy for partial nephrectomy, methods to better control urinary leak or bleeding have been explored. Aside from direct suturing of the collecting system and vessels, fibrin sealants have been the "suspenders" to the "belts" of suturing. The current commercially available sealants are Tisseel "fibrin sealant", (by Baxter, a mix of fibrinogen aprotonin solution, Factor XIII, and human derived thrombin), FloSeal "gelatin matrix" (by Baxter, a mix of human derived thrombin and bovine derived gelatin matrix), and BioGlue "surgical adhesive" (by Cryolife, a mix of bovine serum albumin and gluteraldehyde).

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PATHOLOGY

Xp11.2 Translocation Renal Cell Carcinoma with Very Aggressive Course in Five Adult Patients

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Mod Pathol Suppl. 1 2006; 19: 150A

Background: Renal cell carcinomas (RCC) associated with Xp11.2 translocations (TFE3 gene fusions) are rare tumors occurring predominantly in children and young adults. Although, thus far, only limited data is available, these tumors are believed to be rather indolent even when diagnosed at advanced stages.
Design: Five cases of TFE3-RCC were evaluated in patients aged 18 or older (mean age 31). Diagnosis was confirmed by IHC detection of increased TFE3 fusion protein. Morphology was examined by HE, IHC and electron microscopy (EM) and correlated with clinical picture.
Results: HE showed clear cells, arranged in a pseudopapillary architecture, with retention of morphology in the metastatic tumor deposits. By IHC there was strong nuclear positivity for TFE3 in all cases and focal stain for AE3 and vimentin; stains for HMB45, calretinin, pankeratin and AE1 were all negative. By EM (2/5 cases examined) there were junctional complexes and rudimentary microvilli. In one case there were abundant lipid droplets and glycogen; in a second case, rare rhomboid crystals, similar to those seen in alveolar soft part sarcoma, were present. All patients (3 Caucasian, 2 Hispanic) presented with innocuous complaints, abdominal/flank pain and hematuria, and lacked any significant prior history. All but one patient presented with distant metastases at the time of diagnosis, and all patients were diagnosed with additional metastases or tumor recurrence within 5 months of presentation. Treatments included tumor resection, interleukin-2 therapy, combination chemotherapy, and radiation therapy, all with minimal success. Patients followed a rapidly terminal course, with a mean survival of 15 months post-diagnosis (range 10-20 months). One patient is currently undergoing chemotherapy at 13 months post-diagnosis (with brain metastasis), and another patient is alive at 6 months post-diagnosis, with metastases.
Conclusions: The patients presented here were older than typically described for TFE3-RCC. Although tumor morphology was similar to pediatric patients, these adult patients had a very aggressive clinical course compared to pediatric TFE3-RCC and even to conventional, adult-type RCC. Consistent use of antibodies against TFE3 in all tumors, regardless of patient age, may expand the spectrum of Xp11.2 translocation RCC with respect to age, clinical behavior and molecular abnormalities.

Editorial Comment

These carcinomas are defined by several different translocations involving chromosome Xp11.2. The t(X; 1) (p11.2; q21) translocation results in the fusion of TFE3 gene in chromosome X to PRCC gene in chromosome 1; the t(X; 17) (p11.2; q25) translocation results in the fusion of TFE3 gene in chromosome X with the ASPL gene in chromosome 17. This latter translocation is also seen in the alveolar soft part sarcoma.

These carcinomas predominantly affect children and adolescents and are believed to be rather indolent even when diagnosed at advanced stages. The most distinctive histopathologic appearance is that of a carcinoma with papillary architecture comprised of voluminous clear to eosinophilic cytoplasm, discrete cell borders, vesicular chromatin and prominent nucleoli. Scattered hyaline nodules and psammomatous bodies can be seen. The most distinctive immunohistochemical feature of these tumors is nuclear immunoreactivity for the chimerical (mutant) TFE3 protein (1).

The present study by Meyer et al. reported 5 patients of TFE3 renal cell carcinoma aged 18 or older (mean age 31). All but one patient presented with distant metastases at the time of diagnosis, and all patients were diagnosed with additional metastases or tumor recurrence within 5 months of presentation. The authors emphasize the fact that although tumor morphology was similar to children and adolescents, these adult patients had a very aggressive course. It is noteworthy a Brazilian female 58-year old recently reported with renal cell carcinoma associated with Xp11.2 translocation TFE3 (ASPL-TFE3) gene fusion (2). Metastases were seen in 3 of the 6 dissected lymph nodes, thus determining a final staging (TNM, 2002) pT1b, pN2, pMX (stage IV). After approximately 6 months of follow-up, the patient showed favorable outcome, without manifesting disease or any other signs or symptoms.

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Papillary Renal Cell Carcinoma: Assessment of Clear Cell Change and Clinicopathologic Correlation

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Mod Pathol Suppl 1. 2006; 19: 138A

Background: Papillary renal cell carcinoma with clear cell change and chromosome 3p21 aberration has been described. The significance of this finding, however, remains unclear. We perform the first study to investigate the significance of clear cell change and its clinicopathologic correlation.

Design: Nineteen cases of papillary renal cell carcinoma between 1992 and 2005 were retrieved from the slide archives in the Department of Pathology, Westchester Medical Center. Cytogenetic findings were obtained in 2 cases. All tumors were subclassified as type 1 or 2 and were evaluated for clear cell change and Fuhrman nuclear grade. American Joint Committee on Cancer TNM Staging of Renal Cell Carcinoma (2002) was used and clinical charts were reviewed retrospectively to obtain clinical stage.
Results: The patient age ranged from 11 to 77 years (mean 56). Sixteen patients were males and 3 were females. Tumor size ranged from 1.8 to 10 cm (mean 4.6 cm). All tumors contained clear cells ranged from 0 to 85%. Of the 12 tumors with 0 to 25% clear cells, 9 cases presented with stage I, 2 with stage II, and 1 with stage III disease. Seven tumors possessed clear cell change ranged from 30 to 85%. Of these 7 patients, 2 cases presented with stage I, 1 with stage II, 3 with stage III, and 1 with stage IV. Cytogenetics findings in a tumor with 30% clear cells revealed 49-50X,-X, der(3)add(3)(p21),+7,+17,-19,+21 and the case with 5% clear cells showed 57,XXY,+2,+3,+4,+7,+8,+12,+16,+17,+20. Nine cases (47%) were classified as type 1 and 10 cases (53%) type 2. Of the 9 type 1 tumors, 2 cases had grade 1 nuclei, 6 grade 2, and 1 grade 1. Six of these patients presented with stage I, 2 with stage 2, and 1 with stage IV. In comparison to type 1, 5 cases of type 2 lesions had a nuclear grade of 2 and 5 had grade 3 nuclei. Five patients presented with stage I, 1 with stage II, and 4 with stage III disease.
Conclusions: Type 2 papillary renal cell carcinomas have higher nuclear grade and stage than that of type 1 lesions. Type 2 lesions have poorer prognosis than type 1. Patients bearing tumors with greater than 30% clear cells present with higher stage of disease. Therefore, clear cell change may be a useful pathologic prognosticator in evaluating clinical behavior of these tumors.

Editorial Comment

Papillary renal cell carcinoma has a tendency to present at a lower stage, but with a distinct potential for progression and aggressive behavior (1). Papillary renal cell carcinomas comprise approximately 10% of renal cell carcinoma in large surgical series. The tumor is characterized by malignant epithelial cells forming varying proportions of papillae and tubules. The tumor papillae contain a delicate fibrovascular core and aggregates of foamy macrophages and cholesterol crystals may be present. Solid variants consist of tubules or short papillae resembling glomeruli.

Two morphological types of papillary renal cell carcinoma have been described (2). Type 1 tumors have papillae covered by small cells with scanty cytoplasm, arranged in a single layer on the papillary basement membrane. Type 2 tumor cells are often of higher nuclear grade with eosinophilic cytoplasm and pseudostratified nuclei on papillary cores. Type 1 tumors are more frequently multifocal. Sarcomatoid dedifferentiation is seen in approximately 5% of these tumors and has been associated with both type 1 and type 2 tumors. In series of papillary renal cell carcinoma containing both type 1 and 2 tumors, five year survivals for all stages range from 49% to 84% with tumor grade, stage at presentation and the presence of sarcomatoid dedifferentiation being correlated with outcome. Longer survivals have been demonstrated for type 1 when compared with type 2 on both univariate and multivariate analysis that included both tumor stage and grade.

Uropathologists are aware of the fact that some papillary renal cell carcinomas show clear cell differentiation. Torres-Cabala et al. (3) showed that some of papillary renal cell carcinomas with clear cell differentiation show 3p deletion that is a common finding in conventional clear cell carcinoma. They suggested that this finding might represent an early event in tumor progression to conventional clear cell carcinoma. The study of Dasgupta and Yeh is a further evidence that clear cell differentiation in papillary renal cell carcinomas may have prognostic implications. Patients bearing tumors with greater than 30% clear cells presented with higher stage of disease. Pathologists should report on presence of clear cell differentiation in papillary renal cell carcinomas.

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INVESTIGATIVE UROLOGY

Immunohistochemical Distribution of cAMP- and cGMP-Phosphodiesterase (PDE) Isoenzymes in the Human Prostate

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Eur Urol. 2006; 49: 740-5

Objectives: With the introduction of sildenafil citrate (VIAGRA trade mark), the concept of phosphodiesterase (PDE) inhibition has gained tremendous interest in the field of urology. Cyclic nucleotide second messengers cGMP and cAMP have been assumed to be involved in the control of the normal function of the prostate. The aim of the present study was to evaluate by means of immunohistochemistry the expression and distribution of some cAMP- and cGMP-PDE isoenzymes in the prostate.
Material & Methods: Cryostat sections (10muM) of formaldehyde-fixated tissue segments excised from the transition zone of human prostates were incubated with primary antibodies directed against the PDE isoenzymes 3, 4, 5, and 11. Then, sections were exposed to either fluorescein isothiocyanate- (FITC) or Texas Red- (TR) labeled secondary antibodies and visualization was commenced by means of laser fluorescence microscopy.
Results: TR-immunofluorescence indicating the presence of PDE4 (cAMP-PDE) was abundantly observed in the fibromuscular stroma as well as in glandular structures of the transition zone. In contrast to the distribution of PDE4, immunoactivity indicating PDE5 (cGMP-PDE) and 11 (dual substrate PDE) was mainly observed in glandular and subglandular areas. No immunostaining for PDE3 (cGMP-inhibited PDE) was detected.
Conclusion: Our results confirm the presence of PDE isoenzymes 4, 5 and 11 in the transition zone of the human prostate and present evidence that these isoenzymes are not evenly distributed. These findings are in support of the hypothesis that there might be a rationale for the use of PDE inhibitors in the pharmacotherapy of BPH and LUTS.

Editorial Comment

Lower urinary tract symptoms (LUTS) and erectile dysfunction (ED) association is a very much discussed theme in urology practice and many papers have been published during the last few years. Prostatic obstruction may be clinically treated either by alpha-blockers (effect on bladder neck) or by 5-alpha-reductase inhibitors (reducing effect on gland volume) (1). Recent research (2,3) suggests that the combination of an alpha-blocker and a phosphodiesterase type 5 inhibitor may be useful in patients with (LUTS) associated with erectile dysfunction. The present paper demonstrates the pharmacological background for previous clinical findings.

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Is Pelvicaliceal Anatomy a Risk Factor for Stone Formation in Patients with Solitary Upper Caliceal Stone?

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Urology. 2006; 67: 1159-63

Objectives: To investigate the effect of pelvicaliceal anatomy on stone formation in patients with solitary upper caliceal stones.
Methods: The records of patients with solitary upper caliceal stones between 1996 and 2004 were reviewed. After the exclusion of patients with hydronephrosis, major anatomic abnormalities, noncalcium stones, metabolic abnormalities, history of recurrent stone disease, multiple stones, and previous renal surgery, 42 patients (24 male, 18 female) and 42 healthy subjects (22 male, 20 female) with normal results on intravenous pyelography (IVP) were enrolled into the study. With a previously described formula, upper pole infundibulopelvic angle (IPA), infundibular length (IL) and width (IW), and pelvicaliceal volume of the stone-bearing and contralateral normal kidney of patients and bilateral normal kidneys of healthy subjects were measured from IVP.
Results: Forty-two stone-bearing and 126 normal kidneys (42 contralateral, 84 healthy) were assessed. The mean stone size was 153.47 mm2 (range, 20 to 896 mm2). There were no statistically significant differences in terms of upper caliceal specifications between stone-bearing and normal kidneys. The mean (+/- standard deviation) pelvicaliceal volume of 42 stone-bearing and 126 normal kidneys was 2455.2 +/- 1380.2 mm3 and 1845.7 +/- 1454.8 mm3, respectively (P = 0.019). These values were 2114 +/- 2081.5 mm3 (P = 0.34) and 1709.5 +/- 989.1 mm3 (P = 0.001) for contralateral normal kidneys (n = 42) and normal kidneys of healthy subjects (n = 84), respectively.

Conclusions: Explanation of the etiology of the upper caliceal stone by the anatomic features is very difficult, and these caliceal anatomic variables (IPA, IL, IW) seem not to be a significant risk factor for stone formation in the upper calyx.

Editorial Comment
The study is interesting and demonstrated that there is any statistically significant difference between the stone-bearing and the normal kidneys of patients with upper caliceal stones and healthy individuals in terms of infundibulopelvic angle (IPA), infundibular length (IL) and width (IW) of upper caliceal system. Previous anatomical findings on pelvicaliceal features are well presented and discussed.

The mean pelvicaliceal volume of 42 stone-bearing was 2455,2±1380,2 mm3 and contralateral kidneys was 2114±2081,5, with no statistical difference between stone-bearing and contralateral normal kidneys (p=0,34). When comparing to bilateral kidneys of healthy individuals not bearing stones the difference was significant. Nevertheless, as the authors stated, these finding must be viewed with caution.

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UROLOGICAL ONCOLOGY

Is A Second Transurethral Resection Necessary For Newly Diagnosed Pt1 Bladder Cancer?

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J Urol. 2006; 175: 1258-61

Purpose: We evaluated the potential benefit of a second transurethral resection in patients with newly diagnosed pT1 transitional cell carcinoma of the bladder.
Materials and Methods: Between January 2001 and May 2003, 80 patients with stage T1 bladder cancer were included in this protocol in which all patients prospectively received second TUR within 2 to 6 weeks following the initial resection. Patients with incomplete resections were excluded from study. The pathological findings of the second TUR were reviewed.
Results: Of the 80 patients who underwent second resection, 18 (22.5%) had macroscopic tumors before resection. However, with the addition of microscopic tumors, overall residual disease was determined in 27 (33.8%) patients. Of the 27 patients 7 had pTa, 14 had pT1, 3 had pT1+pTis and 3 had pT2 disease. Residual cancers were detected in 5.8%, 38.2% and 62.5% in G1, G2 and G3 tumors, respectively. The risk of residual tumor directly correlated with the grade of the initial tumor ($p = 0.009$).
Conclusions: Although second TUR dramatically changed the treatment strategy in a small percentage of cases, we strongly recommend performing second TUR in all cases of primary pT1 disease, especially in high-grade cases.

Editorial Comment
This paper highlights the usefulness of a second transurethral resection in superficial bladder cancer by providing own data and a review of the meanwhile large body of literature evidence.

In their own data the authors found at least 18.8% residual tumor at second TUR with an increasing rate up to 33.8% in large and/or multifocal tumors. In the literature, up to 74% of T1G1-3 tumors had residual disease. A second TUR is highly recommended at least in large tumors and all T1 tumors.

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Guidelines on TaT1 (Non-muscle Invasive) Bladder Cancer

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http://www.uroweb.org/files/uploaded_files/guidelines/05%20TaT1%20Bladder%20Cancer.pdf

No abstract avilable

Editorial Comment

These guideline represent and evolutional development from the “old” EAU bladder cancer guidelines, which were well received worldwide. They incorporate recommendations for such major steps in superficial bladder cancer treatment as postoperative single shot instillation with chemotherapy and maintenance therapy with BCG.

The most important information, which led to these steps forward, came from recently published metaanalyses, which were prepared in close cooperation predominantly from members of the guidelines group.

Specifically, the following changes appear as of highest importance and are commented below. Guidelines for superficial and invasive bladder cancer are generated from different groups and are distinct.

Use of histological classification - However, until the 2004 WHO classification has been validated by more clinical trials, tumors should be graded according to both the 1973 and the 2003 WHO classification.

Fluorescence cystoscopy - This investigational method has not yet been implemented on a regular basis in daily practice.

Second resection is recommended in most intermediate and all high-risk tumors.

Single-shot postoperative instillation of chemotherapy is strongly recommended.

Intravesical BCG is superior to intravesical chemotherapy in reducing recurrences and is the only drug to interfere with progression of SBC. BCG immunotherapy is indicated in intermediate risk and high-risk bladder cancer. The use of maintenance therapy of at least 1 year is strongly recommended.

An algorithm for predicting tumor recurrence and progression is extensively provided in these guidelines.

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NEUROUROLOGY & FEMALE UROLOGY

Is There A Role For Periurethral Collagen Injection In The Management Of Urodynamically Proven Mixed Urinary Incontinence?

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Urology. 2006; 67: 725-9; discussion 729-30

Objectives: To investigate the effectiveness of periurethral collagen injection (PCI) in patients presenting with symptoms of mixed urinary incontinence (MUI) and urodynamically demonstrated sphincter deficiency and detrusor overactivity.
Methods: A retrospective review was performed on all patients undergoing PCI from February 1999 to February 2003, during which those with MUI were treated with PCI as first-line therapy. The inclusion criteria were MUI symptoms, detrusor overactivity on urodynamic study, stress urinary incontinence due to sphincter deficiency (determined from physical examination, stress test, urodynamic study with Valsalva leak point pressure, and cystography findings, without urethral hypermobility). The primary outcome measures were the Urogenital Distress Inventory (UDI), Incontinence Impact Questionnaire, and quality-of-life score and the need for anticholinergic medications or additional surgery. Comparisons were performed using the Wilcoxon signed ranks test and paired t test.
Results: Of the 56 patients who underwent PCI, 43 presented with symptoms of MUI, and 16 of these (29%) had both detrusor overactivity and stress urinary incontinence on urodynamic study. The mean follow-up after PCI (without additional PCI) was 18 months (range 6 to 39). The mean age was 65 years (range 40 to 84). The mean Valsalva leak point pressure was 54 +/- 40 cm H2O (range 18 to 146). Ten patients had undergone previous anti-incontinence procedures, and anticholinergic medications had failed in six. The questionnaire scores, indicating severe MUI/poor quality of life before PCI, improved after PCI: UDI question 1, 2.3 +/- 0.8 versus 1.3 +/- 1.0 (P = 0.021); UDI question 2, 2.1 +/- 1.2 versus 1.4 +/- 1.0 (P = 0.068); UDI question 3, 2.9 +/- 0.4 versus 1.8 +/- 1.2 (P = 0.010); and quality-of-life question, 8.6 +/- 2.1 versus 5.2 +/- 3.5 (P = 0.026). The mean injected volume/patient was 8.5 cm3 (range 5 to 17) within a mean of 1.9 treatments (range 1 to 3). Four patients continued taking anticholinergic medications and one proceeded to sling placement.
Conclusions: The use of PCI as the primary/initial intervention in patients with MUI may be the preferred approach, particularly in patients with an elevated risk of anticholinergic medication side effects or when voiding dynamics preclude sling placement.

Editorial Comment

The authors describe a retrospective review involving the performance of periurethral collagen injection for patients plagued with mixed urinary incontinence. The detrusor overactivity was diagnosed on urodynamics as an increase in detrusor pressure and/or a sensation of urgency with or without incontinence during the filling phase of the study.

The authors found a significant improvement in both the symptoms of stress urinary incontinence and overactive bladder (urinary frequency and urinary urge incontinence). These findings somewhat echo those found by McGuire & Savastano (1) from greater than 2 decades ago. This mirror success rate does give some merit to the argument of detrusor overactivity having a definite urethral component in its etiology. Based on the findings of these authors, injectable therapy seems to be a very reasonable option for patients with mixed urinary urge incontinence and has a higher success than those patients tried with pharmacologic therapy alone.

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Treatment for Unsuccessful Tension-Free Vaginal Tape Operation by Shortening Pre-Implanted Tape

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J Urol. 2006; 175: 2196-9; discussion 2199-200

Purpose: We studied the efficacy of shortening the pre-implanted suburethral tape in patients with recurrent urodynamic stress incontinence after a TVT operation.
Materials And Methods: A total of 14 women, including 6 with ISD, were treated for recurrent urodynamic stress incontinence after the initial TVT operation by performing the shortening procedure under local anesthesia. Urodynamics, a 1-hour pad test, introital ultrasonography of the urethra and a cotton swab test were done before the procedure and 1 year postoperatively.
Results: All 14 patients completed the shortening procedure. Mean patient age was 47.2 years (range 43 to 66). Mean time between initial TVT and the shortening procedure was 4 months (range 3 to 14). Ten patients (71.4%) were objectively cured and treatment failed in 4 (2 with ISD and 2 with a fixed urethra). Mean operative time was 17 minutes (range 10 to 25). No intraoperative surgical complications were observed. The 1-hour pad test showed a decrease from a median of 9.0 gm to 1.0. Median postoperative hospital stay was 1 day (range 1 to 4). Spontaneous voiding with adequate post-void residual urine was noted in all patients before discharge home.
Conclusions: Shortening a pre-implanted TVT tape for the treatment of recurrent urodynamic stress incontinence is a safe, effective and minimally invasive option requiring only a short hospital stay. However, ISD and an immobile urethra seem to be risk factors for failure. Long-term followup is needed to determine if this surgery achieves long-lasting results.

Editorial Comment

The authors describe a method to address recurrent urinary incontinence after failed TVT by transvaginal plication of the in situ TVT tape. The authors managed to objectively cure 10 out of the 14 patients (71.4%) with this maneuver while 4 continued with recurrent stress incontinence.

Addressing of recurrent urinary incontinence after TVT has been a topic of discussion in the literature. The above method as described appears to be quite technically facile with a very reasonable salvage success rate. The authors, while performing the transvaginal procedure, did not have any difficulty in locating the in situ sling. Secondary to the actual nature of the TVT procedure, the in place tightening of sutures cannot be performed as described by Choe (1). Repeat transvaginal tape (2) may be considered but carries with it the duplicate expense for the repeat tape. Though multiple options exist for the failed TVT (including repeat TVT

procedure, suburethral sling using an alternative material, versus injectable) this procedure appears to be inexpensive, straight forward, with an acceptable level of success.

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PEDIATRIC UROLOGY

Prediction of Vesicoureteral Reflux after a First Febrile Urinary Tract Infection in Children: Validation of a Clinical Decision Rule

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Arch Dis Child. 2006; 91: 241-4

Aims: To test the reproducibility of a highly sensitive clinical decision rule proposed to predict vesicoureteral reflux (VUR) after a first febrile urinary tract infection in children. This rule combines clinical (family history of uropathology, male gender, young age), biological (raised C reactive protein), and radiological (urinary tract dilation on renal ultrasound) predictors in a score, and provides 100% sensitivity.
Methods: A retrospective hospital based cohort study included all children, 1 month to 4 years old, with a first febrile urinary tract infection. The sensitivities and specificities of the rule at the two previously proposed score thresholds (< or =0 and < or =5) to predict respectively, all-grade or grade > or =3 VUR, were calculated.
Results: A total of 149 children were included. VUR prevalence was 25%. The rule yielded 100% sensitivity and 3% specificity for all-grade VUR, and 93% sensitivity and 13% specificity for grade > or =3 VUR. Some methodological weaknesses explain this lack of reproducibility.
Conclusions: The reproducibility of the previously proposed decision rule was poor and its potential contribution to clinical management of children with febrile urinary tract infection seems to be modest.

Editorial Comment

The authors attempt to validate a previously proposed decision-rule that can be used to decide when to obtain a VCUG in children who have had a first febrile UTI. This is potentially valuable, as any method of limiting the number of catheterized studies in young children would be beneficial. The proposed decision-rule takes into account the age, gender, family history, C-reactive protein and dilation noted on ultrasound. These are all clinically relevant features of the child presenting with a febrile UTI.

Unfortunately, the current study population did not support the use of the decision-rule. In order not to miss a positive VCUG, only 3 of the 143 patients would have been excluded. Nineteen could have been excluded if the clinician would be willing to miss 8% of the refluxing patients, including 1 of the 14 with at least grade 3/5 reflux. Moreover, it is well known that VCUGs themselves are only about 80% sensitive. Hence, the reported analysis is likely an overly positive estimate of the benefits of the decision-rule.

Hanging over this study is the possibility (that this author does not agree with) that diagnosing reflux, is itself of no value. Some have proposed giving temporary prophylactic antibiotics to all patients with febrile UTIs. Others have suggested that prophylactic antibiotics themselves are of no value; if so, why bother diagnosing reflux? In clinical practice, most clinicians still want to diagnose reflux. Therefore, a decision-rule like the one proposed would be of great value. At this time, unfortunately, none exists.

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Testicular Growth from Birth to Two Years of Age, and the Effect of Orchidopexy at Age Nine Months: A Randomized, Controlled Study

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Aim: To study whether surgical treatment at age 9 mo in boys with congenital unilaterally palpable undescended testes (cryptorchidism) is followed by improved growth of the previously retained testes compared to non-treatment.
Methods: At the age of 6 mo, 70 boys were randomized to surgical treatment at 9 mo and 79 boys to treatment at 3 y of age. The boys were then followed at 12 and 24 mo. Ultrasonography was used to determine testicular volume.
Results: After orchidopexy, the previously retained testes resumed growth and were significantly larger than the non-operated testes at 2 y (0.49 ml vs 0.36 ml, $p < 0.001$). Testicular growth after orchidopexy was also demonstrated by a higher mean ratio between the previously retained and the scrotal testes of the individual boys at 2 y: 0.84 for the surgically treated group, compared to 0.63 for the untreated group ($p < 0.001$).
Conclusion: Surgery at 9 mo has a beneficial effect on the growth of previously undescended testes.

Editorial Comment

The authors performed an excellent, randomized study of surgery at 9 months vs. delayed surgery (planned for 3 years of age) for undescended testes. They report that 1) undescended testes are slightly smaller than their descended contralateral matches are shortly after birth; 2) these testes lose considerable ground during the first 6 months of life; 3) those operated on grow much better than those non-operated on during the first 24 months of life.

This is the first randomized trial of early surgery in these patients and demonstrated a clear benefit in terms of testicular size. It is extremely important from that standpoint and it is rewarding for most surgeons in that it supports early surgery. On the other hand, there are a number of questions that the study raises. First, the size measurements were difficult to blind. Those still undescended clearly were notable at the time of the ultrasound and there might well be observer bias. Second, one has to wonder if the increased size is at all

related to lymphatic obstruction. Doing a proper orchiopexy may well require damaging most lymphatics, resulting in a large testis in the first year or 2 postoperatively. This type of enlargement might not be discernable on ultrasound. Third, the study results are reported after 24 months, so we do not know if those children operated on later might have the same increase in growth and therefore, there may not be any benefit to early surgery. Fourth, we do not know if the larger testis is any better functionally. Indeed, most studies suggest that the undescended testis contributes little to ultimate fertility. This is an early report of a much larger study and we can expect that the answers to some of these questions will be forthcoming.

Overall, the authors are to be congratulated on a careful randomized study of this complex problem. We eagerly look forward to further reports from this study.

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