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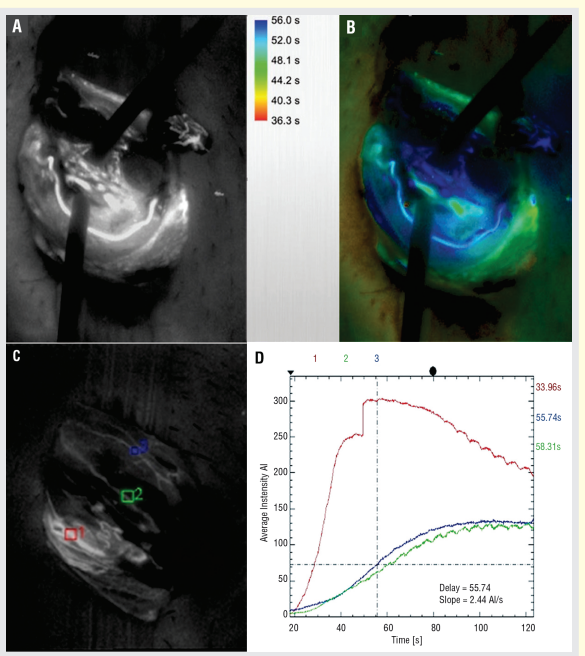

Figure 2 - Built-in fluorescence modules of the operating microscope provided analysis of the vascular dynamics. A) Infrared 800 module demonstrates the relative intensity of indocyanine green signal. B) Flow 800 module illustrates the sequences the flow dynamics into a visual map. C) Interpretation of specific area on the angiographic image can bemarked and D) Flow dynamic of each region can be illustrated in the form of curves. (Page 976)

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CONTENTS

Volume 43 | number 5 | September . October, 2017 | INT BRAZ J UROL

EDITORIAL IN THIS ISSUE

796 *Stênio de Cássio Zequi*

DIFFERENCE OF OPINION

798 Which is the best way to treat a stone on a flexible ureterorrenoscopy? | *Opinion: Fragmentation*
Alex Meller

802 Which is the best way to treat a stone on a flexible ureterorrenoscopy? | *Opinion: Dusting*
Antonio Correa Lopes Neto

REVIEW ARTICLE

805 Short-term efficacy and safety of low-intensity extracorporeal shock wave therapy in erectile dysfunction: a systematic review and meta-analysis
Zi-jun Zou, Liang-you Tang, Zhi-hong Liu, Jia-yu Liang, Ruo-chen Zhang, Yu-jie Wang, Yong-quan Tang, Rui Gao, Yi-ping Lu

822 Update on complications of synthetic suburethral slings
Cristiano Mendes Gomes, Fabrício Leite Carvalho, Carlos Henrique Suzuki Bellucci, Thiago Souto Hemerly, Fábio Baracat, Jose de Bessa Jr., Miguel Srougi, Homero Bruschini

835 Management of prostate abscess in the absence of guidelines
Haitham Abdelmoteleb, Fatima Rashed, Amr Hawary

ORIGINAL ARTICLE

841 Adjuvant radiotherapy for the primary treatment of adrenocortical carcinoma: are we offering the best?
Victor Srougi, Jose Bessa Junior, Fabio Y. Tanno, Amanda M. Ferreira, Ana O. Hoff, João E. Bezerra, Cristiane M. Almeida, Madson Q. Almeida, Berenice B. Mendonça, William C. Nahas, Jose L. Chambô, Miguel Srougi, Maria C. B. V. Fragoso

849 Partial nephrectomy for T3aN0M0 renal cell carcinoma: shall we step forward?
Ding Peng, Zhi-song He, Xue-song Li, Qi Tang, Lei Zhang, Kai-wei Yang, Xiao-teng Yu, Cui-jian Zhang, Li-qun Zhou

857 Laparoscopic partial nephrectomy for tumors 7cm and above. Perioperative outcomes
Matvey Tsivian, Efrat Tsivian, Yury Stanevsky, Roman Bass, A. Ami Sidi, Alexander Tsivian

863 Comparison of two different suture techniques in laparoscopic partial nephrectomy
Onur Kaygisiz, Sinan Çelen, Berna Aytac Vuruşkan, Hakan Vuruşkan

871 The influence of previous robotic experience in the initial learning curve of laparoscopic radical prostatectomy
José Anastácio Dias Neto, Marcos F. Dall'oglio, João Roberto Colombo Jr., Rafael F. Coelho, William Carlos Nahas

880 Quality of life and urolithiasis: the patient - reported outcomes measurement information system (PROMIS)
Nishant Patel, Robert D. Brown, Carl Sarkissian, Shubha De, Manoj Monga

887 Early term effect of ureterorenoscopy (URS) on the Kidney: research measuring NGAL, KIM-1, FABP and CYS C levels in urine
Erdal Benli, Sema Nur Ayyildiz, Selma Cirrik, Tevfik Noyan, Ali Ayyildiz, Abdullah Cirakoglu

896 New concept for treating female stress urinary incontinence with radiofrequency
Patrícia Lordelo, Andrea Vilas Boas, Danielle Sodré, Amanda Lemos, Sibele Tozetto, Cristina Brasil

903 Laparoscopic pectopexy: initial experience of single center with a new technique for apical prolapse surgery
Ahmet Kale, Alper Biler, Hasan Terzi, Taner Usta, Ebru Kale

910 Editorial Comment: Laparoscopic pectopexy: initial experience of single center with a new technique for apical prolapse surgery
Bruno Nicolino Cezarino

911 Inflatable penile prosthesis as tissue expander: what is the evidence?
Paul H. Chung, Jordan A. Siegel, Timothy J. Tausch, Alexandra K. Klein, Jeremy M. Scott, Allen F. Morey

917 Unilateral extravesical ureteral reimplantation via inguinal incision for the correction of vesicoureteral reflux: a 10-year experience
Michael Yap , Unwanabong Nseyo, Hena Din, Madhu Alagiri

925 An unanswered question in pediatric urology: the post pubertal persistence of prepubertal congenital penile curvature correction by tunical plication
Ünsal Ozkuvanci, Orhan Ziylan, M. Irfan Dönmez, Omer Baris Yucel, Tayfun Oktar, Haluk Ander, Ismet Nane

932 Outcomes of miniaturized percutaneous nephrolitotomy in infants: single centre experience
Eyyup Sabri Pelit, Bülent Kati, Cengiz Çanakci, Süleyman Sağir, Halil Çiftçi

939 Effect of Mitomycin - C and Triamcinolone on Preventing Urethral Strictures
Omer Kurt, Fethullah Gevher, Cenk Murat Yazici, Mustafa Erboga, Mucahit Dogru, Cevat Aktas

946 Attenuation of partial unilateral ureteral obstruction - induced renal damage with hyperbaric oxygen therapy in a rat model
Eyup Burak Sancak, Yusuf Ziya Tan, Hakan Turkon, Coskun Silan

957 The prostate after castration and hormone replacement in a rat model: structural and ultrastructural analysis
Bruno Felix-Patrício, Alexandre F. Miranda, Jorge L. Medeiros Jr., Carla B. M. Gallo, Bianca M. Gregório, Diogo B. de Souza, Waldemar S. Costa, Francisco J. B. Sampaio

966 Dipyridamole reduces penile apoptosis in a rat model of post-prostatectomy erectile dysfunction
Omer Kutlu, Ersagun Karaguzel, Ali Ertan Okatan, Ahmet Mentese, Esin Yulug, Ilke Onur Kazaz, Selcuk Kutlu, Eyup Dil, Huseyin Eren, Ahmet Alver

SURGICAL TECHNIQUE

974 Use of indocyanine green angiography in microsurgical subinguinal varicocelectomy - lessons learned from our initial experience
Chak-Lam Cho, Kwan-Lun Ho, Wayne Kwun-Wai Chan, Ringo Wing-Hong Chu, In-Chak Law

980 Editorial Comment: Use of indocyanine green angiography in microsurgical subinguinal varicocelectomy - lessons learned from our initial experience
Marcello Cocuzza

CHALLENGING CLINICAL CASES

982 Synthetic mesh repair of an anterior perineal hernia following robotic radical urethrocystectomy
Horacio J. Alvarez Garzón, Thomas Maubon, Camille Jauffret, Pierre Vieille, Brigitte Fatton, Renaud de Tayrac

RADIOLOGY PAGE

987 Anastomosing hemangioma simulating renal cell carcinoma
Mariana Athaniel Silva Rodrigues, Eduardo Kaiser Ururahy Nunes Fonseca, Fernando Ide Yamauchi, Ronaldo Hueb Baroni

990 A solitary urothelial tumor arising from one of bilateral ureteroceles
Yu Xi Terence Law, Irfan Khan Sagir, Lincoln Tan Guan Lim

VIDEO SECTION

994 Robotic assisted laparoscopic augmentation ileocystoplasty
Peter A. Caputo, Daniel Ramirez, Matthew Maurice, Onder Kara, Ryan Nelson, Ercan Malkoc, Jihad Kaouk

995 Focal cryotherapy: step by step technique description
Cristina Redondo, Victor Srougi, José Batista da Costa, Mohammed Baghdad, Guillermo Velilla, Igor Nunes-Silva, Sebastien Bergerat, Silvia Garcia-Barreras, François Rozet, Alexandre Ingels, Marc Galiano, Rafael Sanchez-Salas, Eric Barret, Xavier Cathelineau

997 Robotic assisted laparoscopic excision of a retroperitoneal Ganglioneuroma
Lucas Medeiros Burttet, Fernando Jahn da Silva Abreu, Gabrielle Aguiar Varaschin, Brasil Silva Neto, Milton Berger

LETTER TO THE EDITOR

998 Re: Insufficient conclusions regarding the association between overactive bladder symptoms and degree of dementia
Jae Heon Kim

1000 Re: Preliminary assessment of neck circumference in benign prostatic hyperplasia in patients with metabolic syndrome
Huseyin Besiroglu, Emin Ozbek

1002 Re: Assessment of sexual functions in partners of women with complaints of urinary incontinence
Mustafa Kadihasanoglu, Emin Özbek

1004 Re: Persistent Mullerian Duct Syndrome: a rare entity with a rare presentation in need of multidisciplinary management
Lisieux Eyer de Jesus

1005 REPLY BY THE AUTHORS: Re: Persistent Mullerian Duct Syndrome: a rare entity with a rare presentation in need of multidisciplinary management
Lin Da Aw, Murizah M. Zain, Sandro C. Esteves, Peter Humaidan

1007 **INFORMATION FOR AUTHORS**

EDITORIAL
IN THIS ISSUE

Volume 43 | number 5 | September . October, 2017 | INT BRAZ J UROL

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The fate of some urologic innovations from the last century

Around the 1980's the external shockwave lithotripsy (ESWL) promoted a revolution in the millenary open surgical approach of urinary stones. After the ESWL, the Endourology procedures and its devices progressed a lot, but several controversies persist in this area, as: What is the best approach during the flexible ureteroscopic lithotripsy, to promote stone fragmentation or dusting? These two visions were put under debate in the Difference of Opinion Section (page 798), respectively by the doctors Meller and Lopes Neto, from Brazil. During this time, ESWL had expanded its applications in in Orthopedics and in Pain Medicine. More recently, new ESWL devices, were developed for new a urologic use: The treatment of erectile dysfunction, but this approach is subject of doubts and some skepticism. To help our readers in understanding this kind of treatment, a Chinese Group performed a review of 15 studies and a metanalisys of 4 controlled randomized trials, focusing in the early treatment results (30 days after intervention) They concluded that low intensity ESWL results in better improvement of erectile function in comparison with the sham treatment groups (page 805).

Returning for urinary lithiasis, to treat small infants usually is a challenge. Colleagues from Istanbul reported their single center experience with the use of miniaturized percutaneous nephrolithotomy (other development of stone management), in 72 children younger than 3years old (page 932).

Other significant modification, verified in the end of the 20th century, was the use of synthetic meshes in urogynecologic surgeries, but after years of use, complications are well known, and resulted in significant amount of legal demands. Gomes et al. evaluated the main complications of the synthetic sub urethral slings utilized in the treatment of female stress urinary incontinence (page 822).

The concept of elective nephron sparing surgeries for the treatment of kidney cancer, was born in the end of the last century, initially for the resection of small tumors (<4.0 cm), and has been progressively consolidated and popularized. Consequently, the indications of partial nephrectomy have been expanded in challenge cases. In this issue of Int Braz J Urol., we have from Pekin, evaluations about the use of partial nephrectomy in pT3a cases; a group from Tel Aviv, reported the outcomes of laparoscopic partial nephrectomy for tumors larger than 7 cm (pages 849-857).

The group of Cleveland Clinic led by Dr. Monga found through the interviews with specific scores, that quality of life of patients with urinary lithiasis is worse than general United States population. With these data, they reinforced the needs of stone prevention measures to improve quality of life of these patients (page 880).

Among the translational papers, there is an interesting study performed in rat models undergone unilateral ureteral obstruction, by the group from Canakkale University,

Volume 43 | number 5 | September . October, 2017 | INT BRAZ J UROL

in Turkey. They demonstrated that the Hyperbaric Oxygen Therapy can reduces the functional renal damage changes (measured through biochemical, histological and scintigraphy parameters).

Focal therapy is other new approach of prostate cancer, under intense discussion. Several equipments are in development around the world, project to promote focal gland ablation. In the video section, the Group of L' Institute Mutualist Montsouris, from Paris, presents a case of focal cryotherapy for patient with anterior prostate cancer (page 995).

Let us following the next urological steps in this century...

Stênio de Cássio Zequi, MD, PhD

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DIFFERENCE OF OPINION

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Which is the best way to treat a stone on a flexible ureterorrenoscopy? | *Opinion: Fragmentation*

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Keywords: Calculi; Lasers, Solid-State; Kidney

Since the introduction of Holmiun YAG (Ho-YAG) laser to treat kidney or ureteral stones, a dramatic change in techniques of stone treatment has occurred, especially how to adjust the ideal laser setting to achieve ideal fragmentation.

First reports of Ho-YAG laser clinical application had been focused on tissue cutting or destruction (1), but few years later, the ability to fragment stones through a thermal mechanism was demonstrated (2). The laser emission superheats water surrounding the laser fiber tip, thus creating a microscopic vaporization bubble that is able to destabilize or vaporize tissue or a stone. Based on this mechanism, the ideal energy setting to treat a stone had been discussed and evaluated.

Nowadays, the concept of dusting and fragmentation settings are very well documented, but the studies failed to prove which technique is superior. In dusting technique, the goal is to pulverize a stone creating small particles and dust (<1-2mm in size) to theoretically enable spontaneous passage of the small particles. In fragmentation and retrieving technique, stones can be fragmented into pieces (1-4mm) depending on the access sheath lumen used and will be extracted with a grasper or basket thoroughly cleaning the collecting system or ureter.

There are three different parameters related to laser settings: energy, frequency and pulse. The laser power delivered in Watts is obtained multiplying energy X frequency, enabling a lot of combinations. Older publications demonstrated that increasing pulse energy (Joules) will increase fragmentation rate (3) but frequency was not evaluated. An elegant study *in vitro* from Kronenberg et al. (4) evaluated different settings and its stone ablation rate, using pulse energy and frequency. It has concluded that stone ablation increased while increasing pulse energy, regardless of frequency or total power (Watts), but this combination can produce bigger fragments (5) and its removal could be time consuming. Conversely, increases in frequency will slower fragmentation rate (6) at the same pulse energy, but it will produce smaller fragments (5) that can be cleared spontaneously, avoiding the need to retrieve all particles.

In newer lithotripter models, the urologist can adjust different pulse durations, i.e., the traditional short-pulse mode (330µs) or a long-pulse mode (650-1250µs) (7). Conceptually, pulse duration is the period of time that energy will be

delivered during a single laser pulse, which can modify stone ablation rate. Preliminary studies showed that short-pulse mode is more ablative than the long-pulse mode (7), but at cost of more retropulsion effect (8). Others suggested that short-pulse mode could produce bigger fragments than long-pulse mode, but it couldn't be proved experimentally (9). More studies are needed to define the ideal pulse duration to achieve best performance, but in the author's opinion, long-pulse mode could perform better in softer stones and, theoretically, produce a better dust effect with less retropulsion.

The questions that emerge from these two concepts (dusting or basketing) are related to clinical outcomes, auxiliary procedures, absence of stone specimen to be analyzed and costs.

Comparative studies about clinical outcomes are rare. The only published study that compared dusting versus basketing for ureteral stones randomized 60 patients (30 in each arm) to undergo active retrieval or wait for spontaneous passage after laser lithotripsy with a semirigid ureteroscope. The primary study outcome was difference in unplanned medical or emergency room visits up to 30 days after surgery. Secondary outcomes evaluated included need for analgesia, need for auxiliary procedures, stone free rate and difference in hospitalization. Overall, the dusting group had a higher rate of unplanned visits than the basketing group (30% versus 3%, OR 12.4, 95% CI 1.8-80.3, P=0.01) (10). Other parameters as stone free rate, re-hospitalization rates, need for analgesia and need for auxiliary procedures hadn't shown significant statistical differences, but all of them tend to be worst in dusting group. Despite its randomized design, this study has many problems (multiple surgeons, variable laser settings, exclusion of patients using ureteral stents, etc.), compromising the outcomes.

Chew et al. are prospectively evaluating both strategies for renal stones (5-20mm) in a multicenter study (EDGE consortium) involving 8 high volume tertiary stone centers. They enrolled 152 patients (basketing = 82, dusting = 70) and followed then for 3 months. The preliminary results evaluated stone free rates as primary outcome, and presence of residual fragments, readmission rate, duration of procedure, amount of energy used and need for additional procedures. Stone free rates at initial follow up were 86.3% in the basketing group versus 59.2% in the dusting group, with fewer patients who underwent basketing having symptoms from residual fragments or requiring secondary interventions. Besides the higher presence of residual fragments in the dusting group, the readmission rate was not statistically different in both groups in a short-term follow-up. The dusting approach results in shorter operative time and lower use of ureteral access sheath (UAS) than basketing group. However, there are problems in this important study: the short follow up duration, multiple surgeons and use of KUB and ultrasound to evaluate residual fragments could bias its results.

The natural history of residual fragments was evaluated in several studies. A retrospective study from Chew and associates evaluated 232 subjects with residual fragments 12 months after ureteroscopy between 2006 and 2013. The stone event rate was 44%, where 29% required intervention and 15% experienced complications without intervention. Fragments larger than 4mm were more likely to grow with time ($p<0.001$) and were associated with more complications ($p=0.039$). Fragments larger than 2mm are more likely to grow ($p<0.001$) but were not associated with complications or re-intervention. Re-intervention rates were predictable based on fragments size ($p=0.017$) (11). Other studies demonstrated that presence of hydronephrosis and lower-pole stones are predictors of failure on residual fragments clearance (12, 13).

These studies highlighted the importance to achieve the real stone free status to prevent re-intervention or stone re-growth, but failed to prove it statistically. But, between 20 to 30% of patients with residual fragments will need an additional procedure and this fact cannot be underestimated.

Basketing technique needs to be performed with UAS elevating the risks of ureteral injury (14), but it also means that intrarenal pressure will be lower during flexible procedure (15), preventing risks of SIRS. This is a controversial point, where cost and benefits still has to be evaluated.

Additionally, immediate costs will be higher in basketing technique procedure where use of a basket device and UAS is mandatory. But none of studies evaluated the global cost including the higher rate of unplanned emergency room visits, additional procedures and re-growth of residual fragments in the patients submitted to dusting technique. Then, more sophisticated cost evaluation studies should be done to answer this question.

Other criticism of dusting technique is the lack of specimen to be analyzed. Assuming that stone disease has a high recurrence rate, with at least 50% of individual experiencing another stone in 5 years, medical prevention is the key to minimize this condition. Knowing the stone composition is one of the major points to prevent recurrence.

New high power lasers (120W) developed for prostate ablation have been used for stone treatment a few years ago. Since then, dusting technique seems to be more efficient and widespread the idea that truly pulverizes the stone. Few studies tested this new technology and none compared head to head basketing and high frequency laser technique. Emiliani and cols. tested different frequencies and pulse energy in an experimental study. They demonstrate that high power was more efficient in reduction of stone volume than lower frequencies (OR 1.14, 95% CI 1.09 -1.20) (16) This new concept could improve dusting results and establish a new paradigm, but the laser unit is very expensive, making it difficult to be used worldwide. Maybe in the future the costs will lower and availability of high power lasers will become the new standard.

Besides all literature, a subjective parameter has to be cited. The perfect dusting technique to produce smaller fragments as possible (real dust) may be less related to laser settings and more dependent on the surgical technique. Studies comparing dusting (high frequency/low energy) versus fragmentation (low frequency/high energy) settings used irregular hand-held approaches or automated testing systems, which failed to reproduce real life situation. The way that urologists approach the stone with the laser, i.e. repeatedly perforating, chipping or fragmenting in comparison with working on its surface, “painting” the stone surface could be the most important factor, and this remains to be investigated.

Finally, the debate still ongoing, but some considerations could be done at that point. Every stone needs a personalized approach, if they are softer, harder, smaller, bigger or located in renal collecting system or ureter. It seems reasonable that a harder stone will need more energy and fragmenting should perform better, but if it is too big, it could produce a prohibitive amount of fragments. On contrary, in softer stones, a technically correct dusting could pulverize the stone and achieve good stone free rates, but sometimes, smaller stones are technically challenging to be pulverized. The urologist must be aware of the fragments size produced during lithotripsy and adjust settings accordingly it in a dynamic way.

Our patients wish to be free of stones, with less pain, less additional procedures and lower complications. Then, in our opinion, the best approach is to reduce stone burden in bigger stones (over 10mm) with dusting technique and fragmenting the residual stone (less than 10mm) in pieces to be retrieved, combining both techniques. When treating smaller stones (less than 10mm), fragmenting and basketing seems to be preferable to meet the patient goal, the higher immediate stone free rate.

CONFLICT OF INTEREST

None declared.

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DIFFERENCE OF OPINION

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Which is the best way to treat a stone on a flexible ureterorrenoscopy? | *Opinion: Dusting*

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Keywords: Calculi; Lasers, Solid-State; Kidney

Flexible ureterorenolithotripsy is rapidly developing and becoming the treatment of choice around the World for the invasive treatment of lithiasis (1). According to calculi dimensions, they can be removed integrated or by using an intracorporeal lithotripter.

According to laser parameters adjustments, it is possible to vaporize calculi ("dusting"). In this case, it is necessary to use high frequency of impulses (>15HZ), low energy (<0.5J) and long pulses (800 μsec), whenever the equipment allows for these options.

Recently, it has been debated which is the best way to program the equipment at the moment of calculi lithotripsy. There are few evidences in literature to conclude, but it seems that dusting has some advantages in relation to fragmentation + basketing.

An experimental work performed in 1999 showed that the use of high energy during lithotripsy increased the quantity of larger fragments; the authors suggested the use of <1 J energy and high frequency of impulses, that characterizes dusting (2). Another more recent experimental study also verified that, by using several potencies and frequencies, that the produced fragments were lower than 1 mm in almost all groups that used 0.2J of energy. Those fragments increased proportionally to the increase of Joules of Holmium laser (3). At present, endourologic post-surgical residual calculi have become a future concern, since they can cause pain, urinary tract obstruction and need of reintervention. The EDGE group collected data from 6 centers and verified that among 232 patients with residual lithiasis, 44% evolved with some colic event and 29% needed surgical reintervention. Fragments bigger than 4 mm were the most probable to grow ($p<0.001$) and associated with bigger complications ($p=0.039$) (4). Also, when bigger fragments are produced, the need for basket removal generates more movement of the appliance through the sheath, increasing the risk of displacement and ureteral lesions.

It is possible to treat efficiently calculi generating power or very tiny fragments that don't need to be removed, dismissing the need of a basket and lowering costs (3). Morhardt, using a 120 W Holmium Laser and dusting, showed efficient resolution of renal and ureteral bigger calculi (1.5–1.7cm) (5). A prospective multicenter study (EDGE group) compared dusting method to fragmentation and basketing in the treatment of intra-renal calculi with 5 to 20mm. 59 patients were studied. Calculi were bigger in the dusting group and stone-free rate was lower (60.9%). But only 17% of residual fragments

were bigger than 4mm and there was no difference in relation to reintervention, hospital readmission or pain. Dusting was favored by shorter surgical time and only 27.5% of procedures used sheath (6). Glickman analyzed laser adjustments during ureterorenolithotripsy in 103 patients. One group used dusting adjustment with low energy (0.2-0.4J) and high frequency (50HZ) and another used higher energy (0.5-1J) with frequency from 5 to 10HZ. In only 3.8% of dusting cases it was inefficient and it was necessary to change to higher energy. The authors concluded the procedure is efficient, with finer fragments and without the need of basketing (7).

In the specific treatment of ureteral calculi, the use of lower energy during dusting reduces the incidence of retropulsion of fragments and eventual return to the intra-renal collector system. Several studies showed that this situation is more frequent when it is used higher energy of laser (2, 3, 7-9). In an experimental model, retropulsion of ureteral calculi was higher and faster when it was used 0.6J/5Hz. With these parameters, 100% of calculi had retropulsion in less than 3 minutes of fragmentation. Fragmentation with 0.2J/15HZ (dusting) caused 60% of retropulsion, but only after 10 minutes of exposure of calculi to impulses, allowing for the resolution of calculi before retropulsion. In a longer time, it was possible to fragment bigger calculi (10). When it was used higher energy, anti-retropulsion devices increased the efficiency of lithotripsy (3), but it must be considered that the need of another material increases the costs. When Ho Yag laser equipment allows for change of pulse length, retropulsion is lower when a longer pulse is used, resulting in better results, since the calculus remains immobile for longer period under fragmentation (11, 12).

Another advantage observed in a comparative work was that dusting fragmentation preserved more the laser fiber: the need to trim the tip during the procedure was less frequent when this adjustment was used (6). An in vitro experiment using holmium laser and dusting showed that the use of longer pulses also generates less degradation of the fiber tip (12).

Dusting, a recent method with few studies and strong evidences, has several advantages in relation to fragmentation and basketing. In summary, the main benefits are:

1) Generation of powder or little fragments, minimizing the risk of recurrence and future complications;
2) Lower costs, since it does not use baskets and spares the laser fiber, with less degradation of its tip. Also, there is no need to extract fragments and it is possible not to use the ureteral sheath, reducing even more the costs.
3) Lower retropulsion of ureteral calculi, reducing the risk of migration to the kidney and inefficiency of the procedure.

I believe that dusting must be the initial choice for intracorporeal lithotripsy. In case of failure during the procedure, it is possible to increase energy, reduce frequency and pulse length, modifying the method to fragmentation and basketing.

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REVIEW ARTICLE

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Short-term efficacy and safety of low-intensity extracorporeal shock wave therapy in erectile dysfunction: a systematic review and meta-analysis

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ABSTRACT

Aim: The role of low-intensity extracorporeal shock wave therapy (LI-ESWT) in erectile dysfunction (ED) is not clearly determined. The purpose of this study is to investigate the short-term efficacy and safety of LI-ESWT for ED patients.

Materials and Methods: Relevant studies were searched in Medline, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), WANFANG and VIP databases. Effective rate in terms of International Index of Erectile Function-Erectile Function Domain (IIEF-EF) and Erectile Hardness Score (EHS) at about 1month after LI-ESWT was extracted from eligible studies for meta-analysis to calculate risk ratio (RR) of effective treatment in ED patients treated by LI-ESWT compared to those receiving sham-treatment.

Results: Overall fifteen studies were included in the review, of which four randomized controlled trials (RCTs) were for meta-analysis. Effective treatment was 8.31 [95% confidence interval (CI): 3.88-17.78] times more effective in the LI-ESWT group (n=176) than in the sham-treatment group (n=101) at about 1 month after the intervention in terms of EHS, while it was 2.50 (95% CI: 0.74-8.45) times more in the treatment group (n=121) than in the control group (n=89) in terms of IIEF-EF. Nine-week protocol with energy density of 0.09mJ/mm^2 and 1500 pluses seemed to have better therapeutic effect than five-week protocol. No significant adverse event was reported.

Conclusion: LI-ESWT, as a noninvasive treatment, has potential short-term therapeutic effect on patients with organic ED irrespective of sensitivity to PDE5is. Owing to the limited number and quality of the studies, more large-scale, well-designed and long-term follow-up time studies are needed to confirm our analysis.

ARTICLE INFO

Keywords:
Erectile Dysfunction; Therapeutics; Meta-Analysis as Topic

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INTRODUCTION

Erectile dysfunction (ED) is a common male sexual dysfunction and oral phosphodiesterase type 5 inhibitor (PDE5i) is a first-line therapy (1). Although ameliorating erectile function (EF) significantly, PDE5is are not curative approaches and patients have to plan sexual activity with the aid of medication. In addition, a part of ED patients poorly respond to PDE5is and need to turn to invasive treatments such as intra-cavernosal injection of vasoactive agents

and surgical implantation of penile prostheses. Therefore, a novel treatment that improves EF in a noninvasive and enduring manner is required.

Shockwave is characterized by acoustic wave generating pressure impulses. It has been used widely in the field of medicine, where the role of shockwave therapy varies with the level of energy intensity (2). Different from high- and medium-intensity shockwave with focused mechanical destructive and anti-inflammatory nature, low-intensity extracorporeal shock wave therapy (LI-ESWT) probably has angiogenic property based on resultant cell membrane microtrauma and mechanical stress that are associated with the release of angiogenic factors (3) and recruitment of circulating endothelial progenitor cells (4). Therefore, LI-ESWT has been used for vasculogenic disease containing peripheral artery disease (5), chronic wounds (6), and cardiac ischemic diseases (7).

Based on the potential stimulation of angiogenesis and local vascularization (8), LI-ESWT was also used for vasculogenic ED and had considerable effectiveness in terms of sexual performance, penile blood flow and endothelial function (9-11). It will hopefully make up the defects in the treatment of ED given that 1) the potential property of altering spontaneous erectile function in an enduring and pathophysiological way (9); 2) reversing insensitivity to PDE5is (11). Meanwhile, penile LI-ESWT was proved to be safe during and after the treatment in the pilot studies (9-11).

Although underlying mechanism is still under investigation, LI-ESWT has been listed in the chapter of first-line therapy since 2013 European Association of Urology (EAU) guidelines on male sexual dysfunction (1), supported by a series of prospective trials containing randomized controlled trials (RCTs) (9-11). Nevertheless, defined recommendation cannot be given because current evidences are relatively limited. Recently, two systematic reviews and meta-analyses (12, 13) on the topic were published. However, the result of the study by Lu et al. (12) was less convincing because significant heterogeneity existed among included studies with ED patients originating from different pathology, and the evidence level of Angulo's study (13) was lowered by including single-arm trials. Therefore, a systematic review and meta-analysis focusing on RCTs regarding LI-ESWT for organic ED without Peyronie's disease (PD) and chronic pelvic pain (CPP) is essential.

MATERIALS AND METHODS

The systematic review and meta-analysis was performed following PRISMA criteria (14).

Criteria for study inclusion/exclusion

Studies, which contained RCT, single-arm trial and respective study, reporting LI-ESWT in the management of ED patients without PD and CPP, were included for this systematic review. If data regarding effective and/or complication rate could be extracted, those included RCTs were further performed for meta-analysis. In addition to eligible original articles, reviews in the field were also identified for further searching of reference lists to ensure the completeness of the literature search. Case reports, letters to the editor, conference abstract, comment and basic studies were excluded.

Two authors reviewed the included articles independently. Disagreements were resolved by discussion and consensus. Duplicate publications were excluded, and when different literatures discussed a same cohort, the most informative one was used for further analysis.

Search strategy

Two authors independently searched Medline, Embase, Cochrane library and Chinese medical electronic databases including China National Knowledge Infrastructure (CNKI), WANFANG and VIP by using one of "shockwave" and "shock wave" combined with one of "erectile dysfunction" and "ED" as a search term with overall 4 combinations. English and Chinese literatures between January 2010 and December 2015 were included. The reference lists of eligible studies and relevant reviews were searched in case of possible missing articles.

Assessment of risk of bias in included studies

Risk of bias in the RCT was assessed according to the Cochrane Collaboration's tool

for assessing risk of bias (15), which addresses sequence generation, allocation concealment, blinding, handling of incomplete data, and selective reporting. The quality of other studies was assessed by the Methodological Index for Non-randomized Studies (MINORS) (16) and global ideal score is 16 points for non-comparative study.

Data extraction

Data extraction was done by two authors independently, and disagreements were resolved by discussion. Titles and abstracts were used to screen for initial study inclusion. Full-text review was carried out on the remaining papers that matched inclusion/exclusion criteria. The same reviewers performed all data extraction including study characteristics and outcome data. A data-extraction form was used with variables containing author, publication year, type of study, country, LI-ESWT protocol, ED type, previous sensitivity of PDE5i, endpoints, and outcomes.

In the meta-analysis, effect size (ES) was risk ratio (RR) of effective treatment in ED patients receiving LI-ESWT and sham treatment. International Index of Erectile Function--Erectile Function Domain (IIEF-EF) score and Erectile Hardness Score (EHS) were validated and most widely used in clinical trials to evaluate erectile function. The numbers of total participants and effective ones measured with them were extracted from included literatures. Short-term effective treatment was defined as 5-point or greater improvement in the IIEF-EF between baseline and score at about 1 month after LI-ESWT or an increase in EHS from 2 or less at baseline to 3 or more at about 1 month after the intervention. The definitions were accepted because most participants and studies could be included. Adverse event outcome was also summarized and analyzed.

Statistical analysis

Random effects model was selected for the calculation of RR based on acknowledging heterogeneities in our samples with several protocols of LI-ESWT and populations with different sensitivity of PDE5is. A chi-squared test was conducted for heterogeneity evaluation and p value less than 0.05 was considered to be statistically significant. I^2 index was used to quantify between-study heterogeneity's contribution to overall heterogeneity. Funnel plot was conducted for evaluation of publication bias. Sensitivity analysis was conducted to explore the heterogeneity via excluding every study one by one. Subgroup analysis according to different protocols, energy densities and doses of LI-ESWT, the consistency of risk factors between the treatment and control group, and sensitivity to PDE5is, was conducted. Statistical calculation was conducted using Review Manager (version 5.3) software.

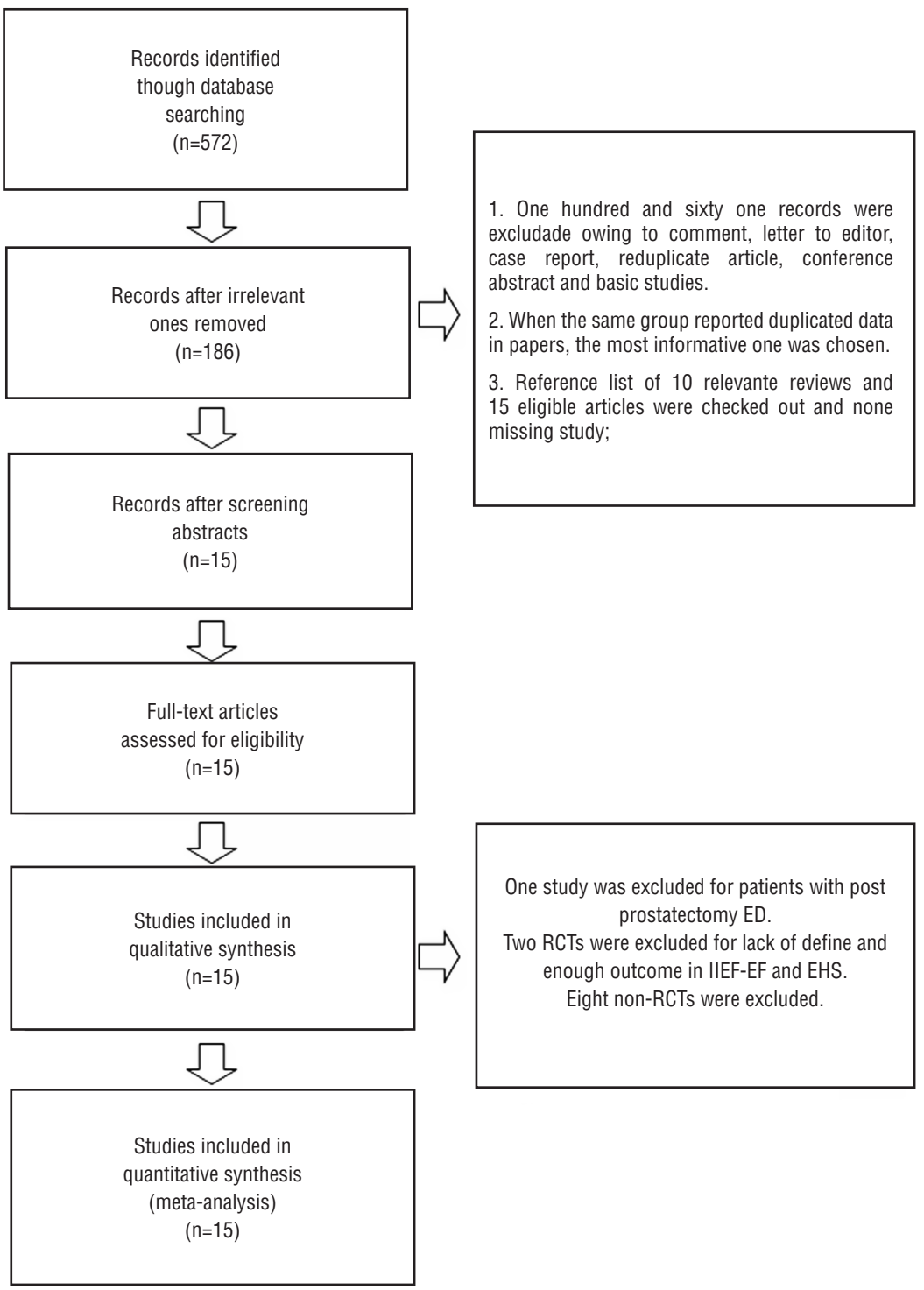
RESULTS

Literature search results

The search process is shown in Figure-1. The first search yielded 572 potentially relevant studies, of which 386 were irrelevant and were excluded after reviewing their titles. Abstracts of the remaining 186 studies were considered for detailed evaluation. One hundred and sixty one studies were excluded in that stage due to reduplicate cohorts, and being letter to the editor, case report, conference abstract and comment. No more eligible articles were found in search of the reference lists of 10 relevant reviews and the 15 original literatures.

Finally, 15 original articles (9-11, 17-28) were included in the systematic review after full-text evaluation. Table-1 shows the characteristics of the eligible studies with 6 RCTs (10, 17, 18, 21, 25, 28) and 9 prospective, single-arm trials (9, 11, 19, 20, 22-24, 26, 27). There was a study (27) about ED secondary to nerve-sparing prostatectomy, while the other studies focused on organic ED that was mainly considered to be vasculogenic. Although the protocol, device, energy density and dose of LI-ESWT were not uniform, all treatments had positive effects on ED in the studies. The details of the methods were summarized in Table-2. A RCT from China (21) compared the efficacy of LI-ESWT and va-

Figure 1 - Flow diagram outlining search results and final included and excluded studies.



cuum erectile device for ED. With two RCTs (18, 21) with lack of sufficient data, overall 4 RCTs (10, 17, 25, 28) were included for quantitative synthesis.

The quality of the included studies

The risks of bias in two RCTs were considered to be high owing to high dropout rate (25) and not performing blind method in performance (21). Three RCTs (10, 17, 28) had unclear risks of bias without details of randomization and/or blind method, and only one RCT was evaluated as being low risk of bias (18). According to MINORS (16), all non-comparative studies were 12 scores with lack of information of blind evaluation of endpoints and prospective calculation of the study size.

Evaluation of the effect of LI-ESWT on ED in terms of IIEF-EF and EHS, and its safety

Three RCTs (10, 17, 28) comparing IIEF--EF-based effective rate (ER) in patients receiving LI-ESWT (n=121) and sham treatment (n=89) were included for the calculation of RR. Effective treatment was 2.50 [95% confidence interval (CI): 0.74-8.54] times higher in the LI--ESWT group than in the sham-controlled group at about 1 month after last session and heterogeneity may be substantial (p=0.02; I^2: 75%). In terms of EHS, including 4 RCTs (10, 17, 25, 28) of 277 patients, RR is 8.31 with 95% CI ranging from 3.88 to 17.78 (p=0.42; I^2: 0%), as seen in Figure-2. Funnel plot was asymmetrical showing publication bias. Sensitivity analysis in IIEF-EF revealed that the study by Olsen et al. (17) influenced heterogeneity significantly and when the study was excluded, I^2 and p value was 24% and 0.25, respectively, while RR was 4.40 (95%CI: 1.18-16.38). Sensitivity analysis indicated that the result was stable in EHS.

In subgroup analysis, as seen in Figures 3 and 4, it was showed that in EHS 9-week protocol with energy density of 0.09mJ/mm^2 and 1500 pluses (RR: 22.59; 95% CI: 4.65-109.79) was probably more effective than 5-week protocol with energy density of 0.15mJ/mm^2 and 3000 pulses (RR: 6.14; 95% CI: 2.58-14.64) based on possibly substantial between-group heterogeneity, although the difference did not reach statistical significance. Similar result was observed in IIEF-EF with RR of 4.40 (95% CI: 1.18-16.38) in 9-week group and 1.16 (95% CI: 0.71-1.90) in 5-week group with the p value of subgroup differences being 0.06. In our analysis, LI-ESWT for PDE5i non-responders was more likely to contribute to effective treatment (RR: 15.50, 95% CI: 0.98-245.34, in IIEF-EF; RR: 20.50, 95% CI: 1.31-320.94, in EHS), than for responders (RR: 1.81, 95% CI: 0.64-5.11, in IIEF-EF; RR: 8.58, 95% CI: 3.17-23.23, in EHS), but difference was not statistically significant. To explain whether the consistency of risk factors of ED, such as age, cardiac disease, diabetes mellitus (DM), et al., between treatment and control group influenced analysis outcome, we summarized the baseline characteristics of study population from the 4 RCTs (Table-3) and performed subgroup analysis according to consistency of risk factors. It was found that the outcome of studies with consistent risk factor was lower (RR: 7.41; 95% CI: 3.36-16.38), than that with inconsistent risk factors (RR: 32.16; 95% CI: 2.09-495.35), but it did not reach statistical significance either (p=0.31).

There was no reported severe complication, which needed medical intervention.

DISCUSSION

Since 2010 when Vardi et al. (9) published the first literature on LI-ESWT for ED, most of published clinical studies (9-11, 17-28) on the topic have favored the modality with the ability of ameliorating patient's EF. It has been written in the EAU guideline as a potential first-line therapy for ED since 2013, although detailed recommendation has not been given since then. On the basis of current literatures, our meta-analysis also suggested that penile LI-ESWT probably represents an effective approach in the treatment of ED, when evaluated by using IIEF-EF and EHS. Hemodynamic improvement was measured objectively via flow mediated dilatation (FMD) technique in some well-designed RCTs (10, 28), although these data were limited and not suitable for

Table 1- Characteristics of the included studies in the systematic review.

ID	Study	Country	Sensitivity to PDE5i	No. of patients	Intervention+	End points	Outcomes
Vardi Y. 2010 (9)	Single arm	Israel	Responders	20	1; without PDE5i	A change in the IIEF-ED domain score of >5 points was used as the main measure of treatment success.	At 1 mo follow-up, 1) 20.9±5.8 vs. 13.5±4.1(baseline), p < 0.001 in IIEF-ED scores remaining unchanged at 6 mo; 2) Significant increasing in the duration of erection and penile rigidity, and significant improvement in penile endothelial function; 3) Ten men did not require any PDE5-I therapy after 6-mo follow-up.
Vardi Y. 2012 (10)	RCT	Israel	Responders	40 (treatment) vs. 20 (placebo)	1; without PDE5i	**Primary end point:** A 5-point or greater improvement in the IIEF-EF between baseline and at 4 w after treatment. **Secondary end point:** Significant increase in the IIEF subcategories. An increase in EHS from ≤2 at baseline to ≥3 at 4w after treatment, and an improvement in penile blood flow.	1) Increase in IIEF-EF score: 6.7±0.9 (LI-ESWT) vs. 3.0±1.4 (sham), p=0.0322; 2) 19 (LI-ESWT) vs. none (sham) in patients with baseline EHS ≤2 having EHS≥3 after treatment; 3) 8.2 vs. 0.1 ml /m/dl in FMD, p< 0.0001.
Gruenwald I. 2012 (11)	Single arm	Israel	Non-responders	29	1; without PDE5i at 4w after completing LI-ESWT (FU1) and use it after 8w (FU2).	Change in IIEF-ED, EHS and three parameters of penile hemodynamics and endothelial function.	1) Mean IIEF-ED scores increased from 8.8±1 (baseline) to 12.3±1 at FU1 (P = 0.035). At FU2 (on active PDE5i treatment), their IIEF-ED further increased to 18.8±1(P < 0.0001); 2) 72.4% (P < 0.0001) reached an EHS of≥3; 3) A significant improvement (P = 0.0001) in penile hemodynamics and this improvement significantly was correlating with increases in the IIEF-ED (P < 0.05).
Olsen A.B. 2014 (17)	RCT	Denmark	Responders	51 (treatment) vs. 54 (placebo)	5; without PDE5i	**Primary end point:** The treatment success threshold was set at EHS 3-4. **Secondary end point:** An increase in IIEF-EF domain score of at least 5 points.	Twenty-nine men (57%, active group) were able to have sexual intercourse without the use of medication vs. 5 men (9%, placebo group, p = 0.0001) after 5 weeks of completing LI-ESWT. But no significant result was found with the use of the IIEF-EF.

Yee C.H. 2014 (18)	RCT	China	Unknown	30 (treatment) vs. 28 (placebo)	1; whether other modality being used was unknown.	**Primary end point:** The 13-week change from baseline for IIEF-ED score after one course of Li-ESWT. **Secondary end point:** The interval change of EHS and adverse events from LI-ESWT therapy.	At 4w follow-up, 1) mean IIEF-ED score: 17.8±4.8 (LI-ESWT) vs. 15.8±6.1 (sham), p=0.156; 2) mean EHS: 2.7±0.5 (LI-ESWT) and 2.4±0.9 (sham), p = 0.163.
Bechara A. 2015 (19)	Single arm	Argentina	Non-responders	25	3; use PDE5i	Whenever patients improved on all IIEF-6, SEP2 and SEP3 and to respond positively to the GAQ at 3 months post-treatment.	60% (12/20) of the patients responded to the treatment.
Chung E. 2015 (20)	Single arm	Australia	Failed or unsatisfactory outcome with oral PDE5i and/or vasoactive agents	30	4; Whether other modality being used was unknown.	Change in IIEF-5 and EDITS scores, and overall satisfaction rate were recorded at 6 weeks and 4 months after completion of LI-ESWT.	At 6 weeks and 4m, 60% of patients reported an improvement in IIEF-5 score by 5 points, 70% improvement in EDITS Index score by > 50%. 67% of patients satisfied (scoring 4 out of 5) and 80% would recommend the therapy.
Qi T. 2015 (21)	RCT	China	Unknown	30 (LI-ESWT) vs. 30 (vacuum erectile device)	7; unknown	At 1 mo after LI-ESWT. 1) Cure: IIEF-5 score ≥ 22pts, or SEP, GAQ and EHS is 5, 2 and 4pts, respectively; 2) Relief: when IIEF-5 score<22pts, a 5-point or greater improvement in the IIEF-5, or SEP≥4pts, GAQ≥1pts, EHS≥3pts; 3) Fail: IIEF-5 score<21pts and improvement score ≤4pts , SEP<3pts, GAQ=0pts, EHS<2pts.	The number of cured patient was 14 and the number of relief was 8. Effective rate was 73% (22/30) in LI-ESWT group.
Pelayo-Nieto M. 2015 (22)	Single arm	Mexico	Unknown	15	3; unknown medication history	In IIEF-EF, success of treatment was defined as an increase of >2 points and >5 points in groups of mild and moderate, respectively. Results were evaluated by using IIEF, EHS, SEP, GAQ at 1 and 6 months after treatment.	The rate of success was 80%. 1) IIEF: 15 (11-18) pts at baseline vs. 20 (11-23) pts at 1 and 6 mo, p<0.013; 2) EHS: 2 (2-3) pts at baseline vs. 4 (2-4) pts at 1 mo, p<0.01; 3) SEP3: 7 patients at baseline vs. 12 patients at 1 mo, p=0.0013.
Reisman Y. 2015 (23)	Single arm	Netherlands, et al	Responders and Non-responders	58	2; without PDE5i until 1 month post treatments.	**Primary end point:** An increase of IIEF-EF score from baseline to the third follow-up (6m post treatment) according to the initial ED severity: >2-point increase for mild symptoms; >5 points for moderate symptoms; and >7 points for severe symptoms.	47(81%) had a successful treatment.

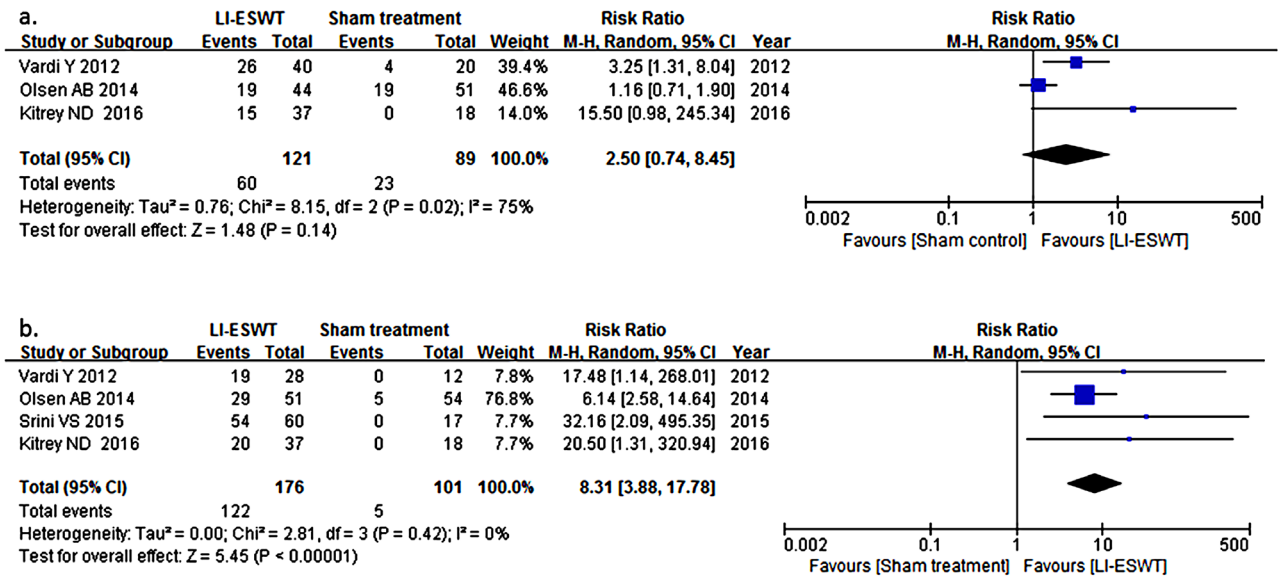
Ruffo A. 2015 (24)	Single arm	Italy	Non-responders	31	2; without PDE5i during treatment.	**Primary end point:** An increase of IIEF-EF score from baseline to 1 and 3 months after LI-ESWT. **Secondary end point:** Improvement in SEP2, 3 and GAQ.	1) IIEF-EF: 16.54±6.35 (baseline) vs. 21.13±6.31 (1 mo), 21.03±6.38 (3 mo). 2) SEP2 (yes): 61% (baseline) vs. 86% (1mo), 89% (3 mo). 3) SEP3 (yes): 32% (baseline) vs. 58% (1mo), 62% (3 mo); all $p<0.05$. 4) GAQ: at 1 and 3 mo, difference is not significant.
Srini V.S. 2015 (25)	RCT	India	Responders	60 (treatment) vs. 17 (placebo)	1; without PDE5i	**Primary end point:** ≥5 points improvement in the IIEF-EF between baseline and 1 mo (also 12 mo). **Secondary end point:** Significant increase in the CGIC and an increase in EHS from ≤2 at baseline to ≥ 3 at FU1 and FU5.	1) Increase in IIEF-EF: at 1 mo, 12.5 pts in LI-ESWT group vs. 1.4 pts in control group; at 12 mo, 8.7 pts in LI-ESWT group vs. NA in control group. 2) Effective rate in EHS: 90% (1m), 83% (12m) vs. none (placebo group). 3) Data about CGIC were not provided.
Hisasue S. 2016 (26)	Single arm	Japan	Unknown	56	1; use PDE5i on-demand after LI-ESWT.	Assessing the patients with SHIM, EHS, and MPCC at 1, 3 and 6 months after the final LI-SWT.	64.2% patients showed improvement in SHIM scores, and 57.1% patients achieved an EHS 3 or 4 without PDE5i within 6 months after LI-SWT. MPCC showed significant improvement in 64% patients from 1 month after treatment, maintaining it until 6 months.
Frey A. 2016 (27)	Single arm	Denmark	Postprostatectomy ED with unknown sensitivity to PDE5i	16	6; use of erectogenic aids	**Primary end point:** Changes in IIEF-5 scores. **Secondary end point:** A global satisfaction question ranging from “very dissatisfied” to “very satisfied”.	The median change in IIEF-5 scores was +3.5 (range -1 to 8; p=0.0049) and +1 (range -3 to 14; p=0.046); 11 and 7 patients reported being either satisfied or very satisfied at 1 mo follow up and 1 year follow up, respectively.
Kitrey N.D. 2016 (28)	RCT	Israel	Non-responders	37 (treatment) vs. 18 (placebo)	1; use PDE5i when evaluating results.	**Main outcomes:** 1) EHS was 3 or greater; 2) A change in IIEF-EF was greater than 7 points for severe ED and 5 points for moderate ED. **Secondary outcome:** FMD penile time-flow AUC as an indicator of penile endothelial function and the CGIC questionnaire. They were evaluated at 1 month after the end of treatment.	1) 54.1% (LIST) vs. none (sham) had EHS=3, $p<0.0001$; 2) in IIEF-EF, 40.5% (LIST) vs. none (sham), p=0.001; 3) 56.3% of the patients treated with active LIST after sham treatment achieved an erection hard enough for penetration ($p<0.005$); 4) The change in penile hemodynamic parameters was statistically significant; 5) According to CGIC, 56.8% of patients (LIST) vs. 27.8% (sham)(p=0.051) reported clinical improvement.

+ Number in the column of intervention represents different protocol of LI-ESWT and is consistent with the ID in table 2.

Table 2-The reported protocols of LI-ESWT in included studies.

ID	Device	Energy density	Frequency	Distribution of energy	Cycle of treatment
1	Omnispec ED1000 (Medispec Ltd., Yehud, Israel / Germantown, MD, USA)	1500 shocks of 0.09mJ/mm^2	120 shocks /min	300 shocks were delivered at each of the 5 treatment points (the distal, mid and proximal penile shaft, and to the left and right crura).	Nine-week treatment period: two LI-ESWT sessions per week for 3 weeks, repeated after a 3-week no treatment interval / twice a week for 4 weeks
2	Renova ®(Direx Group LTD)	3600 shocks of 0.09mJ/mm^2	a maximum rate of 300 shocks/ min	900 shocks were delivered at each of the 4 treatment points (left and right corpus cavernosum, left and right crus).	One session per week for 4 weeks.
3	Renova ®	5000 shocks of 0.09mJ/mm^2	300 shocks/min	900 shocks at left and right corpus cavernosum; 1600 shocks at left and right crus.	One session per week for 4 weeks.
4	Duolith® SD1 ultra (Storz Medical AG, Tägerwilen, Switzerland)	3000 shocks of 0.25mJ/mm^2	6Hz	Distal penis(1000 shocks), base of penis (1000 shocks), and corporal bodies on perineum(500 shocks to each crura)	Twice weekly for 6 weeks
5	Duolith® SD1 ultra (Storz Medical AG, Tägerwilen, Switzerland)	3000 shocks of 0.15mJ/mm^2	5Hz	Six treatment sites (distal, central and proximal part of each corpus cavernosum)	One session per week for 5 weeks.
6	Duolith® SD1 T-Top (Storz Medical, Tägerwilen, Switzerland)	1000 shocks of 20mJ/ mm^2,15mJ/ mm^2 and12mJ/ mm^2	5Hz	Shocks of 20mJ/mm^2, 15mJ/mm^2, 12mJ/mm^2 were applied to the root of penis, to the shaft, and at a few millimeters proximal to the glans, respectively.	Twice sessions every other week for six weeks
7	LGT-2500B(Long Zhi-jie Ltd, Guangzhou, China)	1500 shocks of 1bar	2Hz	300 shocks were delivered at each of the 5 treatment points (the distal, mid and proximal penile shaft, and the left and right crura).	Twice a week for 4 weeks

Figure 2 - Forest plots of random effects model of risk ratio of effective treatment of LI-ESWT for ED in terms of International Index of Erectile Function-Erectile Function Domain (a) and Erectile Hardness Score (b).

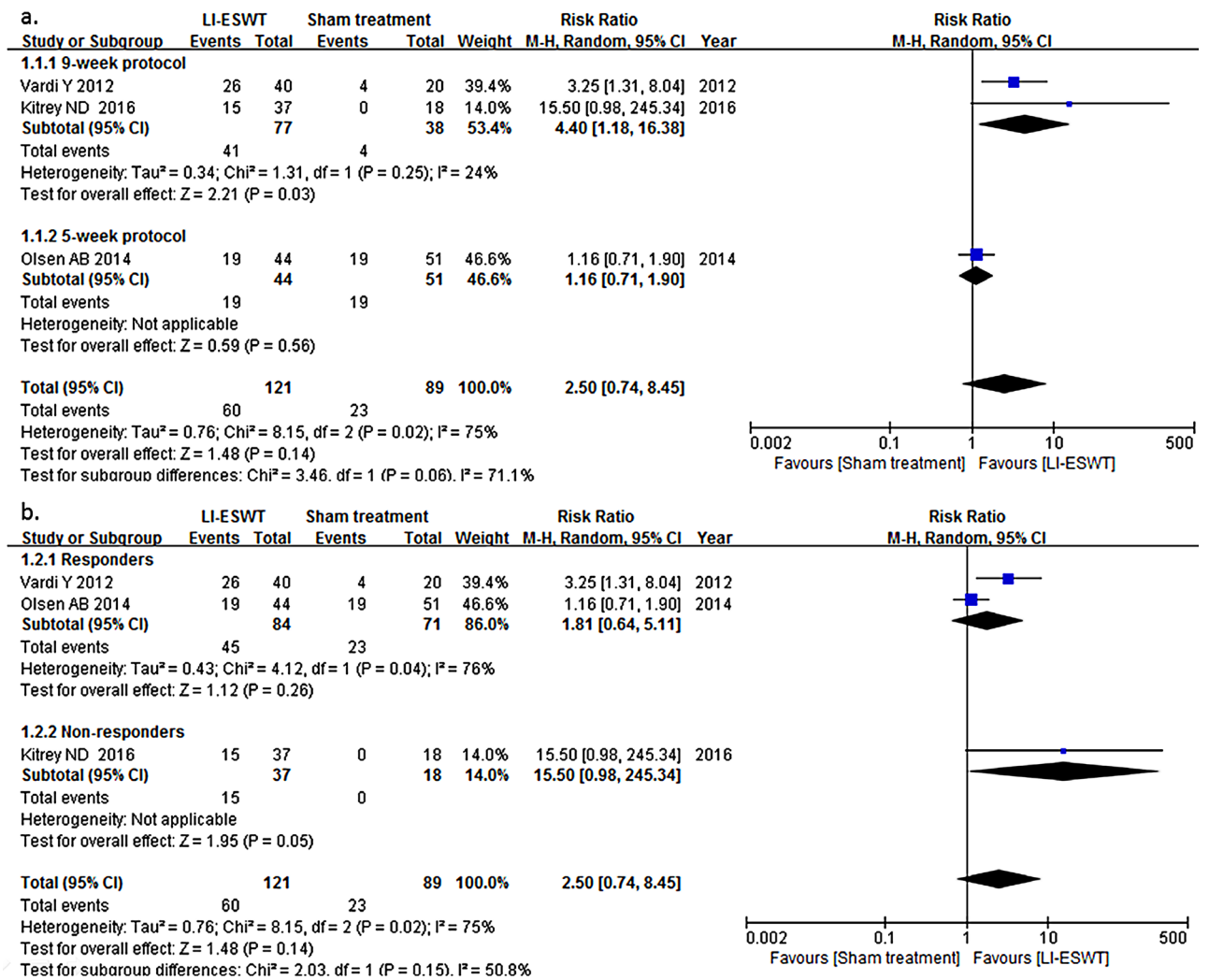


cumulative analysis. In preclinical researches, it was revealed that LI-ESWT could induce angiogenesis, nerve regeneration, progenitor cell recruitment, endothelial functional improvement, tissue remodeling reverse, and microenviroment improvement to improve EF (29, 30). In addition, there was no adverse side effect reported. Overall, current evidences support LI-ESWT as a potential choice for ED clinically and preclinically.

Recently, two systematic reviews and meta-analyses (12, 13) on the topic were published and their conclusions were similar to ours. However, there were some limitations in their study designs. The study by Lu et al. (12) included seven RCTs on LI-ESWT for organic ED and ED associated with PD and CPP. Heterogeneity was evident pathologically and clinically among the three types of ED (31). Furthermore, a recent meta-analysis proved that PD-associated ED could not benefit from extracorporeal shockwave therapy (32). Therefore, the application possibility of cumulative results was reduced and subgroup analysis was not convincing enough when explaining the exact source of heterogeneity based on their inclusion criteria. It is more reasonable to separate different ED according to pathogenesis when the efficacy of LI-ESWT was evaluated. The other study by Angulo et al. (13) included single arm trials with evidence level 2, inevitably lowering the quality of their meta-analysis. Our meta-analysis focused on RCTs regarding organic ED with similar inclusion/exclusion criteria and excluded studies on CPP- and PD-associated disease. In our opinion, our design is the most reasonable among the three meta-analyses.

Different protocols of LI-ESWT likely influence its therapeutic effect on ED, and more frequent treatment and longer treatment course seems to be more effective, although there is no comparative trial to define the best protocol. Our analysis revealed that 9-week protocol with 12 sessions, which was proposed by Vardi et al. (9) and used most frequently, was more effective than 5-week protocol with 5 sessions. In a study evaluating additional shock wave therapy, it was demonstrated that "second round" LI-ESWT was essential for patients with poor response to the previous treatment (33). Nevertheless, shorter LI-ESWT protocols were also investigated because repeated visits to hospital and long duration of treatment could compromise patient's compliance

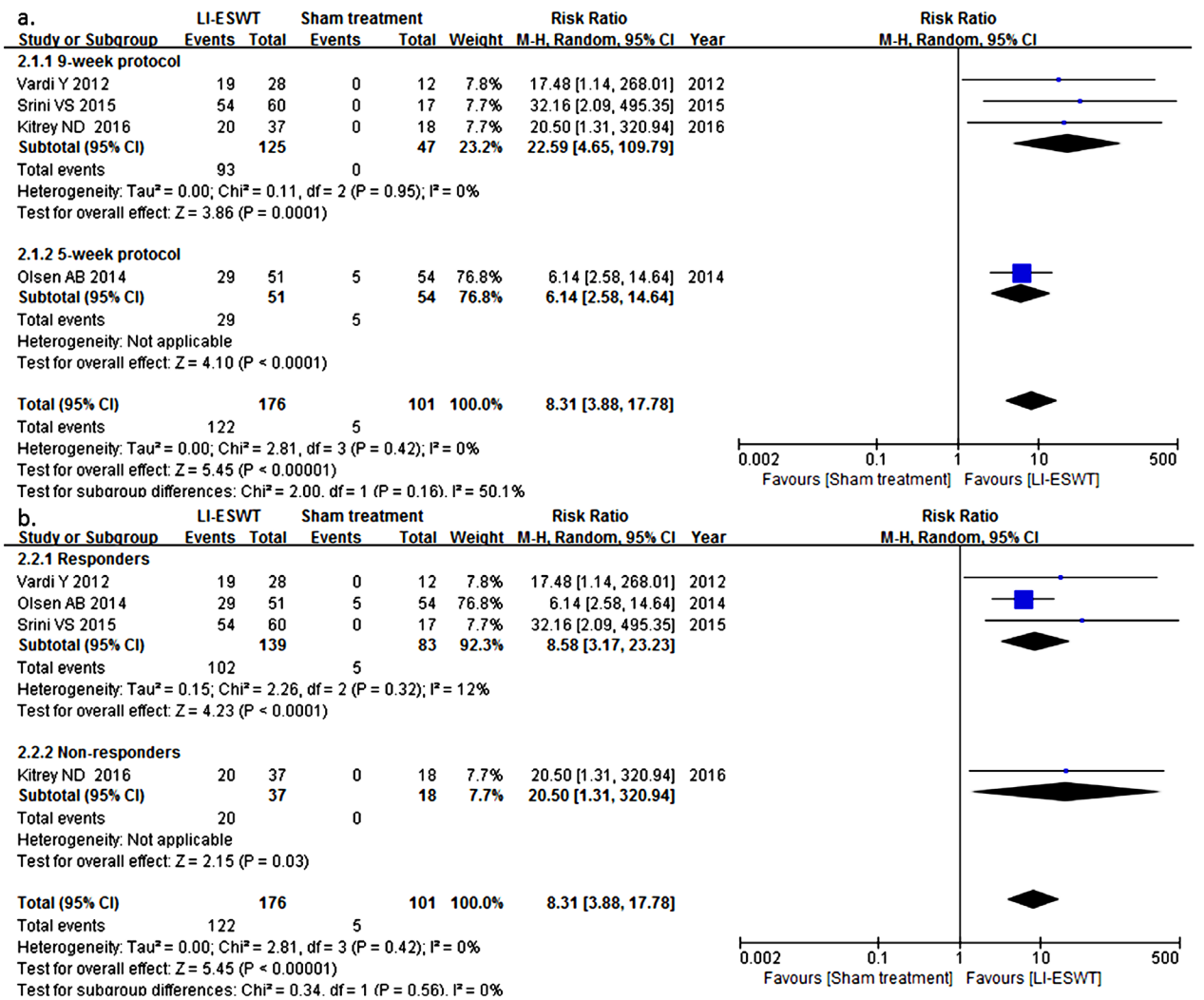
Figure 3 - Relationship of clinical variables and treatment procedures in International Index of Erectile Function-Erectile Function Domain (IIEF-EF). (a) The studies using the 9-week protocol of LI-ESWT more possibly contributed to effective treatment (risk ratio [RR]: 4.40; 95% confidence interval [CI]: 1.18-16.38; p=0.25), than using 5-week protocol (RR: 1.16; 95% CI: 0.71-1.90), although it did not reach statistical significance (p=0.06). (b) LI-ESWT for PDE5I non-responders more possibly contributed to effective treatment (RR: 15.50; 95% CI: 0.98-245.34), than for responders (RR: 1.81; 95% CI: 0.64-5.11; p = 0.04), but it did not reach statistical significance neither (p=0.15).



(18, 25), and favorable results of short protocols were also proven (22-24). Therefore, additional comparative studies among different protocols are demanded to create an optimal protocol.

Energy density (2) and dose (30) of shock wave therapy are considered to be relative to physiological effect. As regard to penile tissue, high energy level causes apoptosis and collagenization of corporal smooth muscle with consequently deteriorating EF (34). When low energy shock wave therapy was conducted in the treatment of diabetic ED, EF was significantly improved with increased smooth muscle and endothelial content. Meanwhile, it was proven that improvement was more significant in the 300-shock group than in the 100- and 200-shock groups (30). The cumulative analysis revealed that 9-week protocol with energy density of 0.09mJ/mm^2 and 1500 pulses

Figure 4 – Relationship of clinical variables and treatment procedures in the Erection Hardness Score (EHS). (a) The studies using the 9-week protocol of LI-ESWT more possibly contributed to effective treatment (risk ratio [RR]: 22.59; 95% confidence interval [CI]: 4.65-109.79; p=0.95), than using 5-week protocol (RR: 6.14; 95% CI: 2.58-14.64), although it did not reach statistical significance (p=0.16). (b) LI-ESWT for PDE5I non-responders more possibly contributed to effective treatment (RR: 20.50; 95% CI:1.31-320.94), than for responders (RR: 8.58; 95% CI: 3.17-23.23; p=0.32), but it did not reach statistical significance (p=0.56). (c) The outcome of studies with consistent risk factor of ED between treatment and control group is lower (RR: 7.41; 95% CI: 3.36-16.38; p=0.52), than that with inconsistent risk factors (RR: 32.16; 95% CI: 2.09-495.35), but it did not reach statistical significance (p=0.31).



(300 for each treatment site) seemed to be superior to 5-week protocol with energy density of 0.15mJ/mm² and 3000 pulses (500 for each site). However, an optimal energy density and number of pulses could not be further defined separately because of limited literature. In fact, no agreement exists on optimal energy and dose range for LI-ESWT and current literature reveal that energy density and dose applied in the field of ED with promising effect usually range from 0.09mJ/mm² to 0.25mJ/mm² and 1500 to 5000 times (300-1600 shocks for each site) respectively. Direct comparative trials and more precise preclinical researches are essential to make optimal parameters.

Compared to second- and third-line therapy for ED, intracavernosal injection of

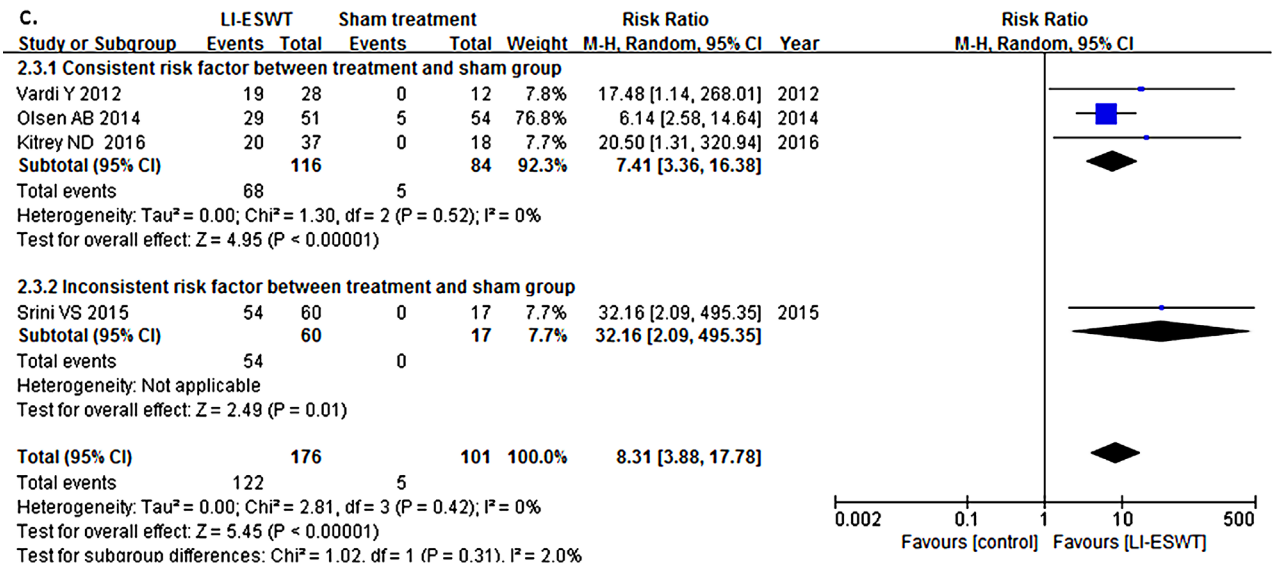


Table 3 - Baseline characteristics of study population in 4 RCTs for meta-analysis.

Study	Age[median(years), range]	EHS	IIEF	Diabetes	Hypertension	Heart disease	Smoking	Alcohol	Lipids
Vardi 2012 (10)	58 (27-72) vs. 57 (35-77)#	≤2	IIEF-EF < 19	30 vs. 30%#	ND	20 vs. 10%#	ND	NA	ND
Olsen 2014 (17)	59 (41-80) vs. 60(37-79)	< 2	IIEF-EF < 20	18 vs. 13%#	33 vs. 37%#	4 vs. 11%#	ND	ND	NA
Srini 2015 (25)	NA	≤2	IIEF-EF < 18	ND	22.11 vs. 5% (p=0.0219)	3.16 vs. 25% (p=0.0003)	ND	23.16 vs. 47.5% (p=0.0074)	20 vs. 47.5% (p=0.0017)
Kitrey 2016 (28)	60 (28-78) vs. 64 (29-81)#	≤2	IIEF-EF ≤ 12	56.8 vs. 72.2%#	ND	48.6 vs. 38.9%#	ND	NA	ND

The former is a LI-ESWT group and the latter is a controlled group in the blank. **#:** No significant differences between groups. **ND:** no significant differences. **NA:** not applicable.

vasoactive drugs and surgical implantation of penile prostheses, LI-ESWT is noninvasive and rehabilitative. Severe ED patients who didn't respond to the first-line therapy of PDE5is could benefit from the treatment (11, 19, 20, 28). Our analysis revealed that non-responders, moderate to severe EDs with baseline IIEF-EF ≤12, appeared to have more possibility to benefit from LI-ESWT than responders with baseline IIEF-EF <20. Interestingly, the only RCT (18) with low risk of bias suggested that although improvement in IIEF-EF in the LI-ESWT group didn't reach significant difference compared to the sham group as a whole, the former's elevated IIEF-EF score was significantly higher than the latter's in subgroup analysis of severe ED patients with Sexual Health Inventory for Men (SHIM) score 5-7. Nevertheless, underlying association between the severity of ED and therapeutic impact of LI-ESWT is not clear and requires further investigation.

In addition to baseline EF, other patient characteristics, such as age, DM, hypertension, heart disease, smoking and/or alcohol consumption, and lipid level, potentially influence the effect of LI-ESWT on ED and thus different proportion of age and comorbidities between the treatment and control group, among different RCTs, likely commits the result of a RCT and meta-analysis. Almost

all included RCTs provided participant's information regarding age and comorbidities, but there was no further investigation to determine the impact of age and comorbidities on the effect of LI-ESWT. In the study by Srini et al. (25), comorbidities were inconsistent between the treatment and control group with higher incidence in the latter. Although RR appeared to be far higher in the Srini's study than the other three studies (10, 17, 28) having consistent comorbidities between the treatment and control group, our analysis still cannot answer the question on whether comorbidities are associated with the effectiveness of LI-ESWT because the difference did not reach statistical significance. Therefore, RCTs with stratification of age and comorbidities are needed to determine the impact of these factors on the effect of LI-ESWT for patients with ED.

Short-term effective treatment defined as "participant's score increased by at least 5 points more than baseline in IIEF-EF, or a patient (baseline EHS ≤2 pts) with EHS ≥3 pts at about 1 month after LI-ESWT" was accepted because most participants and RCTs could be included for meta-analysis. Data about the change of IIEF-EF after treatment in the manner of mean and standard deviation, which were used in the other two meta-analyses, were available in only one (18) of the five RCTs (35). The minimal clinically important difference (MCID) of IIEF-EF is considered to be ideal to assess the true clinical efficacy of an intervention (36) and has been gradually used in the clinical trials about LI-ESWT for ED (23, 28). With more RCTs being published, meta-analysis on the topic using MCID as evaluation criteria is essential in the future.

The initial and optimal functional time of LI-ESWT is still unclear. The effect of LI--ESWT appears to be time-dependent in clinical practice. In the studies using 9-week protocol, the majority of patients felt improvement in EF initially between the sixth and eighth session (10, 11). The efficacy reached peak at 4-6 weeks after all sessions, then declined (17, 20, 25). For about half of the patients, the positive effect would gradually wane over two years, most of whom were severe and diabetic ED patients (37). With aid of PDE5i, however, the peak effect could be showed at 6 months (23, 26). In the laboratory, it was identified previously that shockwave-induced neovascularization was evident at 4 weeks after the treatment and persisted for 12 weeks with angiogenesis-related factors beginning to rise in 1 week, keeping high for 8 weeks, and then decline at 12 weeks (3, 38). Based on aforementioned clinical and preclinical results, it is rational to evaluate the short-term effect on ED at about one month after LI-ESWT in the review.

There are few evidences on LI-ESWT for ED other than vasculogenic type. Nerve sparing prostatectomy ED could benefit from the method (27), while patients suffering from non-sparing nerve surgery probably not (20, 39). Nonetheless, it was revealed that LI-ESWT alone or combined with human adipose-derived stem cells (h-ADSCs) seemed to have ability to promote erectile function recovery in a rat model of ED with bilateral pelvic nerve injury (40, 41).

There are some limitations in this study. First, detailed individual patient data were not available from all the studies. In the review, not all included studies were used for meta-analysis due to heterogeneous endpoints. Nevertheless, the non-quantitative analyzed studies were listed as describable summary to support the use of LI-ESWT. Second, there was substantial variability among the studies, e.g., the severity of ED, age, comorbidity, device, energy density and distribution, frequency of treatment, interval between sessions, and aid of medication. These are confounding factors which likely influence efficacy and should be considered when defining optimal modality strategy. Third, although the confidence interval of RR exceeds the nullity line when efficacy was evaluated by IIEF-EF, the effective treatments were far more in the LI-ESWT group than in the controlled group in the Vardi's (10) and Kitrey's studies (28). After excluding the study by Olsen et al. (17) with obviously influencing stability of cumulative result, RR was 4.40 (95%CI: 1.18-16.38). The authors (17) explained that inconsistent results between using IIEF-EF and EHS

were caused by a part of patients having some problems of understanding the questionnaires of IIEF-EF. Fourth, the quality and number of the eligible studies were relatively limited and none of the 4 RCT was elevated as low risk of bias. Meta-analysis on the basis of these RCTs likely influenced its reliability as level 1a evidence. Fifth, publication bias existed because of four factors: 1) only English and Chinese literatures were included; 2) other language, unpublished studies and conference abstracts were excluded; 3) inflated estimates by a flawed methodological design in smaller studies; 4) and/or a lack of publication of small trials with opposite outcomes. Sixth, objective measured results, and middle- and long-term effects were unavailable in our meta-analysis due to lack of sufficient data.

CONCLUSIONS

In summary, LI-ESWT, as a noninvasive treatment, with potential short-term therapeutic effect on patients with organic ED irrespective of sensitivity to PDE5is. Owing to the limited number and quality of the studies, more large--scale, well-designed and long-term follow-up time studies are needed to confirm our analysis.

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Zi-jun Zou and Liang-you Tang contributed equally to this work

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Update on complications of synthetic suburethral slings

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ABSTRACT

Synthetic suburethral slings have become the most widely used technique for the surgical treatment of stress urinary incontinence. Despite its high success rates, significant complications have been reported including bleeding, urethral or bladder injury, urethral or bladder mesh erosion, intestinal perforation, vaginal extrusion of mesh, urinary tract infection, pain, urinary urgency and bladder outlet obstruction. Recent warnings from important regulatory agencies worldwide concerning safety issues of the use of mesh for urogynecological reconstruction have had a strong impact on patients as well as surgeons and manufacturers. In this paper, we reviewed the literature regarding surgical morbidity associated with synthetic suburethral slings.

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Urinary Incontinence; Polypropylenes; Postoperative Complications

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INTRODUCTION

Stress urinary incontinence (SUI) is defined as the involuntary leakage of urine with effort or exertion, such as physical exercise, sneezing or coughing (1). Approximately 50% of all women experience SUI symptoms (1), and many of these women are sufficiently bothered by their symptoms to seek treatment from a physician. Pelvic floor muscle exercises and other nonsurgical treatments can be effective therapies, but many women choose to undergo surgery to treat their SUI symptoms. Suburethral synthetic sling (SSS) placement is the most common surgery currently performed for SUI and extensive data support their use for the treatment of female SUI. Compared to other surgical techniques, the advantages include shorter operative time/anesthetic need, reduced surgical pain and hospitalization time, and lower incidence of postoperative voiding dysfunction (2-10), The technique is based on the placement of a thin tape of synthetic mesh under the middle urethra which is passed through the retropubic space with a passing needle and exits the abdominal wall just above the pubis (Figure-1). It was introduced by Petros and Ulmsten in 1996 (11). By 2007, over 1.200.000 SSS had been performed worldwide and the numbers continue to increase exponentially (12, 13). A significant modification of the technique was the use of a transobturator route for the placement of the synthetic tape which was introduced by Delorme in 2001 (Figure-2) (14). The purpose of that was to eliminate the risks of complications associated with the passage of a needle in the retropubic space.

Figure 1 - Haematoma of the right thigh (arrow) on postoperative day 3 of a transobturator SSS, with spontaneous resolution.

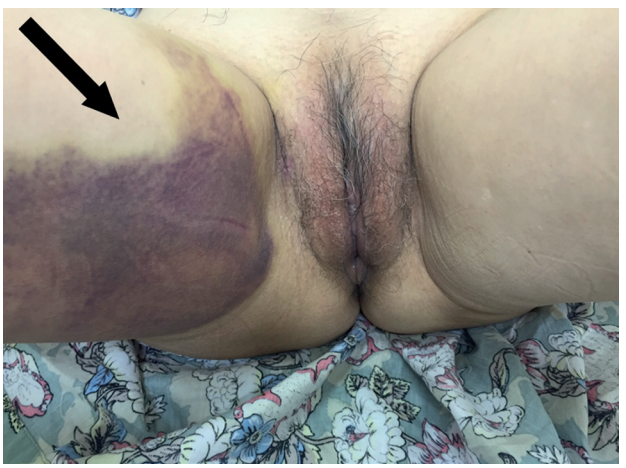
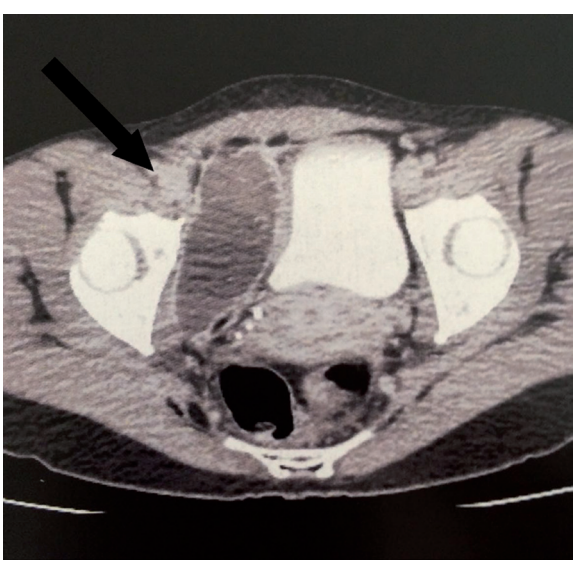


Figure 2 - CT scan in the first postoperative day following a retropubic SSS demonstrates large pelvic hematoma (arrow) compressing the bladder laterally.



In the American Urological Association's opinion, any restriction of the use of SSS would be a disservice to women who choose surgical correction of SUI (15). However, despite the high success rates of the technique, a growing number of complications and adverse effects have been reported (9, 16-26). Recent reports indicate complication rates of 4.3% to 75% for the retropubic slings (2, 18) and 10.5% to 31.3% for the transobturator ones (Table-1) (27-30).

Complications associated to SSS can be classified as immediate or late. Immediate complications include injuries during surgery as well as urinary retention and postoperative infections. Lesions may involve blood vessels, bladder, bowel, urethra, and nerves. Late complications occur weeks or months after surgery and include bladder outlet obstruction, urgency or urge-incontinence, recurrent urinary infections, erosion of the synthetic mesh to the urethra or bladder and extrusion of the tape to the vagina (31).

In a recent communication, the United States Food and Drug Administration (FDA) released an update on the safety and effectiveness of transvaginal placement of mesh (32). Although it was mainly directed to the placement of mesh for the treatment of pelvic organ prolapse, the use of mesh for the treatment of SUI was also included. The communication informed that mesh complications are not rare in transvaginal surgeries and may include serious adverse events (32). As a consequence, meshes from important manufacturers have been removed from the market. Moreover, women have been increasingly worried about the safety of SSS since they do not properly understand the differences between using mesh to treat pelvic organ prolapse as opposed to SUI.

MATERIALS AND METHODS

There is a large body of evidence and review articles evaluating the complications of SSS. The goal of the current study was not to conduct a complete or systematic review or meta-analysis of the topic, but rather to perform a comprehensive overview based on published original and review articles augmented by a literature search. We performed a MEDLINE literature review using the "MeSH" (Medical Subject Heading) and "free text" protocols. The MeSH search was conducted with the following terms: "suburethral sling", "surgical tape", "urinary incontinence", "female". Multiple "free text" searches were performed using the following terms individually through all fields of the records: "sling", "midurethral sling", "transvaginal tape", "transobturator tape", "tension-free tape". The search was restricted to the English language.

Table 1 - Postoperative complication rates after syntethic suburethral sling surgery.

Complication	Retropubic	Transobturatory
Bleeding	0.7 to 8% [27, 29, 45, 81, 83]	0-2% [27, 29, 36, 37]
Bladder Injury	0.7 to 24% [28, 47]	0-15% (12, 29, 48-50) [12, 29, 48-50]
Urethral Injury	0.07 to 0.2% [44, 45]	0.1 to 2.5% [36, 51]
Urethral Erosion	0.03-0.8% [45, 52]	0.03 to 0.8% [45, 52]
Intestinal Injury	0.03 to 0.7% [18, 63-65]	0%
Vaginal Erosion	0-1.5% [28, 29]	0 to 10.9% [27, 29, 66, 67]
UTI	7.4 to 13% [4, 27, 28, 37]	7.4 to 13% [4, 27, 28, 37]
Pain	4% [75]	9.4% [75]
Urgency "de novo"	0,2% -25% [28, 81, 82]	0 to 15.6% [27, 28, 83]
Bladder Outlet Obstruction	6 to 18.3% [12, 24, 26, 75, 94]	3.0-11% [12, 24, 26, 75, 94]
Urinary Retention	4.1% -19.5% [2, 28, 29]	2.7% -11% [28, 29, 37]

We divided the results in different topics regarding complications of synthetic suburethral slings, including bleeding, bladder and urethral injuries, bladder and urethral erosions, bowel injury, vaginal extrusion, urinary tract infection, postoperative pain, de novo urgency, urinary retention and bladder outlet obstruction.

RESULTS

Bleeding

The difficulty in reporting bleeding rates begins by defining this complication. It may vary from a simple hemorrhage during periurethral dissection that is self-limited and easily contained by compression to major vascular injuries with hemodynamic instability requiring aggressive treatment. The reports range from vaginal haematomas (Figure-1) to large vessel injuries with catastrophic outcomes (33). Insignificant haematomas may be common postoperatively after retropubic slings, and are occasionally found in 25% of patients undergoing magnetic resonance imaging (34). Haematomas of less than 100mL are rarely symptomatic, while the larger ones frequently cause abdominal discomfort (35).

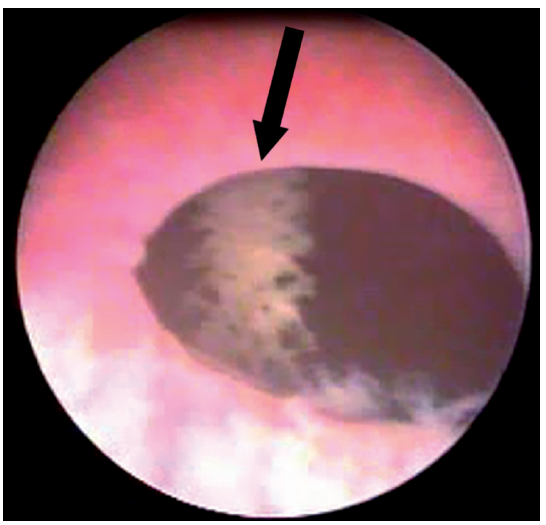
Overall, bleeding rates vary from 0.7% to 8% for the retropubic slings and from 0% to 2% for the transobturator slings (24, 27, 36). Large series (28, 37-39) and metanalyses (24, 33, 40) have shown a significant lower risk of hemorrhagic complications with the transobturator technique. Deng et al. (41), reviewing twenty-eight series from 2001 to 2005, identified that 0.1% of the patients required blood transfusion.

Large haematomas in the retropubic space usually require surgical drainage (Figure-2), since aspiration appears to be ineffective (2, 35, 42). Injuries to major vessels during surgery require immediate surgical exploration with repair, ligation or reconstruction when possible (2). However, intraoperative bleeding is usually mild to moderate and under these circumstances transvaginal exploration is frequently ineffective and should be avoided. Since most of these cases are effectively managed by vaginal packing, the surgeon facing this complication should try and complete the procedure as fast as he can. Rarely, endovascular embolization has been used for the treatment of hemorrhagic complications of SSS surgery (43).

Bladder and urethral injuries

Bladder injury during SSS surgery occurs in 2.7 to 6% of the patients (44, 45). Perforation by the needle is generally the cause of the lesion, which is thus more frequent at the lateral bladder walls (Figure-3). Rarely, the lesion may occur at the time of vaginal dissection and, in this circumstance, the bladder base is affected and the diagnosis is made by the observation of urine drainage at the injury site.

Figure 3 - Cystoscopic view of sling mesh (arrow) in the bladder after a retropubic sling surgery.



Risk factors for bladder injury are previous anti-incontinence surgery, previous surgeries in the retropubic space and surgeon inexperience (46). For retropubic slings, the incidence ranges from 0.7 to 24% (28, 47), while for transobturator slings, the reported rates vary from 0% to 15% (12, 48-50). Most bladder perforations, if recognized during surgery, are treated by repositioning the needle and maintaining bladder drainage with a Foley catheter for 2-7 days (51).

Intraoperative urethral injury occurs in 0.07% to 0.2% for retropubic slings (44, 45) and 0.1% to 2.5% for transobturator (36, 52). It usually occurs during vaginal dissection of the paraurethral space and the diagnosis is made by visualization of the Foley catheter. However, inadvertent needle passage is also a possible cause. In these cases, the diagnosis is made during urethrocystoscopy. The lesion must be repaired immediately and placement of a synthetic sling at the same surgery is contraindicated (15). Prolonged bladder drainage with a Foley catheter (7-14 days) is recommended (51, 53, 54).

Bladder and urethral erosion

Erosion is the extrusion of synthetic mesh to the lumen of the bladder or urethra, which occurs in the late postoperative period. Urethral erosion rates vary from 0.03% to 0.8% (45, 55). Typically, patients with bladder or urethral erosion present filling lower urinary tract symptoms such as urgency and urinary frequency, pelvic pain, dyspareunia, recurrent urinary tract infections, voiding symptoms and microscopic hematuria. Some cases with late diagnosis, may in fact be secondary to urethral or bladder injury during surgery that was overlooked. The eroded mesh may be calcified and present as a fixed bladder stone (Figure-4a). These patients may remain asymptomatic for several months, or present mild symptoms that increase gradually. The diagnosis of urethral or bladder erosion is confirmed by urethrocystoscopy (Figure-4b).

Late urethral erosion is caused by excessive tension of the sling under the urethra, leading to progressive atrophy and subsequent erosion. Hypoestrogenism, prior vaginal or

Figure 4a - Pelvic CT scan shows calcified sling tape (arrow) eroding the bladder wall at the left side 2 years after a retropubic SSS.

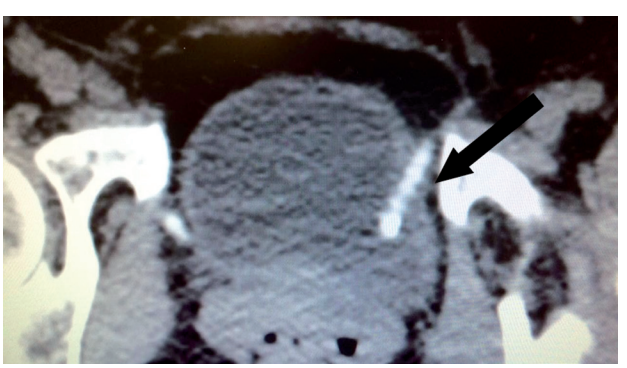
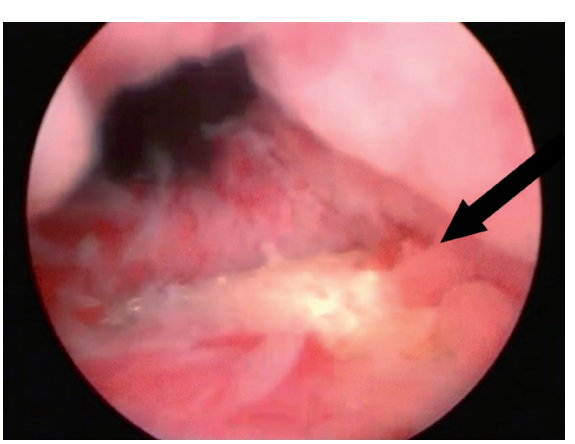
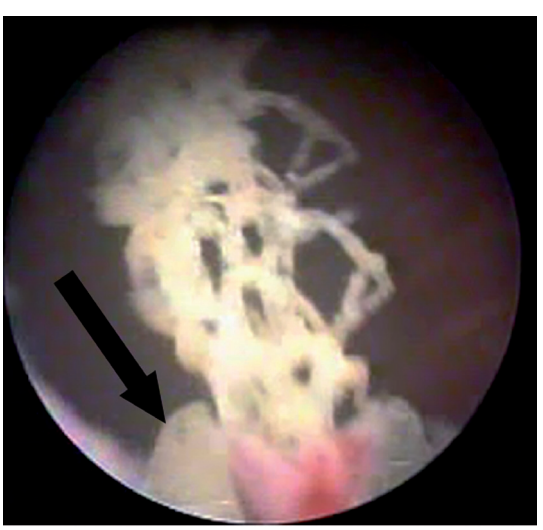


Figure 4b - Mesh erosion in the urethra found in urethrocystoscopy two years after SSS (arrow).



urethral surgery and pelvic radiation are conditions that determine worse urethral vitality and may contribute to a higher risk of erosion (55, 56). Treatment requires mesh removal and urethral repair (56). Total removal is usually performed by vaginal surgery. Laparoscopy may be used in selected cases of retropubic slings (57). Transvaginal partial removal is indicated for small erosions with little tissue loss and absence of infection. An endoscopic approach has also been proposed, consisting in removing the eroded mesh transurethrally and keeping a urethral catheter for 7-14 days (Figure-5) (58-60). In cases requiring urethral reconstruction with extensive tissue mobilization and long suture lines, a Martius flap should be associated to minimize the risk of a fistula (61, 62).

Figure 5 - Endoscopic treatment of mesh erosion in the bladder using laparoscopic scissors (arrow).



Voiding dysfunction after mesh removal is common. Starkman et al. evaluated 19 patients and reported that only 4 (21%) became completely asymptomatic after mesh removal. SUI recurred in 8 (42%) patients and only 9 (47%) considered themselves to be completely dry after surgery (63). Velemir et al. reviewed 17 cases of urethral erosion and obtained only 35.3% of complete urinary continence after transvaginal mesh removal (64). The same authors obtained a continence rate of 57.1% after endoscopic mesh removal. These results may reflect a milder severity of the erosion in patients who underwent endoscopic treatment. According to all authors, the simultaneous placement of a new SSS is contraindicated (15, 65). An autologous pubovaginal sling, however, may be considered (56, 63).

Bowel injury

Bowel perforation is a life-threatening complication that has only been described with the retropubic technique. Few cases have been reported, with an estimated incidence of 0.03% to 0.7% (18, 66-68). The most important risk factor is previous pelvic surgery, which supposedly increases the risk of bowel fixation in the retropubic area. Clinical presentation may include abdominal pain, fever, malaise, leukocytosis, sepsis and bowel fluid discharge from the surgical wound.

Treatment consists of exploratory laparotomy for bowel repair and sling removal. A temporary bowel diversion may be warranted in cases with later diagnosis and bad tissue quality in which a primary repair is considered of high risk. It should be noted that the fact that the transobturator technique avoids the retropubic space makes this serious complication virtually impossible.

Vaginal extrusion

Vaginal extrusion rates vary from 0% to 1.5% for the retropubic slings (28, 29) and from 0% to 10.9% for the transobturator (27, 69, 70). Regardless of the route used, the risk factors include inadequate closure of the vaginal incision, atrophic vaginal mucosa, local infection and unrecognized vaginal lesions during needle passage (17).

Vaginal extrusion (Figure-6) rates depend greatly on the type of synthetic mesh used. Polypropylene monofilament, malleable and macropore meshes are the standard meshes used in contemporary sling surgeries. They have been associated with lower extrusion rates in comparison to other meshes that were used in the past (71, 72). Those characteristics promote better tissue incorporation and facilitate local immune reaction reducing the risk of local infection. When extrusion is associated with infection,

Figure 6 - Vaginal extrusion (arrow) of mesh at the left anterolateral vaginal wall.

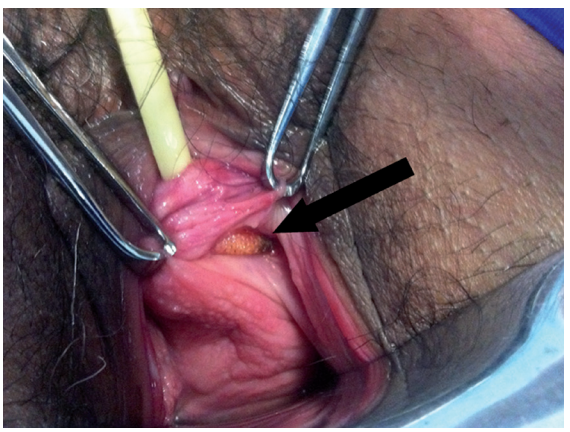
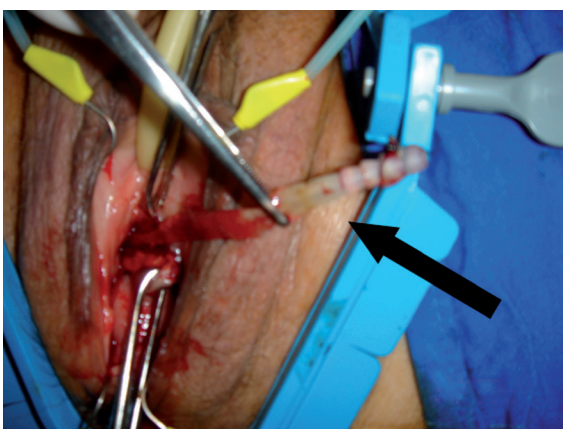


Figure 7 - Transvaginal removal of an infected and extruded sling mesh (arrow).



patients generally present with local pain, vaginal discharge and dyspareunia. The extruded mesh may be identified during vaginal examination. This presentation usually occurs within the first postoperative months and must be distinguished from that which occurs early and, in general, is caused by wound dehiscence, inadequate closure or inadvertent needle passage in the vaginal wall that remained unrecognized during surgery (66, 73, 74).

If the extrusion is small and not associated with infection, conservative treatment and sexual abstinence may be adopted in order to permit second intention healing, with resolution in few weeks (75). Topical estrogen appears to improve the outcomes of conservative treatment (72). Authors recommend surgical removal of the eroded mesh segment if conservative treatment failed and when local infection is suspected (62, 76). This technique is accompanied by high resolution rates and the chance of recurrent stress urinary incontinence is very low. Re-intervention for total mesh removal should be considered in cases of recurrence after the initial procedure (23). Erosions presenting with thorough purulent vaginal discharge, extensive vaginal inflammation or signs of systemic infection require aggressive treatment with total mesh removal (Figure-7). In this situation, the rates of recurrent stress urinary incontinence are approximately 20% (77).

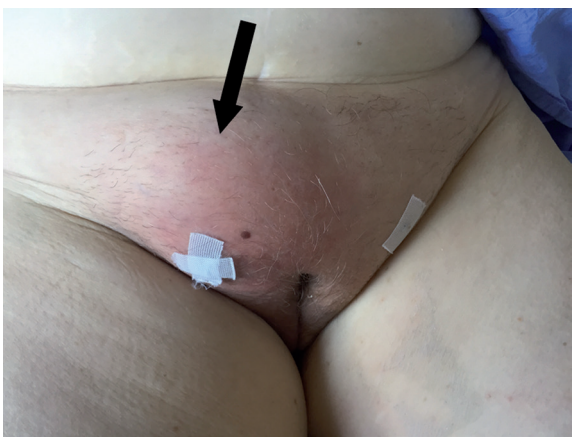
Urinary tract infection (UTI)

Recurrent UTIs after SSS surgery may represent a complication secondary to the presence of urethral/bladder erosion or bladder outlet obstruction. Anger et al. reported that 33.6% of the patients who underwent sling surgery had a UTI within the first 3 postoperative months, which increased to 46.7% within the first 12 months (66). Recently, other authors reported lower rates, ranging from 7.4% to 13%, with no significant difference between the retropubic and transobturator techniques (4, 24, 27, 28). Cases of recurrent UTI due to bladder outlet obstruction require surgical treatment, including mesh lysis or even urethrolysis, as needed. In cases of erosion, removal of the eroded sling and urethral reconstruction are indicated.

Surgical Site Infection

Surgical site infections after a SSS are rarely described and include superficial soft tissue infection and deep abscesso (78, 79). Clinical manifestations of these infections may include pain, tenderness, swelling (Figure-8) and fever, which begins during the first week after the procedure (80). It is easily identified during physical examination and the treatment is based on the use of large spectrum antibiotics (81). Occasionally, ultra-sonography, computer tomography or magnetic ressonance imaging may be used to evaluate the presence of an abscess and

Figure 8 - Large subcutaneous abscess (arrow) after transobturatory SSS treated with ultrasound guided puncture.



its exact extension as well as to guide its drainage (82). Although surgical site infections generally occur in the early postoperative period, cases of deep infections with delayed presentation have been described (82). Noteworthy, cases of severe necrotizing fasciitis after a SSS procedure has also been described (83, 84).

Postoperative pain

Pain in the groin and thighs is one of the most common complications of suburethral sling procedures. The TOMUS trial, a prospective series of 597 patients followed-up for 12 months, comparing the transobturator and retropubic techniques, showed a lower incidence of so called neurological symptoms (pain) for the retropubic slings (4.0%) compared to the transobturator ones (9.4%) (85). In most cases, pain disappears within the first weeks after surgery, but it may persist for more than 4 weeks in 1% to 2.7% of the patients (12, 52, 70, 86).

Several factors may contribute to postoperative pain such as needle passage through pelvic muscles, infection, haematoma, and, more rarely, obturator nerve injury, a complication observed in less than 1% of the cases (24).

It was hypothesized that the inflammatory reaction of the sling material may lead to tissue retraction and hypertonia of the obturator muscle, which may simulate a pinched pudendal nerve, inducing groin and perineal pain (87, 88).

Treatment should be directed to the etiological factor and may vary from the use of common analgesics until drainage of an abscess or haematoma (24, 55, 89-91). In cases of severe or persistent infection, sling removal must be considered. Additionally, occasional patients that persist with pain despite adequate conservative treatment may also be considered for sling removal (23, 92).

De novo urgency

Postoperative urgency is a common complication after SSS procedures, with rates ranging from 5.9 to 25% for the retropubic technique (93, 94) and from 0 to 15.6% for the transobturator slings (27, 95). When considering treatment for this condition, one should first exclude the possibility of sling erosion, local hematoma or bladder outlet obstruction. In these cases, treatment should be directed to the cause. If urethrolysis is required because of bladder obstruction, urgency symptoms may improve in up to 85% of the cases (96). When conditions such as sling erosion, urinary tract infection and bladder outlet obstruction have been ruled out, the principles of clinical management of urgency symptoms should follow those used for patients with the overactive bladder syndrome (97).

Urinary retention

Urinary retention is a common early postoperative complication of all surgical procedures for SUI. Its prevalence varies from 2.5 to 19.5% for retropubic (2, 55, 93, 98) and from 1.5 to 8.6% for transobturator slings (4, 24, 27). The majority of these patients present transient voiding dysfunction with spontaneous resolution in a period of 48 hours to 21 days. The initial management should be to provide a bladder emptying method (indwelling catheter or clean self intermittent catheterization). However, 0.3 to 4.5% of patients treated with a SSS persist with urinary retention for more than 4 weeks and require surgical mesh lysis (2, 4, 24, 27, 55, 93, 98).

Bladder outlet obstruction (BOO)

Bladder outlet obstruction can be easily suspected when patients present with persistent urinary retention (longer than 4 weeks) or have

overt symptoms of incomplete emptying, weak urinary stream and straining to void. However, a significant number of patients demonstrate less evident symptoms and the diagnosis often requires a high index of suspicion, frequently triggered by presentation with symptoms such as urgency, frequency and nocturia. The diagnosis of BOO in women may be challenging and should be made by taking into account the history, physical examination, imagining of the lower urinary tract and the urodynamic pressure-flow parameters (Figure-9a) (99, 100).

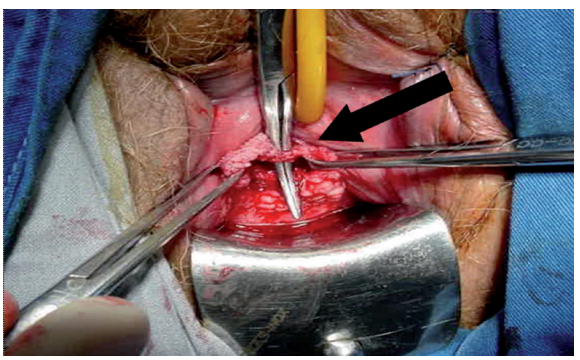
transobturator sling (0%; p=0.004) (85). The surgical options for BOO after a SSS surgery include sling incision (Figures 9b and 9c), sling lysis and partial removal and extensive vaginal or retropubic urethrolysis, with removal of the sling and disruption of the fibrosis surrounding the urethra and bladder neck (Figure-10). When outlet obstruction is diagnosed a long time after sling surgery, single mesh transection may be insufficient to improve BOO because of the possible fixation of the urethra to the pubis and the periurethral fibrotic process. In these cases,

Figure 9a - Urodynamics findings of a patient with BOO secondary to a retropubic SSS, showing high detrusor pressures (short arrow) and low maximum flow rate (long arrow).

In order to improve symptoms and to prevent progression of bladder dysfunction, postoperative BOO should be surgically relieved. The Tomus trial showed higher re-operation rates for treatment of voiding dysfunction in patients undergoing retropubic sling (2.7%) compared to those who underwent

urethrolysis associated with mesh transection is recommended, with satisfactory results ranging from 70 to 85% and SUI recurrence in about 19% (96). If a second urethrolysis is needed, the resolution rate is about 92%, with recurrence of incontinence similar to the observed after the first one (22%) (101).

Figure 9b - Sling incision (arrow) in the same patient after vaginal incision.

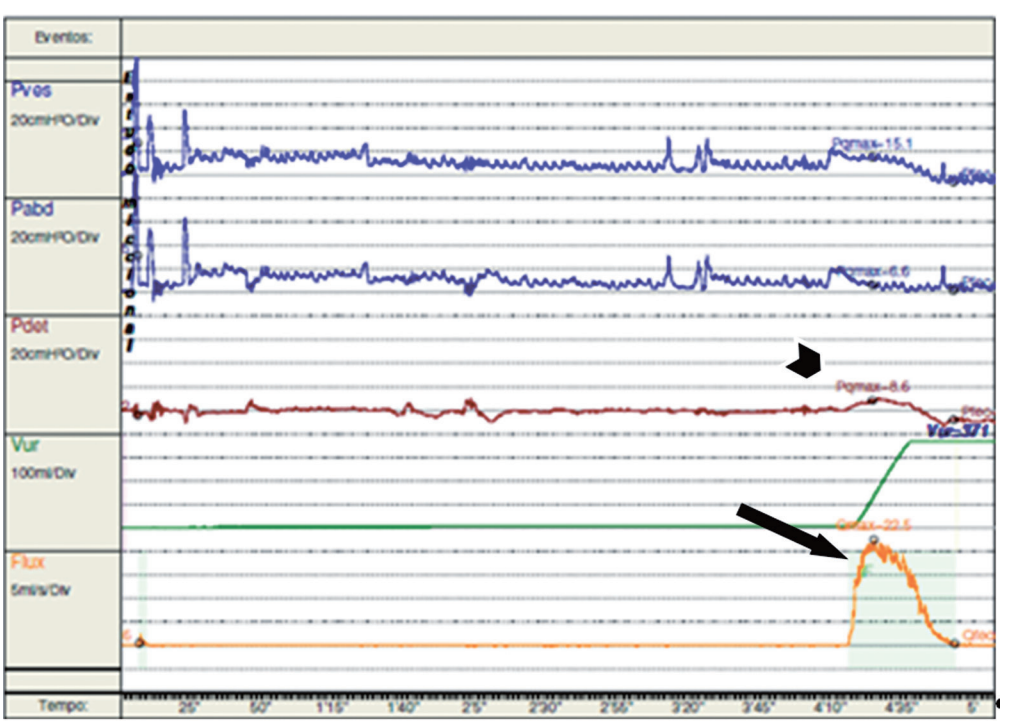


thus become a major concern to all vaginal surgeons. Given the potential risks involved, as well as the readily available legal recourse for patients who experience complications, it is important to deter litigation by appropriately counseling patients about the risks and documenting informed consent in the medical record (102-106).

CONCLUSIONS

This review highlights the surgical morbidity of synthetic suburethral slings, which may include bothersome and even life-threatening complications.

Figure 9c - Postoperative urodynamics demonstrates resolution of the BOO, with low detrusor pressures (PdetQmax 8cm H20 – short arrow) and good flow (Qmax 42mL/s – long arrow).



Medicolegal problems with vaginal mesh surgery

In addition to the medical problems, surgeons must be aware of potential litigation resulting from complications of vaginal surgeries with implantation of meshes. Since the FDA released a warning on the safety and effectiveness of transvaginal placement of meshes in 2011, the number of lawsuits has increased exponentially and has

There is an increasing body of evidence to suggest that the number and severity of complications are underestimated, both by surgeons and patients.

As SSS surgery is the most common procedure performed for the treatment of female stress urinary incontinence, urologists and gynecologists must be aware of these complications, the strategies to avoid them and how to appropriately diagnose and manage the complications. Moreover, to lessen

the chance of medicolegal problems, surgeons using transvaginal meshes should inform patients of potential complications associated with the products and document informed consent in their medical records.

CONFLICT OF INTEREST

None declared.

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REVIEW ARTICLE

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Management of prostate abscess in the absence of guidelines

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ABSTRACT

In contemporary practice, the number of patients presenting with prostatic abscess have significantly declined due to the widespread use of antibiotics. However, when faced with the pathology, prostatic abscess tends to pose a challenge to clinicians due to the difficulty of diagnosis and lack of guidelines for treatment. Treatment consists of an array of measures including parenteral broad-spectrum antibiotic administration and abscess drainage.

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INTRODUCTION

Prostatic abscesses are a rare clinical entity in the current practice due to the widespread use of antibiotics. Management usually imposes a challenge to urologists, that is due to the difficult diagnosis, as it may mimic other diseases of the lower urinary tract and the lack of guidelines for treatment (1). Prostate abscess (PA) usually develops in immunocompromised patients including diabetic and HIV patients as a consequence of acute bacterial prostatitis (2). The reason for the lack of guidelines as regards to PA is that most of the published data in the literature are case reports due to the declining incidence of the disease nowadays.

The incidence of PA in men with HIV has been reduced by the use of antiretroviral therapy (ART), which has decreased the incidence of opportunistic infections, and also by the use of long-term antibiotics in HIV men with bacterial or atypical urinary tract infections (UTIs) (3). In their series of 209 HIV patients, Leport et al. found that the incidence of PA in their patients was 5.3% (4). Both HIV and gonococcal urethritis are sexually transmitted disease. In HIV positive patients, PCR done for urethral swabs showed that the presence of urethral HIV DNA was significantly associated with gonococcal urethritis (5).

The extensive use of antibiotics for the treatment of diverse pathological infections and the decrease of the gonococcal urethritis associated with urethral stenosis, which previously favoured chronic genitourinary infections, have, without doubt, had a great impact on the declining incidence and mortality from prostatic abscesses. This shift was due to the early diagnosis and treatment

of the pelvic and prostatic infections mainly acute bacterial prostatitis. It is estimated that the frequency of prostatic abscess can be as high as 0.5% of urologic diseases and that the mortality rate is between 1% and 16%. The most common bacteria related with prostatic abscesses is E. coli, with an occurrence of up to 70% in such cases (6).

Aetiology and pathogenesis

Some authors suggest that PA is mostly a complication of bacterial prostatitis whether acute or chronic, most commonly seen in men in their fifth or sixth decade but can occur at any age (7). Before the advent of modern antibiotic therapy, 75% of prostatic abscesses were attributable to Neisseria gonorrhoea, and the mortality rate was between 6% and 30% (8). Currently, Enterobacteriaceae, especially E. coli, are the predominant pathogens in acute bacterial prostatitis. Less commonly found organisms are Klebsiella sp, Proteus mirabilis, Enterococcus faecalis and Pseudomonas aeruginosa (9). More recently, there has been a rise in the reported cases of methicillin-resistant Staphylococcus aureus (MRSA) as the causative agent of PA in literature. Risk factors for MRSA infection include: urinary catheter use, health care exposure, history of genitourinary surgery, presence of comorbidities and increasing age (10).

As with most urinary tract infections, prostatic abscess tends to develop from urinary reflux from the urethra toward the prostatic acini, favoured by the different phases of ejaculation and micturition (11). This means that prostatic abscesses are made up of small micro abscesses that coalesce in order to form larger ones which, eventually, on their natural course, could complicate spontaneous drainage through the urethra (8). Haematogenous dissemination has also been described from a septic focus from respiratory, digestive, urinary tracts or of soft tissue. In these cases, the most frequent microorganisms are S. aureus, M. tuberculosis, Escherichia coli and Candida sp (12).

Predisposing factors for PA include an indwelling catheter, instrumentation of the lower urinary tract, bladder outlet obstruction, acute and chronic bacterial prostatitis, chronic renal failure, hemodialysis, biopsy of the prostate, diabetes mellitus, cirrhosis, and, more recently, acquired immunodeficiency syndrome (6). Urologists should have a high index of suspicion of PA in those groups of patients which are the high risk groups.

Clinical Presentation

Prostatic abscess can cause a diagnostic dilemma because, in the early stages, prostatic abscess shares signs and symptoms of others diseases of the lower urinary tract. Symptoms and clinical findings of prostatic abscess are extremely variable. Initially the disease manifests as dysuria, urgency, and frequency in 96% of the cases, fever in 30% to 72%, perineal pain in 20% and urinary retention in 1/3 of the patients (6, 8).

Prostatic abscess should be suspected in high risk group patients presenting with fever and persistent lower urinary tract symptoms that do not respond to antibiotics. A prostatic abscess may progress to spontaneous fistulisation into the urinary bladder, prostatic urethra, rectum, or perineum. In some cases, it can lead to severe sepsis and death (13). One of the theories proposed for development of sepsis in PA is panton-valentine leukocidin (PVL) which is a toxin produced by Staphylococcus aureus that leads to persistence of infection and aids in the spread of infection (14).

DIAGNOSIS

Clinical

The most typical sign of prostatic abscess is a severely tender prostate with areas of fluctuation on digital rectal examination, although those findings diverge between 16% and 88% (15). Other focal symptoms include perineal pain, obstructive urinary symptoms and/or acute urinary retention (13). Systemic signs could be fever, leucocytosis and leucocyturia as well (15).

RADIOLOGICAL

Trans-rectal Ultrasound (TRUS)

The diagnostic method of choice, which also serves as a treatment and follow-up tool for patients with prostatic abscess, is transrectal ultrasonography of the prostate. The most common finding is the presence of one or more hypoechoic

areas, which contain thick pus primarily in the transition zone and in the central zone of the prostate, and which are permeated by hyperechogenic areas and distortion of the anatomy of the gland. Transrectal sonography usually underestimates the real periprostatic extension of the abscess (8).

Tomography (CT)

The role of CT examinations is highlighted in diagnosing PA in cases of extraprostatic collections, as CT can accurately detect the extent of spread of the abscess, particularly to the ischiorectal fossa and perineum (16).

Magnetic Resonance Imaging (MRI)

The use of MRI in PA hasn't been standardised and only limited studies are available. The MRI characteristics of an abscess are a hypointense signal on T1and hyperintense on T2 (17).

TREATMENT

Medical

Initial management entails the use of broad spectrum parenteral antibiotics. This is usually feasible as a single treatment in cases of monofocal abscess cavity <1cm in diameter. An abscess that fails to respond quickly to antibiotics with no signs of clinical improvement needs surgical intervention and drainage of the abscess with or without urine diversion (18). Usually, two weeks are needed before antibiotic treatment are deemed a failure and further surgical intervention would be warranted (19).

Surgical

Several methods have been proposed for surgical drainages all with reported efficacy and feasibility; these are ultrasound guided drainage, transurethral drainage or open drainage (20-22).

Ultrasound guided aspiration

There is a preference for minimally invasive procedures such as TRUS-guided aspiration or transperineal ultrasound guided aspiration. These procedures are considered as the standard procedure for drainage of PA as they are easy to perform under local anaesthesia, have low morbidity and can be repeated in case of failure or incomplete drainage (23, 24). Culture of pus that is aspirated is important because pathogens isolated are often different from those found in urine culture (25).

The first of two percutaneous methods to drain PA is the transrectal approach that utilises a transrectal ultrasound (TRUS) to guide a needle through the rectal wall and into the PA for drainage. This procedure is performed under local anaesthesia with the patient lying in the left lateral decubitus position. Lavage following drainage allows for antibiotics to be introduced directly into the post-drainage cavity (26). TRUS is usually safe to perform except in a few cases where TRUS is contraindicated such as in patients with severe haemorrhoids, anal fistulas, fissures or after abdominoperineal resection (27).

Regarding the outcome of TRUS-guided aspiration, only few studies are available due to the rarity of the condition. In their series, Gogus et al. and Collada et al. had a similar success rate following TRUS-guided aspiration of 83.3%. Success was defined as complete resolution of PA on subsequent US and complete resolution of PA after second TRUS guided aspiration respectively. The reasons for failure were abscess size >3cm, anechoic appearance and ultrasonographically heterogeneous. Transurethral drainage was used following failure of TRUS-guided aspiration and was successful (23, 28).

The other approach is the transperineal route that also entails the use of TRUS to guide a needle puncturing the perineum into the prostatic abscess. This is usually done under general anaesthesia but local anaesthesia can be used. The patient is placed in the lithotomy position and a needle is advanced from the perineum into the prostate. Following complete drainage of the abscess, a guidewire is placed into the cavity and dilatation of the puncture tract is achieved via the Seldinger technique. A loop catheter is then placed for further drainage and is left in place for several days. Varkarakis et al. reported a high success rate with a complete resolution of PA after transperineal drainage (22).

Transurethral

If the abscess recurs or cannot be completely evacuated, transurethral deroofing is a more

appropriate approach, leading to better drainage of the abscess cavity with early recovery of the patient (29). The site of the abscess cavity can be pre-operatively anticipated with the findings from digital rectal examination, transrectal ultrasonography, and CT scans. Additionally, the release of pus to the prostatic urethra, by intra-operative prostatic massage, can indicate the site of the abscess. Another method is to induce pus release to the prostatic urethra by creating several incisions with a Colling's knife in the expected site of the abscess, thus avoiding excessive resection of prostatic tissues. Once the site of the abscess has been localised, proper deroofing of the cavity is performed by resection of prostatic tissues around the cavity's neck (21).

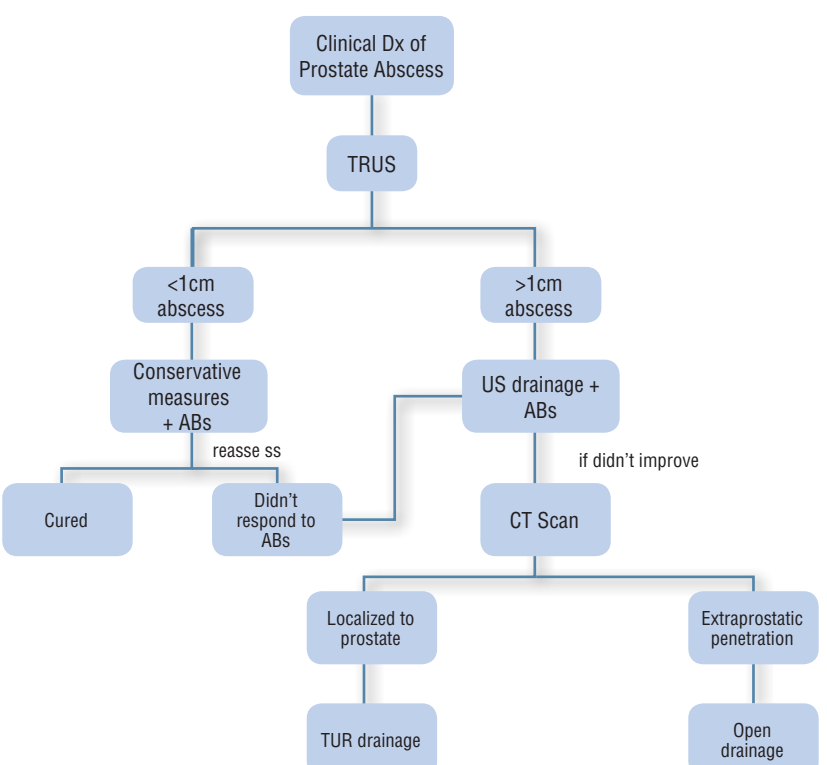
Previously being the standard approach by urologists to treat PA, transurethral drainage has been replaced by the less invasive percutaneous drainage (30). However, transurethral deroofing of PAs is still employed for persistent abscesses that recur despite minimally-invasive treatment (31).

Open drainage

Very rarely open surgical drainage might be required in patients with extraprostatic involvement (29). This is in the form of transperineal incision and drainage in cases where the abscess has penetrated through the levator ani muscle (13). Based on literature review we developed an algorithm for management of prostatic abscess (Figure-1).

EAU Guidelines (32) states that in the case of a prostatic abscess, both drainage and conservative treatment strategies appear feasible (29). When managing prostatic abscess, size does matter; in one study, conservative treatment was successful if the abscess cavities were <1cm in diameter, while larger abscesses were better treated by single aspiration or continuous drainage (18).

Figure 1 - Algorithm for management of prostate abscess.



Dx: Diagnoses, ABs: Antibiotics, US: Ultrasound, CT: Computed Tomography, TUR: Trans-urethral

CONCLUSIONS

PA is a rare occurrence in current clinical practice due to the widespread use of antibiotics. It tends to affect individuals with impaired immune status. Adequate management leads to a better outcome. Due to lack of guidelines for management we recommend following local antibiotic policy as per microbiology guidance. Several methods are available for drainage that are tailored according to individual cases.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Adjuvant radiotherapy for the primary treatment of adrenocortical carcinoma: are we offering the best?

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ABSTRACT

Purpose: To evaluate the role of ARDT after surgical resection of ACC.
Materials and Methods: Records of patients from our institutional ACC database were retrospectively assessed. A paired comparison analysis was used to evaluate the oncological outcomes between patients treated with surgery followed by ARDT or surgery only (control). The endpoints were LRFS, RFS, and OS. A systematic review of the literature and meta-analysis was also performed to evaluate local recurrence of ACC when ARDT was used.
Results: Ten patients were included in each Group. The median follow-up times were 32 months and 35 months for the ARDT and control Groups, respectively. The results for LRFS (p=0.11), RFS (p=0.92), and OS (p=0.47) were similar among subsets. The mean time to present with local recurrence was significantly longer in the ARDT group compared with the control Group (419±206 days vs. 181±86 days, respectively; p=0.03). ARDT was well tolerated by the patients; there were no reports of late toxicity. The meta-analysis, which included four retrospective series, revealed that ARDT had a protective effect on LRFS (HR=0.4; CI=0.17-0.94).
Conclusions: ARDT may reduce the chance and prolong the time to ACC local recurrence. However, there were no benefits for disease recurrence control or overall survival for patients who underwent this complementary therapy.

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Adrenocortical Carcinoma; Radiotherapy, Adjuvant; Therapeutics

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INTRODUCTION

ACC is a rare and lethal disease. One in 1 million individuals will develop this tumor that have a median overall survival time of 1.7 years (1, 2). Most patients are diagnosed when advanced disease is present (3). While 37% present with a localized tumor, 17% present with regional involvement, and 46% with metastatic disease; the 5-year survival probabilities for these disease stages are 62%, 39%, and 7%, respectively (2). Patients who undergo surgical treatment with curative intent have high risk of tumor recurrence of up to 80% (4-7). Because of its aggressive behavior, ACC has substantial clinical importance and elicits continuous medical debate.

The treatment of ACC is challenging and usually involves a multimodal therapy, including

systemic cytotoxic therapy and ARDT. Robust scientific evidence that supports the use of ARDT after surgery for the primary treatment of ACC is lacking. Only retrospective studies have been performed to date. These studies include only small cohorts of patients, probably due to the low prevalence of the disease.

The results of early case series studies indicate that ACC is resistant to radiotherapy (8-13). Concomitant with the adoption of mitotane and improvement in radiation techniques, it was later reported that ARDT can improve local control and reduce the chance of tumor recurrence (14, 15). However, the largest study of the primary treatment of ACC found that there were no benefits for patients who received ARDT (16). Taken together, the limitations of retrospective small series and the controversial outcomes observed, indicate that the role of radiotherapy in the adjuvant setting should be further studied.

We performed a systematic review and meta-analysis that aimed to evaluate the use of ARDT after surgery, for the control of local recurrences in the primary treatment of ACC. We also report our clinical experience with ACC by presenting the results of a paired comparison between patients who were treated using surgery followed by ARDT or surgery alone.

MATERIALS AND METHODS

Institutional paired match comparison

We performed a retrospective search of our adrenocortical cancer database. We selected data from adult patients who were treated using surgery, between 1 January 1994 and 1 January 2014. The patients were separated into two Groups for analysis based on treatment strategy. The treatment Group consisted of individuals treated with surgery followed by ARDT; the control Group consisted of individuals treated with surgery only. The inclusion criteria comprised reported surgical margins, ARDT performed at our institution, and adjuvant use of mitotane. Mitotane data were not included in the analysis. The periods of use and doses given were inconsistent among patients because of variation in tolerance and toxicity. The exclusion criteria comprised patients that had ARDT for the treatment of recurrence or of secondary lesions, intra-operative rupture of the tumor capsule, and positive macroscopic surgical margins. The required minimal follow--up periods were 2 years after radiotherapy in the ARDT group and 2 years after surgery in the control Group, except for the patients that died before. The Groups were paired for comparison based on surgical margin status and clinical stage according to European Network for the Study of Adrenal Tumors classification guidelines. The Weiss scores among the corresponding pairs never exceeded more than two units. Conformal three-dimensional radiotherapy was applied at the tumor bed for all patients in the ARDT group, within 6 months after surgery. Radiation extension and dose were chosen according to adrenocortical cancer severity (based on margin status, size, stage, and Weiss score). Radiotherapy toxicity was classified according to Radiation Therapy Oncology Group criteria (17).

The Groups were compared using local recurrence-free survival LRFS, RFS and OS outcome variables. Local and distant recurrences were diagnosed using computed tomography magnetic resonance or positron-emitting tomography imaging. The times to local and distant recurrence were considered the periods from the surgery date to the date of the imaging examination that revealed the recurrence. If recurrence did not occur, patients were censored at the date of death or at the date of the last follow-up examination. One patient with single metastatic disease was included in each Group. Both were excluded from the recurrence-free survival analysis. OS time was measured from the surgery date to the date of death. Patients still living at the last date of follow-up were censored in the analysis.

The statistical analysis was performed using Stata® 13.0 (Statacorp, College Station, TX, USA). The Groups were compared using the paired t test for continuous variables and Fisher's exact test for categorical variables. Unpaired t tests were used to compare time to event data. The Kaplan--Meier method was used for the survival analysis (GraphPad Prism® version 6.02 for Windows application). The between-Group differences in endpoints were compared using the log-rank test. All

tests were 2-sided. A p-value <0.05 was considered to indicate a statistically significant result.

Meta-analysis for local recurrence

A systematic review of the Medline, Cochrane, and Scopus databases was used to search for English language articles that included adrenocortical carcinoma and radiotherapy, in October 2016. The key words used were adrenocortical cancer, adrenocortical neoplasia, adrenocortical carcinoma, radiotherapy, and radiation (Medline search example: "adrenocortical" AND ("carcinoma" OR "cancer" OR "neoplasia") AND ("radiotherapy" OR "radiation")). There was no time limit on publication date. The data were extracted and analyzed by two individuals (V.S. and J.B.). We selected studies of the primary treatment of ACC that reported a paired comparison analysis of the outcomes of surgery alone and surgery followed by ARDT. Articles that included the use of radiotherapy as the initial primary treatment for adrenocortical cancer, or for metastasis, were excluded. To minimize the risk of assessment bias, the NOS was used to qualify the selected studies (18). A score ≥7 was used to indicate a high risk of bias, moderate risk was indicated by a score of 4-6, and a low risk was indicated by a score ≤3. An adequate follow-up length was determined to be ≥2 years. A fixed model was used to estimate the HRs for local recurrence, with 95% confidence intervals CIs. Heterogeneity was quantified using the I^2 test. The analysis was performed using the Comprehensive MetaAnalysis® version 2.2.064 application (Biostat, Englewood, NJ, USA).

RESULTS

Institutional paired match comparison

We found 61 patients who underwent surgery as the primary treatment for adrenocortical cancer and who were being followed at our institution. Twelve of these patients met the inclusion criteria for the ARDT Group and 26 met the criteria for the control Group. After the matched pairing process was completed, there were 10 patients in each Group. There were no significant between-group differences in age, gender, tumor laterality, tumor size, or Weiss score. The results for the patient's demographic characteristics are presented in Table-1. The median follow-up times for the ARDT and control Groups were 32 months (range: 17-42 months) and 35 months (range: 11-198 months), respectively. Local recurrence was diagnosed in 4 of the ARDT Group, and in 6 of the control Group, patients (p=0.19). Distant recurrence occurred in 8 of the ARDT Group, and 7 of the control Group, patients (9 patients per Group; p=1.0). Seven patients died in each Group (p=1.0).

Table 1 - Patient demographics.

	ARDT group	Control group	*p*
Age (years)*	40 (24-81)	38 (22-63)	0.53
Gender (%)			**0.40**
Male	4 (40%)	1 (10%)	
Female	6 (60%)	9 (90%)	
Side (%)			**1.0**
Right	3 (30%)	9 (90%)	
Left	7 (70%)	1 (10%)	
Tumor size (cm)*	12.7 (6-17)	10 (4-15)	0.28
Weiss score*	8 (4-9)	7 (3-8)	0.08

*Median (range)
ARDT = Adjuvant radiotherapy

ARDT was well tolerated by most of the patients in this cohort. Grade 1, 2, and 3 toxicity occurred in 2 (20%), 4 (40%), and 4 (40%) patients, respectively. No evidence of late radiation toxicity was reported. The median radiation dose was 54 Gys (range=45-54 Gys). The median time to ARDT was 100 days after surgery (range=27-158 days).

The LRFS times were similar among Groups (p=0.11). The 5-year RFS (p=0.92) and OS (p=0.47) times were also equivalent in both subsets of patients (Figure-1). The mean time for local recurrence was significantly greater in the ARDT Group (p=0.03). The mean times for disease recurrence (p=0.58) and death (p=0.55) were similar in the ARDT and control Groups (Table-2).

Meta-analysis for local recurrence

The database search revealed 335 articles; 3 of these articles met the selection criteria (Figure-2). The data from the present cohort were also included in the meta-analysis. All selected articles included results from matched paired series comparing patients who had surgery as the primary treatment for adrenocortical carcinoma, with or without ARDT. Results from a total of 136 patients were included. The NOS indicated that all articles had a low risk of bias (Table-3). The Sabolch et al. article had the lowest score; this cohort included patients who underwent radiotherapy for surgically treated local recurrence (7). A meta-analysis was performed to evaluate LRFS

Figure 1 - Kaplan-Meier analysis of local recurrence-free survival (A), recurrence-free survival (B), and overall survival (C).

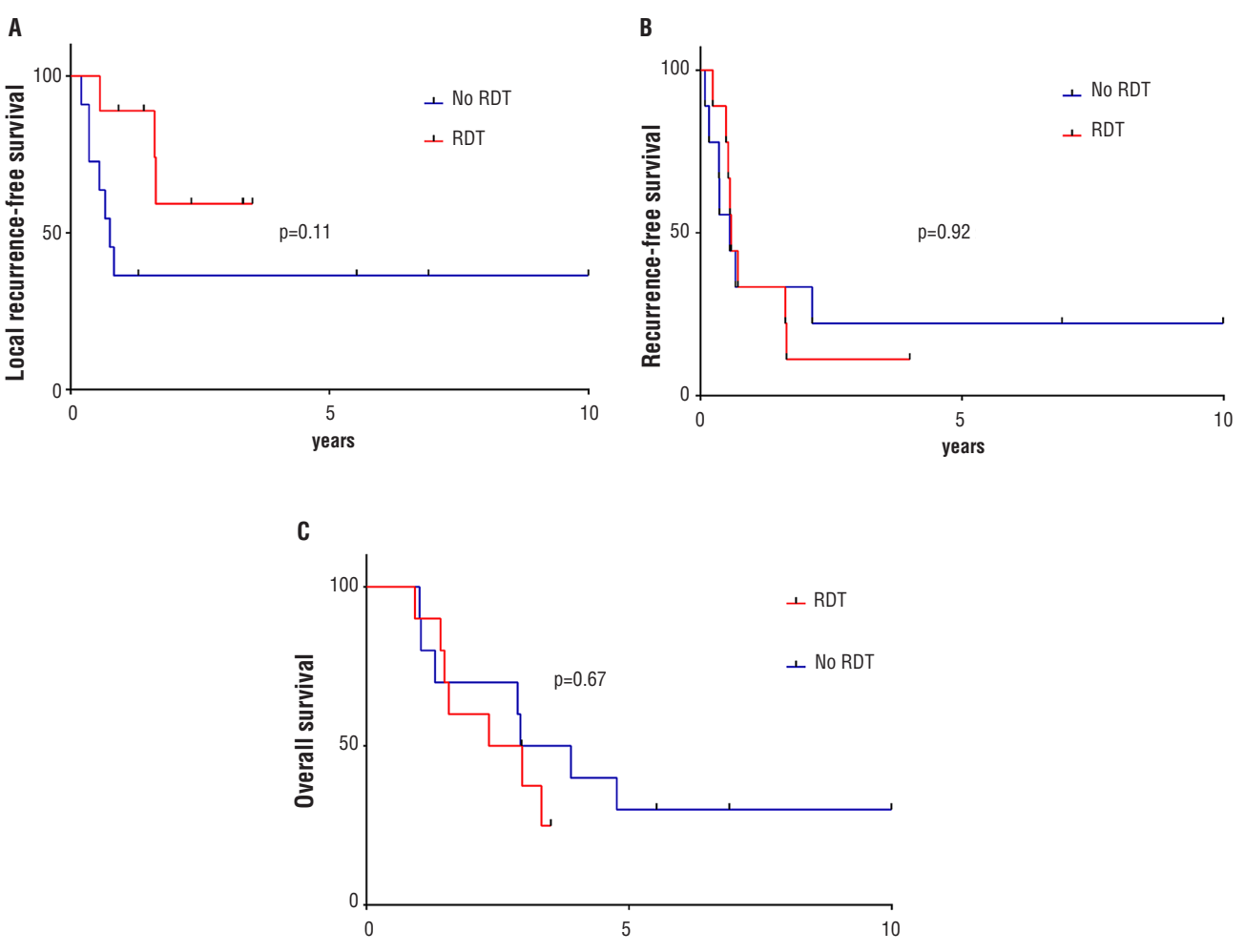


Table 2 - Treatment outcome and time to event results.

	ARDT group	Control group	*p*
Follow-up (months)*	32 (11-43)	35 (11-195)	0.16
Local recurrence			
Number of patients (%)	4 (40)	6 (60)	0.19
Average time (days)	419 ± 206	181 ± 86	0.03
Disease recurrence**			
Number of patients (%)	8 (89%)	7 (78%)	1.0
Average time (days)	291±194	225±255	0.58
Death			
Number of patients (%)	7 (70%)	7 (70%)	1.0
Average time (days)	730 ± 326	929 ± 541	0.42

* Median (range)
** Nine patients analyzed in each group
ARDT = Adjuvant radiotherapy

Figure 2 - Systematic review flowchart.

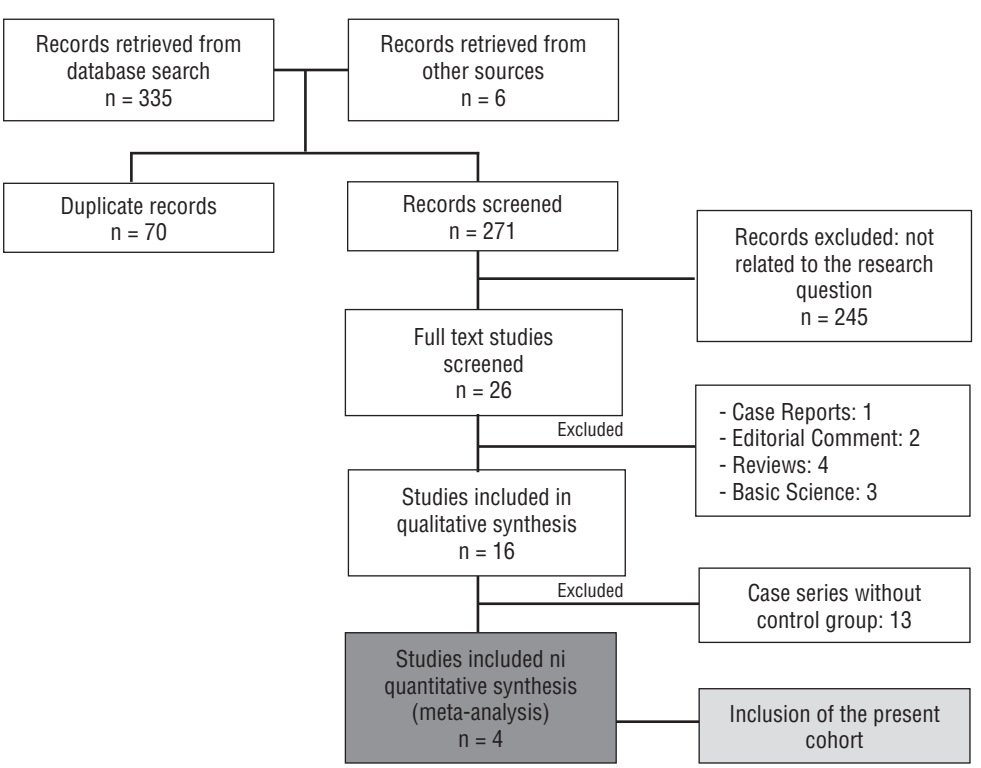
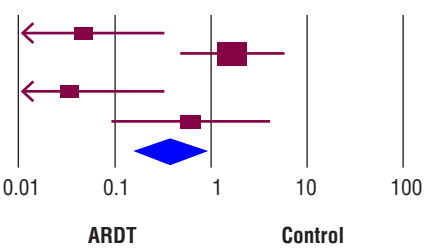


Table 3 - Newcastle-Ottawa Scale assessment for selected cohort studies.

Articles	Selection				Comparability	Outcome			Score
	Representativeness of the present cohort	Selection of non-exposed	Ascertainment of exposure	Outcome not present at start		Assessment of outcome	Adequate follow-up length	Adequate follow-up	
Fassanatch, 2006	★	★	★	★	★★	★		★	8
Habra, 2013	★	★	★	★	★★	★		★	8
Sabolch, 2015		★	★	★	★★	★		★	7
Srougi, 2017	★	★	★	★	★★	★	★	★	9

Figure 3 - Results of meta-analysis for local recurrence-free survival after ARDT for adrenocortical carcinoma (ACC).

Study Name	Statistics for each study					Events / Total		Hazard ratio and 95% CI
	Hazard ratio	Lower limit	Upper limit	Z-Value	p-Value	RDT	Controls	
Fassanatch, 2006	0.045	0.006	0.325	-3.079	0.002	2 / 14	11 / 14	
Habra, 2013	1.711	0.496	5.905	0.850	0.395	7 / 16	10 / 32	
Sabolch, 2015	0.035	0.004	0.317	-2.983	0.003	1 / 20	12 / 20	
Srougi, 2016	0.640	0.100	4.109	-0.470	0.638	4/ 10	6 / 10	
	0.405	0.174	0.942	-2.098	0.036			



(Figure-3). RFS and OS were not analyzed due to the scarcity of data. Patients who had ARDT had a lower chance of local tumor recurrence, compared with the control Group patients (HR=0.4; CI=0.17-0.94; p=0.036; I^2=0.79). The outcomes of the selected articles were considered with substantial heterogeneity.

DISCUSSION

The results for our study cohort showed that there were no benefits from ARDT for local recurrence control of ACC. However, the analysis of published results indicated that the use of this complementary therapy after surgery for the local control of the disease has some benefit. The survival analysis revealed that ARDT did not affect disease recurrence or OS, which was consistent with previously published results.

The pairing criteria among the selected articles included tumor margin status and ACC stage, which are known major risk factors for patient prognosis (3, 19).

Pathological characteristics that are as important as these criteria were not used in any of the series, except by Sabolch et al., who used tumor grade for pairing (15). We aimed to reduce the effects of this difference by minimizing the difference in the Weiss criteria between pairs, which also affects tumor recurrence (20).

Some factors may have changed the results of radiotherapy for ACC treatment over the years. Mitotane has been widely adopted for adjuvant treatment of ACC, and its use is associated with improved survival (7). In experimental studies, Cerquetti et al. found that mitotane is also a sensitizer for radiotherapy and, therefore, can improve ARDT results (21, 22). Recent case series have comprised patients using mitotane, including most of the articles selected for the meta-analysis. Another important factor that has contributed to the improvement in ARDT outcomes is progress in the development of radiation technology. Three--dimension conformal planning reduces the side

effects and enhances the efficacy of external beam radiotherapy. This change has been crucial, considering that the actual recommendation is to irradiate a wide territory because up to 25-30% of the patients may have inter-aortocaval lymph node metastases (2). Consistent with our study cohort results, the analysis of the selected series revealed well-tolerated radiation toxicity; only two cases of late toxicity were reported (14, 16).

The use of ARDT for control of local recurrence is still controversial. Habra et al. found a local recurrence-free rate of 53% for patients who received ARDT, and 67% for a non-ARDT Group; the between-group difference was not statistically significant (16). This finding motivated our study, which shows similar results. Of noteworthy, patients who underwent ARDT did have a longer mean time to development of local recurrence, which was approximately 240 days more than the patients in the control Group. The use of a longer follow-up time could reveal that the chances of local recurrence are the same for patients receiving or not receiving ARDT. However, this finding may justify the use of ARDT for ACC treatment since an incremental increase in the time interval for local disease control could improve quality of life for patients with this aggressive neoplasm.

The results of our meta-analysis suggest that the use of ARDT might increase LRFS. Nonetheless, a definitive treatment paradigm cannot be developed from these results because there was substantial heterogeneity in the outcomes in the published series. Furthermore, it should be emphasized that all evidence to date also indicates that ARDT does not affect disease recurrence or OS (14, 16). It is reasonable to question whether ARDT should be used if it does not improve survival.

This study was limited by its retrospective design and small sample sizes. Our meta-analysis included only four paired retrospective case series. However, given the low prevalence of ACC and the limited number of articles available on the use of ARDT, our work represents the highest level of available evidence. We attempted to minimize sample bias via the strict selection of paired studies; the NOS results indicated the presence of a uniform quality among the articles included in the meta-analysis. Nevertheless, only a multi-institutional randomized trial will provide robust evidence for the role of ARDT in the treatment of ACC.

CONCLUSIONS

ARDT may decrease the chances and delay the time to ACC local recurrence. However, benefits for RFS and OS have not been found. The current evidences lack quality and highlights the need for prospective studies. Considering the rarity of ACC, a joint multi-institutional effort should be implemented to study this problem. Until then, the real advantages of ARDT will remain uncertain.

CONFLICT OF INTEREST

None declared.

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Partial nephrectomy for T3aN0M0 renal cell carcinoma: shall we step forward?

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ABSTRACT

Objectives: To evaluate the prognosis of non-metastatic T3a renal cell carcinoma (RCC) with partial nephrectomy (PN).
Patients and Methods: We retrospectively evaluated 125 patients with non-metastatic T3a RCC. Patients undergoing PN and radical nephrectomy (RN) were strictly matched by clinic-pathologic characteristics. Log-rank test and Cox regression model were used for univariate and multivariate analysis.
Results: 18 pair patients were matched and the median follow-up was 35.5 (10-86) months. PN patients had a higher postoperative eGFR than RN patients (P=0.034). Cancer-specific survival (CSS) and recurrence-free survival (RFS) did not differ between two groups (P=0.305 and P=0.524). On multivariate analysis, CSS decreased with positive surgical margin and anemia (both P <0.01) and RFS decreased with Furhman grade, positive surgical margin, and anemia (all P<0.01).
Conclusions: For patients with non-metastatic pT3a RCC, PN may be a possible option for similar oncology outcomes and better renal function.

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INTRODUCTION

Radical nephrectomy (RN) used to be the standard therapeutic option for localized and locally advanced renal cell carcinoma (RCC) (1). In recent years, the oncology outcomes with partial nephrectomy (PN) were found not worse than those of RN (2). Moreover, PN may improve overall survival by preventing cardiovascular events caused by chronic kidney disease (CKD) for that the incidence of CKD was lower with PN than RN (3-5).

PN was recommended by the European Association of Urology and National Comprehensive Cancer Network guidelines as the preferred option for tumor type 1a-b (T1a-b) RCC 2 (1, 6). In recent years, several studies expanded the application further to T2 RCC patients (7). However, whether PN is a possible option for non-metastatic T3a RCC is unknown. Actually, some non-metastatic patients with pT3a RCC (perinephric and renal sinus fat invasion) have undergone PN for various reasons.

The aim of this study was to analyze the prognostic differences in T3a RCC patients who underwent PN or RN with a strictly case-matched design.

PATIENTS AND METHODS

We searched the renal cancer database in Peking University First Hospital for cases occurring from 2007 to 2012 and retrospectively

identified 2651 RCC patients who underwent nephrectomy, including PN and RN. The study received institutional review board approval. According to the 2010 American Joint Committee on Cancer (AJCC) TNM staging, the patients included 125 with non-metastatic pathological T3a (pT3a) RCC; 18 underwent PN. Patients who underwent PN and RN were exactly matched by gender, age, tumor size, American Society of Anesthesiologists (ASA) score, pathological subtype, surgical margin status, tumor invasion status and Fuhrman grade (Table-1). When more than one RN patient with criteria identified was matched, we chose patients with a smaller difference in tumor size with PN patients.

Table 1 - Criteria for pair matching.

Criterion	Difference allowed
Age	<10 years
Gender	Identical
Tumor size	<3 cm
ASA score	Identical
Pathological subtype	Identical
Tumor invasion status	Identical
Surgical margin status	Identical
Fuhrman grade	Identical

Complete preoperative examinations included chest X-ray, abdominal ultrasonography, abdominal CT, laboratory examinations and other necessary exams for preoperative evaluation. Pathological specimens were assessed by at least two experienced pathologists to confirm the pathologic subtype, surgical margin status, tumor invasion status and lymph-node metastasis status. Histological subtype and Fuhrman grade were stratified according to the 2004 WHO classification system and 1997 WHO recommended standards, respectively. According to 2010 AJCC TNM staging system, T3a staging was diagnosed when the tumor grossly extended into the renal vein or its segmented (muscle-containing) branches or invaded the perirenal and/or renal sinus fat but not beyond Gerota's fascia.

Patients were followed up by the standard strategy for outpatients in our institution, every 3 months post-operatively for the first 2 years and every 6 months for the next 3 years. From the fifth year and thereafter, patients were followed up annually. The general follow-up included imaging examinations (chest X-ray, abdominal ultrasonography or CT) and laboratory examinations (blood, urine and biochemistry). The outcomes investigated during follow-up included cancer-specific survival (CSS) and recurrence-free survival (RFS). The period from the surgery date to the date of recurrence, death or last follow-up was calculated as the follow-up time.

Statistics analysis involved use of SPSS 22.0 (SPSS Inc., Chicago, IL). Student t test was used to compare continuous variables and chi-square test to compare categorical variables. Survival was estimated by Kaplan-Meier method and log-rank test was used for survival difference analysis and univariate analysis. Variables with significant differences on univariate analysis for all T3aN0M0 patients were included in Cox multivariate regression analysis. All comparisons involved two-tailed tests and $P<0.05$ was considered statistically significant.

RESULTS

A total of 18 patients with non-metastatic pT_{3a} renal cell carcinoma underwent PN in our institution. The reasons were solitary kidney (n=3), renal insufficiency (n=3) and preoperative diagnosis of clinical T1 or T2 (cT1 or cT2). From the matching variables, 18 patients who underwent RN were chosen as the control group. For the 36 patients, the median age was 68.5 years (range 36-85); 28 (77.8%) were male and median follow-up was 35.5 months (10-86). The two groups did not differ in baseline characteristics ($P >0.05$) or some post-operative features such as blood loss ($P=0.845$), operative time ($P=0.110$), drainage-tube indwelling time ($P=0.778$) and post-operative stay ($P=0.540$). The preoperative eGFR in both groups is not significant different ($P=0.357$) and the postoperative eGFR in PN group is higher than RN

Table 2 - Baseline characteristics and postoperative outcomes for patients with non-metastatic pT3a renal cell carcinoma (RCC) who underwent radical nephrectomy (RN) and partial nephrectomy (PN) (n=18 each).

Variable	RN	PN	P
Age	64.94±12.62	60.89±13.99	0.368
Male gender	14	14	**Matched**
Histopathologic subtype			**Matched**
ccRCC	13	13	
non-ccRCC	5	5	
Fuhrman grade			**Matched**
1	1	1	
2	11	11	
3	6	6	
ASA score			**Matched**
1	1	1	
2	13	13	
3	4	4	
Tumor size	5.03±1.42	5.27±1.50	0.644
Tumor invasion			**Matched**
Fat	17	17	
Renal vein	1	1	
Surgical margin			**Matched**
Positive	1	1	
Negative	17	17	
Blood loss (mL)	248.89±570.22	287.22±598.03	0.845
Operative time (min)	157.44±45.04	131.61±49.39	0.110
Indwelling drainage tube time (day)	4.94±4.14	4.61±2.77	0.778
Postoperative stay (days)	7.61±2.50	6.44±3.41	0.250
Preoperative eGFR (mL/min/1.73m^2)	82.60±26.53	73.99±27.97	0.357
Postoperative eGFR (mL/min/1.73m^2)	52.35±17.21	68.38±24.40	**0.034***

Data are mean±SD or number. *P<0.05

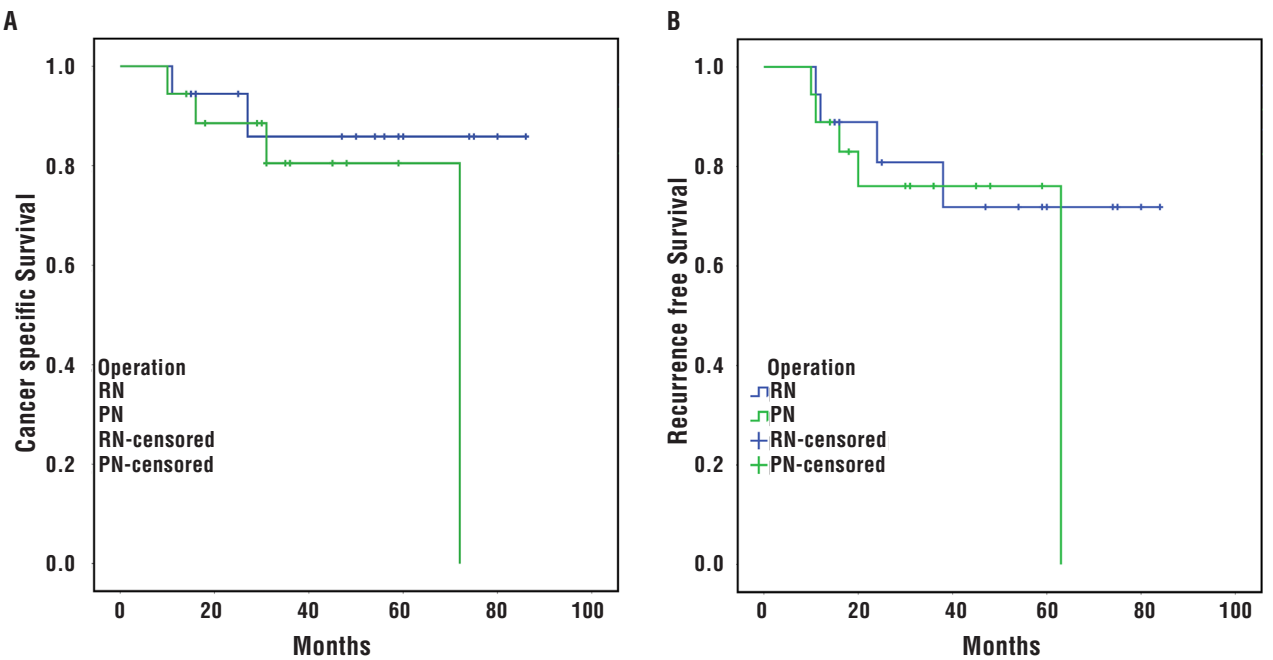
ccRCC = clear cell renal cell carcinoma; **RN =** radical nephrectomy; **PN =** partial nephrectomy; **ASA =** American Society of Anesthesiologists

group (P=0.034) (Table-2).

At the end of follow-up, 4 (22.2%) and 2 (11.1%) patients in the PN and RN groups died due to the disease and 5 (27.8%) and 4 (22.2%) showed recurrence, respectively. The patients who died in the PN group were 1 with renal insufficiency, 3 up-graded after operation and the patients with recurrence in PN group were 1 for renal insufficiency, 1 with solitary kidney and 3 up-graded after operation. The estimated 5-year CSS for the PN and RN patients was 80.5% and 85.9%, and the estimated 5-year RFS was 76% and 80.8%. CSS (P=0.305) and RFS (P=0.524) did not differ between the two groups on log-rank testing (Figure-1).

Univariate analysis revealed that tumor invasion status, Fuhrman grade, positive surgical margin, hypoalbuminaemia and anemia were

Figure 1 - Kaplan–Meier survival analysis of patients with non-metastatic pT3a renal cell carcinoma (RCC) who underwent radical nephrectomy (RN) and partial nephrectomy (PN). A) Cancer-specific survival (P=0.305); B) Recurrence-free survival (P=0.524).



significantly associated with CSS and RFS for all T3aN0M0 patients (n=125) (Table-3). Surgical type (RN vs. PN) was not significantly associated with CSS and RFS. On Cox multivariate regression analysis, CSS was decreased with positive surgical margin (P=0.000) and anemia (P=0.003) and RFS was decreased with Fuhrman grade (P=0.001), positive surgical margin (P=0.003) and anemia (P=0.004) (Table-4).

DISCUSSION

From our institution's data on 125 patients with non-metastatic pT3a RCC, 18 patients with PN and 18 with RN were matched. We compared the outcomes of patients with localized RCC undergoing PN and other patients undergoing routine RN treatment to evaluate the outcomes and effectiveness of PN for non-metastatic T3a RCC. The postoperative eGFR in PN group is higher than RN group. CSS and RFS did not differ between the groups. In the multivariate analysis, positive surgical margin and anemia were independent risk factors for CSS and high Furhman grade, positive surgical margin, and anemia were risk factors for RSS.

A number of studies have shown no significant differences between PN and RN in survival with localized RCC (2, 8, 9). Moreover, several studies suggested that PN could reduce the incidence of CKD and prevent the associated cardiovascular events and improve survival quality (2, 10). However, the therapeutic recommendation is still RN for T3aN0M0 RCC (1, 6). Nevertheless, some T3a RCC patients undergo PN for various reasons such as solitary kidney and renal insufficiency. As well, a few patients were preoperatively diagnosed with cT1-2 cancer and treated with PN, which was pathologically upstaged to pT3a cancer.

In a study by Lee et al. (11), 43 (3.2%) of 1367 patients with small RCC (≤4cm) had pT3a lesions. Gorin et al. (12) retrospectively analyzed 1.096 cT1 patients after PN and found 41 (4.8%) tumors upstaged to pT3a; the 2-year RFS with pT3a tumors was 91.8%, which was lower than

Table 3 - Univariate analysis of clinicopathological variables associated with cancer-specific survival (CSS) and recurrence-free survival (RFS) at 5 years for all $T_{3a}N_0M_0$ patients (n=125).

Variable	n	CSS			RFS		
		CSS	χ^2	*P*	*RFS*	χ^2	P
Gender			2.067	0.151		2.840	0.092
Male	87	65.4			53.1		
Female	38	74.2			69.7		
Age, years			0.736	0.391		0.400	0.527
<55	49	69.6			59.1		
≥55	76	67.5			57.7		
BMI			0.146	0.703		0.230	0.632
<25	68	64.3			59.8		
≥25	57	72.8			55.9		
Tumor invasion			9.772	**0.002***		4.231	**0.040***
Fat	89	78.6			64.6		
Renal vein	36	46.3			42.9		
Histopathologic subtype			0.267	0.605		0.801	0.371
ccRCC	111	68.3			56.0		
non-ccRCC	14	68.8			77.4		
Location			1.206	0.272		0.905	0.341
Left	66	62.9			54.9		
Right	59	74.4			62.9		
Tumor size, cm			0.007	0.935		0.310	0.578
≤4	9	83.3			58.3		
>4	116	68.9			57.8		
Fuhrman grade			8.968	**0.003***		16.623	**<0.001***
1&2	60	85.7			79.6		
3&4	65	53.9			39.5		
ASA score			0.000	0.993		0.834	0.361
1&2	113	67.4			58.6		
3&4	12	76.2			60.0		
Surgical type			0.021	0.885		0.101	0.751
RN	107	67.3			56.6		
PN	18	80.5			76		
Surgical margin			46.172	**<0.001***		16.169	**<0.001***
Positive	2	0			0		
Negative	123	69.1			59.2		
Surgical approach			0.061	0.805		2.023	0.155
Open	80	67.2			54.5		
Laparoscopic	45	74			67.8		
Hypoalbuminaemia			10.934	**0.001***		4.394	**0.036***
No	115	71.9			60.2		
Yes	10	20			28.6		
Anemia			22.03	**<0.001***		13.349	**<0.001***
No	102	75.6			63.7		
Yes	23	33			29.8		

*P<0.05

BMI = body mass index; ccRCC = clear cell renal cell carcinoma; **RN =** radical nephrectomy; **PN =** partial nephrectomy; **ASA =** American Society of Anesthesiologists

Table 4 - Multivariate analysis of clinicopathological variables for CSS and RFS for all $T_{3a}N_0M_0$ patients (n=125).

Variable	CSS			RFS		
	HR	*(95% CI)*	*P*	*HR*	*(95% CI)*	*P*
Tumor invasion						
Fat	1			1		
Renal vein	1.386	0.580-3.315	0.463	1.201	0.593-2.432	0.610
Fuhrman grade						
1&2	1			1		
3&4	1.865	0.701-4.961	0.212	3.688	1.651-8.239	**0.001***
Surgical margin						
Positive	41.318	6.686-255.331	**<0.001***	10.861	2.231-52.873	**0.003***
Negative	1			1		
Serum album, g/L						
≥35	1			1		
<35	1.678	0.580-4.855	0.339	1.300	0.431-3.922	0.642
Anemia						
No	1			1		
Yes	3.633	1.546-8.537	**0.003***	3.201	1.464-7.000	**0.004***

*P<0.05
HR = hazard ratio; **CI =** confidence interval

with pT1-2 tumors (99.2%, P=0.003). Tumor upstaging was associated with a high R.E.N.A.L (radius, exophytic/endophytic, nearness to collecting system or sinus, anterior/posterior and location relative to polar lines) nephrometry score (hazard ratio [HR] 2.97, 95% CI 1.20-7.35, P=0.02), increased tumor diameter (1.66, 1.32-2.08, P<0.001), and hilar location (2.83, 1.43-5.61, P=0.003). In another multi-institutional study, Nayak et al. (13) reported 134 (9%) of 1.448 cT1 patients with upstaging to pT3a. The 3-year RFS with upstaging was 76% as compared with 93% without upstaging (P<0.001). Disease recurrence, increasing age, Fuhrman grade and tumor size were independently associated with pathological upstaging. In our study, we found 11 of 125 (8.8%) patients with non-metastatic pT3a RCC with cT1 cancer treated by PN.

Various risk factors associated with the oncology outcomes of non-metastatic RCC include age, gender, TNM, Fuhrman grade, tumor size, histopathologic subtype, ASA score and tumor invasion status (14, 15). Therefore, strict matching should be conducted to mitigate potential selection bias caused by these features. Lee et al. (11) found no significant differences between T1a and T3a patients in overall survival (P=0.521), CSS (P=0.651) and RFS (P=0.250). However, several variables such as age (P=0.015), tumor size (P <0.001), subtype (P=0.020), and Fuhrman grade (P=0.021) differed between the 2 cohorts. Jeldres et al. (16) matched pT3a RCC by age, gender, tumor size, Fuhrman grade and histopathologic subtype to create a cohort of PN patients (n=30) and RN patients (n=63) and demonstrated no significant difference between the groups in CSS (P=0.9). The authors also included all unmatched 72PN patients and 789RN patients in the multivariate analysis and found PN not associated with worse CSS as compared with RN (HR=0.62, P=0.11). In our study, the matching criteria (gender, age, tumor size, ASA score, pathological subtype, surgical margin status, tumor invasion status and Fuhrman grade) were more stringent than that used by Jeldres et al., and we found no significant differences between the PN and RN groups in CSS

(P=0.305) and RFS (P=0.524). As well, on univariate analysis of all T3aN0M0 RCC patients, surgical type (PN or RN) was not associated with CSS or RFS.

Renal insufficiency has an independent and graded association with risk of death and cardiovascular events (17, 18). RCC patients have about a 25% rate of CKD, which can lead to a series of metabolic disorders and cardiovascular events (19). PN was suggested to benefit renal function as compared with RN (20, 21). Sun et al. found a lower rate of postoperative renal events with PN versus RN (22). Yokoyama et al. (23) found RN as an independent risk factor for new-onset CKD. Jong Jin et al. (24) compared 45 T3a RCC patients who underwent PN and 298 patients who underwent RN and found that renal function, measured by postoperative creatinine (Cr) and estimated glomerular filtration rate (eGFR), was better with PN than RN (Cr: 1.07 vs. 1.37mg/dL, P=0.001; eGFR: 75.4 vs. 59.8mL/min, P <0.001). However, RFS was lower for RN than PN patients (P <0.001). Because the mean tumor size was smaller for PN than RN patients (P <0.001), the authors also analyzed RFS for patients with tumor size ≤4cm (30PN patients, 33RN patients) and found no significant difference (P=0.306). Similar to the results of patients with tumor size ≤4cm in this previous study, we found similar CSS and RFS but higher postoperative eGFR for PN than RN patients (P=0.034) and this could imply that PN may protect renal function.

Positive surgical margin was previously found significantly associated with tumor recurrence, although the development of metastases and CSS were comparable with positive and negative surgical margins (25-27). Borghesi et al. (28) reported that the overall incidence of recurrence after negative surgical margins ranged from 0% to 7%. In our study, 2 of 125 patients (1.6%) with T3aN0M0 RCC showed positive surgical margins and the variable was associated with CSS (P=0.000) and RFS (P=0.000) on Cox multiple regression analysis. However, because of the low rate of positive surgical margins in single-center T3aN0M0 RCC patients, the association with oncological outcomes demands larger cohort studies.

This study has several strengths. The experienced surgeons in a single center ensured that every patient received similar and standard treatment. Furthermore, the sequential and uniform follow-up provided high-quality data for analysis. Moreover, the characteristics of patients in the PN and RN groups were comparable with the strict case matching.

However, this study still presents several limitations. First, it was retrospective and cannot avoid the inevitable disadvantages of a retrospective study. Second, this is a small sample and single-center study, for a low ratio of T3a RCC patients undergoing PN and this cannot avoid the type 1 or 2 error. Third, the median follow-up time was short. Prospective, large-sample and multi-institutional studies are required to further test the use of PN and discover risk factors for non-metastatic T3a RCC patients.

In conclusion, this case-matched analysis demonstrates that for non-metastatic T3a RCC patients, PN may be is a possible option for similar oncology outcomes and better renal function.

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CONFLICT OF INTEREST

None declared.

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Laparoscopic partial nephrectomy for tumors 7cm and above. Perioperative outcomes

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ABSTRACT

Purpose: To assess and report the outcomes of laparoscopic partial nephrectomy)LPN) for T2 renal masses.
Materials and Methods: Retrospective review of patients undergoing LPN for clinically localized renal masses ≥7cm between the years 2005-2016. Descriptive analyses were generated for demographics, lesion characteristics, perioperative variables (operative time, warm ischemia time (WIT), estimated blood loss (EBL), intra-operative and post-operative complications (IOC and POC) and pathologic variables (pathology, subtype and Fuhrman grade).
Results: A total of 27 patients underwent LPN for a T2 renal mass at our institution between 2005 and early 2016 of which 19 were males. The mean age was 66 (52-72). All procedures were transperitoneal with 16 on the right and 11 on the left. Median operative time was 200 minutes (IQR 181-236) and median WIT 19 minutes (IQR 16-23). EBL was 125mL (IQR 75-175). One case was converted to laparoscopic radical nephrectomy due to suspected tumor thrombus in the renal vein. Surgical margins were positive in one renal tumor in a patient with multiple tumors. There was a total of 2 IOC (7.4%) and 3 POC (11%) classified as Clavien grade 3.
Conclusions: To our knowledge, this series is the first to describe the outcomes of LPN for cT2 renal masses. In our series, LPN for larger renal masses appears feasible with favorable perioperative outcomes. Additional data are needed to further explore the benefits of minimally invasive surgical approaches to larger renal masses.

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INTRODUCTION

Laparoscopic partial nephrectomy (LPN) is a valid treatment option for small renal masses (SRM) (1, 2). It has been shown that LPN provides comparable overall survival (OS), cancer specific survival (CSS) and progression free survival (PFS) when compared to open partial nephrectomy (3-5) while maintaining the benefits of nephron-sparing surgery (NSS) in preservation of renal parenchyma and therefore decreased risk of chronic kidney disease.

Studies have described positive outcomes with LPN for stage T1 masses (4-6). Only scarce data exist, however, on the use of Laparoscopy in NSS for T2 masses (7, 8) .While in the widespread of robotics, mainly in the United States has largely replaced the use of pure laparoscopy, in other parts of the world, laparoscopy remains the mainstay of minimally invasive surgery and an extremely re-

levant topic for discussion. At our institution, the standard of care for renal masses is LPN. We have previously reported on our outcomes for tumors larger than T1a (7). Herein, we analyze the outcomes of LPN for tumors of 7cm or larger.

PATIENTS AND METHODS

After approval from our Institutional Review Board we retrospectively reviewed our prospectively collected database to identify patients undergoing LPN for a clinical T2 renal mass. Clinical stage was determined on cross sectional imaging. A total of 27 patients underwent LPN for renal masses ≥7cm between 2005 and early 2016. All surgeries were performed by a single surgeon (AT). The variables that were examined when reviewing our database were demographics (age, gender), lesion characteristics: side, centrality, location and size. Perioperative variables collected included: operative time (OT), warm ischemia time (WIT), estimated blood loss (EBL), concomitant surgery, conversion to laparoscopic radical nephrectomy (RN) or to open surgery, intra-operative complications (IOC) and post-operative complications (POC). POC were classified according the modified Clavien system (9). Pathologic variables included malignant vs. benign pathology, subtype and Fuhrman grade when applicable. Descriptive analyses were generated. Data are reported as median (interquartile range, IQR) or number (%).

Surgical technique

Our surgical technique has evolved over the years. We use the standard transperitoneal approach with three to four trocars as previously described (10). After dissecting the renal vessels and identifying the tumor, the anticipated resection margins are marked with cautery under ultrasound guidance. Typically, a bulldog clamp is applied to the renal artery only, without venous clamping. In cases of central tumors whereby venous clamping is deemed beneficial, a single bulldog clamp is applied to artery and vein en bloc. The mass is excised and trapped in a bag. The defect is then closed in two layers. A running suture secured on both ends with an absorbable clip controls the resection bed (regardless of whether the collecting system is violated) and for the superficial layer a running suture interrupted by absorbable clips on one side of the defect is used (11). With the evolution of our technique we do not routinely use bolsters or other additional hemostatic agents aside from sutures. Routinely, ≥10mm ports sites are closed using the Endoclose TM device (United States Surgical, Norwalk, CT).

RESULTS

A total of 27 patients underwent LPN for T2 (7-15cm) renal masses at our institution be-

Figure 1 - 14cm tumor of the left kidney. Preoperative (A) and 6 months postoperative imaging (B).

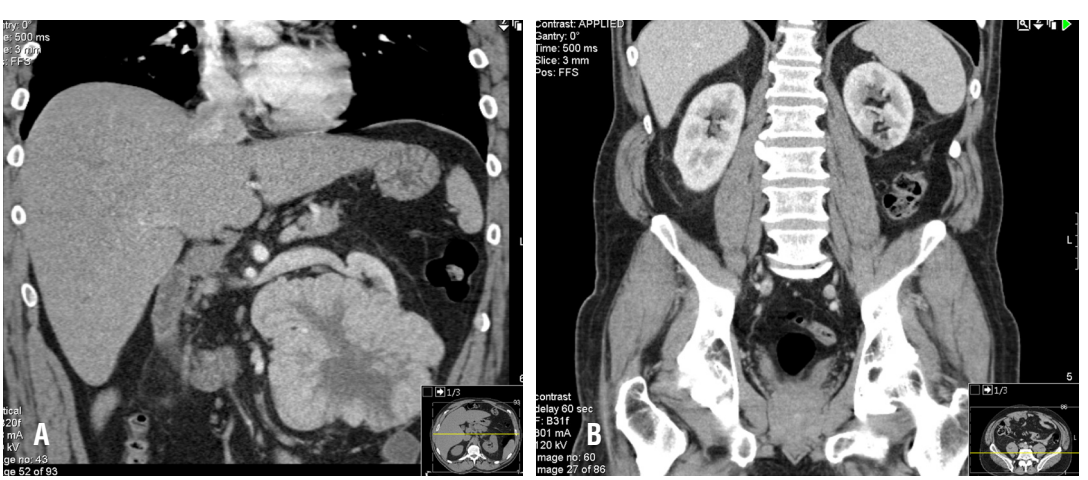
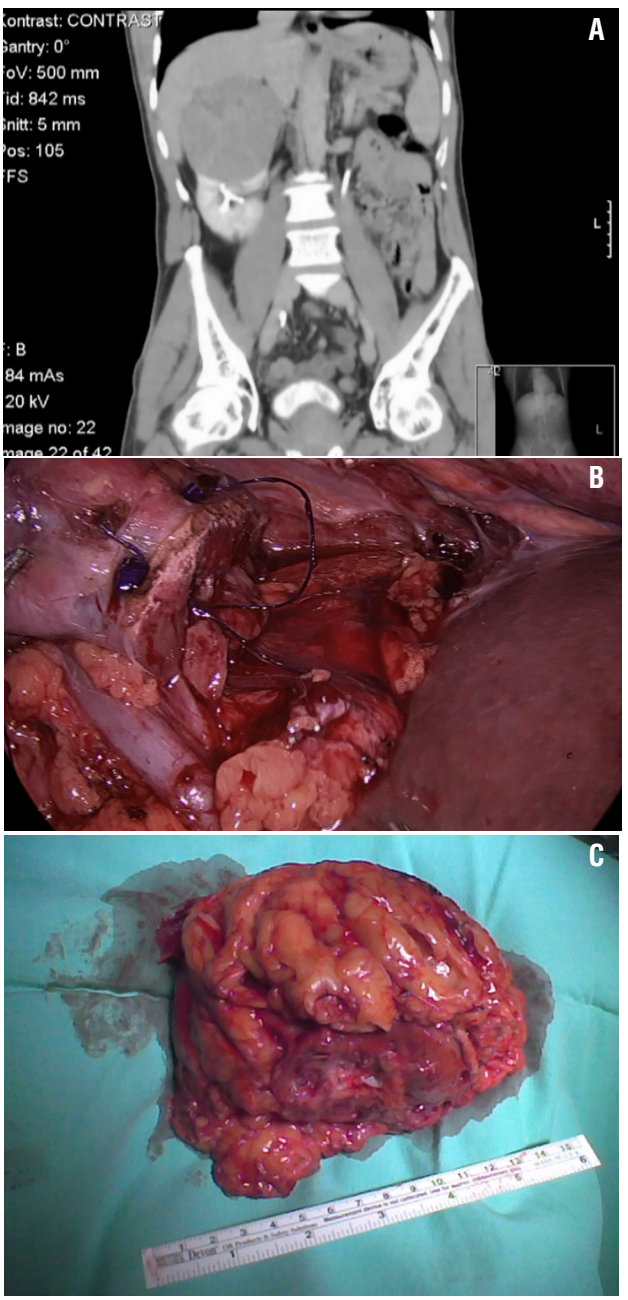


Figure 2 - 10cm right renal tumor. Preoperative imaging (A), intraoperative view of heminephrectomy crater (B) and specimen (C).



tween 2005 and 2016. Patient characteristics are detailed in Table-1. The median age was 66 (IQR 52-78) with male predominance (70.4%). The median radiographic tumor size was 80mm (IQR 72-110). In 2 (7.4%) cases lesions were bilateral. Most of the lesions were central (46.2%) followed by hilar (38.7%) and peripheral (11.5%). Posterior lesions accounted for 53.8% of cases and the upper pole was involved in 53.8% of cases. The majority of masses (63%) were malignant with predominance of the clear cell subtype. All 27 cases were managed laparoscopically with a median operative time of 200 minutes (IQR 180-233) and WIT of 19 minutes (IQR 16-23). Estimated blood loss was 125mL (IQR 88-163). One case was converted to laparoscopic radical nephrectomy due to suspected tumor thrombus in the renal vein. Surgical margins were positive in one renal tumor in a patient with multiple tumors. There was a total of 2 intraoperative complications including a renal vein injury that was repaired intraoperatively and a slipped bulldog clamp resulting in bleeding requiring transfusion. There were 3 postoperative complications, classified as Clavien grade 3: a ureteral injury that was identified postoperatively requiring open ureteroureterostomy on postoperative day 2, urinoma due to obstructing ureteral stone 2 weeks after surgery, requiring stent placement and a delayed bleeding 7 days following the procedure that was managed with angioembolization.

DISCUSSION

Laparoscopic partial nephrectomy is a well-established treatment option for small renal masses that is recommended by the major guidelines for T1 renal masses (1); moreover, it has been shown to have comparable short term and long term cancer control as its open counterpart in several studies (12, 13). Although PN for renal masses ≥7cm has already been shown to be a valid alternative for RN (14, 15), evidence of LPN feasibility for larger renal masses is scarce. All published series on NSS for T2 disease reporting on a mixed surgical approach, mostly open, with very small cohorts of patients undergo laparoscopic surgery.

Currently, at our institution, LPN is the preferred management option for most patients with localized renal mass. Here we described our experience with LPN for renal tumors ≥7cm. In the present study, perioperative outcomes were

Table 1 - Cohort characteristics.

Variable	Number (%)/Median (IQR)
Number of patients	27
Age, years	66 (52-78)
Gender	
Female	8(29.6%)
Male	19(70.4%)
Side	
Right	16(59.3%)
Left	11(40.7%)
Bilateral	2(7.4%)
Concomitant surgery	3(11%)
Centrality	
Central	13(46.2%)
Hilar	10(38.7%)
Peripheral	3(11.5%)
Location*	
Anterior	9(34.6%)
Medial	2(7.6%)
Lateral	1(3.8%)
Posterior	14(53.8%)
Pole location	
Low	8(30.8%)
Mid	4(15.4%)
Upper	14(53.2%)
Tumor size, mm	80(72-110)
OT, minutes	200(181-236)
WIT, minutes	19(16-23)
EBL, mL	150(75-175)
IOC	2(7.4%)
POC	3(11.1%)
Conversion to radical	1(3.7%)
Malignancy	
Benign	10(37%)
Malignant	17(63%)
Positive margins	1(3.7%)
Subtype**	
Clear cell	7(41.2%)
Chromophobe	3(17.6%)
Cystic	2(11.8%)
Papillary	5(29.4%)
Fuhrman	
I	4
II	4
III	5
IV	0

* One case of pelvic kidney, therefore centrality, location and pole location could not be classified. / ** percentage out of malignant masses / **T=**operative time; **WIT=**Warm ischemia time; **EBL=**Estimated blood loss; **IOC=**Intraoperative complications; **POC=**Postoperative complications

encouraging with a median OT of200 minutes (181-236). This is in line with what has been previously reported on minimally invasive partial nephrectomy for large renal masses. Brandao et al. reported a similar median OT when they compared Robot-Assisted LPN (RALPN) outcomes for tumors ≥7cm and ≤4cm (16). Karellas et al. reported a median of 170 minutes on their series of 34 patients with cortical renal masses ≥7cm of which 5 were performed laparoscopically (17).

WIT under 20 minutes is considered safe to minimize renal ischemic damage (18). Our median WIT of 19 minutes is comparable to what has been reported previously for renal masses ≥4cm. In a multi-institutional comparative analysis of RALPN Petros et al. reported a median WIT of 24 minutes for masses >4cm and of 17 minutes ≤4cm (19). Ficarra et al. achieved a WIT of 22 minutes with only a minority of cases with WIT >30 minutes (20). A WIT of 38 however was described by Simmons et al. (21) which the authors attributed to a large portion of complex tumors in their series. Most of the tumors in our series had a central location (46.2% central and 7.6% central-hilar). We believe that our WIT times are in line with the literature and are favorable.

Complication rates in our series include 2 (7.4%) IOC and 3 (11%) POC of grade 3 according to the modified Clavien classification (9). Similar rates were described by Ficarra et al. (20). The same percentage of major complications (10.9%) was seen in Becker et al. series of 91 open partial nephrectomies that included only 1 had RALPN (15).

A low percentage of positive surgical margins is described in various studies of minimally invasive partial nephrectomy (19, 22, 23). We only had one patient with positive margins (5.9% out of all malignant masses). The patient had 2 masses on the upper and lower poles. The margins were positive on the smaller mass that measured 2.5cm.

Our present study has several limitations. Its retrospective, single center nature raises difficulty in the application of these results to general practice. It is also important to

consider that these complex cases were done by a single experienced surgeon and therefore, our results may be challenging to replicate in a different setting. Furthermore, even though perioperative outcomes appear excellent, longer follow-up is required for our oncological outcomes to mature.

CONCLUSIONS

To our knowledge, this series is the first to describe the outcomes of pure LPN for cT2 renal masses aside from scattered reports. In our series, LPN for larger renal masses appears feasible with favorable perioperative outcomes. Additional data are needed to further explore the benefits of minimally invasive surgical approaches to larger renal masses and determine oncological outcomes.

CONFLICT OF INTEREST

None declared.

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Comparison of two different suture techniques in laparoscopic partial nephrectomy

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ABSTRACT

Objective: To comparatively evaluate the traditional interrupted knot-tying and running suture renorrhaphy with Monocryl® in laparoscopic partial nephrectomy (LPN).
Materials and Methods: A retrospective analysis of 62 consecutive patients undergoing LPN using traditional interrupted knot-tying suture renorrhaphy (Group 1; n=31) or running suture technique renorrhaphy with 2-0 monofilament polyglecaprone (Monocryl®, Ethicon) (Group 2; n=31) from December 2011 to October 2015 at the University. All patients underwent LPN performed by an experienced laparoscopic surgeon. The demographic, perioperative and postoperative parameters were compared between the groups, and the effect of both suture techniques on the warm ischemic time (WIT) and trifecta were evaluated.
Results: The running suture renorrhaphy with Monocryl® reduced WIT, estimated blood lost and length of hospitalization stay significantly without increasing postoperative complication rate during LPN in comparison with interrupted knot-tying suture.
Conclusion: The renorrhaphy using the running suture with Monocryl® is an effective and safe technique with the advantage of shortening WIT even in more challenging and larger tumors during LPN.

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Nephrectomy; Laparoscopy; Suture Techniques

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INTRODUCTION

Partial nephrectomy (PN) is recommended for localized renal cancers as an alternative to radical nephrectomy (1). Previous studies reported less renal function loss and decreased risk of chronic kidney disease after PN than radical nephrectomy (2, 3). The laparoscopic approach in PN has become more common in recent years due to the advantages of lower morbidity, shorter hospitalization stay, reduced postoperative pain, and increased patient satisfaction compared to the open approach (4).

The success of the PN technique is based on the negative surgical margin for oncological outcome and the minimum warm ischemia time (WIT) for renal function preservation (5). Laparoscopic PN (LPN) and open PN have similar outcomes in terms of positive surgical margin, but LPN has longer WIT compared to open PN (6, 7) due to technical and ergonomic challenges of laparoscopic suturing. A recent study reported that increased WIT plays an important role in renal functional loss in the early postoperative period in elective LPN (8).

It is important to determine the laparoscopic suture technique in PN that minimizes WIT. Different suture materials and techniques have been suggested to speed up the reconstruction un-

der warm ischemia (9-12). A limited number of studies compared the suture techniques using PDS II, self-retaining barbed sutures, and polyglactin sutures (8, 13).

However, to our knowledge, no study has compared suture techniques using poliglecaprone (Monocryl®; Ethicon) for running suture renorrhaphy. Thus, the aim of this study was to comparatively evaluate two alternative renorrhaphy techniques in laparoscopic PN using Monocryl®.

MATERIALS AND METHODS

Medical data from a series of 143 consecutive patients treated with LPN were evaluated between December 2011 and October 2015. The selected patients were operated on by a single experienced laparoscopic surgeon (HV). Sixty--six patients who were operated on by different surgeons were excluded. Ten patients who were followed up for less than 6 months were also excluded, as well as five patients with a solitary kidney, other cancers, or history of kidney operation. The remaining 62 consecutive patients were included in the study. LPN was performed by traditional interrupted knot-tying suture renorrhaphy (Group 1, n=31), and the last 31 patients were treated with the running suture technique using Monocryl® (Group 2).

All patients were assessed with whole blood count, blood chemistry, and triphasic computed tomography. Preoperative variables included age, gender, body mass index (BMI), Charlson Comorbidity Index, size and location of renal mass, hematocrit (HCT) value, and creatinine value. Perioperative and postoperative parameters included the WIT, operative time, estimated blood loss (EBL), transfusion rate, complications, and length of hospital stay (LOS). Intraoperative and postoperative complications were classified according to SATAVA and Clavien-Dindo classifications (14, 15).

Both groups were followed up for a median of 7 months for the evaluation of renal function and cancer status after LPN. Renal function was assessed by eGFR using the Modification of Diet in Renal Disease (MDRD) study equation (16). The R.E.N.A.L. Nephrometry Score was analyzed by preoperative abdominal triphasic computed tomography by one specialist (17). Trifecta was defined as a combination of negative surgical margin, WIT less than 25 minutes, and zero perioperative complications (18). To test the reproducibility of the assessments of scores, the same examiner reassessed all computed tomography scans two weeks after the first evaluation. The differences between double interpretations were statistically tested.

Surgical technique

Transperitoneoscopic PN was performed in all patients. All surgeries were performed by the same experienced laparoscopic surgeon. All patients were placed in a lateral decubitus position. The pneumoperitoneum was established using the Veress technique. After insufflation of the abdomen, three or four ports were placed. After the renal mass was localized, Gerota's fascia was dissected, leaving the tumor with overlying perinephric fat. The renal artery was dissected and mobilized gently. The renal capsule around the mass was incised to mark the position. After mannitol administration, the renal artery was cross-clamped using a Satinsky clamp or bulldog clamp. The renal vein was not clamped. The tumor was excised with cold scissors from the kidney. The renal mass was placed in an endobag at the end of the surgery.

In Group 1, the interrupted suture technique was performed with 2-0 polypropylene suture (Prolene®; Ethicon, Somerville, NJ) and 3-0 polyglactin 910 suture (Vicryl®; Ethicon, Somerville, NJ). The blood vessels were repaired with 2-0 Prolene®, and nodes were done separately for each vessel. If there was an opened pelvicalyceal system, it was sutured with using 2-0 Vicryl® by interrupted suture closure with knot tying. Then, Surgicel® (Ethicon Endo-Surgery, Somerville, NJ) was placed on the parenchyma defect site. The renal parenchymal defect suture was performed using 2-0 Vicryl® over the Surgicel® by interrupted suture closure with knot tying. After the suture closure was completed, the bulldog or Satinsky clamp was removed.

In Group 2, 2-0 Monocryl® (poliglecaprone 25; Ethicon) suture was used. A Hem-o-lok® clip was applied to the suture's terminal end by

cutting to a length of 20cm. If there was an opened pelvicalyceal system, it was firstly closed with 3-0 polyglactin 910 (Vicryl; Ethicon). After the initial suture using prepared 2-0 Monocryl® suture (poliglecaprone 25; Ethicon), the needle was passed from outside to inside through the renal parenchyma. The tumor bed was then sutured two or three times using running sutures.

At the end, the suture was removed from the renal capsule, tension was applied, and the suture was locked with Hem-o-lok® clips (Teleflex® Medical, Research Triangle Park, NC). The clamps were removed, and the tumor bed was inspected to ensure hemostasis. If necessary, additional sutures were supplied or only one Surgicel® (Ethicon Endo-Surgery, Somerville, NJ) was placed in the tumor bed. The outer parenchymal layer was repaired as described above after the clamps were removed.

Statistical analysis

The data were statistically analyzed by using SPSS 23.0 (SPSS Inc, Chicago, Ill, USA). The variables were compared according to groups. The Shapiro-Wilk test was applied to test the normality of continuous variables. The normally distributed variables are presented as the mean±standard deviation and compared using a student's t-test. The non-normally distributed variables are presented as the median (minimum-maximum) and compared using the Mann-Whitney U test. The Wilcoxon signed rank test was used for non-normally distributed related samples. Nominal data are presented as a number or percentage and compared using the chi-square test. A p-value less than 0.05 was considered as statistically significant.

RESULTS

The mean age was 57.8±19.5 years. There were no significant differences between the groups with respect to age, gender, BMI, Charlson Comorbidity Index, preoperative HCT level, preoperative creatinine, preoperative eGFR, or chronic kidney failure rate (Table-1). The intra-examiner correlation coefficient for repeated scores was 0.93, indicating high reliability. The locations and pathology of the renal mass and R.E.N.A.L. Nephrometry Score were found to be similar in both groups, although the renal mass size was significantly higher in Group 2 (Table-1). Renal mass sizes were 3.0±1.03 cm and 3.97±1.47cm for Groups 1 and 2, respectively (Table-1). The median R.E.N.A.L. Nephrometry Scores were 4 (4-6) and 5 (4-10) for Groups 1 and 2, respectively (Table-1). The positive surgical margin rate did not differ between the groups. Positive surgical margins were 2 and 1 for groups 1 and 2, respectively (p=0.612). None of the patients showed progression during a median of 36 months of follow-up.

The median WITs were 21 (13-42) and 13 (6-26) minutes for Groups 1 and 2, respectively, and it was significantly lower in Group 2 than in Group 1 (p<0.001). WIT was over 25 minutes in six cases in Group 2 and in only one case in Group 1. The HCT differences and red blood cell transfusion rates were similar in both groups on the first day, but EBL was higher in Group 1 (Table-2). The perioperative opened pelvicalyceal system rate and operative time were similar between groups (Table-2). There were no significant differences between the groups with regard to perioperative and postoperative complications (Table-2). In Group 1, diaphragmatic rupture was treated with laparoscopy in the same season by the same surgeon. In Group 2, one patient underwent angiography one week after the operation for late hemorrhage. None of the cases were converted to open surgery. However, LOS was lower in Group 2 (2.55±0.96 days) than in Group 1 (3.23±1.26 days; p=0.02, Table-2). Trifecta rates were similar in both groups.

The median serum creatinine levels were significantly increased and eGFR was significantly decreased after LPN in both Groups. However, there were no significant differences between the preoperative values and 6-month follow-up in both Groups (Table-3). The creatinine and eGFR differences were similar in both Groups (Table-2).

DISCUSSION

LPN is a minimally invasive approach for localized renal tumors (1). It has shown

Table 1 - Comparison of demographic, perioperative, and pathological outcomes between interrupted knot-tying suture renorrhaphy and running suture renorrhaphy with polyglecaprone

		Group 1	Group 2	p
Age		53 (32-78)	59 (38-80)	0.123
Gender (Female/Male)		9/22	13/18	0.426
Charlson Comorbidity Index		3 (2-5)	3 (2-5)	0.052
BMI		27.21 (17-47)	27.12 (22-47)	0.833
Preoperative Hct		14.2 (10.3-18)	13.0 (10.3-16.8)	0.058
Preoperative creatinine		0.8 (0.6-2.8)	0.7 (0.6-1.9)	0.250
Preoperative eGFR (mL/min/1.73m^2)		93.77±24.74	92.81±27.60	0.885
CKD 3A or more	3A	1	0	
	3B	1	2	0.597
	4	1	1	
Side (right)		54.5%	45.5%	0.611
Localization	Upper	9	8	
	Middle	11	11	0.950
	Lower	11	12	
Pathology of renal mass	Clear Cell RCCa	10	14	
	Chromophobe RCCa	6	1	0.804
	Papillary RCCa	7	8	
	Multicystic RCCa	2	2	
	Benign	6	6	
Mass size (cm)		3 (2-5)	4 (2-8)	0.006
RENAL score		4 (4-6)	5 (4-10)	0.068

CKD = Chronic Kidney Disease stage

comparable oncologic outcomes to open PN while providing shorter hospital stay, decreased convalescence, and reduced pain (4). Despite the benefits of LPN, it is a technically demanding procedure with a higher rate of intraoperative complications and longer WIT compared to open surgery (19). Becker et al. (20) emphasized that WIT is the strongest modifiable surgical risk factor for postoperative chronic kidney disease. Lane et al. (19) also reported that the major surgical factor in renal function was WIT among the patient-specific, tumor-specific, and surgical factors after PN. Funahashi et al. (21) found that a WIT of 25 minutes or more caused irreversible damage distributed diffusely throughout the operated kidney. Thompson et al. (22) reported that with prolonged WIT, ischemia reperfusion was positively associated with short- and long-term renal consequences, and they suggested that every minute counts for the severity of damage when the renal hilum is clamped. Therefore, WIT should be shortened as much as possible to help preserve renal function (20, 22).

Link et al. (23) stated that longer ischemia time in LPN is likely to result in difficulty in renorrhaphy with laparoscopy. Intracorporeal suturing was the most time-consuming stage during LPN. Thus, simplifying the suture

Table 2 - Comparison of perioperative and postoperative outcomes between groups.

		Group 1	Group 2	p
WIT (min)		21 (13-42)	13 (6-26)	<0.001
WIT ≥25 min		6 (19.4%)	1 (3.2%)	0.052
Positive surgical margin		2 (6.5%)	1 (3.2%)	0.612
Operative time (min)		120 (60/210)	120 (60/210)	0.656
Estimated blood loss		85 (30-300)	50 (30-450)	0.010
Δ Hct 1		-1.6 (-5.2/0.10)	-1.7 (-4.6/0.2)	0.330
Δ Creatinine day 2		-0.1 (-0.7/0.1)	0 (-0.6/0)	0.877
Δ Creatinine month 6		0 (-0.9/0.3)	0 (-0.2/0.1)	0.719
eGFR month 6 (mL/min/1.73m^2)		104 (18-125)	95 (26-133)	0.481
ΔeGFR6 (mL/min/1.73m^2)		-7 (-51/19)	-6 (-31/17)	0.619
ΔeGFR6 (mL/min/1.73m^2)		0(-20/39)	0 (-4/8)	0.680
SATAVA	1	5 (16.1%)	4 (12.9%)	
	2A	3 (9.7%)	3 (9.7%)	0.744
	3	0	1 (3.2%)	
Trifecta rate		71%	80.6%	0.554
Complication Clavien	1	5 (16.1%)	6 (19.4%)	0.809
	2	2 (6.5%)	1 (3.2%)	
LOS (day)		3 (2-7)	2 (2-6)	0.008

Δ **Creatinine 6** - changes in creatinine in postoperative 6 month from baseline
Δ **Hct 1** - changes in hematocrit creatinine in postoperative first day

Table 3 - Renal function changes overtime between groups.

		Preoperative	Postoperative day 2	Postoperative month 6	p1	p2
Median Creatinine level	G1	0.8 (0.6-2.8)	0.8 (0.6-3.5)	0.8 (0.6-3.7)	0.02	0.929
	G2	0.7 (0.6-1.9)	0.8 (0.6-2.4)	0.7 (0.6-2.0)	0.01	0.414
eGFR (mL/min/1.73m^2)	G1	100 (25-138)	93 (18-117)	104 (18-125)	0.014	0.221
	G2	95 (29-133)	90 (22-115)	95 (26-133)	0.03	1

p1 = statistical significance between preoperative and postoperative 2 day value; **p2 =** statistical significance between preoperative and postoperative 6 month value.
G1 = Group 1; **G2 =** Group 2

technique could reduce WIT and better preserve renal function. There are limited numbers of studies considering the effects of simplifying the suture technique on WIT, and none of them used polyglecaprone sutures (9-13). Therefore, the present study aimed to investigate the efficacy of renorrhaphy using running suture technique with monofilament polyglecaprone (Monocryl®, Ethicon) on reducing renorrhaphy time and WIT during LPN in comparison with interrupted knot-tying suture renorrhaphy.

The main goals of PN are providing WIT less than 25 minutes, as suggested by Thompson et al. (22), as well as negative surgical margins for oncological safety without complications defined as trifecta (18). In this study, the trifecta rate was

similar between groups, but WIT was significantly reduced in the group undergoing running suture technique renorrhaphy with Monocryl®. Erdem et al. (12) reported a significantly reduced WIT of 9 minutes in a group treated by self-retaining barbed suture rather than polyglactin suture. Jeon et al. also reported a shorter WIT of 7.4 minutes in a barbed suture group than a polyglactin suture group (24). The advantage of self-retaining barbed suture (V-Loc) in decreasing WIT might result from passing through the tissue in only one direction, preventing the suture from slipping and eliminating the need to maintain continuous tension while suturing and tying knots. In another study, the mean WIT was 21.5 minutes in running suture renorrhaphy using PDS suture, while it was 32.3 minutes in the interrupted suture group (13).

PDS II® suture was reported to be 1.4 times as stiff as Monocryl® suture (25). Bezwada et al. (25) showed that the lower stiffness and pliability of Monocryl® suture resulted in excellent handling and tensile properties with minimal resistance during passage through tissue, and Monocryl® had very good tactile feedback. Vicryl® is a braided multifilament suture that causes resistance when passing through the kidney during LPN. Monocryl® suture stretches more than Vicryl® and PDS at higher loads (26). In this study, Monocryl® suture was preferred for providing faster parenchymal suturing with minimal tissue damage, and it is also more cost-effective than V-Loc.

The median WIT was reduced 8 minutes in patients treated with running suture using Monocryl® than traditional renorrhaphy, despite larger tumors in running suture renorrhaphy Group. Likewise, WIT was higher than 25 minutes for only one patient in Group 2 but for 6 patients in Group 1. During running suture renorrhaphy, the surgeon does not need to see the bleeding vessels clearly to control the hemorrhage after unclamping. Thus, this technique facilitates renal parenchymal suturing and gives confidence to the surgeon for unclamping before repairing the renal parenchymal defect. These features also contribute to decreasing WIT.

The postoperative decline of renal function after LPN was recovered to preoperative baseline values after 6 months post-operation in both groups. There were no significant differences between the groups with regard to renal function. WIT was significantly lower in Group 2. The median WIT was 21 minutes in Group 1, and only 6 patients had WIT ≥25 minutes, which could be a reason for the similarity of renal function.

HCT difference from the first day, transfusion rate, operative time, perioperative and postoperative complications, and trifecta rate were similar in both Groups. However, EBL was found to be higher in Group 1 than in Group 2. Olweny et al. (27) reported that barbed sutures reduce the incidence of serious intraoperative bleeding. Similar results were observed with other V-Loc series (24, 28). Our results are in accordance with these studies. In Group 2, one patient underwent angiography one week after operation for late hemorrhage.

After minimally invasive PN, Omea et al. (29) found an unexpectedly high rate of 21.7% for asymptomatic unruptured renal artery pseudoaneurysm detected by computed tomography arteriography in the early period. However, in a systematic review and comparative analysis, Jain et al. (30) reported that the rate of symptomatic pseudoaneurysm was 1.96%. In our study, only one patient in Group 2 underwent angiography one week after the operation for symptomatic pseudoaneurysm. This ratio represents 1.6% of the total patients, which is in accordance with the literature. It is hard to make a conclusive decision about the comparison of the groups with regard to pseudoaneurysm due to the limited number of the patients.

LOS was shorter in the running suture renorrhaphy Group than the traditional renorrhaphy Group. Running suture renorrhaphy provides a decline of 0.7 days in mean LOS. However, this study cannot provide a definite conclusion about this issue.

One of the limitations of this study is its retrospective nature. However, both Groups were treated by the same surgeon, who had experience with at least 1.000 laparoscopic surgeries, including radical nephrectomy, PN, radical prostatectomy, and radical cystectomy. The same experienced surgeon used the standard surgical technique. Secondly, renal mass, was smaller in the traditional renorrhaphy Group. However, WIT was longer in the tradi-

tional renorrhaphy group, although renal mass was smaller. Thirdly, the sample size was small, and the results should be confirmed with more cases.

CONCLUSIONS

Renorrhaphy using running sutures with Monocryl® is an effective and safe technique that shortens WIT. EBL and LOS are also decreased with this technique.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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The influence of previous robotic experience in the initial learning curve of laparoscopic radical prostatectomy

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ABSTRACT

Introduction: This study analyzed the impact of the experience with Robotic-Assisted Laparoscopic Prostatectomy (RALP) on the initial experience with Laparoscopic Radical Prostatectomy (LRP) by examining perioperative results and early outcomes of 110 patients. LRPs were performed by two ro-botic fellowship trained surgeons with daily practice in RALP.

Patients and Methods: 110 LRP were performed to treat aleatory selected patients. The patients were divided into 4 groups for prospective analyses. A transperitoneal approach that simulates the RALP technique was used.

Results: The median operative time was 163 minutes (110-240), and this time significantly decreased through case 40, when the time plateaued (p=0.0007). The median blood loss was 250mL. No patients required blood transfusion. There were no life-threatening complications or deaths. Minor complications were uniformly distributed along the series (P=0.6401). The overall positive surgical margins (PSM) rate was 28.2% (20% in pT2 and 43.6% in pT3). PSM was in the prostate apex in 61.3% of cases. At the 12-month follow-up, 88% of men were continent (0-1 pad).

Conclusions: The present study shows that there are multiple learning curves for LRP. The shallowest learning curve was seen for the operative time. Surgeons transitioning between the RALP and LRP techniques were considered competent based on the low perioperative complication rate, absence of major complications, and lack of blood transfusions. This study shows that a learning curve still exists and that there are factors that must be considered by surgeons transitioning between the two techniques.

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INTRODUCTION

Laparoscopic Radical Prostatectomy (LRP) was first described by Schuessler in 1992, and the first large series was published by Guilloneau (1, 2). As LRP becomes more established with more long-term follow-up studies available, this approach is showing solid oncological and functional results. The major barriers to the adoption of LRP are the technically challenging nature of the procedure and a steep learning curve (3).

The challenges presented by skill acquisition were overcome in part by the introduction of the da Vinci Surgical System that facilitates robotic-assisted laparoscopic prostatectomy (RALP). In Europe and the United States, RALP is now displacing radical retropubic prostatectomy as the gold standard surgical approach to treat localized pros-

tate cancer, such that RALP may eventually completely replace LRP (4). However, RALP does have limited availability, training facilities and higher direct costs, which is an area of concern given the economic considerations that are becoming increasingly important for reasonable health care resource allocation in light of budgetary constraints and limited resources, especially in developing countries (5).

Surgeons who have experience with LRP could obtain excellent operative outcomes with RALP, accelerate procedural uptake and eliminate the RALP learning curve because of the similarities between the techniques (6). Moreover, given that RALP replicates the laparoscopic technique, experience with RALP should allow surgeons to perform LRP without a learning curve. This situation can occur in developing countries and in regions without access to robotic facilities. However, whether proficiency with one surgical technique ensures proficiency in the other is unclear (7, 8).

This study analyzed the impact of the experience with RALP on the initial experience with LRP by examining perioperative results and early oncological and functional outcomes of 110 prostate cancer cases.

MATERIALS AND METHODS

Between November 2010 and August 2012, 110 LRP were performed by two surgeons to treat aleatory selected patients with clinically localized prostate cancer referred to the Instituto do Câncer do Estado de São Paulo (Cancer Institute of the State of São Paulo). Both surgeons participated in LRP during the residency with the same surgeon and were experienced in upper tract laparoscopic surgeries, coordinating together the oncologic laparoscopic program, mentoring urology residents and performing themselves at least 2-3 challenge surgeries weekly (partial laparoscopic nephrectomy, challenge radical laparoscopic nephrectomy) (9). The surgeons also performed post residency two years of fellowship training in RALP in the United States. At the time of the study, both were RALP proctors, mentoring robotic surgeries in another institution, and used to perform themselves 2-4 RALP weekly for the past three years before the beginning of the study. Nevertheless, it was not possible to evaluate the previous surgical experience of both surgeons because they used to perform in many institutions.

The patients were operated by the surgeons alternately and ordered chronologically. Data were collected prospectively and all the patients were divided into 4 groups of approximated size for analyses. A transperitoneal approach that simulates the RALP technique, as described by Patel et al. (10), was used for all patients, and neuro-vascular bundle preservation was attempted in clinically localized cancers. All complications were graded according to the Clavien-Dindo classification. Prostatic Specific Antigen (PSA) tests were performed after 6 and 12 months. Biochemical recurrence was defined as PSA >0.2µg/L or PSA that never fell below 0.1µg/L. Continence was defined as 0 or 1 (confidence) pad per 24h. All specimens were reviewed by a specialist uropathologist. Positive surgical margins (PSM) were defined as the presence of tumor at the inked surface of the specimen (11).

Statistical analysis was performed with the IBM® SPSS® Statistics 23 program. Statistical analyses were carried out using Fisher's exact test and non-parametric Kruskal-Wallis test for qualitative variables. ANOVA was used to compare continuous values and the Tukey test was applied to explore differences between groups. Logistic regression curves were used to represent the tendencies relative to experience.

RESULTS

Statistical analyses found no statistical difference in age, body mass index, PSA, clinical stage, pathologic staging, and biopsy Gleason score between each phase of the learning curve (Table-1).

The median operative time was 163 minutes (range 110-240), with a significant reduction along the experience (p=0.0007) (Table-2). After a significant decrease until case 40, a plateau was reached. After case 90, a new reduction appeared (Figure-1).

The median blood loss during surgery was 250mL (range 50-1000mL), and there was

Table 1 – Demographic and Clinical Characteristics.

		Group				p value
Characteristic	Total	1	2	3	4	
Age (years)						
Mean	61.7	61.7	63.7	61.2	60.2	0.244[1]
SD	6.30	8.18	5.50	4.91	6.24	
Body Mass Index						
Mean	25.97	25.49	27.10	25.84	25.35	0.180[1]
SD	3.22	2.96	2.70	4.12	2.992	
PSA (µg)						
Median	7.5	7.5	8.3	9.3	5.8	0.072[2]
Range	6.5-63.53	6.9-23.5	6.72-62.4	7.22-16.7	3.26-16.2	
Clinical Stage, (%)						
cT1	64 (58.2)	18 (66.7)	11 (40.7)	17 (63.0)	18 (64.3)	
cT2	45 (40.9)	9 (33.3)	16 (59.3)	10 (37.0)	10 (35.7)	0.579[3]
Biopse Gleason Score n(%)						
<7	77 (70.0)	21 (77.8)	17 (63.0)	18 (66.7)	21 (75.0)	
7	26 (23.7)	6 (22.2)	7 (25.9)	7 (25.9)	6 (21.4)	0.246[3]
>7	6 (5.5)	0 (0.0)	3 (11.1)	2 (7.4)	1 (3.6)	

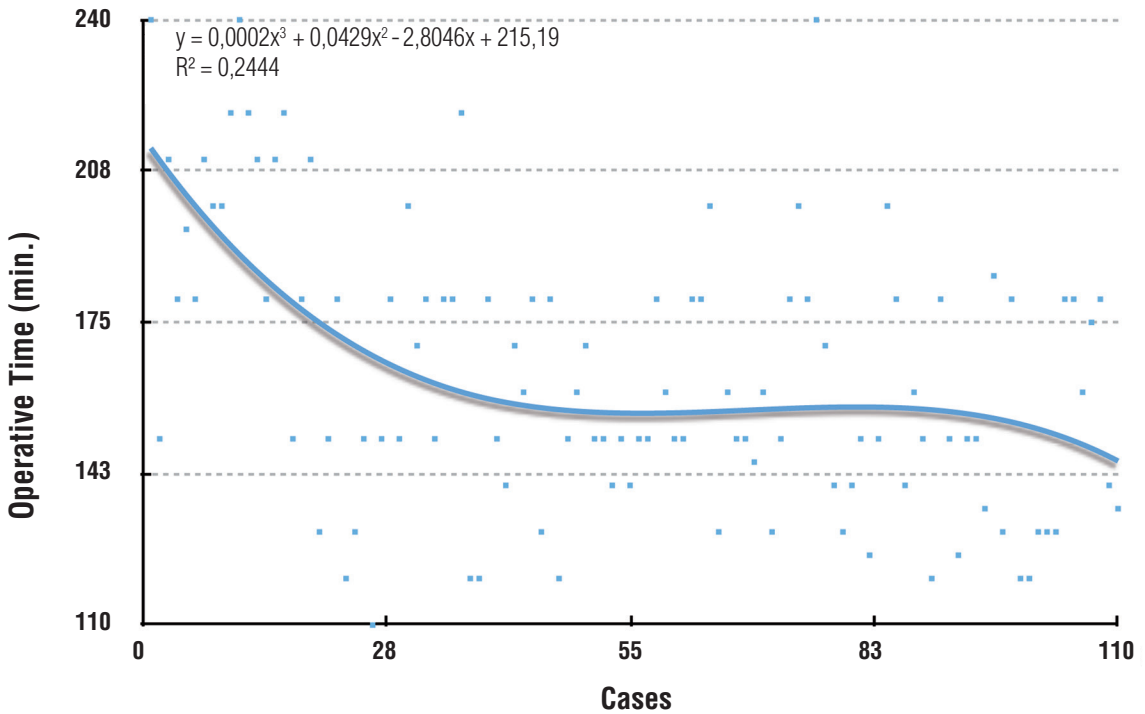
Note: [1] ANOVA, [2] Kruskal-Wallis, [3] Fisher.

Table 2 - Perioperative Data.

		Group				
Characteristic	TOTAL	1	2	3	4	p
Operative Time (min)						
Mean	163.54	182.41	160.37	160.93	151.38	0.0007[1]
SD	29.97	36.88	24.41	25.27	23.98	
Blood Loss (mL)						
Median	250	200	250	250	300	0.6393[2]
Range	250-950	250-900	250-900	300-750	275-800	
Hospital Stay (days)						
Median	1	1	1	1	1	0.0593[2]
Range	0-13	1-2	0-2	0-2	0-13	
Continence (%)	88.0	74.1	92.3	88.9	96.4	0.1012[3]
Complication (%)						
Clavien grade I / II	8 (7.3)	3 (11.1)	2 (7.4)	1 (3.6)	1 (7.2)	0.5619[3]
Clavien grade III	8 (7.3)	2 (7.4)	0 (0.0)	4 (14.3)	2 (7.1)	0.2644[3]
T Stage (%)						
T2	70 (63.6%)	18 (69.2%)	19 (70.4%)	18 (66.7%)	15 (51.7%)	0.2265[3]
T3	39 (35.4%)	8 (30.8%)	8 (29.6%)	9 (33.3%)	14 (48.3%)	

Note: [1] ANOVA, [2] Kruskal-Wallis, [3] Fisher.

Figure 1- Learning curve for operative time.



no statistical difference in the series (P=0.6393) (Table-2). No patients required a blood transfusion. Complications were uniformly distributed along the series (P=0.6401) (Table-2). Rectal lesions occurred in 2 patients (1.81%), and were repaired intra-operatively. Conversion was necessary in 1 (0.90%) patient due to fibrosis after biopsy. There were two incisional hernias at the vertical infra umbilical port that required surgery during the first year of follow-up. In addition, there was one clinical anastomotic leak that required bilateral ureteral stents, one anastomotic stricture that required internal urethrotomy, and one patient required cystoscopy to reposition the urethral catheter on the first post-operative day. There were no life-threatening complications or deaths (Clavien IV and V) in the series.

The overall PSM rate was 28.2%, corresponding to 20% in pT2 and 43.6% in pT3. There was no clear decreasing tendency and the PSM was persistently between 25 and 30% (Figure-2). A comparison of the pT2 (p=0.3818), pT3 (p=0.7993) and overall (P=0.6661) groups showed no statistical difference. PSM was in the prostate apex in 61.3% of cases and the location showed no difference with experience (p=0.7533).

At the 12-month follow-up, 88% of men were continent. The continence rate tended to decrease up to case 70 when it reached a plateau of ~95% continence rate (Figure-3).

DISCUSSION

The feasibility and reproducibility of LRP have been established and long-term oncological and functional outcomes have been shown to be comparable with open retropubic radical prostatectomy. LRP offers advantages over open radical prostatectomy in terms of decreased blood loss, analgesic requirements, hospitalization and convalescence periods (12). However, the steep learning curve is a hurdle to wide uptake of this surgical approach. Previous studies showed that fellowship training significantly reduces the lear-

Figure 2 - Positive surgical margin rate.

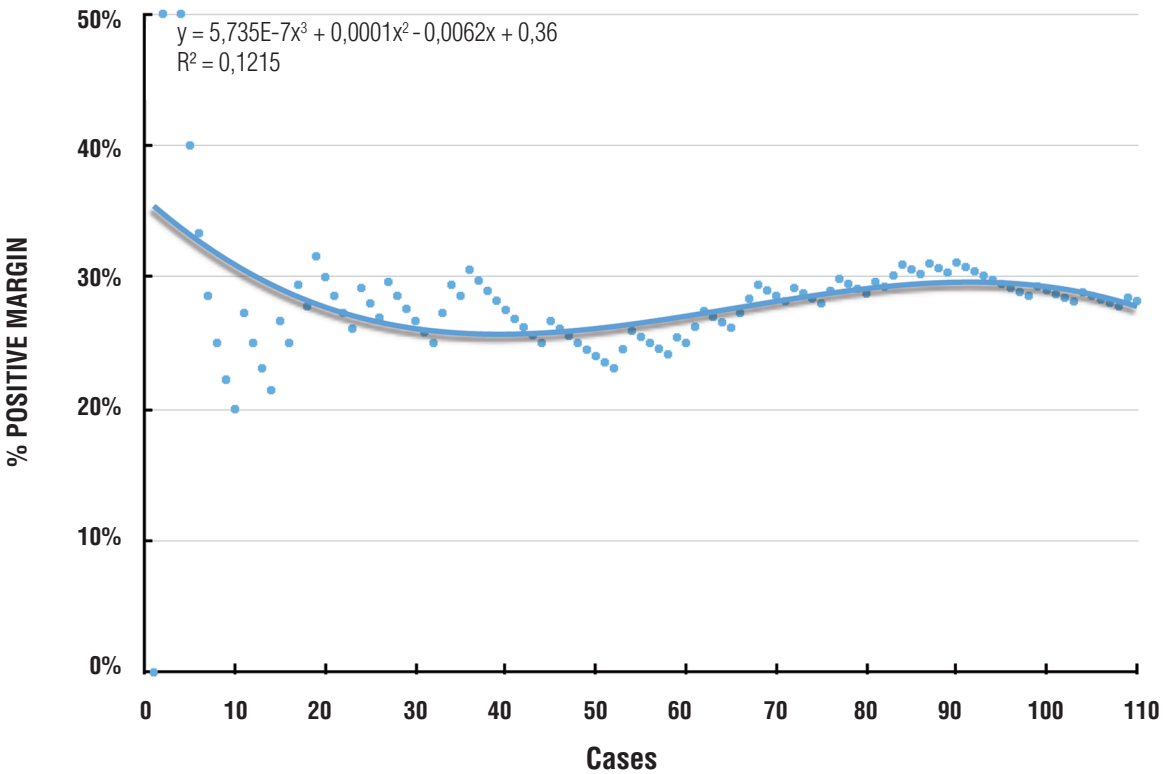
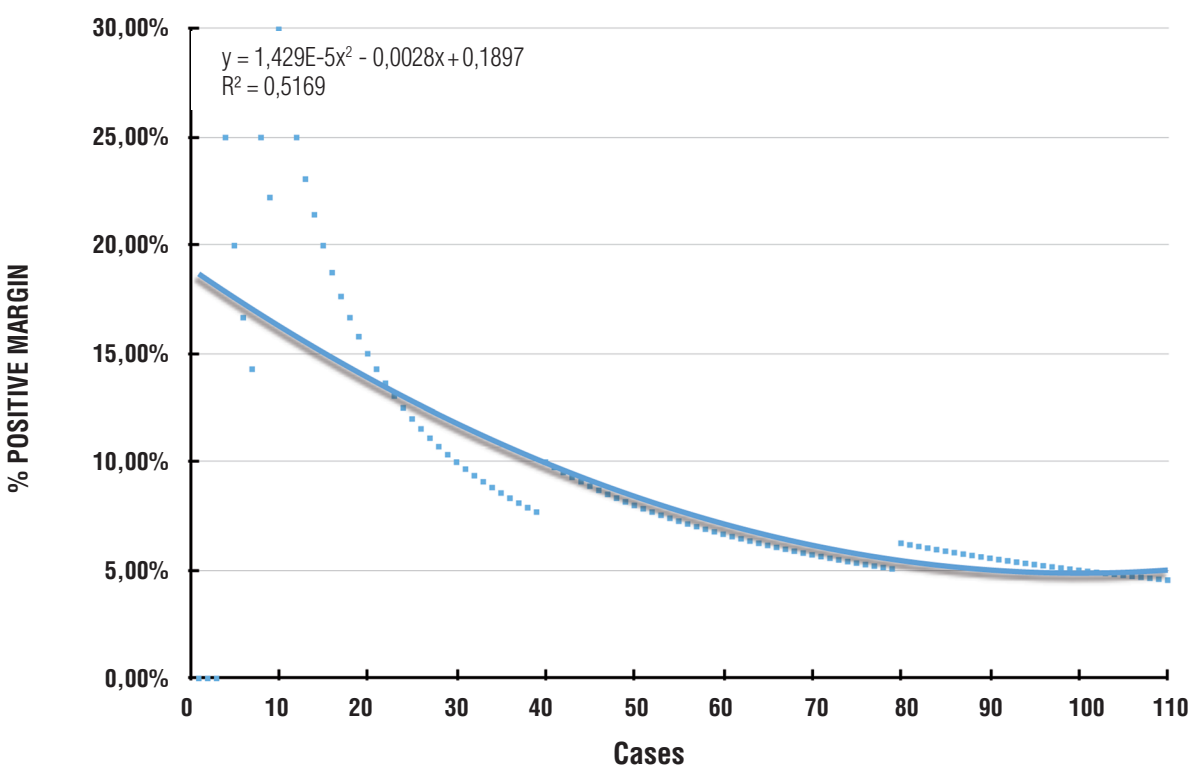


Figure 3 - Incontinence rate.



ning curve without compromising safety or outcomes (7, 13-15).

A limited number of mentorship programs in LRP currently exist in developing countries, and most surgeons who perform LRP were trained in the United States or Europe, where RALP now accounts for 95% of minimally invasive prostate cancer treatment (6). Due to budget limitations, this transition to a robotic surgical interface will be much more gradual in developing countries (9, 16).

Although the open radical prostatectomy would be a more realistic option considering the cost saving (17), LRP remains a cost-effective minimally invasive surgical option especially when the operative time is shorter than 4 hours and the use of reusable instruments are optimized (5).

Many studies have assessed the learning curve of RALP for surgeons transitioning from LRP to the robotic technique. These studies showed that technical similarities between LRP and RALP can help minimize the learning curve, particularly when surgeons are already proficient in antegrate prostate dissection techniques and laparoscopic principles (18). It was suggested that the skill set in other laparoscopic procedures, such as radical and partial nephrectomy is transferable to LRP (16). Hence, the learning curve for LRP would likely be lessened for laparoscopically experienced and RALP-trained surgeons, which in turn translates into improved initial outcomes for patients.

This study analyzed the early results of the first 110LRP performed by two surgeons experienced in RALP and upper tract laparoscopy at a university teaching hospital to describe the challenges that surgeons trained in RALP face when they try to initiate practice in areas without the robotic system.

The mean operative time was 163.5 minutes, with no cases requiring more than 240 minutes, and there was only one conversion. After 40 cases, the learning curve plateaued at 150 minutes, which is comparable to results from large series studies. Even recognizing that the operative time is not as relevant to the patient, the value could represent technical difficulties or indicate the lack of progression in any step of the surgery (3). A similar abrupt reduction in the operative time after only a few cases was described by several studies, suggesting that 15 to 25 cases is sufficient to achieve a mean operative time of 3-4 hours, and could represent the adaptation to laparoscopic instruments and maneuvers, suggesting that the principal steps were already learned (16, 19). The amount of blood loss and length of hospital stay were stable and comparable to large series. There were no cases with high blood loss volumes and none of the patients required transfusions (14, 20).

The complication rate was 14.6%, with half being Clavien I/II and half being Clavien III. No Clavien IV or V complications were seen. There was only one open conversion due to bleeding after prostate removal that may have been caused by post-biopsy fibrosis. Mitre et al. found a significant reduction in the complication rate, mainly limited to transfusions and urinary extravasation (9). Hruza et al. analyzed the complications in 2.200LRP cases and described complication rates of 21.7% (Clavien 1 and 2) and 11.5% (Clavien 3-5), as well as a significant reduction in minor complications when comparing the first and last 200 cases (11). Siqueira et al. warned about the possibility of major complications to occur during the learning curve and found no difference between the trans and extra peritoneal approach (21) The lack of a significant reduction in complications may have been due to the low complication rate since the outset of our study, and favors the hypothesis that expertise transfers between the techniques.

LRP is considered to be a well-established procedure with proven benefits in terms of reduced preoperative bleeding and need for transfusion (20). After 1138 cases, Soares et al. found a median bleeding of 200mL (10-1.300mL) that stabilized after 150 cases and a transfusion rate of 0.5%, which is similar to that seen by Stolzenburg et al. among 2.000 cases (13, 22). Moreover, our initial results were comparable to those described in a study by Good et al., which showed reduced bleeding after 500 cases (23).

Since the main goal of LRP is oncologic success, initial experience could be based on a PSM rate that should be 0%, but in practice 15% is considered acceptable. Our PSM rates were 20% in pT2 and 43.6% in pT3 with no statistical improve-

ment with experience, were comparable to many previous reports (2, 3, 11, 12, 20, 24), although it was higher than series with PSM rates between 7.2 and 13.9%, probable due to the higher proportion of pT3 in our series (22, 25). Many studies also described a plateau in the PSM after 250 cases (3, 7, 23), while for others the plateau occurred after 100 cases (26). All of these studies defended the need for a continuous evaluation of outcomes, modulated teaching methods, and revision of video recordings to provide better outcomes and minimize the learning curve. However, more experience-between 500 and 1.000 cases-may be needed to achieve a PSM plateau for pT3 tumors, which may have the steepest learning curve (23, 27).

The high PSM rates in our series were associated with a high incidence of apical margin that was present in 61.3% of PSM. This outcome could be due to the limited number of cases that was not sufficient to overcome the initial learning curve, to the attempts to preserve the neuro-vascular bundles in clinically under staged patients and to technical difficulties associated with attempts to reproduce the robotic technique in the apex dissection in the absence of the freedom afforded by articulating instruments (6).

McNeill et al. suggested that frozen sections be routinely used to reduce the apical margins that accounted for 53% of their overall PSM (26). Meanwhile, Good et al. compared the learning curves and outcomes for LRP and RALP and found that RALP yielded significant benefits to patients compared to LRP, especially outcomes that were linked to better apical dissection (apical PSM and continence), and considered that this improvement may be related to the technological platform rather than factors associated with individual surgeons (23).

For continence, we had concern that our patients would find the international validated questionnaire to be too complicated. Moreover, different definitions of continence may contribute to a difference of about 10% in continence rates. As such, we chose to use the simplified criteria of 'no drops, no pad', that, in practice, includes the patients who uses one pad a day for his reassurance as well as the patient who leaks a few drops but does not uses a pad. In this study, the continence rate plateaued at 70 cases wherein 95% of patients were continent. This result supports the thinking that previous experience with RALP may facilitate competence with LRP. A study by McNeill et al. described similarly a plateau after 250 cases following modular training. Similar overall continence rates have been described, however more cases are required to reach overall continence rates that exceed 95% (22, 26).

Our study has several limitations. The non - randomized nature, relatively few patients and the short follow-up that limits the usage of biochemical recurrence in our study. Erectile dysfunction was not evaluated in our series due to no application of validated questionnaires. No quality of life measures were recorded to investigate patient perceptions of their outcome. It should be considered that any previous radical prostatectomy experience has potential to improve the results independent of the surgical technique utilized.

In addition, this data relates to two specific surgeons and the results may not necessarily extrapolate to other centers. This limits the applicability of our comments to all surgeons transitioning between the techniques of radical prostatectomy, as differing levels of aptitude and prior exposure will heavily impact on the results. The informative power of an institutional learning curve might be limited, because it is difficult to determine if the surgeons were equally skilled or if one struggle versus the others (11).

CONCLUSIONS

The present study shows that there are multiple learning curves for LRP, and support the idea that self-evaluation and continuous monitoring of surgical outcomes are needed to develop interventions that will improve surgeon performance. The shallowest learning curve was seen for the operative time. The PSM learning curve may need additional experience to improve the results, principally in the apical margin. Surgeons transitioning between the RALP and LRP techniques were considered competent based on the low perioperative complication rate, absence of major complications, and

lack of blood transfusions. This study provides an overview of early LRP results for two surgeons trained in RALP and shows that a learning curve still exists and that there are factors that must be considered by surgeons transitioning between the two techniques.

ABBREVIATIONS

LRP = Laparoscopic Radical Prostatectomy
RALP = Robotic-Assisted Laparoscopic Prostatectomy
PSA = Prostatic Specific Antigen
PSM = Positive Surgical Margins

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Ethical standard

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

Informed consent

Informed consent was obtained from all individual participants included in the study.

CONFLICT OF INTEREST

None declared.

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Quality of life and urolithiasis: the patient – reported outcomes measurement information system (PROMIS)

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ABSTRACT

Background: With a high rate of recurrence, urolithiasis is a chronic disease that impacts quality of life. The Patient Reported Outcomes Measurement Information System is an NIH validated questionnaire to assess patient quality of life. We evaluated the impact of urolithiasis on quality of life using the NIH-sponsored PROMIS-43 questionnaire.

Materials and Methods: Patients reporting to the kidney stone clinic were interviewed to collect information on stone history and demographic information and were asked to complete the PROMIS-43 questionnaire. Quality of life scores were analyzed using gender and age matched groups for the general US population. Statistical comparisons were made based on demographic information and patient stone history. Statistical significance was $P<0.05$.

Results: 103 patients completed the survey. 36% of respondents were male, the average age of the group was 52 years old, with 58% primary income earners, and 35% primary caregivers. 7% had never passed a stone or had a procedure while 17% passed 10 or more stones in their lifetime. Overall, pain and physical function were worse in patients with urolithiasis. Primary income earners had better quality of life while primary caregivers and those with other chronic medical conditions were worse. Patients on dietary and medical therapy had better quality of life scores.

Conclusions: Urolithiasis patients subjectively have worse pain and physical function than the general population. The impact of pain on quality of life was greatest in those patients who had more stone episodes, underscoring the importance of preventive measures. Stone prevention measures improve quality of life.

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INTRODUCTION

Urolithiasis is a common disease with an estimated prevalence of 13% in men and 7% in women and a rising incidence (1, 2). Recurrence of stones is a common problem with a recurrence rate of 2-5% every year, and the risk of recurrence increases with each stone episode (3). For many, urolithiasis is a chronic disease and chronic diseases are known to have a significant impact on the quality of life (QoL) of the sufferers (4). In spite of this, only a few studies have examined QoL of patients who suffer from urolithiasis, with all demonstrating a decrease in QoL but each having varying results (5).

Patient Reported Outcomes Measurement Information System (PROMIS) is an NIH sponsored online system of validated questionnaires that can be used to evaluate multiple domains related to QoL

(6). Results are reported in comparison to both the general population and age and gender matched controls. To date, PROMIS surveys have not been used to evaluate the QoL in those with urolithiasis.

The objective of this study was to compare self-reported QoL in the domains of anxiety, depression, fatigue, pain, physical function, and sleep disturbance of patients diagnosed with urolithiasis to age and gender matched controls using the PROMIS-43 survey.

MATERIALS AND METHODS

Patient Selection

After Institutional Review Board approval, recurrent and first-time kidney stone formers reporting to our kidney stone clinic were recruited to take part in the study. Eligible patients were at least 18 years old with a previous or current diagnosis of kidney stones. All patients were interviewed on the day of their clinic visit to collect basic demographic information including: age, sex, whether primary income earner or primary caregiver, and presence of other chronic illnesses. We also gathered information regarding each patient's history of kidney stone procedures including number and type (ureteral stent placement, shockwave lithotripsy, ureteroscopy, and percutaneous nephrolithotomy), number of stones passed without surgery (based on history), and current dietary (increase in fluids, decrease in oxalate, increase in citrate, decrease in protein, decrease in salt) and medical treatments (use of allopurinol, thiazide diuretic, or potassium citrate).

Quality of Life Survey

Following the office interview, each patient was invited to fill out the PROMIS-43 (Version 1) survey. The PROMIS database is an NIH sponsored program with validated questionnaires designed to assess patient function and quality of life in several domains. The PROMIS-43 survey consists of 43 questions assessing the following categories: anxiety/fear, depression/sadness, fatigue, pain interference, physical function, and sleep disturbance. Individual results are provided for each patient as a T-score percent with the general population mean set at 50% with a standard deviation of 10%. In addition, patients are matched based on age group and sex. For anxiety/fear, depression/sadness, fatigue, pain interference, and sleep disturbance a higher score indicates worse function or quality of life. For physical functioning, a higher score indicates better physical function.

Statistical analysis

A z-test was performed on all overall scores from each PROMIS category to look for significant differences between those with urolithiasis and the general population. Subgroup analysis was performed to look for differences in QoL based on status as a primary care giver (PCG) to a dependent, status as a primary income earner (PIE) for a household, other significant chronic medical illnesses (SCMI), number of stones passed, number of procedures, age, and sex. T-test and ANOVA were used to compare QoL between groups of urolithiasis patients. Significance was considered at $p < 0.05$.

RESULTS

Demographics

Of 200 invitations, 103 patients completed both the office interview and PROMIS-43 survey over the course of the one year study period. 74% were recurrent stone formers, while 26% were first-time stone formers. 64% of the respondents were female, the mean age in years was 51.6, 58% were the household primary income earners, 35% were primary caregivers and 55% had other chronic medical illnesses. 24% were both PIE and PCG while 27% were neither PIE or PCG.

Patients passed a mean of 11.5 stones in their lifetime without surgery; however, 7% had never passed a stone or had a procedure. Patients underwent 2.4 procedures during their lifetime with shockwave lithotripsy and ureteroscopy being the most common. 30% of patients had made dietary changes for stone prevention, and of these, the mean number of dietary changes was 1.9. 26% of patients were on medical

therapy for stone prevention, with 23%, 2% and 1% being on 1, 2 or 3 medications.

Overall

Overall, reported pain interference and physical functioning were significantly worse in patients with kidney stones compared to the general population. Depression/sadness was significantly less than the general population and there was no statistical difference in anxiety, fatigue or sleep disturbance between the two groups. (Figure-1)

Impact of Demographics on QoL

PIE patients had less fatigue, less pain and better physical functioning than those that were not PIE (Table-1). In contrast, stone patients that were PCG had more fatigue and pain than non--PCG patients. When combining PIE and PCG, those that were PIE but not PCG had the best quality of life while those that were PCG but not PIE had the worst quality of life (Figure-2). The presence of co-morbid (SCMI) chronic disease significantly worsened pain and physical functioning. Examining age and gender, those that were under 40 and female had trends showing worse quality of life; however, none of the differences were significant.

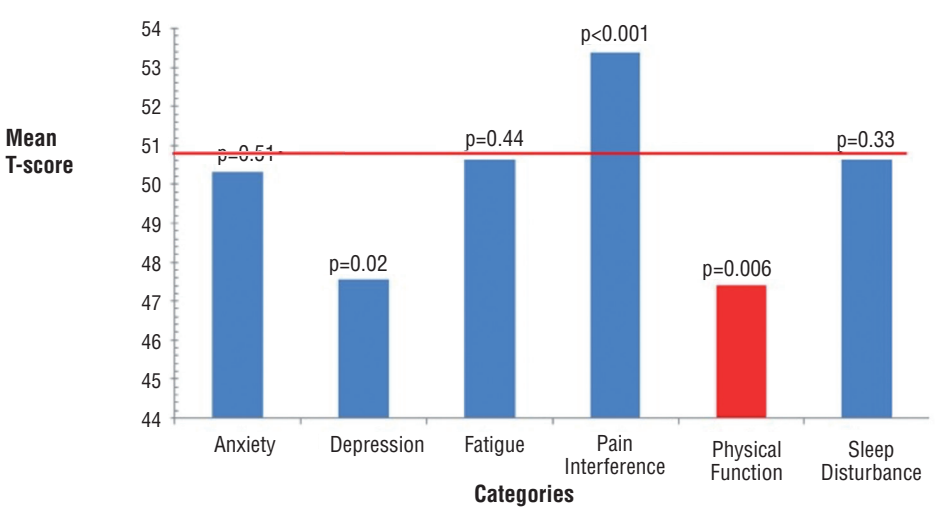
Impact of Stone History on QoL

Patients that passed 10 or more stones and those that had 4 or more procedures in a lifetime had significantly worse pain than those that had fewer stones and procedures (Table-2). Those that made dietary changes had significantly better physical function than those who had not, with other domains trending in the same direction. Patients taking a medication for stone prevention had significantly better depression and anxiety scores.

DISCUSSION

Chronic diseases are known to have an impact on health-related quality of life (4). The NIH sponsored PROMIS database was initially launched in 2004 with the aim to establish a national resource for measurement of patient reported outcomes of health and well-being. Questions were created to measure physical, mental and social health across disease. Several validation studies were performed across multiple diseases by the PROMIS network (6). Further refinement has determined the minimal clinically important differences in PROMIS scores with each domain ranging from 3-6% for the T-score (7). As

Figure 1 - Overall quality of life in patients with urolithiasis.



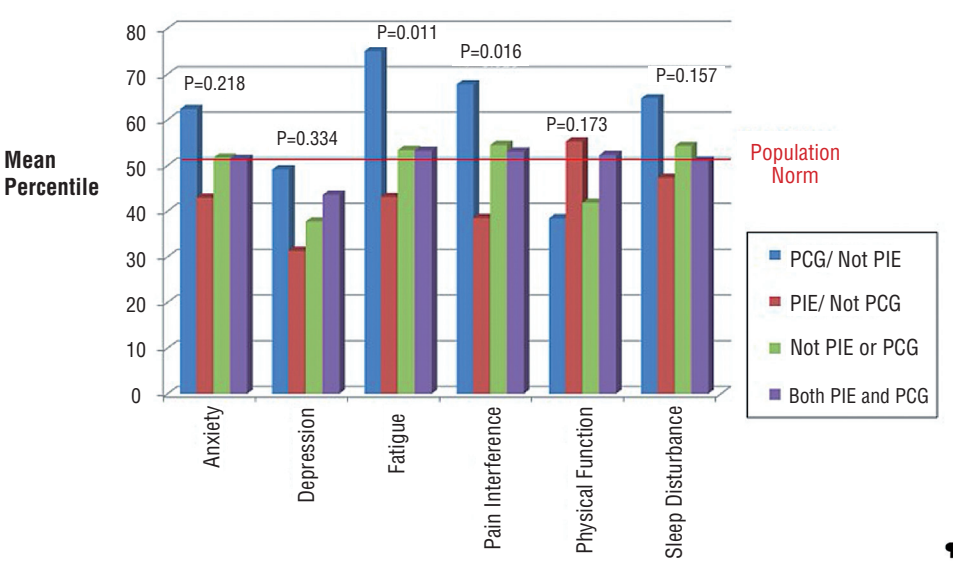
For physical function, a higher T-score indicates better function. For all other categories, a higher T-score indicates worsened quality of life. Population Mean is set at 50% with a standard deviation of 10%.

Table 1 - Quality of life based on patient demographics.

	Anxiety		Depression		Fatigue		Pain Interference		Physical Function		Sleep Disturbance	
Sex												
Female	51.01	p=0.28	47.97	p=0.55	52.07	p=0.06	54.63	p=0.09	46.49	p=0.21	50.82	p=0.77
Male	49.03		46.78		47.92		51.06		49.08		50.31	
Age												
Under 40	53.75		48.10		55.50		55.10		49.1		54.90	
40 to 59	50.86	p=0.16	48.23	p=0.85	50.45	p=0.08	53.18	p=0.67	47.23	p=0.47	49.89	p=0.07
60+	48.91		43.27		48.63		52.67		46.36		50.06	
SCMI												
No	50.38	p=0.78	46.27	p=0.18	50.18	p=0.62	51.00	p=0.03	50.93	p<0.01	51.29	p=0.74
Yes	50.89		48.82		51.25		55.30		44.27		50.73	
Income												
non-PIE/non PCG	50.85		47.81		51.19		54.85		44.59		51.67	
PCG/non-PIE	54.07	p=0.22	50.36	p=0.33	58.50	p=0.01	58.93	p=0.02	45.00	p=0.17	54.64	p=0.16
PIE/non-PCG	48.38		45.56		47.56		49.79		49.28		48.87	
Both PCG and PIE	50.70		48.91		50.35		54.35		48.96		50.00	

Mean T-scores for six PROMIS-43 quality of life measures, p-value is based on T-test measuring in group differences. SCMI (Significant chronic medical illness), PIE (primary income earner), PCG (Primary caregiver)

Figure 2 - PIE and PCG status.



Quality of life based on status as a primary income earner (PIE) and primary caregiver (PCG).

Table 2 - Quality of life based on stone history.

	Anxiety		Depression		Fatigue		Pain Interference		Physical Function		Sleep Disturbance	
Stones												
0	50.14		48.06		50.83		52.36		47.25		50.50	
1 to 2	50.36	p=0.90	47.00	p=0.06	47.96	p=0.28	50.44	p=0.03	49.40	p=0.55	50.28	p=0.34
3 to 9	49.45		43.73		50.05		53.14		47.50		48.68	
10+	51.55		51.55		54.20		59.15		45.05		53.50	
Procedures												
0	51.04		48.12		48.64		52.84		49.12		48.64	
1	51.54		49.92		53.19		54.04		44.88		52.12	
2	49.97	p=0.77	45.79	p=0.40	49.00	p=0.25	50.76	p<0.05	49.21	p=0.27	52.03	p=0.39
3	47.25		44.13		49.25		53.50		47.50		47.63	
4+	49.00		48.70		55.50		61.80		43.40		49.50	
Diet												
No	52.06	p=0.29	49.03	p=0.34	52.68	p=0.24	54.94	p=0.30	44.26	p=0.04	49.94	p=0.41
Yes	50.03		47.06		49.91		52.67		48.62		51.45	
Meds												
No	51.49	p=0.02	48.87	p=0.02	51.65	p=0.09	52.75	p=0.28	47.30	p=0.86	51.17	p=0.29
Yes	46.85		43.65		47.58		55.23		47.69		49.08	

Mean T-scores for six PROMIS-43 quality of life measures, p-value is based on t-test or ANOVA comparison within groups. (Stones - number of stones passed over lifetime, Procedures - number of procedures over lifetime, Diet - has the patient made any dietary modifications, Meds - is patient currently on stone prevention medications)

such, PROMIS questionnaires provide a validated source for determining differences in quality of life across a spectrum of diseases.

Urolithiasis is a common disease with a lifetime prevalence between 10-15% and is increasing in incidence (1, 2). Many of the patients that suffer from urolithiasis will undergo multiple stone episodes with recurrence approaching 100% at 25 years (3). Up to 2 million emergency department visits a year are related to urologic stone disease (5). For many people, urolithiasis is a chronic disease resulting in significant morbidity.

Previous studies have examined the effect of stone episodes on patient psychological well--being. Patients with stressful life factors such as low income, mortgage problems and emotional life events were more likely to have symptomatic stone episodes (8). Miyaoka et al. demonstrated that having multiple stone episodes per year or having symptoms of renal colic were significantly associated with stress (9).

Some studies have linked depression to stone disease. In a prospective study, Angell et al. showed that 30% of stone patients had significant depressive symptoms (10). A large retrospective study in Taiwan found a 1.75 increased risk for a diagnosis of depression in the year following a stone episode (11). There is also a correlation between the frequency and number of stone episodes and anxiety (12).

Other studies have focused on all QoL and these studies have employed the Short Form 36 (SF-36) to evaluate QoL in urolithiasis. While all the studies demonstrate decreased QoL in stone patients, there is little consistency in which health domains are worsened. Diniz et al. showed renal colic was associated with a decrease in QoL in all domains of the SF-36 (13). Bensalah et al. found a

decrease in QoL in 5 of 8 domains within the SF-36, but those with a stone episode within the last month had worse QoL than those with remote episodes (14). Further, other chronic medical illnesses in stone patients significantly worsen QoL (14, 15). Some studies have shown that female stone formers have lower QoL than male counterparts (15, 16). Donnally et al. performed a longitudinal study on QoL with the SF-36 finding that there was no difference in QoL even after improvement in stone symptoms calling into question the validity of the SF-36 (17).

Recently, Penniston and Nakada have developed a new instrument, Wisconsin Stone Quality of Life Questionnaire (WISQOL), to evaluate quality of life in kidney stone patients. Urologists and stone patients identified domains for quality of life that were important in stone disease, and questions were validated on patients presenting to a stone clinic (18). Interestingly, when the WISWOL wad administered to asymptomatic stone formers, a lower QoL was demonstrated in urinary urgency and anxiety (19). The WISQOL performs similarly across multiple sites in regard to health related quality of life (HRQOL) and has thus been internally and externally validated to assess QoL in stone formers (20).

Our results demonstrated an overall decrease in the QoL of stone formers when compared to the general population in two of the six PROMIS-43 categories: pain and physical function. Interestingly, depression scores were lower in the stone forming group. This contrasts with other studies which had shown higher levels of depression within stone formers. The reasons for the differences could be related to the study type. Chung et al. performed a retrospective review that found a correlation between a stone episode and a diagnosis of depression in the following year (11). However, Angell et al. had a prospective study using a validated questionnaire, the Center for Epidemiologic Studies Depression (CES-D) questionnaire, and found an elevation in depression within stone patients (9). Determining the true relationship between depression and urolithiasis will require further study.

A few demographic factors were associated with differences in QoL. Having other chronic medical conditions worsened QoL. Being a household primary income earner meant better QoL while being a primary caregiver worsened QoL. When combining the two, those that were not PIE but were PCG had the worst outcomes. Primary caregivers are known to experience more fatigue and this may impact both self-reported pain and fatigue. In contrast, primary income earners may have been in better overall health to be able to work or may have fewer financial concerns than non-PIE. The reason that non-PIE but PCG has the worst QoL is less clear. It may be that PCG that are not PIE have less financial stability and less support structure than those that are both PIE and PCG. For example, those who work and are primary care givers likely have support at work (sick leave, disability leave) and support at home (daycare, nanny etc.). In contrast, those who are PCG may not have a similar support structure in place. Patients that have other chronic medical illnesses or are primary caregivers may need benefit from more aggressive preventive measures to ward off stone formation, as well as may need consideration for earlier intervention rather than a prolonged course of medical expulsive therapy.

A limitation of our study is an inability to identify where in the continuum of stone disease each patient was at the time of survey. Initially attempting to discern whether stone formers were different from the general population, we treated 'stone patients' as a single entity. Knowing kidney stone disease affects QoL scores measured by PROMIS, future studies will help further assess the role of one's clinical course. Considering responses of first time versus recurrent stone formers, acutely symptomatic patients versus those several years removed from a symptomatic episode may further help understanding whether scores are affected by the episodic nature of stone disease.

We could identify an increased burden of disease as measured by number of spontaneously passed stones or number of procedures, negatively impacted pain interference. However, patients who were treated with medical therapy, both dietary and pharmacologic, had improved QoL dimensions. As such, medical therapy should be strongly considered to help improve QoL in all recurrent stone formers.

CONCLUSION

Urolithiasis negatively impacts quality of life and having more stone episodes worsens quality of life. Certain factors such as chronic medical illnesses and being a primary caregiver for children are associated with lower quality of life. Medical therapy for stones may improve quality of life and should be considered in those with urolithiasis.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Early term effect of ureterorenoscopy (URS) on the Kidney: research measuring NGAL, KIM-1, FABP and CYS C levels in urine

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ABSTRACT

Aim: URS is a very commonly used procedure for treatment of ureter stones. Increased hydrostatic pressure in the collecting system linked to fluids used during the procedure may cause harmful effects on the kidney. The aim of this study is to determine whether the URS procedure has a negative effect on the kidney by investigating NGAL, KIM-1, FABP and Cys C levels in urine.

Material and Methods: This study included 30 patients undergoing ureterorenoscopy (URS) for ureter stones. Urine samples were collected 5 times; before the URS procedure (control) and at 1, 3, 5 and 12 hours following the procedure. NGAL, KIM-1, FBAP and Cys C levels were measured in urine and compared with the control values.

Results: The NGAL levels in urine before the procedure and at 1, 3, 5 and 12 hours after the procedure were 34.59±35.34; 62.72±142.32; 47.15±104.48; 45.23±163.16 and 44.99±60.79ng/mL, respectively (p=0.001). Similarly, the urinary KIM-1, FABP and Cys C levels were found to increase compared to control values; however this increase did not reach statistical significance (p >0.05).

Conclusions: After the URS procedure, there were important changes in NGAL, FABP, KIM-1 and Cys C levels. These changes reached statistical significance for NGAL, but did not reach significance for the other parameters. In conclusion, the URS procedure significantly affects the kidney; however, this effect disappears over time.

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INTRODUCTION

URS, used as an alternative to open surgery and ESWL for stone treatment, has revolutionized treatment of stones located in the upper urinary system. It is reported to be a reliable and effective procedure even for complex cases like solitary kidney, pregnancy and obesity. However, the procedure has potential for serious complications like ureter injury and kidney loss (1, 2).

The majority of complications reported for URS are related to traumatic injury caused by the direct effect of surgical tools on tissue. The effect of the procedure on the kidney has not been sufficiently revealed. Processes related directly to stone disease and to treatment may affect renal functions. There are limited studies on this topic and data are mostly related to the late period. The effect of the procedure on renal functions in the early period is not fully known. The small amount

of data related to renal injury in the post-op period may be due to a lack of focus on the topic or problems with diagnosis. It is well known that markers like urea and creatinine used to monitor renal functions are not sufficiently reliable to determine renal injury in the early period. Another reason may be that patients are discharged from hospital before classic symptoms of renal injury occur. When data is obtained from patients requiring long post-op monitoring in hospital, renal injury appears to be more common than realized. A study on this topic found that renal injury occurred in 40% of patients after cardiac surgery (3).

Recently, some biomarkers have been suggested with the ability to better identify renal damage in the early period compared with traditional markers. The focus has mainly been on markers like neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (Cys-C), kidney injury molecule-1 (KIM-1) and liver-type fatty acids binding protein (L-FABP) and they are reported to identify renal injury earlier compared to creatinine (4).

To the best of our knowledge in the literature to date, the effect of the URS procedure on the kidney has not been investigated using the new biomarkers NGAL, KIM-1, FABP and Cys-C. The aim of this study is to determine whether the URS procedure commonly used for stone treatment has a negative effect on the kidney by measuring these new biomarkers in urine.

MATERIAL AND METHODS

Study Design

This study was approved by the local ethics committee of Samsun University (2014/556). The study included 30 patients submitted to URS procedure due to ureter stones in 2015 and 2016. Before surgery direct urinary system graphy, urinary ultrasound, intravenous pyelography, urine tests, urea, creatinine and other necessary tests were completed. The exclusion criteria for the study were age under 18 years, use of permanent catheter, urinary tract infection, muscular diseases, use of cytotoxic medication, renal failure, and diseases that affect marker levels in urine or serum like protein leak. Additionally, cases with non-functioning kidney occurring due to the stone were excluded from the study. The patients signed a consent form after being informed about the procedure.

The surgical procedure was completed under general anesthesia in the lithotomy position. During the procedure, a 10F semi-rigid ureteroscope (Storz, Germany) and laser lithotriptor (Stonelight laser) were used. Urine samples were taken before surgery with a 10F nelathon catheter and after surgery with the aid of a 14F Foley catheter inserted in the bladder. Urine samples were obtained from patients 5 times; immediately before the URS procedure (baseline) and 1, 3, 5 and 12 hours after the procedure. Samples were stored at - 80°C until laboratory study.

BIOCHEMICAL STUDY

Urinary Cystatin C measurement

Measurements were completed with Biovendor brand Human Cystatin C ELISA kits (Lot No: E15-001, Cat No: RD191009100) using the Sandwich-ELISA method. Urine samples were diluted 1/20 and read at 450nm wavelength with an ELISA reader (BioTek, ELx800).

Urinary FABP measurement

FABP measurements were completed with Elabscience brand Human FABP3 ELISA kits (Lot No: AK0015APR21031 Catalog No: E-EL-H1431) using the Sandwich-ELISA method. Results were read at 450nm wavelength with an ELISA reader (BioTek, ELx800).

Urinary NGAL measurement

Measurements used Boster Immunoleader brand Human Lipocalin-2/NGAL ELISA kits (Lot No: 5031059708 Catalog No: EK0853) with the Sandwich-ELISA method. Samples were diluted 1/10 and results were read at 450nm wavelength with an ELISA reader (BioTek, ELx800).

Urinary KIM-1 measurement

Measurements used the Sandwich-ELISA method with Boster Immunoleader brand Human KIM1 ELISA kits (Lot No: 5299125708 Catalog No: EK0883). Results were read at 450nm wavelength with an ELISA reader (BioTek, ELx800).

Urinary Creatinine measurement

Abbott brand trade creatinine kits (Creatinine Lot No: 78067UN14) were used in an Abbott Architect C8000 autoanalyzer at the Ministry of Health Ordu University Education and Research Hospital Biochemistry Laboratory.

Markers measured in urine were normalized according to 24-hour urine volume and creatinine value.

Statistical analysis

Data obtained from repeated measurements in the study were assessed with variance analysis. The results are given as sample size, mean and standard deviation (SD). All statistical analyses were completed with "SPSS for Windows Version 20.0" program. Data with p value <0.05 were accepted as significant.

RESULTS

The mean age of patients was identified as 52.7±12.7 (28-78 years) (mean±SD) (min-max). According to sex, age distribution for females and males were identified as 53.1±13.8 years (31-78) and 51.6±12.4 years (28-72), respectively (p=0.707). Mean stone size was 9.7±1.8mm and operation duration was 24.8±9.3 minutes. In terms of stone localization, 15 patients (50%) had lower ureter, 11 patients (36.7%) had middle ureter and 4 patients (13.3%) had upper ureter stones. No serious complication was encountered after surgery. No patient had a double-J (DJ) stent inserted. Creatinine values in serum before the procedure and 10 days after the procedure were 0.81±0.15 and 0.89±0.31, respectively, and the variation was not statistically significant (p=0.117).

The NGAL values measured in urine were identified as 34.59±35.34 for baseline, 62.72±142.35 for 1st hour, 47.15±104.48 for 3rd hour, 45.23±163.16 for 5th hour and 44.99±60.79ng/dL for the 12th hour. The variation in NGAL values was statistically significant (p=0.001). Additionally, there were differences in the variation of this parameter within the group (p<0.05) (Table-1).

The variation in FABP (pg/mL) during the URS procedure was similar; 128.59±104.48, 214.50±251.57, 192.25±163.16, 192.76±142.32 and 164.76±218.90, respectively. There was an increase in FABP value during the procedure compared to the baseline value. However, this increase did not reach statistical significance (p=0.292). Additionally, there were no differences in terms of this parameter within the group (p>0.05) (Table-2).

The variation in KIM-1 (ng/mL) was as follows; 2.06±3.71, 3.62±6.43, 2.49±2.49, 2.28±2.75 and 2.26±2.40. Though KIM-1 levels increased during the procedure compared to baseline values, this variation was not significant (p=0.707). Additionally, there were no differences within the group (p >0.05) (Table-3).

The variation in Cys-C (ng/mL) levels occurred as follows 27.38±25.20, 55.70±81.53, 45.70±71.17, 37.60±46.37 and 33.49±27.60. Though the Cys-C levels increased compared to baseline values, this increase did not reach statistical significance (p=0.095). There were no differences in terms of this parameter within

Table 1 - Time-linked variation in NGAL (ng/dL) measured in urine.

Parameter	Mean	Std.Dev	P-value	Linear	Quadratic	Cubic	Order 4
NGAL-0	34.59[a]	35.34					
NGAL-1	62.72	142.32					
NGAL-3	47.15	104.48	0.001	0.010	0.062	0.541	0.157
NGAL-5	45.23[a]	163.16					
NGAL-12	44.99	60.79					

[a] significant difference within the group.

Table 2 - Time-linked variation in FABP (pg/mL) measured in urine.

FABP	Mean	Std. Dev	p-value
Control	128.59	104.48	
1st hour	214.50	251.57	
3rd hour	192.25	163.16	0.292
5th hour	192.25	142.32	
12th hour	164.76	218.90	

No differences between the groups

Table 3 - Time-linked variation in KIM-1 (ng/mL) measured in urine.

KIM 1	Mean	Std. Dev	P -value
Control	2.0662	3.71348	
1st hour	3.6234	6.43728	
3rd hour	2.4924	2.49448	0.707
5th hour	2.2866	2.75137	
12th hour	2.2610	2.40135	

No differences between the groups

Table 4 - Variation in Cys-C (ng/mL) measured in urine.

Cys C	Mean	Std. Dev	P -value
Control	27.38	25.20	
1st hour	55.70	81.53	
3rd hour	45.70	71.17	0.095
5th hour	37.60	46.37	
12th hour	33.49	27.60	

No differences between the groups

the group ($p < 0.05$) (Table-3). The creatinine values measured in serum before and after the procedure (mg/dL) were 0.89 ± 0.31 and 0.81 ± 0.15, respectively ($p=0.117$) (Table-4).

DISCUSSION

This study observed that the URS procedure affected kidney functions with increases measured in urinary NGAL, Cys-C, KIM-1 and FABP levels in the early period. The variations in biomarkers after the procedure only reached statistical significance for NGAL.

The first imaging of the upper urinary system in 1912 brought about significant changes in surgical procedures related to the upper urinary system. The advances in endoscopic systems have brought URS to the forefront of treatment for ureter and kidney stones. Significant advantages of these procedures include effectiveness and

reliability of many procedures performed on the upper urinary system in addition to providing rapid post-op recovery (5). The majority of complications encountered during the URS procedure are insignificant and can be treated with simple approaches. A study investigating complications developing after URS reported the general complication rate after URS was 5.9% for 2436 URS cases. Among the most commonly encountered intraoperative problems are mucosal edema, mucosal injury, false passage, ureteral perforation and ureteral avulsion (6).

The majority of reported complications related to URS are due to traumatic effects of the tools used. The correlation of this procedure to acute kidney injury (AKI) is not fully known. It is known that problems affecting kidney functions like obstructive uropathy, surgical procedures and urinary sepsis are commonly encountered in this patient group. As a result, urologic patients may be considered a risk group in terms of renal functions. As the URS procedure is frequently reliable, post-op renal functions are not monitored. Patients are discharged from hospital on the same day or following day post-op and generally renal functions are not monitored in this period. Additionally, markers like urea and creatinine examined in this early period may be misleading in terms of showing renal functions in the late period. In conclusion, the effect of the URS procedure on renal tissue in the early period has not been fully researched to date. This study was designed to determine the effect of the URS procedure on early period renal functions. One of the rare studies on this topic by Caddeo et al. investigated the incidence of AKI developing after the URS procedure. The results of this study identified that AKI developed in nearly 3.6% of cases (7). However, in this study renal functions were based on serum creatinine evaluated in the late period and no information was given about the early period. Another study by Ghosh et al. assessed the effect of the URS procedure in a solitary kidney. The authors reported that renal functions were not affected by the procedure (8). This study assessed renal functions in the 3rd month post-op and did not study results related to the early period.

In these studies, mostly late stage kidney functions were investigated and no information was given about the early period. As observed in our study results, renal functions are affected in the early period. In the literature, renal functions in the early function after URS are not known due to the scarcity of studies.

The surgical tools and the high-pressure fluid used during the URS procedure are considered to possibly affect renal functions. A study on this topic by Schwalb et al. investigated the effect of fluid pressure in an animal model. This study identified morphologic changes in renal tissue in the group with high pressure fluid used compared to the baseline group in both the early and late period. The authors reported the irrigation fluid used during the procedure had a damaging effect on the kidney (9). However, when the literature is examined most data relating to AKI developing after surgery comes from cardiac surgery studies. The reason for this may be that after cardiopulmonary surgery patients are frequently monitored in surgical intensive care units (ICU) for several days. Thus, there is sufficient time for markers of renal injury in serum to change. The result of this close monitoring is that some studies report about 40% development of AKI post-op (3). One of the rare studies related to urologic surgery by Caddeo et al. reported the incidence of AKI in patients after urologic surgery was 0.7-43% (7). As shown by this study, renal injury after surgery is commonly encountered. However, due to problems with diagnosis of this disease, it may not be noticed. As a result, as interest in this topic increases, it is expected that as with other surgical branches, urology clinics will have an increase in the incidence of renal injury. Diagnosis of AKI, with high morbidity and mortality rates, in the early period is important in order to take necessary precautions, to avoid factors affecting kidney functions and for replacement treatment. Studies have reported that AKI lengthens hospital stays, increases labor losses and treatment costs and causes mortal complications (10).

As with many surgeries, it may be difficult to identify renal injury developing after the URS procedure. The main reasons for this are that patients are discharged on the same day or on the following day post-op and renal functions

are rarely checked in this period. Another reason is the lack of a reliable imaging method or marker to show renal injury in the early period. Markers commonly used for AKI diagnosis like urea and creatinine are reported to be insufficient to identify kidney damage in the early period and to predict severity and results. Additionally, it is known that markers like urea and creatinine measured in serum are affected by a variety of factors like age, sex, fluid and protein intake and muscle mass (4, 11). In conclusion, it may be misleading to assess renal injury occurring in the early period after URS with serum urea and creatinine values. As renal functions are not seriously affected at this point, renal injury may not be noticed by the patient.

Studies in recent times have proposed some newly-emerging markers that are superior to creatinine to identify renal injury in the early period. The most noteworthy of these markers are NGAL, Cys-C, KIM-1 and FABP (12).

NGAL is a small protein from the lipocalin family with 25kDA weight. Recent studies have reported that NGAL begins to increase in the early period of renal injury. A study on this topic reported that NGAL may be effective in terms of identification in the early period after contrast nephropathy (13). Another study compared NGAL with serum creatinine values for identification of early stage renal injury. The authors examined serum creatinine values to diagnose renal injury and reported this was 1-3 days delayed compared to NGAL (14). Another study investigated urinary NGAL levels to identify diabetic nephropathy in the early period. The results of this study reported that it may be a beneficial biomarker to identify renal injury in the early period (15). The same study reported a correlation between severity of renal injury and NGAL levels.

The power of NGAL to identify renal injury in the early period after surgery was investigated by Mishra et al. The authors reported that NGAL can identify renal injury within 2 hours post-op (16). In our study the urinary NGAL levels in the first hours after the URS procedure were significantly increased compared to the baseline value. Later, the levels of this marker reduced in a time-linked fashion. In conclusion, the URS procedure affects renal functions in the early post-op period. This situation should be considered for critical patients in terms of renal functions.

Cys-C is a cystein proteinase enzyme inhibitor. As it has low molecular weight and does not bind to proteins, it is freely filtered by glomerules. Under normal conditions it is reabsorbed by the proximal tubules and has low levels in urine. Any factor affecting the proximal tubule structure affects reabsorption of Cys-C. It is considered a sensitive marker of renal tubular injury (17). The study by Hall et al. reported that it was a beneficial maker to identify renal injury developing in the early period in patients in the ICU after surgery (18). For early identification of renal injury, Pirgakis et al. compared serum creatinine levels with Cys-C levels in surgical patients. The authors reported that the Cys-C value measured in the 6th hour post-op was a strong predictor of late period renal function (19). Another study by Liangos et al. reported that Cys-C increased in urine in the early period in ICU patients developing renal injury (20). The power of Cys-C for early identification of renal injury developing after urologic surgery has been investigated in several studies. One of these studies compared early identification of renal injury after partial/radical nephrectomy with serum creatinine levels on the 1st day post-op. The authors reported Cys-C performance was superior to creatinine to determine renal injury developing in the late period (21). Koyner et al. compared the performance of Cys-C, NGAL, and KIM-1 to identify renal injury developing in the early period after cardiac surgery. This study suggested that Cys-C provided the best performance in terms of identifying renal injury in the early period (22). The authors also reported a correlation between this marker and mortality. The results of our study identified an increase in urinary Cys-C levels in the early post-op period compared to baseline values. This increase reduced over time; however, it did not reach statistical significance.

Studies related to KIM-1 have reported it may be a beneficial marker to identify renal injury in the early period (4). A study by Han et al. investigated the performance of KIM-1 to identify renal damage developing post-op in the early period. This study showed that from the 3rd hour after in-

jury urinary levels began to increase. The authors reported that KIM-1 was a beneficial marker to identify AKI in the early period (23). Liangos et al. reported that urinary KIM-1 levels were a beneficial marker to determine prognosis of patients in the ICU developing AKI (24). Another study by Song et al. investigated the correlation between KIM-1 levels and tissue injury occurring in renal tissue in renal transplant patients developing tissue rejection. The researchers reported a strong correlation between KIM-1 levels and tubular cell and tissue injury shown with biopsy in patients developing rejection. They reported that this marker began to increase before tissue damage developed or before traditional serum markers began to increase (25). In our study the KIM-1 levels measured in urine increased especially in the first hours after the URS procedure compared to baseline values. Though this increase was not statistically significant, the damaging effect of the URS procedure on the kidney was observed in the increase in urinary KIM-1 levels.

Under normal conditions there are trace amounts of FABP in urine, with the amount increasing when renal injury develops. A study by Matsui et al. compared FABP with creatinine in terms of determining AKI in the early period. The results indicate FABP identified renal injury earlier compared to creatinine (26). Yamamoto et al. investigated the performance of FABP to determine early stage renal injury in both animal models and kidney transplant patients. The authors reported that FABP in urine was a beneficial biomarker to predict acute ischemic injury developing after ischemia-reperfusion injury (27). This opinion was later supported by Matsui et al. (28). Another study by Manabe et al. showed that urinary FABP levels were good indicators to predict AKI developing linked to contrast nephropathy (29). Another study investigated the correlation between urinary FABP, KIM-1, VENAG and NGAL levels and prognosis for terminal renal injury. This study reported that FABP and NGAL were effective to predict results of terminal renal injury (30). In our study the urinary FABP values increased in the early post-op period after the URS procedure compared to baseline values. However, this variation did not reach statistical significance. In accordance with our results, in the literature some studies have not shown positive results for FABP.

This study investigated the use of new markers reported to show renal injury in the early period to determine the effect of the URS procedure on the kidney. To the best of our knowledge this study is the first on this topic in the literature. This study showed that kidney functions were affected in the early period with increases occurring in the markers in urine. The results of the study were that levels of all markers increased in urine in the first hours (especially 1st and 3rd hours) and later reduced in a time-linked fashion. The variation in marker levels only reached significance for NGAL. From these results, it is understood that the URS procedure affects kidney functions in the early period. It is very difficult to explain the cause of this injury because there are insufficient studies on the effect of the URS procedure on the kidney in the early period.

A cause of this injury may be reduced renal blood perfusion, though this was not investigated in our study. The high intra-pelvic pressure caused by the fluid used during the procedure may cause a reduction in renal blood perfusion. Another cause may be medications used during anesthesia with contributions from hypotensive attacks occurring during the procedure and many other unknown reasons. There is a need for detailed studies on this topic.

Our study is the first study to evaluate the results of the URS procedure in the early period using new markers in urine. As a result, there is no study in the literature that we can use to directly compare our results.

There are some limitations to this study. Among these are the low number of cases and the fact that the study was completed at a single center. Also, the lack of knowledge about renal blood perfusion during the procedure is another significant limitation. However, as this is the first study on this topic and the results are noteworthy we consider this to be a significant study.

CONCLUSIONS

In conclusion, in our study the URS procedure had significant effects on the kidney with an

increase in NGAL, FABP, KIM-1 and Cys C levels examined in urine. However, these variations only reached statistical significance for NGAL. According to our idea, the URS procedure is not the harmless procedure it is generally accepted to be. As a result, kidney functions should be closely monitored, especially for patients with borderline kidney functions. Classic markers like urea and creatinine are not sufficiently reliable to show damage in the early period. As shown by our results, after more comprehensive studies new markers may be beneficial in identifying renal damage in the early period and in terms of taking necessary precautions.

ETHICAL STANDARD

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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New concept for treating female stress urinary incontinence with radiofrequency

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ABSTRACT

Purpose: To evaluate the clinical response and adverse effects of radiofrequency on the urethral meatus in the treatment of stress urinary incontinence in women.
Materials and Methods: This phase one study included ten women with Stress Urinary Incontinence (SUI). The evaluation consisted of 1 hour Pad tests to quantify urine loss and to assess the degree of procedure satisfaction by using the Likert scale. To evaluate safety, we observed the number of referred side effects.
Results: Average age was 53.10 years±7.08 years. In assessing the final Pad Test, 70% showed a reduction and 30% a worsening of urinary loss. Using the Pad Test one month later, there was a reduction in all patients (p=0.028). The degree of satisfaction was 90% and no side effects have been observed. One patient reported burning sensation.
Conclusion: The treatment of SUI with radiofrequency on the urethral meatus has no adverse effects, being a low risk method that reduces urinary loss in women. However, to increase the validity of the study, larger clinical trials are warranted.

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Keywords:
Pulsed Radiofrequency Treatment; Urinary Incontinence, Stress; Women

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INTRODUCTION

The prevalence of stress urinary incontinence (SUI) in the adult female population varies widely, ranging from 4% to 35% (1, 2). SUI has a high impact on the health condition of patients, with personal and social consequences and high negative impact on psychological and relational well-being (3, 4). This justifies a continuous search for a therapy.

The first line of treatment is pelvic floor muscle training. Medication, or even surgery, could also be recommended. The success rate of therapeutic treatment varies from 25 to 90%, depending on severity, cause and timing of reassessment (5).

Theetiology of SUI is multifactorial, and SUI may be caused by inadequate support of the pelvic organs and anterior vaginal wall suspension and/or a possible change in the intrinsic urethral closure mechanism itself (6, 7). In addition to that, histological studies observed a reduction of collagen in urethra walls in case of loss of urethral support and/or sphincter dysfunction (8), making therapy with radiofrequency an option.

A current treatment proposal is the use of radiofrequency, which is a diathermic process

generated by the radiation of an electromagnetic spectrum, resulting in an immediate retraction of existing collagen and subsequent activation of fibroblasts causing neocollagenesis (9). In studies using radiofrequency to treat SUI, a therapeutic response of 50% was shown (10). Elser et al., used the probe by inserting it in the intra urethral or intravaginal region. Although this technique is minimally invasive, it presented a rate of adverse or side effect of 0.9% to 9.5%, and the need for antibiotic prophylaxis, oral sedation, local anesthesia, while increasing the risk of urinary tract infections and its costs (11, 12).

Female urethra is known for having a maximum length of five centimeters, and its anatomical structure and length justifies the use of radiofrequency on the external urethral meatus. Radiofrequency waves can reach a sufficient depth to induce collagen production in the whole urethra. The hypothesis of this innovative study is that radiofrequency treatment on the urethral meatus reduces urinary loss, in a safe manner and with low risk. Our main objective is to evaluate the clinical response and adverse effects of radiofrequency on the urethral meatus in the treatment of stress urinary incontinence in women.

MATERIALS AND METHODS

These are results of a phase one study, approved by the Ethics Committee and Research of the Bahia School of Medicine and Health Public (CAAE: 20333213.1.0000.5544). Conformed to the standards set by the Declaration of Helsinki. It was registered at ClinicalTrials.gov (NTR: 02623842). All participants provided written informed consent.

The age of the women involved varied from 43 to 66 years, with an average of 53.1±7.1 years. Eligible women were at least 18 years of age, with SUI as the main clinical complaint, without any urgency symptoms (clinical complaint plus voiding diary per three days), and urinary loss of more than 1g in a one hour Pad Test. Patients with organ prolapses, neurological chronic degenerative diseases, residual voiding, pacemakers, copper intrauterine devices, or those who underwent other treatment for SUI (medical, surgical or physical therapy) as well as pregnant women, were excluded.

Evaluation of patients

Initially an anamnesis questionnaire was carried out to assess the presence of comorbidities, associated urinary symptoms and fecal urinary symptoms. After the questionnaire was done, physical examination took place to assess the function of the muscles of the pelvic floor. The examination comprised digital palpation quantified by the modified Oxford scale (13).

Device and procedure description

The non-ablative radiofrequency device Spectra G2 - Tonederm®, has been adjusted for use on the urethral meatus. The device consists of an electromagnetic wave generator - high frequency wave, 0.5MHz - which is connected to a monopolar active electrode with a diameter of 0.5cm, and a passive metal electrode, the return plate (Figure-1). Only equipment with the approval of the national organ (ANVISA) can be used for this treatment method.

The undressed patient lays in lithotomy position, the return plate is placed under the sacrum and the active electrode is positioned on the external urethral meatus.

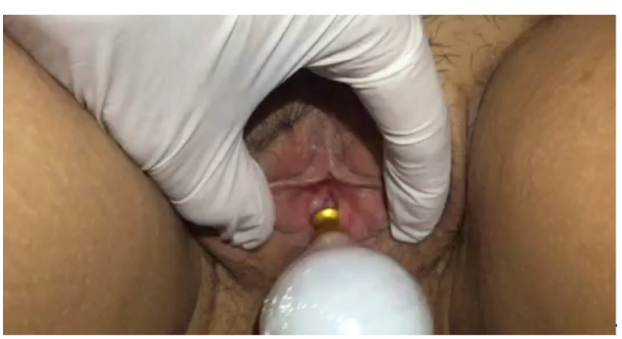
When starting the passage of electromagnetic waves, the active electrode is placed on the urethral meatus and moved in circles (Figure-2). The active electrode is removed regularly to perform the temperature check. The temperature is monitored with an infrared thermometer, and after reaching 39-41°C, this temperature and the motions are maintained for 2 minutes. We used the same principle of the monopolar radiofrequency that is used for tissue repair to genital regions (14). All patients had 5 sessions of treatment, with a weekly frequency, and did not undergo any other therapeutic treatment for urinary incontinence. Women currently taking medications such as hormones, diuretics, or other medications, remained on their usual dose of medicine throughout the study period.

Assessment of response to therapy

As objective evaluation, the Pad test was repeated immediately after the last radiofrequency treatment, and as follow-up one-, two- and three months after the treatment. The categories used in

Figure 1 - Details of the electrodes used in the radiowfrequency apparatus Spectra G3 Tonederm®.

Figure 2 - Demonstration of application of non-ablative radiofrequency in external urethral meatus.



the classification of urinary loss are: loss of 1 to 10g represents mild incontinence, 11 to 50g represents moderate incontinence and >50g represents severe incontinence (3).

As subjective evaluation, the level of patient satisfaction was measured using a 5-point Likert scale, which measured the response to treatment as follows: 1) very dissatisfied, 2) dissatisfied 3) neutral; 4) satisfied; 5) very satisfied.

The expected adverse effects were edema, redness, increased local temperature or presence of secretion.

Statistical Design

To prepare the database and descriptive analysis, the Statistical Package for Social Sciences software (SPSS Inc., Chicago, IL, USA) version 14.0 for Windows, was used. The results are presented in tables and graphs. Categorical variables (patient satisfaction level) are expressed as frequencies and percentages -n (%). Continuous variables with normal distribution are expressed as mean and standard deviation; and those with non--normal distribution, as median and interquartile range. The normality of the numerical variables was assessed using descriptive statistics, graphical analysis and the Shapiro -wilk test.

The analysis of the mean Pad Test comparison was performed by ANOVA repeated measures, and compared the loss in grams at the begginning, the end, after one-, two-, and three months of treatment, considering a significance level of 5% ($p < 0.05$).

RESULTS

The sample consisted of 10 patients with a mean age of 53.10±7.08 years. The clinical characteristics are shown in Table-1. The result of the initial Pad test evaluation showed four (40%) participants classified as having experienced a slight loss, five (50%) a moderate loss and one (10%) a severe loss.

In assessing the final Pad test, seven (70%) showed a reduction of urinary loss, two (20%) showed no further loss and three (30%) a worsening of urinary loss.

Figure-3 shows reduction of the urine loss in grams (g) Pad test at the begginning-, end-, and after one-, two - and three months of treatment (p=0,028).

After one month, all participants showed an improvement in the results of Pad test, compared to the initial examination: two (20%) had no loss, three (30%) had a slight loss, four (40%) had a moderate loss and none had severe loss. One participant did not return for a follow-up review after one month (Table-2).

While assessing patient satisfaction, nine (90%) participants reported to be satisfied with the treatment. One patient indicated to be little satisfied with the treatment as an answer to the Likert questionnaire.

Table 1 - Clinical characteristics of 10 patients who underwent non-ablative radiofrequency treatment on the external urethral meatus, Salvador - BA, 2015.

Patient	Age	Pelvic floor muscle strength*	Pregnancies	Normal deliveries	Surgeries	Medicins for CNS and LUTS	Hormonal status	Smoking
01	56	4	0	0	Hemorrhoidectomy	HRT	Menopause	No
02	62	1	5	5	TAH	HRT	Menopause	No
03	49	4	4	4	No	High blood pressure Clordalidone Elanapril	Fertile	No
04	43	3	2	1	Myomectomy	Captopril pressure Puran t4	Fertile	No
05	47	4	2	0	Caesarean section	OC, Nifedipine, Hydrochlorothiazide	Fertile	No
06	49	3	3	3	TAH	No	Fertile	No
07	51	2	6	4	No	No	Menopause	No
08	57	1	7	5	No	No	Menopause	Yes
09	66	1	8	4	TAH	Losartan, Hydrochlorothiazide	Menopause	No
10	51	4	2	1	TAH + Perineoplasty	Estradot + Testosterone	Menopause	Yes

CNS = Central Nervous System; **AO =** Anticoncepcional Oral; **OC =** Oral Contraceptive; **LUT =** Lower Urinary Tract; **TAH =** Total Abdominal Hysterectomy
***** measure by modified Oxford scale.

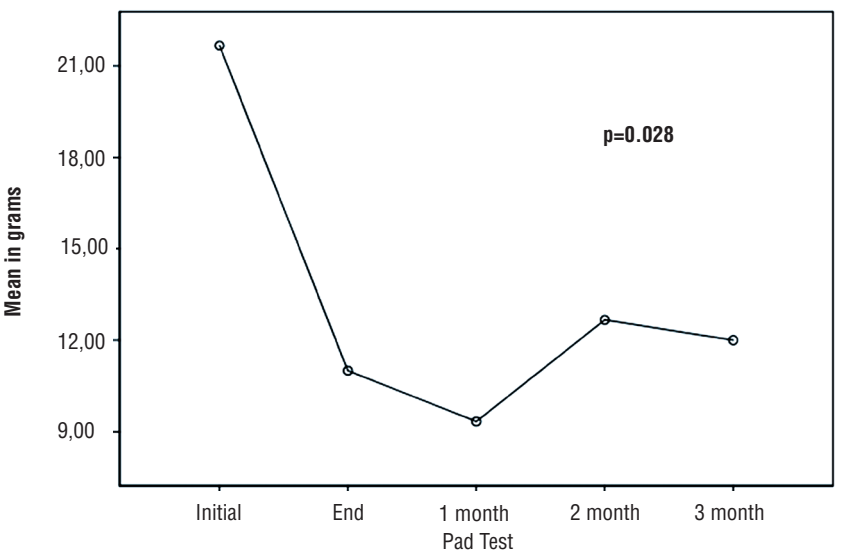
Table 2 - Results of urinary loss in grams (g) of 10 patients who underwent non-ablative radiofrequency treatment on external urethral meatus measured by Pad Test, Bahia, 2015.

Patient	Initial Pad test (g)	Final (End) Pad test (g)	Pad test after 1 month (g)	Pad test after 2 months (g)	Pad test after 3 months (g)
01	2	1	0	2	2
02	6	2	0	5	4
03	13	23	10	12	--
04	16	21	10	31	29
05	7	2	5	3	--
06	6	3	5	11	--
07	11	10	4	3	6
08	25	27	20	19	16
09	70	5	22	16	15
10	16	0	--	2	--

Assessing whether the use of non-ablative radiofrequency on urethral meatus is regarded safe, nine (90%) out of 10 participants presented no adverse or side effects. One participant indicated to have felt an unexpected burning sensation in the area of the urethral meatus, just after the menstrual period. This participant returned for the radiofrequency treatment a week later, without any complaints.

During her physical examination, there was no edema, redness, increased local temperature or presence of secretion. Nothing was prescribed in order to improve this discomfort. No other complications were observed. All patients completed the five sessions.

Figure 3 - Comparison of mean urinary loss in grams (g) Pad Test at the begginning-, end-, and after one-, two- and three months of treatment.



DISCUSSION

We present a new technique of a conservative treatment of SUI. It follows a principle that already exists, but applied in a different way. We applied the technique on the urethral meatus after an animal experimental study has demonstrated the possibility of increasing collagen production of anal sphincter (9) and we used temperatures ranging from 39 to 41ºC, as it was proved to be safe and effective in the human genital region (14).

We demonstrated that the method is painless and reliable. Besides the fact that we indicate its lower risk of adverse effects during the technical treatment; only one patient reported a burning sensation during a session right after menstruation. In this case, a possible difference in resistance of tissue could be due to friction of the pad with a change in impedance of the passage of electric waves. For the electric current to perform the desired action on the tissue, it needs to overcome the barrier imposed on its flow and reach the target tissue in the right intensity. This is what we call tissue impedance. The impedance is composed of the extra flow resistance and capacitive reactance of cell membranes. The electric current will always take the path of least resistance. The tissue impedance may change the density, intensity and path of the current and of the biological response (15).

The method has no adverse effects; the observed results were similar to those of the studies of Meillheiser et al. where radiofrequency was used for treatment of the vaginal introitus to treat vaginal laxity; and a pilot study conducted to test tolerance and safety showed that there has been no adverse effect (using frequency 75-90 Joules/ cm^2) (16). In addition to the low risk, one advantage of this new treatment technique is that it is not necessary to place the device in the urethra, which reduces the side effects and eliminates the need for prophylactic antibiotics or the use of anesthetics, as used in prior studies. In the systematic review on the intraurethral radiofrequency technique, a relative risk (RR) of 5.76 of pain / burning-, a RR of 1.36 of a hyperactive destrusor-, and a RR of 0.95 of urinary retention was found (17).

The clinical response related to urinary loss was satisfactory for this group of patients studied. This is a very small number of patients to show therapeutic effectiveness, but considered a necessary phase study when to present a new therapy. Randomized clinical trials are being developed by our group to assess the effectiveness of the method.

The improvement in urinary loss is shown in the final Pad test. Seven out of ten participants showed an improvement in reducing stress urinary

incontinence. By treating with radiofrequency, local temperatures increase, which enables vasodilation and the opening of capillaries, the gain of oxygen, and an improved drainage. This phenomenon can improve the circulation of the venous plexus which is a layer of spongy erectile tissue, that contributes to the urethral closure mechanism (7). The decrease in urinary loss measured by the Pad test was most evident one month after the radiofrequency treatment. The result we found is probably due to the period of collagen denaturation and neo production that remains until 28 days after treatment. Since those collagen changes favor the urethral closure mechanism (18), it could be explained why there was a better response on the pad test after one month. Rechberger et al. demonstrated that collagen content has been correlated with the urethral pressure, the length of the urethra and maximum closure pressure of the urethra (19).

Nine out of ten patients indicated to be satisfied with the treatment, although seven out of ten patients experienced a reduction of urinary loss after treatment with radiofrequency. This finding shows that satisfaction is not only linked to the therapeutic outcome, but possibly also to the level of expectations of the people involved. This means that degrees of satisfaction do not always correspond to the results. However, the degree of satisfaction should be measured to stablish a subjective response of patients. Satisfaction is the feeling of pleasure or disappointment which resulted from comparing a perceived performance or outcome against one´s expectations. When considering the answers of patients on satisfaction, the Hawthorne-effect can be taken into consideration. Hawthorne said that when individuals believe they are experiencing a form of treatment, they are more likely to respond to be satisfied with therapeutic responses (20). Another factor that should be taken into consideration is that the complaint regarding urinary loss is not directly proportional to the volume of urine loss (21, 22).

A disadvantage of this new technique is that qualified professionals are required to perform the procedures. Another issue is a need to schedule five sessions, however, there is no consensus on parameters and treatment frequency in literature regarding radiofrequency treatment.

Hence, it can be considered a conceivable perspective to carry out a clinical trial to measure the response to radiofrequency treatment on the external urethral meatus of woman with SUI, with a control on variables such as age, parity, degree of muscle strength, BMI, and with a long-term control of the response to therapy on the external urethral meatus. A limitation found was the loss of 4 patients during the follow-up phase, due to their lack of finances to finish the study.

CONCLUSIONS

The preliminary results of our study (phase 1) look promising. However, to increase the validity of the study, larger clinical trials are warranted. Our study showed that the treatment of stress urinary incontinence with radiofrequency on the urethral meatus had no adverse effects and reduced urinary loss in women.

CONFLICT OF INTEREST

None declared.

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Laparoscopic pectopexy: initial experience of single center with a new technique for apical prolapse surgery

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ABSTRACT

Objective: To share our first experience with laparoscopic pectopexy, a new technique for apical prolapse surgery, and to evaluate the feasibility of this technique.
Materials and Methods: Seven patients with apical prolapse underwent surgery with laparoscopic pectopexy. The lateral parts of the iliopectineal ligament were used for a bilateral mesh fixation of the descended structures. The medical records of the patients were reviewed, and the short-term clinical outcomes were analyzed.
Results: The laparoscopic pectopexy procedures were successfully performed, without intraoperative and postoperative complications. De novo apical prolapse, de novo urgency, de novo constipation, stress urinary incontinence, anterior and lateral defect cystoceles, and rectoceles did not occur in any of the patients during a 6-month follow-up period.
Conclusion: Although laparoscopic sacrocolpopexy has shown excellent anatomical and functional long-term results, laparoscopic pectopexy offers a feasible, safe, and comfortable alternative for apical prolapse surgery. Pectopexy may increase a surgeon's technical perspective for apical prolapse surgery.

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Laparoscopy; Pelvic Organ Prolapse; Vagina

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INTRODUCTION

Pelvic organ prolapse (POP) affects millions of women worldwide, and is a health problem for 50% of parous women aged over 50 years (1). At the same time, the number of surgical procedures performed for prolapse has increased enormously in recent years, as a result of changes in population distribution; while 12.7% of women in the United States were aged over 65 in 2000, this figure will rise to 20% by 2030 (2). Similarly, the percentage of women in Germany aged over 65 was 20% in 2011, and this proportion will increase to 35% by 2060 (3).

Apical prolapse refers to the downward displacement of the vaginal apex, uterus, or cervix. It may be associated with various signs and symptoms, including vaginal bulging, palpable or visible tissue protrusion, pelvic pain, dyspareunia, or obstructed intercourse. Women with apical prolapse often experience altered bladder and bowel functions, such as irritative or obstructed voiding, urinary retention or urinary incontinence, obstructed defecation, and fecal urgency or fecal incontinence (4).

Numerous previous studies have shown that sacrocolpopexy or sacrouteropexy represents the most effective option for apical prolapse surgery (4-6); sacrocolpopexy remains the most suitable surgical procedure for restructuring the physiological axis of the vagina (4-6). In contrast

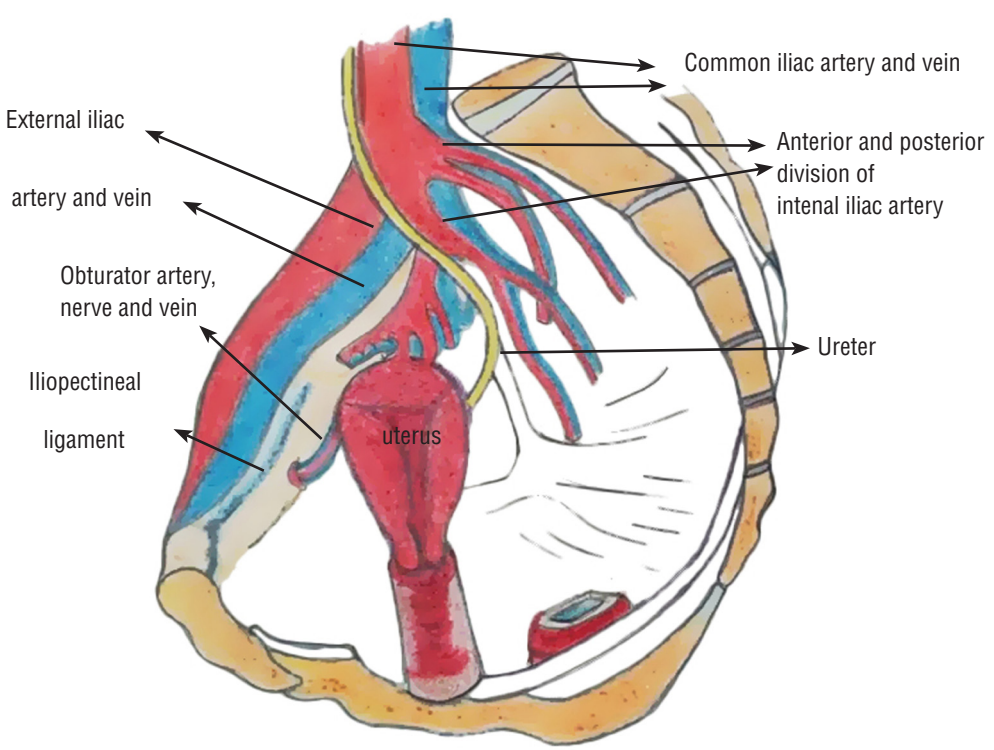
with abdominal sacrocolpopexy, laparoscopic and robot-assisted approaches avoid the need for a large abdominal incision and minimize bowel manipulation, potentially leading to less postoperative pain and a shorter recovery time (7, 8).

Although sacrocolpopexy has been the most effective option over time, the procedure is still associated with some problems, and the most frequently reported complications include defecation disorders and stress urinary incontinence (SUI) (9). Previous studies have consistently reported that gastrointestinal complications, such as small bowel obstruction, ileus, or defecation disorders occur in approximately 0.1 to 5% of sacrocolpopexy procedures. The mesh placed between the sacrum and vagina (cervix) always narrows the pelvis, and the cause of the defecation disorders may be reduced space in the pelvis (outlet obstruction), adhesions, or trauma of the hypogastric nerves (5, 7, 9-11). However, presacral hemorrhage is the most worrying intraoperative complication of sacrocolpopexy, and may have life-threatening consequences (11).

POP is more associated with obese patients (12), and the advantages of laparoscopic surgery are more important for this patient Group. However, this method may be restricted, due to the difficulty of the surgical field. In 2007, Banerjee and Noe described a new method of endoscopic prolapse surgery that was especially developed for obese patients, in which the lateral parts of the iliopectineal ligament are used for bilateral mesh fixation of the descended structures (13). In this method, the mesh follows round and broad ligaments without crossing the ureter or bowel; therefore, the pelvic outlet does not shrink. In addition, the hypogastric vessels are also a safe distance from any danger (13).

The ilipectineal ligament is an extension of the lacunar ligament that runs on the pectineal line of the pubic bone (14) (Figure-1), and is significantly stronger than the sacrospinous ligament and the arcus tendineus of the pelvic fascia (15). The structure is strong, and holds suture well. It is

Figure 1 - Anatomic details of the iliopectineal ligament.



also possible to find sufficient material for a suture in the lateral part of the iliopectineal ligament, facilitating reconstruction of the pelvic floor (16). This segment of the ligament is situated at the second sacral vertebra (S2) level which is the optimal level for the physiological axis of the vagina. S2 level is the anchor point for the physiological axis of the vagina (16).

We recently successfully performed prolapse surgery in seven patients, without any complications, using a new laparoscopic pectopexy technique. This was the first short-term Turkish experience with this technique, and it is described and shared in this paper.

MATERIALS AND METHODS

A total of seven women who underwent laparoscopic pectopexy between May 2014 and January 2015 at the Kocaeli Derince Educational and Research Hospital, Kocaeli, Turkey, were included. The patients presented with either symptoms related to apical prolapse, such as sensation of pressure on the vagina, seeing or feeling a bulge/protrusion, lower back pain, dyspareunia, and other sexually related symptoms, or associated urinary symptoms, such as incontinence, frequency, urgency, and urinary retention. All operations were performed by the same surgical team, and all patients underwent surgery after their informed consent was obtained. The study was approved by the Ethics Committee of the Kocaeli Derince Educational and Research Hospital (Registration number KÜ GOKAEK 2016/204).

The extent of the genital prolapse was assessed not only by a gynecological examination, but also via ultrasonography. The pelvic organ prolapse quantification system (POP-Q) for prolapse assessment was used. In order to assess the influence of pressure, the patients were examined both in a lying and in a sitting position; this assessment was important to avoid an over--or under-correction. Only symptomatic primary vaginal or uterine prolapse patients with POP Q II and above were included. Exclusion criteria were previous operations for vaginal prolapse correction, pelvic inflammatory disease, and previously identified, or strongly suspected, massive adhesions in the pelvic cavity.

The patient's medical records and video recordings of the operations were reviewed. All patients were analyzed in terms of age, body mass index (weight in kilograms divided by the square of the height in meters), estimated blood loss (EBL), operation time, intraoperative complications and postoperative complications.

The patients were followed up for at least 6 months after surgery, and the relapse occurrence of apical prolapse, anterior and lateral defect cystoceles, as well as the incidence of de novo urinary symptoms, rectoceles, and defecation disorders, were recorded. We used the defecation section of the International Consultation on Incontinence Ouestionnaire to document the defecation disorders.

Surgical procedures

All the operations were performed under general anesthesia with endotracheal intubation, and standard intramuscular cephalosporin antibiotics were used for prophylaxis. The patients were then placed in a modified lithotomy position, with the hips at an approximate 180º extension, the knees flexed at almost 90º, and with the table tilted in a nearly 45º Trendelenburg position. Both arms were tucked along the patient's side. A 10mm trocar (Endo Ethicon) was inserted directly from the umbilicus, and pneumoperitoneum was generated until an intra-abdominal pressure of 14mmHg was achieved. Three additional 5mm ports were inserted under direct visualization of the lower intra abdominal area; median, left, and right from 2 cm medial and superior to the anterior superior iliac crests. Following sterilization of the skin and covering of the patient, a RUMI© uterine manipulator with a Koh Cup™ colpotomizer (Cooper Surgical; Trumbull, Connecticut, US) was trans-vaginally introduced at the beginning of the procedure. The surgeon stood on the patient's left, and the first assistant handled the scope on the patient's right. The second assistant was positioned between the legs of the patient. Operation time began with the first skin incision and ended with the final closure of an incision.

Pectopexy technique

We performed this procedure as previously described by Banerjee and Noe (13). First, we opened the peritoneal layer along the right round ligament toward the pelvic side wall (Figure-2A). An incision in the medial and caudal direction was made with an Harmonic scalpel, and the right external iliac vein was visualized. Soft tissue in this area was dissected with blunt dissection, so an approximately 4-5 cm segment of the right iliopectineal ligament (Cooper ligament) adjacent to the insertion of the iliopsoas muscle could be identified (Figure-2B). The same procedure was then repeated on the left side of the patient. The peritoneal layers on both sides were opened toward the vaginal apex, and the anterior and posterior areas of the vaginal apex were prepared for the mesh fixation. In patients with a preserved uterus, the anterior peritoneum of the uterus was dissected, and the lower anterior segment of the uterus was prepared for the mesh fixation (Figure-2C). After completion of dissections, a polyvinylidene fluoride monofilament mesh (DynaMesh© PVDF, 3x15 cm) was inserted into the abdominal cavity. The ends of the mesh were sutured to both iliopectineal ligaments via the intracorporeal suture technique, using nonabsorbable sutures (Figures 2D and 2E). The mesh in the tension-free position was fixed to the vaginal apex or uterus with polydioxanone sutures (Figure-2F), and the vaginal apex or uterus was provided with a hammock-like fixation. Finally, the peritoneum above the mesh was sutured with an absorbable suture material (Figure-2G).

Low-dose vaginal estriol treatment was postoperatively initiated, and it was recommended that all patients continue with this for at least 6-8 weeks following the procedure. We also advised the performance of regular pelvic floor exercises to provide adequate healing and scar tissue formation.

Statistical analysis

Statistical analysis was carried out using Statistical Package for the Social Sciences software, version 20.0 (SPSS Inc., Chicago, Illinois, USA), and descriptive statistics were used to describe the study. Data were expressed as number and percentage or mean with standard deviation.

RESULTS

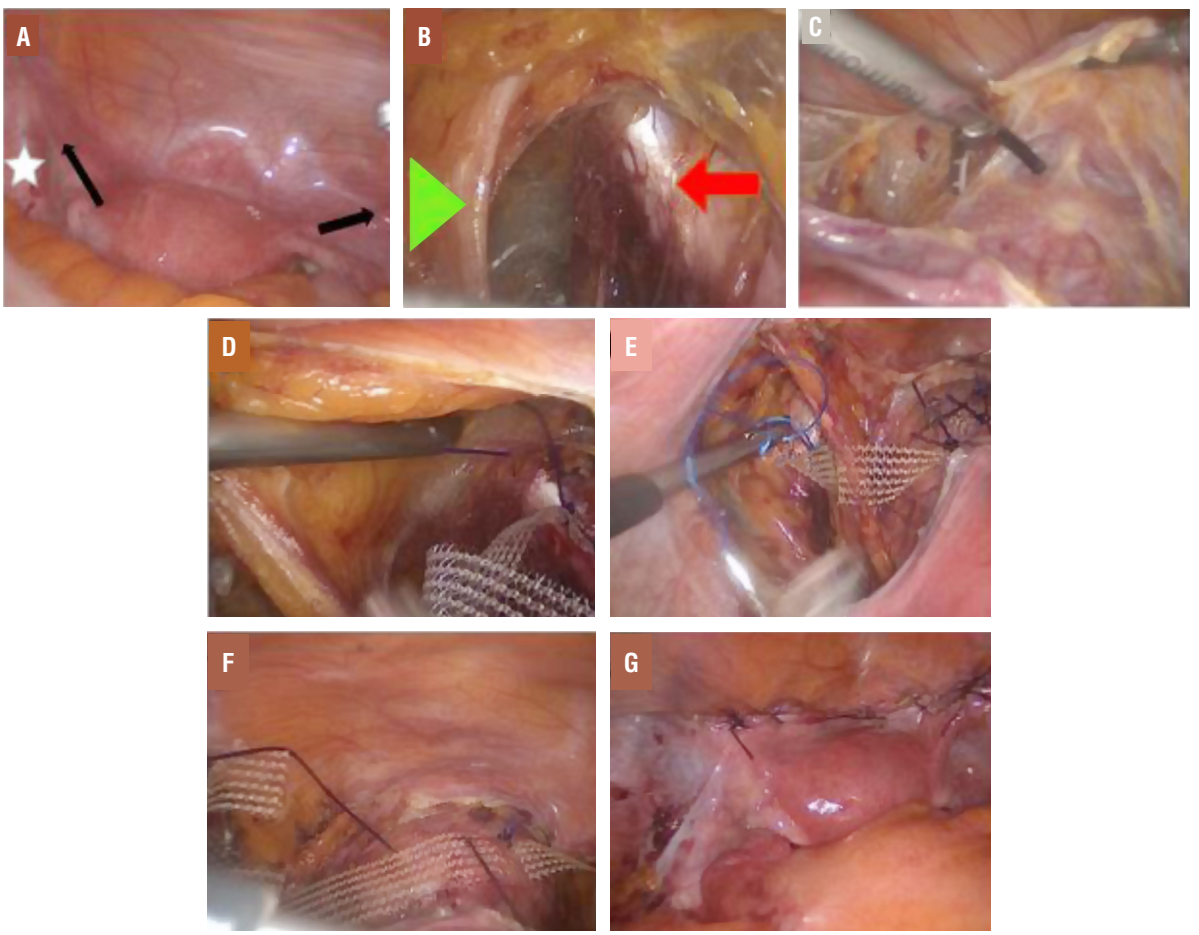
Over the study period, seven patients underwent laparoscopic pectopexy procedures. EBL was no more than 50 mL and operation time was no longer than 80 minutes (Table-1). Laparoscopic pectopexy was successfully performed, without intraoperative or postoperative complications. Conversion to laparotomy was not required in any of the cases and nor were postoperative blood transfusions. The patients remained in hospital for a maximum of 24 hours and were discharged in good health. The therapy satisfaction rates were high in all patients, who were followed up in the outpatient clinic at 1 week and then at 6 months after discharge. De novo apical prolapse, de novo urgency, de novo constipation, SUI, anterior and lateral defect cystoceles, and rectoceles did not occur in any of the patients during the 6-month follow-up period.

DISCUSSION

Several previous studies have shown that both abdominal and laparoscopic sacrocolpopexy for apical prolapse surgery is related to excellent anatomical and functional outcomes in long-term follow-up (4-6, 17). Apical prolapse repair has been performed laparoscopically for over 20 years (10, 18), and, although it depends on the surgeon's ability, potential problems may arise during laparoscopic sacrolcolpopexy; the sigmoid is retracted to the left, allowing identification of the sacral promontory, and when working in the area of the sacrum, care should be taken to avoid damage to the sigmoid, presacral veins, and right ureter. Another issue is accessibility to the surgical area at the ventral side of the sacrum; therefore, many surgeons have modified the technique and have fixed the mesh to the top of the promontory. However, this change of mesh localization results in a positional change in direction to the abdominal wall (10, 16).

Laparoscopic pectopexy is a new type of endoscopic prolapse surgery. It uses the late-

Figure 2 - Intraoperative stages.



Determination of the round ligaments (arrows) and external iliac vessels (star). The peritoneal layer is opened along the right round ligament toward the pelvic side wall. Soft tissue in this area was dissected with blunt dissection. The iliopectineal ligament (arrow) and the medial umbilical ligament (triangle) are demonstrated. The same procedure is then repeated on the left side of the patient. The peritoneal layers on both sides are opened toward the cervix. After completion of dissections, the ends of the mesh are sutured to both iliopectineal ligaments via the intracorporeal suture technique, using nonabsorbable sutures. The middle of the mesh is fixed at the lower anterior segment of the uterus with three stitches. The peritoneum above the mesh is sutured with an absorbable suture material.

ral parts of the iliopectineal ligament for a bilateral mesh fixation of the descended structures, so fewer potential long-term problems are expected (19). The pelvic outlet does not narrow with this procedure, as is expected with sacrocolpopexy, and, compared to the latter, laparoscopic pectopexy is not associated with a high intraoperative risk (19). In the present study, there were no intraoperative complications or postoperative complications. Noe et al. compared the laparoscopic pectopexy and sacrocolpopexy procedures in a randomised comparative clinical trial that was conducted in 83 patients who had only symptomatic primary vaginal prolapse POPQ ≥2 (19). They showed that mean operation time and blood loss were reduced in the pectopexy Group.

The incidence of de novo SUI following sacrocolpopexy is 15.9-37.6% (17, 20, 21). North et al. reported de novo SUI in half of women without concomitant continence surgery with sacrocolpopexy (18). In contrast with other studies, Noe et al. observed de novo SUI in approximately 5% of women in both laparoscopic pectopexy and laparoscopic sacrocolpopexy groups (16). Although we are not capable of analyzing the long-term outcomes of the patients in the current

Table 1 - Details of laparoscopic pectopexy procedures.

Patient no	Age (years)	BMI (kg/m^2)	Pelvic examination	Operation time (min.)	EBL (mL)	Intraoperative Complications	Postoperative Complications
1	67	23.4	Vaginal vault prolapse	80	40	None	None
2	56	20.5	Vaginal vault prolapse	74	20	None	None
3	59	23.6	Vaginal vault prolapse	60	30	None	None
4	61	22.9	Vaginal vault prolapse	70	35	None	None
5	50	19.5	Vaginal vault prolapse	72	40	None	None
6	40	23.5	Uterine prolapse	55	50	None	None
7	39	24.4	Uterine prolapse	59	45	None	None

BMI = body mass index; **EBL =** estimated blood loss.

study, no occurrences of de novo SUI were recorded.

One important problem that is observed following sacrocolpopexy is that of gastrointestinal complications; defecation problems, particularly constipation, are most common (18, 22, 23). As expected, Noe et al. showed a statistically significant difference in the incidence of de novo defecation problems following laparoscopic pectopexy and sacrocolpopexy- 0% and 19.5%, respectively (16). In accordance with these results, we did not observe defecation problems. This may be explained by the fact that pectopexy neither reduces the space of the pelvis (outlet obstruction) nor carries the risks of trauma to the hypogastric nerves.

It has been reported that this technique may be protective against de novo anterior and lateral defect cystoceles, due to the lateral placement of mesh (16). In our study, de novo lateral defects were not observed.

We successfully performed laparoscopic pectopexy procedures in seven patients, without intraoperative and postoperative complications. As already mentioned, de novo apical prolapse, de novo urgency, de novo constipation , SUI, anterior and lateral defect cystoceles, and rectoceles did not occur in our patients during the 6-month follow-up period. However, the number of cases included was one of the main limitation of this study. Besides there was no control group to compare the results.

We believe that laparoscopic pectopexy offers several practical advantages: (1) it enables the surgeon to use a wide area in the pelvis, that reacts more satisfactorily in complex surgical conditions; (2) it does not reduce the pelvic space, so postoperative defecation and urinary disorders are not expected; (3) the iliopectineal ligament is very strong, thus it is expected that there will be a very low rate of postoperative recurrence of apical prolapse; (4) the iliopectineal ligament fixation of apical prolapse does not change the physiologic axis of the vagina because S2 level is the anchor point for the physiological axis of the vagina; and (5) the iliopectineal ligament is far from the ureter, intestines, sigmoid, and presacral veins. During surgery, there is very little damage to these structures, so the iliopectineal ligament is a safe area for apical prolapse reconstructive surgery.

CONCLUSIONS

We have shown in our study that pectopexy may be a feasible, safe, and comfortable procedure that can be performed in the apical prolapsus surgery. Laparoscopic pectopexy might be an alternative technique to sacrocolpopexy. However, this case series displays the initial experience of a new pro-

cedure, and further prospective comparative studies are necessary to show long-term effectiveness.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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EDITORIAL COMMENT: LAPAROSCOPIC PECTOPEXY: INITIAL EXPERIENCE OF SINGLE CENTER WITH A NEW TECHNIQUE FOR APICAL PROLAPSE SURGERY

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Pelvic organ prolapse (POP) affects millions of women worldwide, and is a health problem for 50% of parous women aged over 50 years (1). Multiple procedures and surgical techniques have been used, with or without the use of vaginal meshes, due to common treatment failure, reoperations, and complication rates in some studies. Randomized trials comparing the use of mesh to native tissue repair in POP surgery have now shown better anatomical but similar functional outcomes, with transvaginal meshes being associated with more complications. Surgeons so on started to use again classic techniques to correct POP using minimally invasive surgery as laparoscopy and robotic surgery (2).

Laparoscopic sacrocolpexy has been used over the time as a good option for apical prolapse correction, with some reported complications as defecation disorders due to pelvic narrowing and hypogastric nerves lesions, specially in obese populations. This retrospective analysis shows an alternative technique to correct apical prolapse, using the iliopectineal ligament (Cooper ligament) to fixate a tension free mesh to vaginal apex instead to classic sacrum fixation. In this method, the mesh follows round and broad ligaments without crossing the ureter or bowel; therefore, the pelvic outlet does not shrink. In addition, the hypogastric vessels are also a safe distance from any danger (3).

Seven patients were submitted to Laparoscopic pectopexy without intraoperative and postoperative complications. Recurrence of apical prolapse, urgency, constipation, stress urinary incontinence, anterior and lateral defect cystoceles, and rectoceles did not occur in these seven patients during the 6-month follow-up period. Despite of the inherent limitations of this retrospective study with limited number of patients, this is a promising techinique that can be used alternatively to sacrocolpopexy, specialy in obese patients or limited surgeons experience in minimally invasive approaches. Randomized controlled trials are still needed to compare results with the gold - standard procedure and to best define indications to this new technique.

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Inflatable penile prosthesis as tissue expander: what is the evidence?

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ABSTRACT

Objective: Many patients who undergo inflatable penile prosthesis (IPP) replacement are often upsized to larger cylinders, suggesting the IPP may serve as a tissue expander and increase internal penile length. The objective of this study is to evaluate whether cylinder length increases with subsequent IPP insertion.

Materials and Methods: We queried American Medical Systems and Coloplast Patient Information Form databases to identify patients who underwent IPP placement and replacement between 2004-2013. Patients were grouped by device type and time to replacement (<2 or ≥2 years). We selected the 2-year mark for subgroup analysis to allow time for tissue expansion to occur and to exclude patients who underwent early explantation (e.g. erosion or infection).

Results: Two thousand, seven hundred and forty nine patients (1,532 AMS 700 LGX, 717 AMS 700 CX, and 500 Coloplast Titan) met the inclusion criteria. Mean time between implants was earlier for LGX (29 months) than CX (39 months) and Titan (48 months) patients (p<0.001). Patients who underwent device replacement at <2 years did not experience an increase in mean cylinder length. On the contrary, patients who underwent device replacement at ≥2 years did experience significant increases in mean cylinder length (LGX 1.2 cm, CX 1.1 cm, and Titan 0.9 cm, p<0.001). The mean increases in length at ≥2 years were similar between the 3 devices (p=0.20). Sixty percent of patients demonstrated increases of >0.5 cm and 40% demonstrated increases of ≥1 cm.

Conclusions: As demonstrated, the IPP may provide tissue expansion over time. Further evaluation is needed to determine if increased cylinder length correlates to increased functional length and patient satisfaction.

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INTRODUCTION

Although patients report high rates of satisfaction with penile prosthesis surgery, penile shortening has long been recognized as a common patient complaint (1-6).

Patients often attribute penile shortening to the prosthesis; however, many patients fail to acknowledge that radical prostatectomy, Peyronie's disease, priapism, long-standing erectile dysfunction, and obesity can all affect penile length even prior to device placement (7). The largest study to evaluate post-operative penile length showed that prosthesis do not shorten post-operative stretched penile length (5). In addition, another study suggested that the combination of aggressive sizing with a penile rehabilitation inflation protocol may actually help to increase post-operative stretched penile length (4).

We have often observed that patients are often upsized to larger cylinders during inflatable penile prosthesis (IPP) replacement surgery. We hypothesized that IPP may serve as tissue expanders, stretching the corpora gradually over time when inflated regularly and increase internal penile length. We used IPP cylinder length as a surrogate for internal penile length and queried industry data to evaluate on a nationwide scale whether IPP cylinder length increases at the time of device replacement.

MATERIALS AND METHODS

Study requests were submitted to and approved by both American Medical Systems (AMS, Minneapolis, MN, USA) and Coloplast (Minneapolis, MN, USA) to obtain Patient Information Form (PIF) data for patients who had IPP placement and replacement (AMS 700LGX, AMS 700CX, and Coloplast Titan) between 2004 and 2013. Cylinder lengths were calculated as the total length of both cylinders plus rear tip extenders from each side. The average length from both sides was used for patients with mismatched lengths. Differences in IPP length were stratified by device type and by the interval duration between surgical dates of device replacement (<2 or ≥2 years); reason for device replacement was not available. Devices were also stratified by interval changes in cylinder length. The 2-year mark was selected for subgroup analysis to allow for sufficient time for tissue expansion to occur and to reduce the influence of early device explantation. Patients who underwent early explantation (e.g., infection, erosion, or oversizing) were likely treated with shorter cylinders due to immediate salvage techniques, development of corporal fibrosis, and need for device downsizing.

Data were tabulated and analyzed in SPSS® (IBM, Armonk, NY, USA). Analyses of categorical and continuous variables were performed using chi-squared test, t-test, and ANOVA analyses. Statistical significance was set at $p < 0.05$.

RESULTS

During the ten-year study period, 2.749 patients (1.532AMS 700LGX, 717AMS 700CX, and 500 Coloplast Titan) met the inclusion criteria (Table-1). Mean age at the time of first device placement (61 years) was similar between LGX and CX patients (p=0.37); age was not available for Titan patients. Mean time between implants was shorter for LGX (29 months), compared to CX (39 months) and Titan (48 months) patients ($p < 0.001$). Mean initial length of LGX cylinders (19.7 cm) was shorter compared to CX (20.0 cm) and Titan (20.1 cm) ($p < 0.001$) patients.

At the time of device replacement, mean cylinder length (LGX 0.6cm, CX 0.5cm, and Titan 0.5 cm, p=0.86) and percent change of cylinder length (LGX 3.3%, CX 3.6%, and Titan 3.6%, p=0.77) increased equally for all three devices. The Titan increased 0.7 cm, 0.9 cm, 1.0 cm, and 1.3 cm at the time of device replacement 1, 2, 3, and 5 years after the initial placement, respectively. Data for LGX and CX patients was not available for all of those time intervals.

Table 1 - Patient and Device Characteristics for AMS 700 LGX, AMS 700 CX, and Coloplast Titan.

	LGX	CX	Titan	p
Patient Characteristics				
Number of patients	717	1532	500	-
Mean age at first implant, yrs	61	61	-	0.37
Mean time to replacement, mos	29	39	48	<0.001
Device Characteristics				
Mean initial cylinder length, cm	19.7	20.0	20.1	<0.001
Mean change in length, cm	0.6	0.5	0.5	0.86
Mean percent change in length, %	3.3	3.6	3.6	0.77

At ≥2 years, mean cylinder length (LGX 1.2 cm, CX 1.1 cm, and Titan 0.9 cm), p=0.20) and percent change of cylinder length (LGX 6.5%, CX 6.2%, and Titan 5.5%, p=0.53) increased equally for all three devices (Figure-1). Mean cylinder length did not increase when replaced at <2 years. At ≥2 years, 60% of patients increased >0.5 cm and 40% increased ≥1cm in cylinder length (Table-2). LGX and CX patients both demonstrated increased cylinder length more frequently and in greater magnitude compared to Titan patients (p<0.0001). LGX patients did not demonstrate increased cylinder length compared to CX patients (p=0.12).

DISCUSSION

Tissue Expansion in Surgery

Tissue expansion was first described in 1957 for auricular reconstruction and is most commonly employed today with plastic and breast

Figure 1 - Significant increases in mean cylinder length (A) and mean percent change in cylinder length (B) were seen with device replacement at ≥2 years compared to <2 years for AMS 700LGX, AMS 700CX, and Coloplast Titan (all p <0.001). LGX, CX, and Titan performed similarly within each subcategory (see depicted p values).

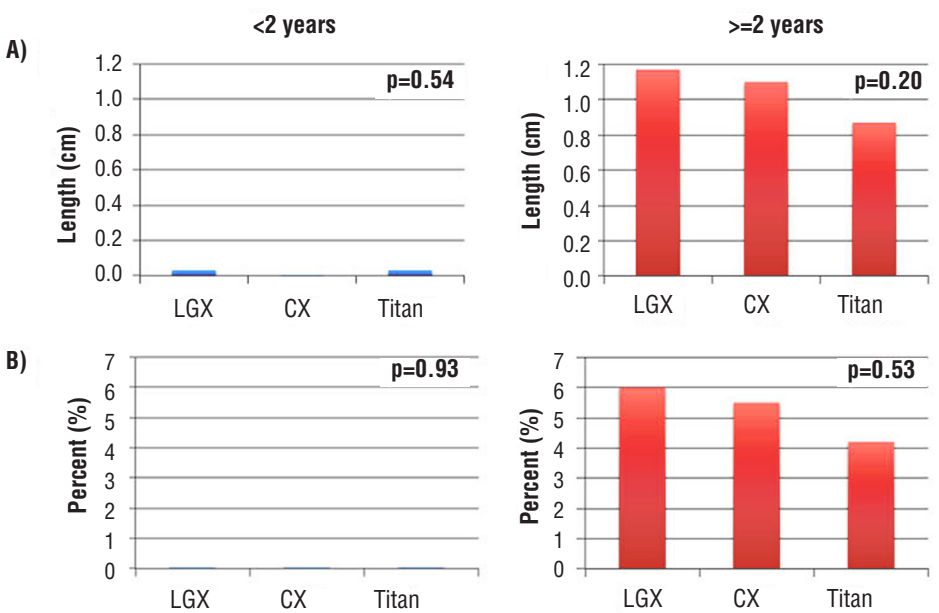

Table 2 - Interval Changes in Cylinder Length for AMS 700 LGX, AMS 700 CX, and Coloplast Titan with Device Replacement at ≥2 Years.

	LGX	CX	Titan
Any decrease in length	33 (10%)	105 (12%)	63 (21%)
0-0.5 cm increase in length	79 (25%)	247 (28%)	55 (18%)
0.5-1 cm increase in length	72 (23%)	196 (22%)	63 (21%)
≥1 cm increase in length	133 (42%)	331 (38%)	119 (40%)

LGX vs. Titan (p<0.0001); CX vs. Titan (p<0.0001); LGX vs CX (p=0.12)

reconstructive surgery (8). Descriptions of tissue expansion within Urology are limited. Case reports have described good success with expanding penile tissue in children and young adults with scarred skin who required phallic reconstruction in the setting of multiple prior hypospadias and epispadias surgeries (9, 10), Several small studies suggest that an IPP may expand corporal tissue with regular inflation among patients with and without corporal scarring (4, 11). Wilson et al. demonstrated fibrotic corpora secondary to priapism or infection could be stretched with aggressive cycling (11).

We have frequently observed that many patients who undergo IPP replacement are often upsized to larger cylinders, thus prompting our effort to further validate the concept that IPP cylinders may serve as tissue expanders. This unique nationwide, industry-generated database confirmed that 40% and 60% of men undergoing device replacement after two years from initial placement experienced mean increases in device length of ≥1cm and >0.5 cm, respectively.

Penile Lengthening Procedures and Length Assessment

Evaluating whether an IPP may serve as a tissue expander is clinically important because penile shortening is known to be a frequent source of patient dissatisfaction after IPP insertion (1-6). Patient self-assessment of penile length is notoriously problematic because it tends to be a subjective, emotional, and multifactorial process. One evaluation of over 52,000 men and women identified that although 85% of women were satisfied with their partner's penis size, only 55% of men were satisfied with their own penis size (12). Many concomitant anatomic and technical factors may contribute to the perception of penile shortening after IPP (e.g., prior prostatectomy, Peyronie's disease, priapism, suprapubic fat pad, lack of glans engorgement, inadequate corporal dilation, inappropriate device sizing). In addition, men with refractory erectile dysfunction may suffer from recall bias, since they may not have had any recent, rigid erections. Prior studies evaluating stretched penile length to better characterize length change after IPP placement vary (5, 13). Therefore, without good objective measures of penile length, careful pre-and post-operative counseling becomes even more important to appropriately set patient's expectations.

Numerous ancillary maneuvers (sliding technique, suprapubic lipectomy, suspensory ligament release, autologous fat injections, stretching devices, vacuum protocols, glans injection, ventral phalloplasty) have been developed for penile enlargement, illustrating the importance of penile size among IPP patients (14-16). Complications from these strategies may include penile lumps, nodules, and shaft deformities (7, 17, 18). Our large PIF dataset suggests that aggressive IPP cycling after initial implantation, followed by eventual device upsizing may constitute a treatment strategy for patients with legitimate penile shortening; however, evidence of increased functional length and improved patient satisfaction with device replacement is required before implementing such a treatment strategy.

Penile Length in IPP Patients

Henry et al. prospectively evaluated penile length and girth measurements for 1 year following Titan IPP placement using an aggressive sizing and cycling protocol. These patients underwent daily inflation for 6 months followed by maximal inflation for 1-2 hours daily for 6-12 months. After 1 year, 65% of patients were pleased with their length, 74% perceived increased length, and most experienced about 1cm increase in stretched penile length with this aggressive cycling regimen. Our nationwide PIF data study similarly identified that many IPP patients who underwent device replacement after two years experienced increased cylinder length. Further evaluation is required to identify the correlation between internal (cylinder) and external (stretched penile and inflated) length.

The selection of which type of prosthesis to use may depend on several characteristics, including patient anatomy, history, and surgeon preference. Because the AMS 700LGX was developed to provide both girth and length expansion, it is commonly recommended for patients with shorter penile lengths. Because the AMS 700CX and Coloplast Titan devices provide only girth expan-

sion, these devices are typically recommended for patients with larger penile lengths. These device features may help to explain why in this study, at the time of first implant, the LGX devices tended to be shorter compared to CX and Titan ($p < 0.001$). Furthermore, LGX devices demonstrated cylinder length increase more frequently and in greater magnitude compared to Titan ($p < 0.0001$), but not CX devices ($p = 0.12$).

Limitations

Although this 10 years, nationwide dataset study is the largest of its kind to evaluate device length changes over time after IPP implantation, many important limitations exist in this analysis. Conclusions from this study are based on industry obtained PIF data, which lacks important clinical details such as the reason for device explantation or replacement. The reason for device replacement can affect the choice of subsequent device sizing, as men explanted due to infection experienced significant corporal fibrosis and contraction. Furthermore, the method for device sizing is unknown without description of whether some implanters attempted cylinder oversizing during IPP placement or prescribed aggressive postoperative cycling protocols. It is possible that men who inflated their IPP more regularly may have produced more tissue expansion and those who inflated rarely did not.

This nationwide, patient information form data study suggests that increased cylinder length may translate into increased functional length. Further evaluation needs to be conducted to confirm this hypothesis. One counter argument is that implants may compress the flaccid glans and corporal tissue, allowing for increased cylinder length, without increased functional length. Future studies will benefit from patient satisfaction data to evaluate whether increased cylinder length at the time of replacement are of functionally and subjectively beneficial to patient.

CONCLUSIONS

The IPP does appear to provide some degree of tissue expansion over time, which challenges the common patient perception of penile shortening after IPP insertion. Additional evaluation is needed to evaluate whether increased cylinder length at the time of replacement increases patient satisfaction. Furthermore, the relationship between increased internal corporal length and external penile length remains to be established.

ABBREVIATIONS

IPP = inflatable penile prosthesis
PIF = data: patient information form data

CONFLICT OF INTEREST

Author Allen Morey receives honoraria for being a meeting participant and lecturer for American Medical Systems and Coloplast Corp.

Other authors

None declared.

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ORIGINAL ARTICLE

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Unilateral extravesical ureteral reimplantation via inguinal incision for the correction of vesicoureteral reflux: a 10-year experience

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ABSTRACT

Introduction and Objective: Multiple options exist for the surgical management of vesicoureteral reflux (VUR). We report on our 10-year experience using the inguinal approach to extravesical ureteral reimplantation (EVR).

Materials and Methods: Patient characteristics of age, gender, and reflux grade were obtained and outcomes of operative time, hospital stay, and radiographic resolution were assessed.

Results: 71 girls and 20 boys with a mean age of 74 months (range 14-164) underwent inguinal EVR via a 3.5-cm inguinal mini-incision. Mean follow up was 10.9 months (range 0.4-69.7). Average grade of reflux was 2.80. Average operative time was 91 minutes (range 51-268). The procedure was successful in 87 of 91 patients (95.6%). The 3 cases of reflux that persisted were all grade 1 and managed expectantly. Contralateral reflux developed in 9 cases, all of which resolved after treatment with either Deflux or ureteral reimplant. There were 4 case of urinary retention that resolved after a brief period of CIC or indwelling catheterization. There were no cases of ureteral obstruction. Most patients were discharged on post-operative day 1 (85/91) and no hospitalization extended beyond 3 days.

Conclusions: The inguinal approach to extravesical ureteral reimplantation should be considered as a potentially minimally invasive alternative to endoscopic and robotic treatment of VUR with a success rate more comparable to traditional open approaches. We feel it is the method of choice in cases of unilateral VUR requiring surgical correction.

ARTICLE INFO

Keywords:
Urinary Incontinence; Minimally Invasive Surgical Procedures; Vesico-Ureteral Reflux

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INTRODUCTION

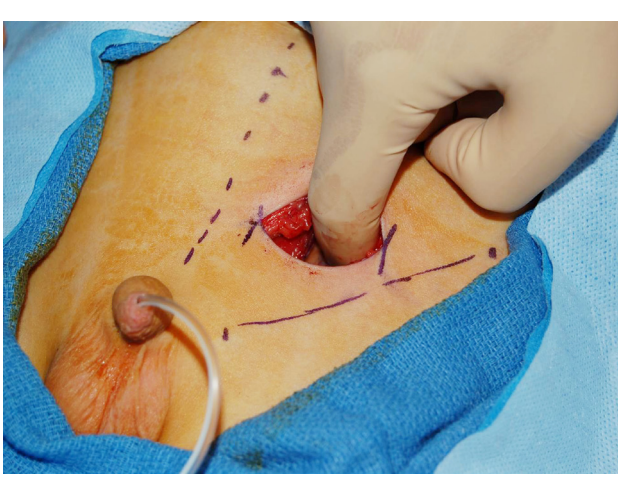
Multiple options exist for the surgical management of vesicoureteral reflux (VUR). Since Lich (1) and Gregoir et al. (2) first popularized extravesical reimplantation (EVR) in the early 1960s, various refinements and modifications have been described. In 2002, Chen et al. reported on EVR performed through an inguinal approach rather than through the standard Pfannenstiel incision (3). They showed that inguinal EVR was safe, effective, and associated with a shorter hospital stay, shorter operative time, and less postoperative pain when compared to both standard EVR and intravesical reimplantation (4). We now report on our 10-year experience with inguinal EVR for the management of VUR. To our knowledge, this is the largest single series to report on extravesical ureteral reimplantation through an inguinal incision. We hypothesized that unilateral inguinal

EVR would remain a safe and effective procedure with opportune cosmesis when evaluated within a large cohort.

MATERIALS AND METHODS

After obtaining IRB approval, we retrospectively reviewed the charts of 157 patients who underwent unilateral inguinal EVR between July 2002 and October 2012. All surgeries were performed by a single surgeon. Average inguinal incision was 3.5cm in length (Figure-1). Baseline characteristics assessed included patient age at the time of surgery, gender, presence of duplicated system, and indication for surgery. We also reviewed length of hospitalization and operative time. The primary objective of our study was to determine surgical success, which was defined as the absence of reflux in the ipsilateral ureter on postoperative voiding cystourethrogram (VCUG). Secondary objectives included determining the presence of de novo contralateral VUR, postoperative urinary retention, and postoperative urinary obstruction. Urinary retention was defined as the need for Foley catheter replacement or clean intermittent catheterization (CIC) postoperatively. Urinary obstruction was defined as postoperative hydronephrosis requiring intervention. Patients were excluded from the study if they had secondary VUR, lack of preoperative or postoperative VCUG, incomplete records, or if surgery was performed through a Pfannenstiel incision.

Figure 1 - Intraoperative example of inguinal incision.



RESULTS

A total of 71 girls and 20 boys met study criteria for a total of 91 patients in the cohort. Patient demographics are presented in Table-1. Mean patient age was 74 months (range: 14-164 months), with females being significantly older than males at the time of surgery (50.3 months vs. 30.6 months, p=0.006). Average grade of reflux was 2.80, with the distribution of grades shown in Figure-2. Indication for surgery in the majority of patients was persistent asymptomatic VUR and parental preference (62 of 91 patients). The remainder of patients underwent surgery for renal scarring, parental preference, or recurrent UTI. Eight patients had previously undergone ipsilateral surgery for VUR. Seven patients had prior subureteric injection of Deflux® and one patient had prior ureteroneocystostomy. Common sheath reimplantation for duplicated collecting systems was performed in 14 patients. 88 patients underwent inguinal EVR alone with no other concomitant procedures. Average operative time in these patients was 91 minutes (range: 51-268 minutes). No intraoperative complications occurred. Average hospital stay was 1.08 days (range: 1-3 days), with the majority of patients discharged on postoperative day 1 (85 of 91 patients). Follow-up ranged from 0.4 to 69.7 months, with a mean of 10.9 months.

The overall success rate in our series was 95.6% (87 of 91 patients) (Table-2). Persistent reflux was grade 1 in all four cases and none required intervention in the follow-up period. Follow--up VCUG was not performed in any patient to assess for resolution of persistent reflux.

Nine patients (9.9%) developed de novo contralateral reflux postoperatively (Table-3). Of the patients with de novo reflux, four (44%) had a history of reflux that had resolved prior to surgery. Eight patients had resolution of contralateral reflux following either Deflux® or formal reimplantation. One patient had spontaneous resolution of de novo contralateral reflux. One patient was lost to follow-up.

Urinary retention developed in 4 children (4.4%) and was transient in all cases (Table-4). Three of these four patients resumed normal voi-

Table 1 - Patient characteristics.

Total Number of Patients	91	
Gender, n (%)		
Male	20 (22.0)	
Female	71 (78.0)	
Mean (range) age, months	74.4 (14-164)	p = 0.006
Male	55.8 (15-164)	
Female	79.7 (14-159)	
Indication for surgery, n (%)		
Recurrent UTI	8 (8.8)	
Persistent Asymptomatic VUR	62 (68.1)	
Parental Preference	6 (6.6)	
Renal Scarring	15 (16.5)	
Duplicated System, n (%)	14 (15.4)	
Prior Ipsilateral VUR Surgery, n (%)	8 (8.8)	
Deflux	7 (7.7)	
Reimplant	1 (1.1)	

Figure 2 - Distribution of preoperative reflux grades.

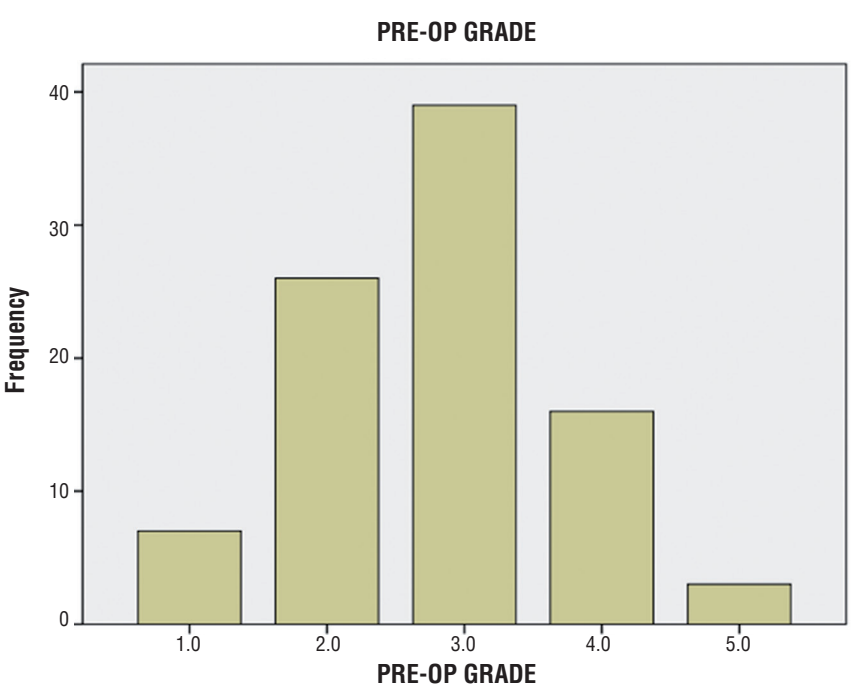


Table 2 - Outcomes.

Resolved reflux, n (%)	87 (95.6)
Contralateral de novo reflux, n (%)	9 (9.9)
Urinary retention, n (%)	4 (4.4)
Urinary obstruction, n (%)	0 (0)
Operative time, mean (range) min	91 (51-268)
Hospital stay, mean (range) days	1.08 (1-3)

ding after CIC for one day or less. The other patient failed multiple voiding trials and ultimately required prolonged indwelling Foley drainage. This patient had a significant history of voiding dysfunction and ultimately resumed spontaneous voiding 20 days after surgery. Ureteral obstruction did not occur in any patient.

DISCUSSION

Ureteral reimplantation is a definitive surgical therapy with a high success rate for elimina-

Table 3 - Characteristics of patients with *de novo* contralateral VUR.

Patient	Age (months)	Gender	Preoperative VUR Grade	Contralateral VUR Grade	History of Bilateral VUR	Intervention (Resolution)	Resolution
1	50.3	Female	4	1	No	Deflux®	Yes
2	50.4	Female	2	2	No	Lost to follow-up	Lost to follow-up
3	42.5	Female	4	2	No	Observation	Yes
4	54.4	Female	3	2	Yes	Reimplantation	Yes
5	112.5	Female	4	2	Yes	Reimplantation	Yes
6	112.5	Female	4	2	No	Deflux®	Yes
7	71.5	Female	3	2	Yes	Deflux®	Yes
8	72.5	Female	4	3	Yes	Reimplantation	Yes
9	86.0	Female	3	3	No	Deflux®	Yes

Table 4 - Characteristics of patients with postoperative urinary retention.

Patient	Age (months)	Gender	Intervention	Duration (days)	Resolution
1	30.6	Male	Indwelling Foley	20	Yes
2	89.9	Female	CIC	1	Yes
3	68.2	Female	CIC	1	Yes
4	77.8	Female	CIC	1	Yes

CIC = Clean intermittent catheterization

ting VUR. The Lich-Gregoir extravesical reimplantation technique was first introduced in the early 1960s as an alterative to traditional transvesical repair and has since been shown to be effective in greater than 90% to 95% of patients (5-7). This technique is thought by many to be less morbid than intravesical techniques that require cystotomy and direct urothelial manipulation (8). In a prospective, randomized trial comparing open intravesical reimplantation to EVR for unilateral reflux, Schwenter et al. (6) showed that the extravesical approach resulted in shorter operative time, avoidance of gross hematuria, and less postoperative pain and bladder spasms (8).

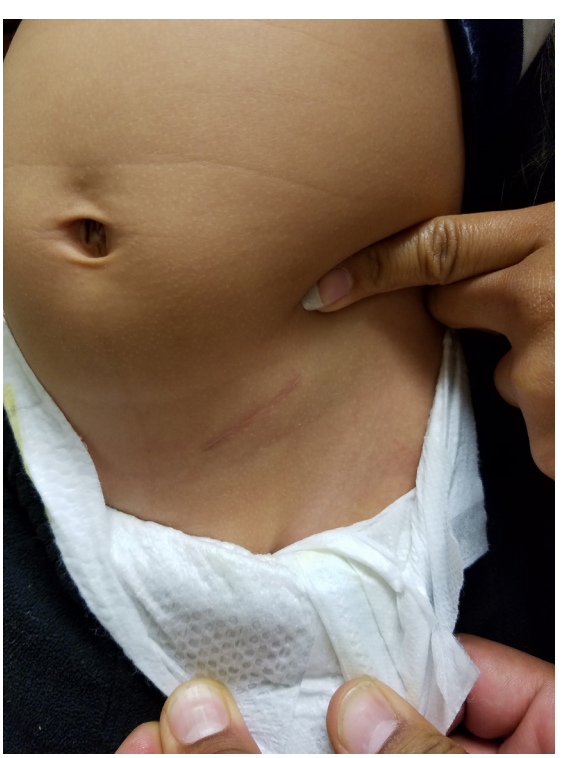
Traditionally, extravesical reimplantation has been performed through a standard Pfannenstiel incision. In 2002, Chen et al. (3) were the first to describe EVR through an inguinal approach, which they successfully and safely performed in the outpatient setting (3). They later compared inguinal EVR to conventional EVR through a Pfannenstiel incision and reported decreased operative time, shorter hospital stay, and reduced postoperative analgesic requirements with the inguinal approach (4).

The ability to perform inguinal EVR in the outpatient setting potentially marginalizes the benefits of traditional minimally invasive techniques, such as endoscopic injection of dextranomer/hyaluronic acid (Deflux®) and robotic ureteral reimplantation. Transurethral injection of Deflux® offers a less invasive alternative to open surgery but at the expense of lower success rates and questionable long-term durability (9-12). Additionally, when compared to outpatient EVR in unilateral cases of reflux, Deflux® was been shown to be the more expensive of the two procedures (13).

The use and applicability of robotic surgery for correction of VUR remains a highly debated topic. Advocates cite advantages of improved cosmesis, decreased pain, reduced hospital stay, and high success rates (14-16). A recent multi-institutional review by Grimsby et al. (15), however, showed a lower success rate, higher complication rate, and longer operative times when compared to open ureteral reimplantation (17). Long-term durability has also yet to be documented for robotic surgery and its use may ultimately be limited by higher costs, a steep learning curve, and limited accessibility (18). In regards to cosmesis, we maintain that a small inguinal incision, that can be concealed below the underwear or bathing suit line, provides a superior cosmetic result when compared with 2 to 4 abdominal scars associated with the robotic approach. This is supported by validated scar surveys in pyeloplasty patients which have shown that parents and patients prefer incisions that can be hidden over laparoscopic incisions that are more conspicuous (19). An example of our inguinal incision 3 months post-operatively is shown in Figure-3.

To our knowledge, we report on the largest single series experience with inguinal EVR for the management of VUR. In our 10-year cohort, we report a collective 95.6% success rate in treating 91 patients with unilateral inguinal EVR. This is comparable to success rates reported by prior studies describing their experiences with inguinal EVR (3, 4, 8, 20). Previously, Chen et al. (3) reported 1 failure in 89 patients and Schwenter et al. (6) reported a 100% success rate in 22 patients after

Figure 3 - Inguinal incision 3 months postoperatively.



inguinal EVR (3, 8). In 2011, Wiygul and Palmer (9) reported on their experience with inguinal EVR in 45 patients (20). Although postoperative VCUG was not routinely obtained in their study, the 3 patients in their series with febrile UTIs postoperatively did not have persistent reflux when VCUG was repeated.

Previous studies have looked at potential risk factors for persistent VUR after open reimplantation and identified male gender, high preoperative VUR grade, dysfunctional voiding, preoperative hydronephrosis, ureteral tapering, and younger age as features that might increase the chances of failed repair (21-24). The small number of patients with persistent VUR in our series limited our ability to detect associations or to perform large multivariate analyses; however, we did note that all 4 patients with persistent reflux in our study had a prior history of contralateral reflux that spontaneously resolved prior to surgery. While we did not repeat VCUG in any patient with persistent VUR, studies suggest that the natural history is eventual resolution (21). Hubert et al. (25) reported persistent VUR in 27.8% of their cohort, with spontaneous resolution in all cases that were grade 1. In our series, all 4 cases of persistent VUR were grade 1 (24).

De novo contralateral reflux developed in 9.9% of our cohort. Studies have previously identified younger age, smaller than expected bladder capacity, and history of preoperatively resolved contralateral VUR as risk factors for de novo contralateral VUR after open unilateral reimplantation (24, 26, 27). In our series, we noted that nearly 50% of patients with de novo contralateral VUR had a history of resolved contralateral VUR, although no statistical analysis was performed.

Hubert et al. (25) evaluated the natural history of contralateral VUR in 39 patients and reported a 78% rate of spontaneous resolution at a median of 23 months (24). In our series, all 7 patients who underwent intervention for de novo contralateral reflux were asymptomatic at the time of surgery; accordingly, it may have been reasonable to manage these patients with observation alone. In patients who are asymptomatic but whose parents prefer surgery, however, Deflux® seems to be a good first option.

There were 14 duplicated systems in our cohort with successful correction of VUR in 13 of these patients (92.9%). Radojicic et al. (28) previously described their experience using inguinal EVR for reflux in duplicated ureters and reported successful repair in all 14 patients in their series (25). These findings suggest that inguinal EVR can be successfully used for correcting reflux in both straightforward and complex anatomy.

While postoperative urinary retention remains a feared complication following EVR, particularly in bilateral cases, it seems to be less of a concern after unilateral procedures (6, 29, 30). In our study, only 4 of 91 patients (4.4%) developed post-operative urinary retention, which was transient in all cases. While transvesical techniques may be more appropriate for bilateral cases of VUR, we believe our findings support the use of EVR as the technique of choice in open reimplantation for unilateral reflux.

Ureteral obstruction is a rare complication after extravesical reimplantation and no patients in our series experienced urinary obstruction requiring intervention.

In our study, a total of 7 patients were excluded from the analysis due to the absence of post-operative VCUG. All resulted of loss to follow-up. It is possible that these patients may have had follow-up care elsewhere, in which case we may have missed surgical failures and/or post--operative complications (i.e. urinary retention, ureteral obstruction, etc.). However, it is our belief that they these patients were actually more likely to have had a successful outcome and less likely to have experienced post-operative complications and therefore did not feel the need to follow-up. This would then have led to an underestimation of the efficacy of inguinal EVR and overestimation of its associated complications, such as urinary retention and ureteral obstruction.

CONCLUSIONS

Ureteral reimplantation may be safely and successfully performed through an inguinal hernia incision by using the extravesical technique. In unilateral cases, postoperative urinary retention following inguinal EVR is rare. This approach

avoids the adverse effects of entering the bladder and can offer an outpatient alternative to endoscopic therapy. This technique should be considered as a potentially minimally invasive alternative to endoscopic and robotic treatment of VUR with a success rate more comparable to traditional open approaches. Accordingly, we feel it is the method of choice in cases of unilateral VUR requiring surgical correction. Our study adds to the limited literature regarding use of inguinal EVR for the management of vesicoureteral reflux.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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An unanswered question in pediatric urology: the post pubertal persistence of prepubertal congenital penile curvature correction by tunical plication

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ABSTRACT

Objective: The aim of this study is to analyze post pubertal results of pre pubertal tunica albuginea plication with non-absorbable sutures in the correction of CPC.
Materials and Methods: The files of patients who underwent tunica albuginea plication without incision (dorsal/lateral) were retrospectively reviewed. Patients younger than 13 years of age at the time of operation and older than 14 years of age in November 2015 were included. Patients with a penile curvature of less than 30 degrees & more than 45 degrees and penile/urethral anomalies were excluded. All of the patients underwent surgery followed by circumcision.
Results: The mean age of patients at the time of the operation was 9.7 years (range, 6-13 years). The mean degree of ventral penile curvature measured during the operation was 39 degrees while it was 41 degrees in the lateral curvatures. All of the patients were curvature-free at the end of the operation. At the time of the follow-up examination, the mean age was 16.7 years (range, 14-25 years). Six patients had a straight (0-10 degrees) penis during erection and seven patients had recurrent penile curvatures ranging from 30 to 50 degrees.
Conclusion: Pre pubertal tunica albuginea plication of congenital penile curvature (30-45 degrees) with non-absorbable sutures performed without incision is a minimal invasive method especially when performed during circumcision. However, recurrence might be observed in half of the patients after puberty.

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INTRODUCTION

Congenital penile curvature (CPC) is a condition in which the erect penis is not straight and there are no urethral or penile anomalies such as epispadias or epispadias. Curvature is typically ventral, but it can also be dorsal, lateral or mixed (1). The prevalence of CPC ranges between 0.04-0.6% (2, 3). Skin tethering, abnormal Buck's or Dartos fascia, corporeal body disproportion, and rarely, short urethra are thought to play a role in the etiology (4). CPC may be recognized in early childhood by parents during morning erections, but it is more often diagnosed during puberty when the erections become frequent and the penis enlarges. CPC might decrease the individual's quality of life after adolescence by causing esthetic, functional, and psychological problems.

Currently, the EAU congenital penile curvature guidelines endorses post pubertal surgical correction as the mainstay treatment, while EAU pediatric urology guidelines indicates surgical correction of CPC over 30 degrees without identifying any age interval (5, 6). In a survey among American pediatric urologists, surgery has been shown to be recommended in patients with a degree of curvature greater than 20-30 degrees and in patients who feel the appearance of the penis is not esthetic during erection (7). However, the optimal technique and timing for surgery are controversial. In addition, there is limited data regarding the long-term follow-up of those patients. Our aim was to analyze the post pubertal persistence of CPC correction with tunica albuginea plication using non-absorbable sutures performed in children at prepubertal age.

MATERIALS AND METHODS

After obtaining permission from the local board, the files of patients who underwent circumcision and congenital penile curvature correction between 1991 and 2012 were retrospectively reviewed. Patients who were found to have moderate (30-45 degrees) CPC during surgery were analyzed. Children aged younger than 13 years at the time of operation and older than 14 years in November 2015 were included. The exclusion criteria were having a penile curvature less than 30 degrees and more than 45 degrees after degloving, having undergone other correction techniques including plication with incision or Nesbit, and presence of penile or urethral anomalies (urethral hypoplasia and divergence of corpus spongiosum). Operation reports were reviewed in order to obtain per operative curvature specifications (laterality and degree).

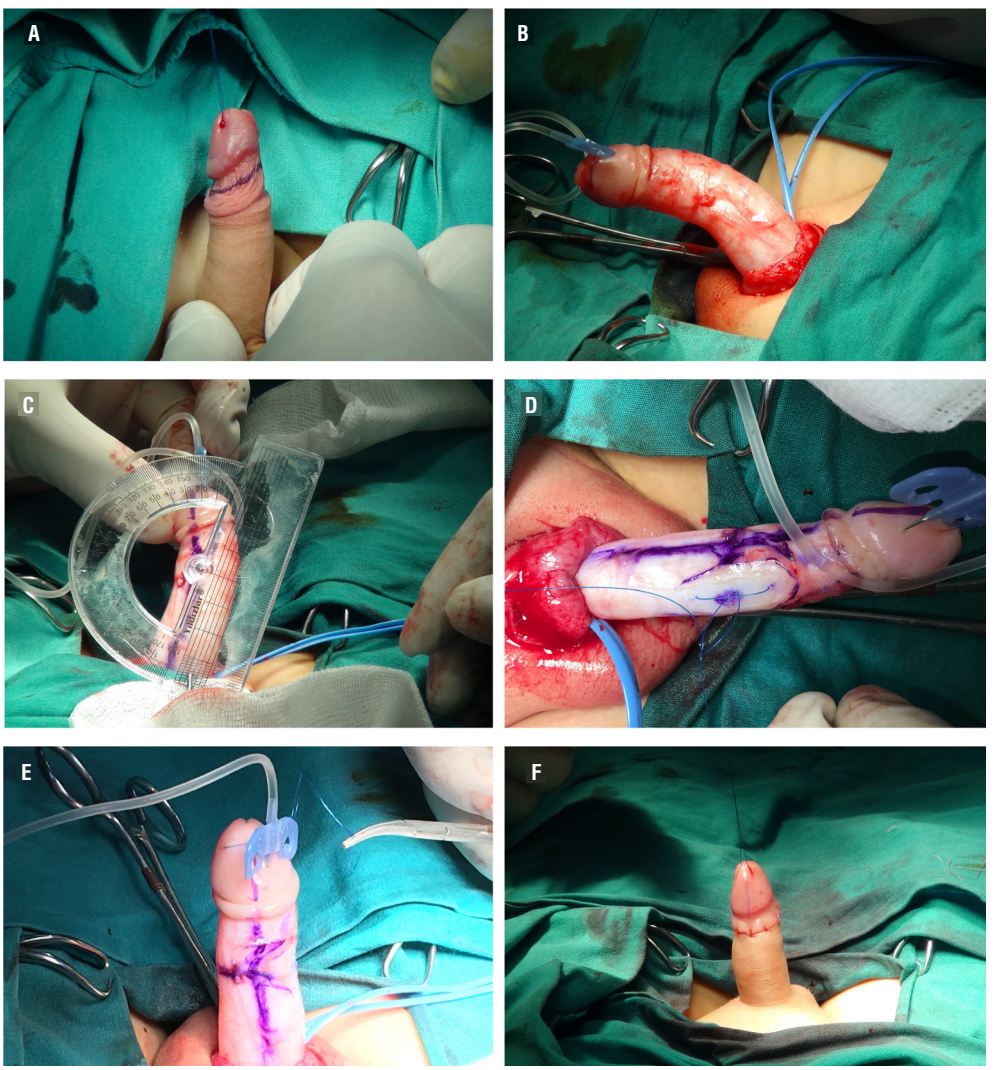
All patients underwent tunica albuginea plication with non-absorbable sutures for patients with disproportional corpora cavernosa by one of two surgeons (OZ, TO), followed by circumcision. During the surgical procedure, a urethral catheter was inserted to assure the integrity of the urethra. Following a complete penile degloving and even release of the Dartos fascia until Buck's fascia, an artificial erection was obtained using saline injection after placing a proximal tourniquet. Afterwards, curvature degree was measured using a goniometer. The contralateral side to the maximal curvature of the corpus cavernosum was marked. Upon opening Buck's fascia, a 4.0/5.0 non-absorbable inverted suture was placed in the 12 o'clock position while preserving the dorsal vein in the ventral curvature or on the opposite side of the bend in the lateral curvature (Figure-1). Afterwards, straightening of the penis was checked again and residual curvature less than 10 degrees was accepted as successful. If the first plication was not sufficient to correct the curvature, additional plication sutures were placed where necessary. The procedure was finished after circumcision using the sleeve method. A self-adhesive dressing was applied for two days after the procedure. The urethral catheter was left in situ for one day.

Early postoperative results were obtained from patient files. Furthermore, patients were contacted by telephone and requested to attend a follow-up examination. The parents were consulted, and approval of the patients and their parents were both obtained. After physical examination, patients were questioned about what they thought of their current penile curvature. In addition to this, we also asked them to send us digital photos of the erect penis taken from the side and from the top. Photos were digitally reviewed and the degree of penile curvature was measured on the digital picture as the angle between the perpendicular lines originating from the glans and base of the penis. Preoperative and current curvature degrees of all patients were compared.

RESULTS

A total of 13 patients who underwent prepubertal CPC correction and circumcision between 1991 and 2012 were studied. The mean age at the time of operation was 9.7 years (range, 6-13 years). All patients were admitted for circumcision and correction curvature at the same time. The mean ventral and lateral curvatures were 39 degrees and 41 degrees, respectively. Among these patients, nine had ventral curvatures, one had a ventral and a right lateral curvature, one had a left lateral curvature, and two

Figure 1 - a) Marking prior to degloving of the penis; b) Artificial erection using saline; c) Measurement of the curvature using a goniometer; d) Correction of curvature by tunical plication; e) Control of curvature after plication; f) Circumcision.



had right lateral curvatures. Seven patients underwent one-suture midline dorsal plication, two had two-suture lateral plication, one had one-suture lateral plication, one had triple-suture lateral plication, one had two-suture midline dorsal plication, and another had a two-suture midline dorsal plication and a triple-suture lateral plication (Table-1). The mean operation time was 42 minutes (range, 29-51 minutes). All of the patients were curvature-free at the end of the operation. Furthermore, there were no signs of recurrence at the early postoperative control (3-6 months). The mean age at the time of examination was 16.7 years (range, 14-25 years) indicating a mean of 7 years of follow-up including the fastest growing interval of penis.

All follow-up photographs were digitally assessed in terms of curvature. Five patients had straight penises, one patient had less than 10 degrees of curvature, and the remaining seven patients had recurrent curvatures varying between 30-50 degrees. None of the patients had postoperative complications of wound healing, hemorrhage or urethral damage.

Table 1 - Summary of the patients.

	Age at operation (years)	Per operative curvature	Operation type	Age at final follow-up (years)	Current curvature
#1	12	Ventral 45º	OMDP	25	Straight
#2	6	Ventral 30º + Right 45º	TMDP + ThLP	16	Straight
#3	11	Left 30º	OLP	16	Straight
#4	7	Ventral 30º	OMDP	17	Straight
#5	8	Ventral 45º	OMDP	17	Straight
#6	12	Ventral 45º	OMDP	15	Ventral 10º
#7	8	Ventral 45º	TMDP	14	Ventral 45º
#8	9	Ventral 45º	OMDP	15	Ventral 30º
#9	13	Ventral 45º	OMDP	17	Ventral 30º
#10	10	Right 45º	TLP	18	Right 50º
#11	7	Ventral 30º	OMDP	14	Ventral 30º
#12	11	Right 45º	TLP	17	Right 30º
#13	8	Ventral 30º	TMDP	16	Ventral 40º

OMDP = One-suture midline dorsal plication; **TMDP =** Two-suture midline dorsal plication; **TLP =** Two-suture lateral plication; **ThLP =** Triple-suture lateral plication; **OLP =** One-suture lateral plication

Patients were questioned about their penile perception. None of the patients reported erectile dysfunction. Furthermore, none of the patients reported feeling suture bumps although they were palpable in every patient during physical examination. Patients without recurrent curvature at the follow-up visit reported neither penile discomfort in erection nor penile deformity. However, every patient with recurrent curvature stated that they were unhappy with the appearance of their penis.

DISCUSSION

The current literature does not provide comprehensive knowledge about the natural history of congenital penile curvature. As a result, there is no consensus/algorithm regarding technique and timing of the operation.

The process of penis development begins in the fetal period and continues until the end of puberty. Therefore, some authors suggest that penile correction surgeries should be performed after puberty (8), claiming that penile curvature can only be completely assessed after puberty (9).

On the other hand, it is known that having normal appearing external genitalia during puberty is necessary for healthy psychosexual development. The delay in the diagnosis of CPC has negative consequences on psychosocial development and quality of life (10). As a result, it is recommended to correct penile abnormalities at an early age (6-12 months) before sexual awareness begins (11). In our daily practice, patients/parents request surgery for CPC at school age, concomitantly with circumcision.

There are several methods for the correction of CPC, but none of these techniques is considered as a gold standard. Stepwise correction of anatomic abnormalities is recommended. The method of surgery is chosen according to the degree of curvature measured after the penis has been degloved. The two main methods are shortening and lengthening procedures. Lengthening is performed via urethral mobilization, corporotomy, and grafting of tunica albuginea of the curvature side, whereas shortening is achieved through various methods of plication and excision of the contralateral side. According to a survey of pediatric urologists, shortening procedures are recommended for mild or moderate curvatures, whereas lengthening procedures are recommended for severe curvatures (7).

Lengthening techniques are definitely more invasive than shortening techniques. Those who favor lengthening procedures consider that the pathology belongs to the shorter side, and therefore they find lengthening more logical (12). The authors proposed that most ventral curvatures develop due to urethral disorders. Chordee correction was possible by mobilization of urethra after penile degloving in 76% of cases, and dorsal plication after urethral mobilization in 8%. Only 16% required division/resection of hypoplastic urethra. None of them had residual chordee in a follow-up period of 6 months-3 years (mean: 26 months).

However, recent histopathologic studies have revealed that CPC is caused by abnormal development of the tunica albuginea of the corpora cavernosa and increased elasticity of tunica on the longer side, rather than urethral anomalies or short urethrae (13). In cases with ventral curvatures, asymmetric corporal development is responsible and the urethra is mostly normal, but in cases with lateral, dorsal or mixed curvatures, the abnormal development is always on the convex side of the tunica albuginea. We believe that CPC secondary to urethral abnormalities is less frequent and should be considered as hypospadias variants and therefore, should be managed accordingly.

Shortening techniques such as the Nesbit procedure or 16-dot plication have been shown as effective in adult CPC correction, but the use of these techniques in children is questionable. Baskin et al. showed penile neurovascular anatomy in hypospadiac and normal penises, and they also defined their technique of avoiding neurovascular damage (14). Their technique is effective, simple, and less invasive. As a result, penile deglovingand dorsal midline plication has gained popularity over time in chordee correction, hypospadias repair, and CPC correction among pediatric urologists. In a report regarding the long-term efficacy of dorsal plication with 83 patients, only 13 (16%) had CPC. The authors reported that dorsal plication of the tunica albuginea with sutures to 11-12-1 o'clock positions were successful in all cases and no recurrence was reported during a six-year follow-up period (15). However, it should be noted that the mean age at the time of surgery was 1.8 years and the mean follow-up period was 6 years, which does not include the fastest development period of the penis. Additional studies have reported good outcomes of dorsal plication without complications among the pediatric age group, whereas follow-up data after puberty is missing. Midline plication was performed for 43 children with penile curvatures. Only six had isolated penile curvatures and midline plication was successful for mild and moderate curvatures during the 16-month follow-up period (16). In another study, the authors performed midline plication for seven of ten penile curvatures caused by corporeal disproportion and reported no recurrent curvature during a 14.8-month follow-up period (17). In summary, the number of cases is small and the period of follow-up is short and information pertaining to puberty is lacking in the studies mentioned above. In the unique study regarding the post pubertal outcomes of prepubertal correction of CPC, Dipaola et al. showed that Nesbit dorsal plication had excellent results in cases of hypoplastic Dartos fascia. Also, they reported a 36% failure rate in more severe forms such as deficiency of corpus spongiosum, hypoplasia of the Buck's and Dartos fascia. Thus, the authors concluded persistence is related to the severity of the curvature rather than the age at surgery (18).

In our study, we aimed to evaluate the post pubertal results of our patients who underwent prepubertal dorsal and/or lateral tunica albuginea plication with non-absorbable sutures without incision, concomitantly performed with circumcision. Short-term follow-up examinations of these patients revealed no signs of recurrence. However, in the late follow-up after puberty, 7 out of 13 patients had recurrent curvature that required surgery. It is not certain whether this was a problem related to the technique or the nature of an ongoing developmental process. Although patients who required more sutures in order to obtain a straight penis during surgery seemed to be prone to recurrence, the numbers of patients are not enough to make a solid statement.

The post pubertal results of lengthening or tunical incision/excision techniques in children are scarce and as such, it is not clear whether these techniques have better outcomes. However, it is clear

that tunica albuginea plication with non-absorbable sutures without incision is the least invasive technique compared with its counterparts. Moreover, prepubertal correction with this technique may also eliminate psychosexual disorders that may arise from CPC in half of the patients.

We believe that prepubertal correction of moderate CPC (30-45 degrees) using tunica albuginea plication with non-absorbable sutures, especially during circumcision, remains an alternative. Our current practice is to offer this technique to our patients along with circumcision because circumcision is a ritual in our country. If the patient has already undergone circumcision, the correction of curvature may be postponed until the post pubertal period. Finally, parents should be counseled in terms of a roughly 50% recurrence rate after puberty.

The limitations of our study are its retrospective nature, the limited number of patients, lack of a comparative arm, and deficiency of a validated questionnaire and comparatively subjective assessment of patients via digital photography. The use of questionnaires such as the International Index of Erectile Function or Self-Esteem and Relationship Questionnaire were not applicable in our population because the mean age at the time of first intercourse in boys is 17 years in our country (19). The strengths of the study are the post pubertal outcomes of a single operation technique from a single center.

CONCLUSIONS

Prepubertal tunica albuginea plication with non-absorbable sutures without incision for corporal disproportion can be performed along with circumcision in moderate CPC. However, recurrence might be observed in half of the patients after puberty. It is not certain whether this is a problem related to the technique or the nature of an ongoing developmental process. Prospectively designed, comparative, and longitudinal studies are needed to form firm conclusions.

Ethical Standard

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Formal consents were obtained from both partents and the children.

CONFLICT OF INTEREST

None declared.

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Outcomes of miniaturized percutaneous nephrolitotomy in infants: single centre experience

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ABSTRACT

Objectives: The present study was aim to evaluate the safety and efficacy of Mini-PNL to treat kidney stones in patients aged <3 years. This is the one of the largest series in the literature in this age group of patients.
Material and methods: From May 2012 to April 2016, the medical records of 74 infant patients who underwent mini-PNL for renal stones were reviewed retrospectively. All infants were evaluated with the plain abdominal radiograph, urinary ultrasound, non-contrast computerized tomography and/or intravenous urogram. Pre-operative, intra-operative and post-operative data were analyzed.
Results: A total of 74 infant (42 male, 32 female) with a mean age 21.5±8.2 (10-36) months were included in this study. The mean size of the stones was 22.0±5.9 (14-45) mm. A 17 Fr rigid pediatric nephroscope with a pneumatic intracorporeal lithotripsy were used through 20-22 Fr access sheath. The stone-free rate was 84.7% at 1 month after the operation. Mean operative time was 74.0 (40-140) min. Mean fluoroscopy screening time was as 4.3(3.1-8.6) min. Average hospitalization time was 3.8 (2-9) day. Auxiliary procedures were performed to 11(15.3%) patients (7 extracorporeal shock wave lithotripsy, 3 re- percutaneous nephrolitotomy, 1 retrograde intrarenal surgery). No major complication classified as Clavien IV-V observed in study group.
Conclusions: Mini-PNL with pneumatic intracorporeal lithotripsy can be performed safely and effectively to manage kidney stones in infants with high stone free rate and low complications.

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INTRODUCTION

Childhood urolithiasis is a major health problem in developing countries especially in endemic regions. The incidence of childhood urolithiasis ranges between 4-6% and the incidence increases up to 14.8% in endemic regions of the World such as Turkey (1, 2). Pediatric patients generally have underlying metabolic, anatomical, functional abnormalities and/or recurrent urinary tract infections that cause urinary stone. Children with kidney stone are classified as high-risk patients for recurrence and requirement of multiple interventions (3).

In this century, with the advancement of technology, minimal invasive treatment modalities such as extracorporeal shock wave therapy (ESWL), percutaneous nephrolitotomy (PCNL) (micro-, mini-), flexible ureteroscopy (f-URS) are routinely used for the treatment of pediatric renal stones (4). Open surgery is still an option for stones with anatomic renal abnormalities (5). According to the European Urology Guidelines (EAU) for the treatment of pediatric kidney stones, ESWL is the

first treatment option for stones smaller than 2cm. Although it is the least invasive method it may require more auxiliary procedures than the other methods and most of the pediatric patients requires anesthesia during the ESWL procedure (6). PCNL should be the preferred treatment method in stones larger than 2cm and ESWL resistant hard stones (7). Since the first series of mini-PCNL technique was published in 1998, mini-PCNL has reached higher stone free rates (SFR) in pediatric patients with lower complication rates (8).

In published literature, there are few studies about mini-PCNL in infancy and number of patients included in these studies are limited. The present study aims to evaluate the safety and efficacy of mini-PNL to treat kidney stones in patients aged <3 years. To our best knowledge, this study is one of the largest series in the literature in this age group of patients.

MATERIALS AND METHODS

From May 2012 to April 2016, the medical records of 72 infant (42 boys, 30 girls) patients who underwent mini-PNL for renal stones were reviewed retrospectively in a referral tertiary institution in Turkey. The presence of renal stones larger than 2cm, history of previous unsuccessful ESWL and ESWL resistant stones smaller than 2cm were accepted as indications for mini-PNL. ESWL resistance was accepted as two ESWL session failures. Patients who have stones with renal congenital anomaly such as ureteropelvic junction obstruction were excluded from the study. Serum biochemistry, complete blood count, urine analysis and urine culture were performed for all patients prior to surgery. All infants were evaluated with plain abdominal radiography (KUB), urinary ultrasound (USG), non-contrast computerized tomography (NCCT) and/or intravenous urogram (IVP). All patients had sterile urine culture prior to surgery. Urinary tract infection was treated according to bio-sensitivity result of the urine culture. Stone size was accepted as the longest axis measured on NCCT and if multiple stones exists, stone burden was assessed as the sum of longest diameter of each stone.

All patients received intravenous antibiotic prophylaxis 1 hour before the surgery. Patients were placed in the low lithotomy position on heater blanket laid operation Table. Irrigation fluids at room temperature and heater blanket were used to prevent hypothermia in infants. Initially, 3-4Fr open end ureteric catheter was placed into the renal collecting system via semirigid pediatric URS (6Fr Karl Storz, Germany) or pediatric cystoscopy (12Fr Karl Storz, Germany) under fluoroscopic control. Foley urethral catheter (8-10Fr) was used to fix the ureteric catheters. The patient was then turned into the prone position with chest padding not to disturb ventilation and perfusion. Lead aprons were placed over the patient's gonadal region to protect gonads from radiation exposure. Caliceal system of the kidney was punctured with 18g diamond tip needle after opacification of collecting system with retrograde injection of contrast agent under fluoroscopy guidance. A guidewire was inserted to the renal collecting system through the needle and after certification of guidewire location in the renal collecting system, Amplatz renal dilatators were used for tract dilatation up to 20-22Fr. Pneumatic lithotripter 17F nephroscope (Karl Storz, Germany) was used for fragmentation of the stones. Stone fragments were collected with grasping forceps. At the end of the operation renal collecting system was checked for residual stone fragmentation via fluoroscopy; a 10-12Fr nephrostomy catheter was subsequently inserted into the renal pelvis. Antegrade pyelography was performed through the nephrostomy catheter to control the extravasation of the urine. Operation time was clocked from insertion of ureteral catheter to the nephrostomy tube placement. We performed USG and KUB in the 1st and/or 3rd months of follow-up. The frequency of visits and imaging method (BT/USG and KUB) to be used in each visit was determined according to residual fragment burden, localization and presence of obstruction and symptoms of patients during follow-up. Procedure was accepted as stone-free when there was no residual fragmentation on radiological imaging method on 3-month follow--up. Metabolic assessment was performed in all stone free patients at 1 month postoperatively. Prophylaxis was started according to the results of stone analysis and/or metabolic assessment.

All statistical analyses were conducted by using SPSS statistical software (version 15.0; SPSS, Inc., Chicago, IL, USA). A probability value (p value) of <05 was considered statistically significant.

RESULTS

A total of 72 infants (42 male, 30 female) with a mean age 21.5±8.2 (10-36) months were included in this study. The mean size of the stones was 22.0±5.9 (14-45) mm. Renal stones were located in renal pelvis (n=20), lower pole (n=17), middle pole/upper pole (n=11), all calyx (n=24). Patients had no hydronephrosis (n=12), grade 1(n=15), grade 2 (n=37) and grade 3 hydronephrosis (n=8). All intrarenal access was performed in the prone position and under fluoroscopic guidance. Mean operative time was 69.0 (40-140) min. Mean fluoroscopy screening time was 4.3 (3.1-8.6) min. The stone-free rate was 84.7% at 1 month after the operation. Nephrostomy tube was not inserted postoperatively in 6 (8.4%) patients with no residual stone, extravasation and perioperative hemorrhage and especially in single access, short-running procedures. Auxiliary procedures were performed to 11(15.3%) patients (7 ESWL, 3 re- PCNL, 1 RIRS). Seven out of these 11 patients were completely stone free and these additional procedures increased the overall success rate from 84.7% to 94.4%. The stone size was 15±4.2mm in the clinically successful procedures and 22±4.9 in the failed procedures (P=0.004). Additionally, renal pelvis or single calyceal location was 73.7% in the clinically successful procedures, whereas it was 27.2% in the failed procedures (P=0.002). Four patients were followed via ultrasonography for insignificant fragments. Average hospitalization time was 3.0 (2-9) days. Complications classified as Clavien IV-V were not observed, however one major complication classified as Clavien III was observed in the study group. Five patients required blood transfusions. Extravasation of urine to the retroperitoneum then pleura after withdrawal of the nephrostomy tube was observed in 1 infant and in this patient spontaneous resolution was observed after DJ stent insertion. Bowel perforation was seen in 1 patient which was diagnosed when colonic content was seen in nephrostomy tube and perforated area of descending colon was primarily repaired on postoperative day 3; 1 patient had hydrothorax due to pleural injury during the upper pole access and thorax tube was inserted. Seven patients developed urinary infections and they were treated according to antibiogram results of the urinary culture.

Nine uric acid stones, 11 cystine stones, 16 calcium oxalate-calcium phosphate stones and 7 struvite stones were detected during the postoperative stone analysis Stone composition was not known in 29 patients because of the discontinuation of the follow-up. Demographics, preoperative, intraoperative, postoperative findings of patients, stone composition and factors that affect the stone free status of the patients are summarized in Tables 1-4.

DISCUSSION

The high risk of recurrence of the stones in the pediatric age group and necessity of multiple surgical interventions has led to development of

Table 1 - Patients' demographics and preoperative data.

Age of patients (months)	21.5±8.2 (10-36)
Male/Female	42/30 (58.3% / 41.7%)
Stone size (mm)	22±5.9 (14-45)
<20 mm	49 (68.1%)
>20 mm	23 (31.9%)
Stone location	
Renal pelvis	20 (27.8%)
Lower pole	17 (23.6%)
Middle pole/Upper pole	11 (15.3%)
Partial/complete staghorn	24 (33.3%)
Laterality L/R	41/31
Hydronephrosis	
Grade 0	12 (16.6%)
Grade 1	15 (20.8%)
Grade 2	37 (51.4%)
Grade 3	8 (11.2%)

Table 2 - Intraoperative data.

Puncture location	
Subcostal	67(93.1%)
Supracostal	5 (6.9%)
Number of puncture	
Single	68 (94.4%)
Multiple	4 (5.6%)
Operative time (mean mins)	69 (40-140)
Hospitalization time (mean days)	3 (2-9)
Fluoroscopic screening time (mean mins)	3.6(1.2-9.8)
Tubeless PNL	6 (8.4%)
Tube PNL	66(91.6%)

Table 3 - Postoperative data.

Initial Stone free rate(after 1 month)	61 (84.7%)
Stone free rate after additional therapy	68(94.4%)
Additional procedures	
ESWL	7
Re-PNL	3
URS	1
Minor (Clavien I-II) complications	14 (19.4%)
Major (Clavien III-V) complications	1 (1.3%)
Preoperative hemoglobin level	12.3 (9.8-15.3)
Postoperative hemoglobin level	11.3 (8.9-13.9)
Stone composition	
Uric acid	9 (12.5%)
Cystine	11 (15.3%)
CaOx-CaP	16 (22.3%)
Struvite	7 (9.7%)
Unknown	29 (40.2%)

minimally invasive treatment methods with maximal efficiency. ESWL, RIRS, PCNL (micro-, mini-) and laparoscopic surgery are the standard minimal invasive procedures to treat renal stones in pediatric patients.

ESWL is the least invasive and first-line treatment method that is used for the management of pediatric renal stones. Despite its widespread use in adults, ESWL for pediatric renal stones was first performed in 1986 by Newman (9). Reports have showed the safety and efficacy of the ESWL even in low birth weight infants (10). Limited reports about ESWL in infancy exist because of the rarity of renal stones in infancy. The success rate of ESWL in infant patient was 84.6-100% (11, 12). Despite these high stone free rate of the procedure, ESWL has some disadvantages such as requirement of anesthesia, ureteral obstruction in high volume renal stones and higher additional intervention rate (13). In current literature ESWL is a safe method of treatment from the point of view of development of new onset diabetes mellitus and hypertension; however, long term detrimental effect of ESWL on kidney which can cause diabetes mellitus and hypertension is still controversial (12, 14).

With the advancement of small caliber f--URS, management of renal stones in childhood have become possible even in infant patients. Cannon et al. published the first series of the RIRS in pediatric patient (15). Stone free rate in pediatric RIRS studies varies between 76-99%. However age of patient in these series was generally greater than 3 years old (15, 16). Li et al. published first series of RIRS in infant patient with SFR of 94.6%. Ten out of 55 infants underwent simultaneous bilateral RIRS (17). One of the major problems during the procedure in this age group of patient was ureteral access sheath (UAS) insertion. The younger the child was, the harder the insertion of UAS. In reported series of pediatric RIRS, UAS was inserted in 43.7-61.5% of patients (16-18). Li et al. did not use UAS, rather they inserted DJ stent in all patients before the procedure and after a while 8Fr f-URS was advanced over the hydrophilic guidewire (17). Generally, major complications were not observed in these procedures. Urinary system infection, postoperative hematuria, ureteral mucosal injury and ureteral perforation were the most commonly observed complications in pediatric RIRS series (16, 17).

The first mini-PNL series was published in 1998 by Jackman et al. in which they used the 11Fr sheath and 7Fr rigid cystoscope in 11 procedures without any complication (19). Success rate of mini PNL procedure in recent infant series varies between 70.8-92.5% after single session and 81.2-92.5% after additional session. Bodakci et al. showed that stone free rate was 70.8% at the end of the posto-

Table 4 - Factors that affect the stone free status of the patients.

	Initional stone-free status (84.7%)	Residual stone without additional treatment (15.3%)	P value
Gender			0.820
Male	36 (59.1%)	6 (54.5%)	
Female	25 (40.9%)	5 (45.5%)	
Laterality			0.223
Right side	27 (44.2%)	4 (36.3%)	
Left side	34 (55.8%)	7 (63.7%)	
Stone size (mm)	15±4.2	22±4.9	**0.004**
Stone location			**0.002**
Renal pelvis or single calyx	45 (73.7%)	3 (27.2%)	
Partial/complete staghorn	16 (26.3%)	8 (72.8%)	
Hydronephrosis Grade			0.065
Grade 0-1	22 (36.1%)	5 (45.4)	
Grade 2-3	39 (63.9%)	6 (54.6)	

perative 24 hour and 81.2% at the end of the first postoperative week in 48 infant mini-PNL procedures (20). Bo Xiao et al. performed all mini-PCNL with ultrasound-guidance in 67 renal units of 56 patients aged <3 years. They found that SFR during the hospital discharge was 92.5% (21). In the retrospective study of Brodie et al. which was conducted in 46 patients under age of 16, 76% of patients achieved 100% stone clearance after a single session of mini-PCNL and 100% of patients achieved stone clearance of greater than or equal to 80% (22). SFR was 76.9% in a prospective study of Kareem Daw et al. and SFR increased to 85% and 92.3% after ESWL and auxiliary therapy respectively (23). Pelit et al. reported a SFR of 84.4% and 91.1% after initial and additional treatment respectively (18). In our study, we reached SFR of 84.7% and 94.4% after single and additional session respectively. Further analysis of SFR revealed that stone size and stone location were factors that affected the stone free status of the patients. In our observation, although hydronephrosis grade did not affect the success of the procedure it facilitated the access to the collecting systems and shortened the operation time. We believe that an SFR of 94.4% for mini PNL procedure in infants is acceptable. In parallel to the literature on mini PCNL in infants, stone free rates of our series after initial and additional therapy is higher than some studies in infant patients. This is because we have an increased experience in childhood urolithiasis due to the location of our hospital in an endemic stone area.

Holmium: yttrium-aluminum-garnet (h--YAG) laser and pneumatic intracorporeal lithotripsy tecniques were both used for stone fragmentation in infant mini-PCNL. As it was in our study, Bodakci et al. used only pneumatic lithotoripsy for fragmentation and SFR was 81.2% in their series (20). Brodie and Bo Xiao et al. used both pneumatic and laser lithotripsy for fragmentation depending on the surgeon's preference and SFR was 76% and 92.5% in their studies,respectively (21, 22). Kareem Daw et al. used only h-YAG laser for stone fragmentation and they obtained a 76.9% of SFR (23). However in current litarature, there was no study that compare the effect of lithotripsy techniques on SFR in infant mini-PCNL.

Although the stone-free rates were higher after mini PNL, complications were not uncommon in infancy, such as bleeding, urosepsis, colon perforation, hypothermia and urinary leakage. Pediatric patients were more likely to bleed during system dilatation because of the fragile renal parenchyma and delicate collecting system. In mini PNL series of infancy, blood transfusion rates were lower than the

pediatric age patients and varied between 0% and 7.5% (20, 21). Studies showed that blood transfusion rates were higher with the use of 24-26Fr sheaths than with ≤18Fr (5.9%) sheaths (24). We dilate the renal tract up to 20Fr or 22Fr according to the stone size and age of patients. In our opinion, the 22Fr sheath should be kept for stones larger than 2cm to reduce the bleeding if the patient's age and physical development is appropriate.

Children can easily become hypothermic due to the long-running operations, cold irrigation fluids and operation room (25). Roberts et al. showed that hypothermia is directly related with the duration of the operation and they also stated that preoperative preparation, anesthesia induction and patient positioning contribute the fall of the body temperature as much as the surgical procedure itself (26). In our patients, we did not observe any hypothermic complications. We think that irrigation fluids at body temperature and heater blanket prevent infants from being hypothermic and shortening the duration of all surgical steps including preoperative procedures, anesthesia induction and positioning preserve the core body temperature of the patients.

One of the important issues of mini-PCNL in infants is radiation exposure. Some methods have been tried to minimize radiation exposure. Bo Xiao et al. punctured the collecting system under USG guidance to reduce radiation exposure (21). Bodakci et al. achieved US-guided intrarenal access in 7 of 40 to decrease the fluoroscopy time (22). In all series, lead aprons were used to protect patient's gonads like our studies.

Bowel perforations are also rare complications, however carry high morbidity and mortality risk. It is observed as 0.2% to 0.3%. Dilated collecting tubules, horseshoe kidney, and retro-renal colon are risk factors for colon injury (27). To avoid colon perforation in PCNL, some techniques have been proposed. Ultrasound-guided puncture or CT-guided puncture of the pelvicaliceal system in patients with anatomic abnormalities could prevent colon perforation (28, 29). However, these access techniques were not routinely applied during PCNL procedures. For this reason, especially the left renal lower pole access with other retro-renal colon risk factors, the bowel injury should be considered during PNL. Conservative treatment with drainage of urinary system and gastrointestinal system separately is generally the first choice of method (30). In our patient, we observed colonic content in nephrostomy tube at postoperative 3 day and we decided to repair the colon primarily with pediatric surgeons. The patient was discharged uneventfully at postoperative 9 day following laparotomy.

The overall incidence of hydrothorax after PCNL procedures was between 0% and 3.3%. The risk of injury increased with the supracostal access due to the position of the pleura (31). As in our case that we have performed supracostal puncture, respiratory distress developed on postoperative day 1 and hydrothorax was diagnosed. This patient was managed successfully by intercostal chest tube drainage.

Our study is limited by its retrospective nature. On the other hand, it is strengthened by the high number of patients.

CONCLUSIONS

Mini-PNL with pneumatic intracorporeal lithotripsy can be performed safely and effectively to manage kidney stones with high stone free rate and low complications in patients under the age of 3. Exposure of infant patients to hypothermia and radiation must be kept in mind during the operation. This method of treatment provides an acceptable SFR in experienced center.

CONFLICT OF INTEREST

None declared.

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Effect of Mitomycin – C and Triamcinolone on Preventing Urethral Strictures

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ABSTRACT

Urethral stricture is a common disease with high recurrence rate. Several manipulations were defined to prevent the recurrence but the results were disappointing. This study aimed to evaluate the efficacy of triamcinolone and mitomycin-C on urethral stricture formation and their effect on inhibition of urethral fibrosis. A total of 24 New Zealand rabbits were divided into 3 groups. Urethras of rabbits were traumatized with pediatric resectoscope. Resection area was irrigated with 10mL saline, swapped with a cotton wool soaked with 0.5mg/mL MMC and injected by 40mg triamcinolone in groups 1, 2 and 3 respectively. Retrograde urethrogram was performed at 28th day of procedure and the urethra was removed for histopathologic evaluation. There were significant differences in urethral diameters and in lumen reduction rate between the control and study groups ($p<0.001$). Compared to control group, all treatment groups showed mild fibrosis, less collagen bundle irregularity, and lower numbers of fibroblasts ($p=0.003$). The Tunnel assay showed that the number of apoptotic cells in the submucosal connective tissue was quantitatively higher in control groups ($p=0.034$). In the view of efficacy and safety, MMC and triamcinolone have the potential to replace the use of stents, clean intermittent catheterization, or long term catheters following internal urethrotomy. There were no statistically significant differences between two agents in terms of preventing urethral stricture formation in the present study. Mitomycin C and triamcinolone decreased the recurrence rates of urethral stricture.

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INTRODUCTION

Urethral stricture is one of the oldest known urologic diseases and remains a common problem with high morbidity. Injuries to the urethral epithelium or the underlying corpus spongiosum may result in scar formation leading to urethral stricture which negatively affects quality of voiding (1). Although it can occur anywhere in the urethra, about half of cases are present in the bulbar urethra. The most common causes of urethral stricture are idiopathic causes, iatrogenic causes (catheterization and transurethral surgery), inflammatory causes and trauma (pelvic fracture) (2).

Urethral stricture has been mostly treated with urethral dilation and visual internal urethrotomy (DVIU). Long-term success rate of endoscopic treatments, however, is not high. Santucci et al. showed that the long term success rate of single DVIU was nearly 8% and significantly

decreased with repeated urethrotomies (3). Because of this low success rate, several manipulations have been defined to prevent stricture recurrence such as indwelling Foley catheter, home self--catheterization, and urethral stents. Unfortunately, repeated instrumentation may exacerbate scar formation and complicate subsequent reconstruction and may lead to several complications (1, 4).

Excessive collagen synthesis and changes in composition of the extracellular matrix are the key events in the pathogenesis of urethral stricture. Several previous studies had evaluated the effect of antifibrotic drugs on urethral strictures, such as halofuginone, mitomycin C, botulinum toxin A, somatostatin analog, and glucocorticoids (5-9). Corticosteroid-based drugs were reported to decrease collagen production, and many studies have shown their efficacy on treatment of urethral stricture (10). Mitomycin C (MMC) is also a potent agent that exerts chemotherapeutic and antibiotic activity by inhibiting DNA synthesis. It inhibits mitosis, fibroblast proliferation, protein and collagen synthesis and angiogenesis. This agent plays an important role in tissue healing and scar formation by reducing the release of matrix proteins via the inhibition of proliferative fibroblasts (11).

Clinical studies have shown that MMC has the potential to prevent urethral stricture (6). Both triamcinolone and MMC have anti-proliferative and anti-scarring properties and can be suitable candidates for the treatment of urethral stricture (6, 11, 12). In our study, we compared the efficacy of triamcinolone and MMC on urethral stricture formation and their effect on the inhibition of urethral fibrosis.

MATERIALS AND METHODS

This study was performed at Namik Kemal University Experimental Animals, Application and Research Center with the approval of Ethics Board for Animal Studies of Namik Kemal University. Twenty-four healthy New Zealand white male rabbits (weight, 2.5-3.5kg) were used. Animals were housed in a temperature-controlled ($22\pm1^{o}C$), humidity-controlled, (40%-70%), and light-period controlled (12h/12h light/dark cycle) environment. They were fed with a standard rabbit pellet diet and had access to tap water ad libitum. Before the interventional procedures, ketamine HCl at a dose of 15mg/kg and xylazine at a dose of 6mg/kg were administered intramuscularly for general anesthesia. Rabbit urethras were traumatized as described by Faydaci et al. (13). Briefly, the animals were placed in a supine position, and their genitalia were scrubbed with povidone-iodine solution. An 11F pediatric resectoscope was used for the endoscopic operation. A 2 to 3 mm wide resection on anterior urethra at 5 to 7 o'clock position, 10mm proximal to the external meatus, was performed with pediatric resectoscope using electric energy by the same surgeon (O.K.). The resection was deepened enough to uncover the periurethral tissue to allow urine leakage from the lumen. The urine was deliberately not diverted. No antibiotics were administered.

Animals were randomly divided into three groups, 8 rabbits of each. In group 1 (control), the urethra was traumatized and irrigated with 10mL saline without medical treatment. In group 2, the urethra was traumatized and a cotton wool soaked with 0.5mg/mL MMC was applied to the traumatized area for 5 minutes, and then the urethra was irrigated with 10mL saline. In group 3, the urethra was traumatized and 40mg triamcinolone was injected to the traumatized area as 1mL of injection. At the end of 28 days of surgical manipulation, urethral gross morphology was evaluated by retrograde urethrogram and video-urethroscopy. Contrast medium (20mL of 760g/L meglumine amine diluted by 20mL of 9g/l sodium chloride) was injected slowly and through the urethra by the same researcher, under X-ray vision to visualize the configuration of urethral lumen. The urethral caliber was measured as described by Jaidane et al. (14). For estimation of the percentage of urethral stricture, urethrograms and video-urethroscopy were used. The rate of stricture was defined as the division of the diameter in the narrowest part of stricture to normal diameter of urethra just distal to stricture. Strictures were considered as significant if the urethral lumen diameter decreased more than 50%. The rabbits were euthanized with high dose of pentothal, and whole urethra was removed for histopathologic evaluation.

Histologic examination

The urethra specimens were individually immersed in Bouin's solution, dehydrated in alcohol and embedded in paraffin. 5µm thick sections were obtained and subjected to hematoxylin and eosin and Masson trichrome staining to assess fibrosis, epithelium, and collagen density. The urethra tissues were examined and evaluated in random order under blindfold conditions with standard light microscopy by a histologist. The Masson's trichrome staining method was used to investigate fibrotic degree. A score of 0 to 3 was assigned as follows based on the degree of staining and fibrosis: Negative, absence of staining and fibrosis (0 points); mildly positive, slight staining and fibrosis (<25%, 1 point); moderately positive, moderate staining and fibrosis (25%-50%, 2 points); and strongly positive, strong staining and severe fibrosis (>50%, 3 points). Progression from strongly positive to negative was considered to be significant (15). Sections were photographed using a Nikon 50i photomicroscope and NIS elementary software.

TUNEL assay

Apoptosis was evaluated by the terminal dUTP nick end-labeling (TUNEL) assay. The TUNEL method, which detects fragmentation of DNA in the nucleus during apoptotic cell death in situ, was employed using an apoptosis detection kit (ApopTag® Peroxidase In Situ Apoptosis Detection Kit, Cat. No. S7100, Millipore, USA). The number of TUNEL--positive cell was evaluated semi-quantitatively; 0, no positive cells; 1, less than 10% positive cells; 2, 10-50%; and 3, >50%.

Statistical analysis

All data were analyzed with the Statistical Package for the Social Sciences for Windows software (Version 17.0 SPSS, Chicago, IL). Data were presented as mean and standard deviation or percentage. Data in independent groups were analyzed for normalcy with Kolmogorov–Smirnov test and further evaluated with independent t-test or Mann–Whitney U test. Data in dependent groups were analyzed with paired t-test or Wilcoxon signed test after evaluation of normalcy with Kolmogorov–Smirnov test.

RESULTS

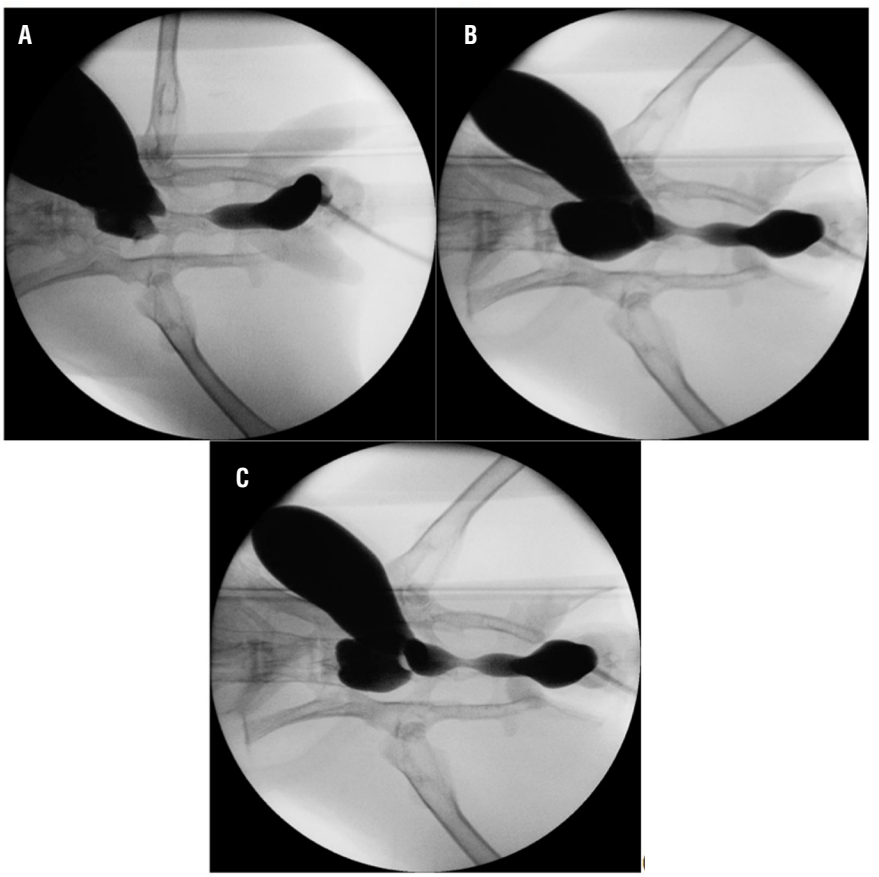
All rabbits survived during the study and voided spontaneously after the procedure. We encountered no major clinical complication. There were statistically significant differences in urethral diameters and in lumen reduction rate, between the control and study groups (Table-1). Both MMC and triamcinolone groups had significantly lower rate of stricture compared to control group (P<0.001). On the other hand, there was no difference between treatment groups in terms of urethral diameters and lumen reduction rate (Table-1), (Figure-1). Light microscopic examination in the control group showed an extensive collagen deposition in the mucosal connective tissue and increased fibroblasts (Figure-2A). Compared to control group, all treatment groups (particularly MMC) exhibited mild fibrosis, less collagen bundle irregularity, and lower numbers of fibroblasts (Figures 2B and 2C) (p=0.003).

Table 1 - Urethral diameter, lumen reduction rate of rabbits in different treated groups.

	Urethral diameter (mm, mean±SD)	Lumen reduction (%) (mean ± SD)	Fibrosis score (Masson) (mean± SD)	TUNEL score (mean±SD)
Control	2,67 ± 0.49	0,91 ± 0.04	2.75 ± 0.46	2,37 ± 0.51
Mitomycin-C	6,85 ± 0.49	0,45 ± 0.13	1.50 ± 0.53	1.50 ± 0.53
Triamcinolone	6,49 ± 0.57	0,49 ± 0.14	2.00 ± 0.53	1.75 ± 0.46
(p) Value	**[a]p= <0.001**	**[a]p= <0.001**	p=0.003	p=0.034
	[b]p= <0.001	**[b]p= <0.001**		
	[c]p = 0.377	[c]p = 0.273		

[a] Statistical analysis between control group and Mitomycin-C group; [b] Statistical analysis between control group and Triamcinolone group; [c] Statistical analysis between Mitomycin-C group and Triamcinolone group

Figure 1 - Urethral stricture in groups on retrograde uretrography on postoperative 28th day.



(a) Control group. (b) Mitomycine-C group. (c) Triamcinolone group.

The Tunnel assay showed that the number of apoptotic cells in the submucosal connective tissue was quantitatively higher in control groups than the treatment groups (Figures 2D, 2E and 2F). Treatment with triamcinolone and especially MMC markedly reduced the number of apoptotic cells (p=0.034) (Table-1).

DISCUSSION

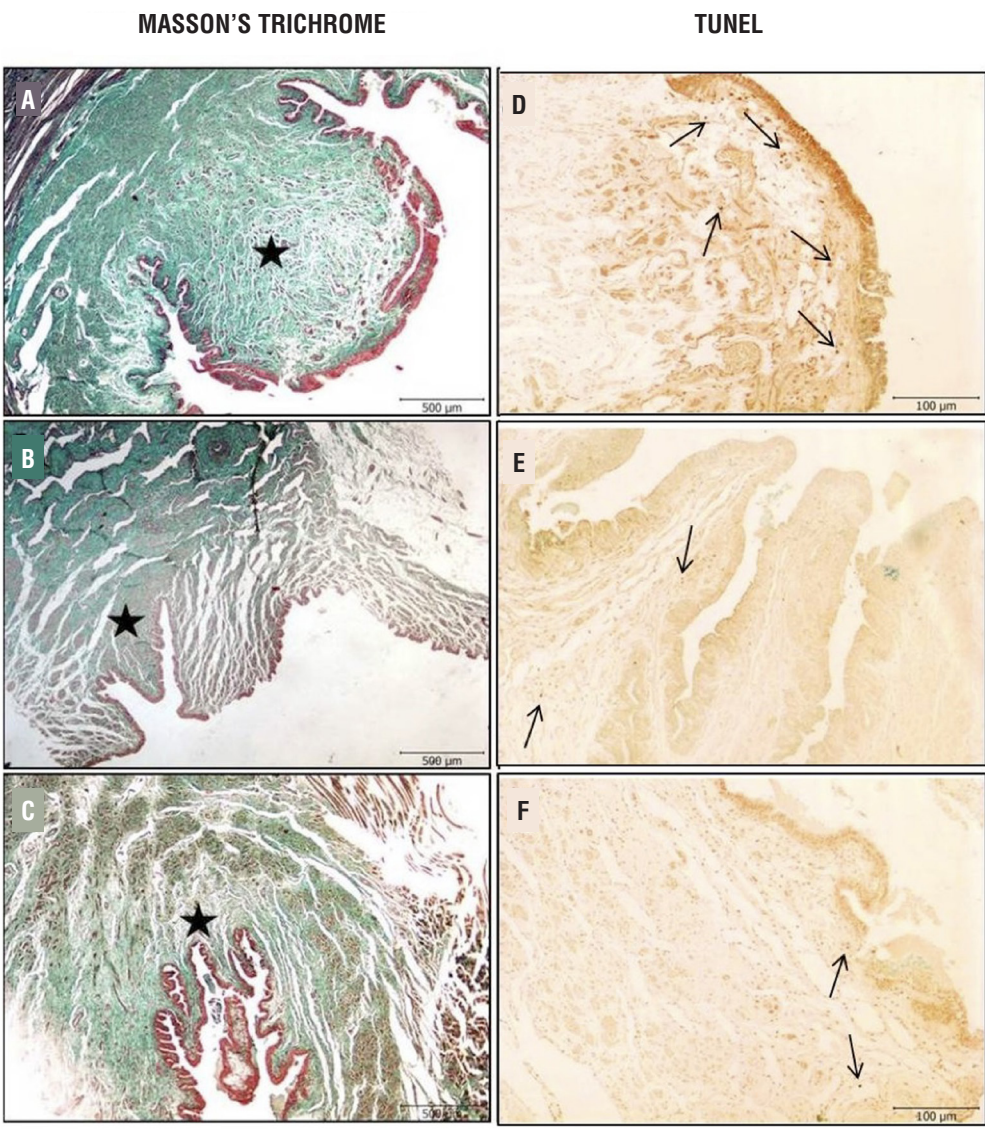
Urethral stricture is a serious disease that causes voiding dysfunction, which adversely affects quality of life and can trigger a chain of events that can lead to renal failure (16). Most of the preferred treatment techniques like DVIU has low success rates for the treatment of urethral stricture. Open surgery is much more effective with long-term cure rates of 90-95%. On the other hand, open surgery is a complicated technique and requires expertise with significant complications (3).

Although the exact pathophysiology of urethral stricture remains unknown, fibrosis caused by excessive collagen synthesis and changes in the composition of the extracellular matrix have been suggested as pathophysiological mechanisms (5, 12). Any drug or procedure that can delay fibrosis and prevent stricture recurrence after internal urethrotomy would ultimately result in an increase of surgical success rates, patient comfort and would decrease treatment costs. Therefore, studies have been performed to explore different molecules for preventing fibrosis and urethral stricture recurrence (5-9, 16, 17).

Halofuginone is a specific inhibitor of collagen type I synthesis by fibroblasts. Nagler

showed that local or oral halofuginone prevented stricture rmation and collagen a1 gene expression, and reduced collagen content (5). In another study rapamycin was shown to be effective in inhibiting fibroblast proliferation and collagen expression (17). Metalloproteinase-1 is another agent that was reported to induce lower collagen concentration in the traumatized region, and it was proposed to be used as an agent to preserve urethral patency (16). All these experimental studies showed that

Figure 2 - Representative urethra tissue photographs of Masson's trichrome and TUNEL staining.



Masson's trichrome; **(a)** Urethral stricture group animals showing extensive collagen deposition are recognized as green in the submucosal connective tissue **(b)** Mitomycin-C treated rats significant less collagen deposition in the urethra **(c)** Triamcinolone treated rats significantly less collagen deposition in the urethra.

Asteriks: collagen fibers (Masson's trichrome, scale bar: 500µm). TUNEL; The number of apoptotic cells in the submucosal connective tissue were quantitatively higher in urethral stricture groups than control groups **(d, e)**. Treatment of mitomycin markedly reduced the number of apoptotic cells **(f)**.

arrow: TUNEL positive cells.

(TUNEL staining, scale bar: 100µm).

inhibition of fibroblast proliferation and collagen expression is critical for preserving the patency of the urethral lumen. In the present study, we used similar criteria to assess the efficacy of MMC and triamcinolone on preventing urethral stricture.

Mitomycine C is an alkylating antineoplastic antibiotic derived from Streptomyces caespitosus. It inhibits DNA synthesis by cross-linking DNA between adenine and guanine. It is not cell cycle specific and suppresses cellular RNA and protein synthesis. By this way, it delays healing process by preventing replication of fibroblasts and epithelial cells and inhibiting collagen synthesis (18). It was shown that MMC improved the success rates of myringotomy and trabeculectomy by preventing fibroblast proliferation and development of fibrosis (19, 20).

Mazdak et al. injected MMC into the urethral submucosa and reported that patients with MMC injection had lower rates of stricture recurrence (6). Opposing this study, some researchers proposed that submucosal injection could increase the complication rate and reduce the duration of the effective dose within the tissue, which yielded a scientific discussion (21). Ayyildiz et al. assessed the efficacy of MMC for preventing urethral scar by applying the agent topically to the traumatized region in rats (22). They concluded that locally applied MMC significantly reduced fibrosis in a dose-independent manner. We also applied MMC topically, and found that it was effective for reducing urethral stricture rate. Urethral diameter was 6.85 (5.90-7.55) and the stricture ratio was 0.45 (0.33-0.59). These values were statistically significant when compared with the control group.

Triamcinolone reduces fibrosis formation by inhibiting collagen synthesis. It increases collagenase production, and lowers the levels of collagenase inhibitors (23). Corticosteroids are extensively used in treating mucosal strictures and skin scars (10, 24). There is a very limited number of studies reporting its efficacy in treating urethral strictures (25, 26). In the present study triamcinolone significantly reduced stricture formation which corroborates with previous studies.

We also compared the efficacy of MMC and triamcinolone to state whether one of them are superior to other in preventing urethral stricture. Although our results demonstrated that differences between MMC and triamcinolone groups were not statistically significant, MMC was slightly superior on preventing urethral stricture. Both agents were statistically superior on preventing urethral stricture compared to control group. Hematoxylin-eosin staining results confirmed that there was less fibrosis and lower collagen content in the two groups treated with MMC and triamcinolone. Also Tunnel assay results showed that the number of apoptotic cells in the submucosal connective tissue was lower in MMC and triamcinolone groups compared to control group.

The considerably short follow-up period can be considered as a study limitation. Many strictures may recur within 2 year following internal urethrotomy. Pansadoro et al. suggested that a minimum follow-up of 5 years is required to assess the results of treatment of urethral stricture (27). On the other hand, the literature fully supports our local data, and despite the limitations, our results may provide useful insight for clinicians who want to offer additional medical therapy in order to prevent urethral stricture recurrence for patient that has undergone internal urethrotomy.

CONCLUSIONS

In the view of efficacy and safety, MMC and triamcinolone hve the potential to replace the use of stents, clean intermittent catheterization, or long term catheters following internal urethrotomy. There were no statistically significant differences between two agents in terms of preventing US formation in the present study. Future studies may provide more detailed information for the usage of these drugs in urethral stricture.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Attenuation of partial unilateral ureteral obstruction – induced renal damage with hyperbaric oxygen therapy in a rat model

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ABSTRACT

Objective: The objective of the present study was to evaluate the effectiveness of HBO therapy on biochemical parameters, renal morphology and renal scintigraphy in rats undergoing chronic unilateral partial ureteral obstruction (UPUO).

Material and methods: Thirty-five rats were divided into five equal groups: Control group; Sham group; HBO group; UPUO group and UPUO/HBO group. The effects of HBO therapy were examined using biochemical parameters and histopathological changes. After calculating the score for each histopathological change, the total histopathological score was obtained by adding all the scores. In addition, dynamic renal scintigraphy findings were evaluated.

Results: Serum parameters indicating inflammation, serum tumor necrosis factor-alpha, ischemia modified-albumin, IMA/albumin ratio and Pentraxin-3 levels, were observed to be high in the UPUO group and low in the UPUO/HBO treatment group. Similarly, in the treatment group, the reduction in malondialdehyde, total oxidant status and oxidative stress index levels and increase in total antioxidant capacity values were observed to be statistically significant compared to the UPUO group ($p<0.001$, $p=0.007$, $p<0.001$, $p=0.001$, respectively). The total score and apoptosis index significantly decreased after administration of HBO treatment. Dynamic 99mTc-MAG3 renal scintigraphy also showed convincing evidence regarding the protective nature of HBO against kidney injury. In the UPUO/HBO therapy group, the percentage contribution of each operated kidney increased significantly compared to the UPUO group (41.73% versus 32.72%).

Conclusion: The findings of this study indicate that HBO therapy had a reno-protective effect by reducing inflammation and oxidative stress, and preserving renal function after renal tissue damage due to induction of UPUO.

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Hyperbaric Oxygenation; Ureteral Obstruction; Apoptosis

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INTRODUCTION

Obstructive uropathy is one of the leading causes of end-stage renal disease in children and adults and is associated with increased intraluminal pressure in the ureter and renal tubules that can cause renal parenchymal damage (1). In clinical practice, although unilateral partial ureteral

obstruction (UPUO) is considerably more common, the pathophysiologic changes in renal tissue due to UPUO are not understood as well as those in complete ureteral obstruction (2). Known factors in the pathophysiology of the partially obstructed kidney are characterized by renal blood flow impairment, intrapelvic pressure elevation, vasoactive and inflammatory mediators (3). Reactive oxygen species (ROS), which form during ureteral obstruction, are recently recognized as responsible for the development of the pathogenesis of UPUO in experimental research (2, 3). Increased lipid peroxidation and oxidative stress in UPUO have been proposed as possible causes that lead to tubule-interstitial lesions and renal fibrosis. Furthermore, apoptotic cell death has been reported to play an important role in renal damage arising from UPUO (4). Despite advances in supportive precautions and preventive strategies, presently there is no specific medication in clinical use for UPUO-induced renal damage. However, because inflammation, oxidative stress and apoptosis combine in the pathophysiology of UPUO, the optimal therapeutic or preventive approach should target these pathways.

Hyperbaric oxygen (HBO) therapy was first used for the treatment of wounds associated with ischemic tissues (5). HBO therapy involves the intermittent inhalation of 100% oxygen at a pressure higher than 1 standard atmospheric pressure (6). This therapy enhances the dissolved oxygen concentration in arterial blood and restores the diffusion of oxygen into poorly perfused tissues (6, 7). Animal studies have shown that HBO therapy attenuates ischemia reperfusion-induced tissue injury by abating oxidative stress, suppressing inflammation, increasing nitric oxide formation and preventing apoptosis (7-9).

The objective of this study was to evaluate the effectiveness of HBO therapy on biochemical parameters, renal morphology and renal scintigraphy in rats undergoing UPUO.

MATERIAL AND METHODS

Animals and Treatments

Thirty-five male Wistar albino rats, weighing 275±25g, were obtained from the University Experimental Research Center. All rats were placed in separate cages at room temperature during the study under standard laboratory conditions with a 12h dark/12h light cycle. The animals were kept in standard housing conditions with temperature of 25±1°C and 45±5% humidity. The rats were given ad libitum food and water. Sterile conditions were provided during operation.

Experimental Protocol

The 35 rats were randomly divided into five equal groups as follows.

Group 1 (Control Group): No procedure administered, taken into the hyperbaric chamber for 14 days but no oxygen administered. On the 14th day under mild ether anesthesia, blood and the left kidney were obtained and rats were sacrificed.

Group 2 (Sham Group): Rats underwent surgical intervention without the final step of partial ureteral ligation. In the 24th hour postoperative the rats were taken to the hyperbaric chamber for one hour but HBO was not administered. The same procedure was repeated on the 14th day postoperative. On the 14th day postoperative renal scintigraphy was performed. Afterwards, blood and tissue samples were taken and rats were sacrificed.

Group 3 (HBO Group): Same procedure as Group 2, however additionally for 14 days HBO therapy was administered.

Group 4 (UPUO Group): Same procedure as Group 2, however UPUO was performed.

Group 5 (UPUO/HBO Group): UPUO was performed. Twenty four hours after operation, the rats were administered HBO. The same procedure was repeated until the 14th day. On the 14th day renal scintigraphy was performed. Afterwards, blood and tissue samples were taken and rats were sacrificed.

Technique

Rats anesthetized with 5mg/kg xylazine (Rompun®, Bayer, Istanbul, Turkey) and 50mg/kg ketamine hydrochloride (Ketalar®, Eczacibasi, Istanbul, Turkey) with spontaneous respiration at room temperature were placed on a sterile disposable towel over a warming pad. The abdominal skin was prepared with povidone-iodine. After mi-

dline incision, the left ureter was located and separated. Psoas muscle was parted 1cm and a tunnel was formed but in Groups 2 and 3 the ureter was not enclosed in the tunnel. In Groups 4 and 5 UPUO was performed according to the technique of Ulm and Miller (10). Psoas muscle was parted 1cm and a tunnel was formed. 1/4 proximal ureter was completely liberated and enclosed in the tunnel. The psoas muscle was closed over the ureter with 6-0 nonabsorbable sutures. The incision was closed with 3-0 silk and rats were returned to cages to recover. The skin was cleaned every day with povidone-iodine to prevent the rats gnawing at the stitches. In Groups 3 and 5, twenty four hours after the operation, the rats were exposed to 100% oxygen for 1 hour at a pressure of 2.5atm in a cylindrical pressure chamber (Barotech Model DB01; BarotechIndustries, Inc., Istanbul, Turkey). In Groups 3 and 5, the final HBO treatment was administered on the postoperative 14th day. One hour after final treatment, the rats in Groups 2, 3, 4 and 5 had renal scintigraphy performed. Immediately afterwards, intracardiac blood samples were obtained and then left nephrectomy was performed immediately. At the end of surgery, all rats were sacrificed by cervical dislocation. Harvested kidneys were divided into two pieces. One piece was put into formalin solution immediately and sent to pathology for histopathological analysis. The others were stored at -800C for biochemical analysis.

Laboratory Analysis

Rat tissue and blood samples were obtained at the end of the experiment for each group of animals. The blood samples taken in tubes without anticoagulants were centrifuged at 4000rpm for 10 min for analyses. The resultant serum samples were aliquoted and stored at -80°C until analysis. Albumin, urea, and creatinine levels were determined with a colorimetric method and potassium, chlorine and sodium levels were determined with ion selective electrode methods on the Cobas c501 Autoanalyzer (Roche Diagnostics, Germany).

Serum Pentraxin-3 (PTX3), tumor necrosis factor- alpha (TNF-**α**) and interleukin-6 (IL-6) concentrations were measured with enzyme--linked immunosorbent assay (ELISA) kit (PTX3, Catalog No: CK-E90725, Hangzhou Eastbiopharm Co. Ltd., Hangzhou, China; TNF-**α**, Catalog No: KRC3011; IL-6, Catalog No: KRC0061, Invitrogen Corporation, Camarillo, CA, US) according to the manufacturer's instructions. The intra-assay and inter-assay coefficients of variations were <10 and <12; <6.9 and <9.0; and <5.8% and <8.8 for PTX3, TNF-**α** and IL-6 respectively.

Ischemia-modified albumin (IMA) level was measured by using colorimetric method discovered by Bar-Or et al. (11). The results were reported as absorbance units (ABSUs). Serum IMA/albumin ratio (IMAR) was calculated. Serum IMAR was expressed as Absolute units per gram (ABSU/g) of albumin.

The tissues were prepared at +4°C for biochemical analysis. After washing with phosphate buffer solution (PBS), kidney tissue of the rats was weighed and cut into small pieces, and stored at -80°C in Eppendorf tubes until biochemical analysis. Tissues from all experimental groups were homogenized using Mixer Mill MM 400 (Retsch, Haan, Germany). The protein contents of the tissues were determined according to the method of Lowry et al. (12). Tissue total antioxidant capacity (TAC; Cat. No: RL0017) and total oxidant status (TOS; Cat.No:RL0024) levels were determined with spectrophotometric kits (Rel Assay Diagnostics, Gaziantep, Turkey) as previously described. The TOS/TAC ratio was used to calculate the oxidative stress index (OSI), an indicator of the degree of oxidative stress. Tissue malondialdehyde (MDA) and superoxide dismutase (SOD) levels were measured using commercial available kits according to the manufacturer's directions (OxiSelect MDA and SOD Activity Assay Kits, Cell Biolabs, Cat No: STA-330, STA-340, respectively).

Histopathologic evaluation

The removed kidney tissues were immersed in 10% buffered formaldehyde, dehydrated, embedded in paraffin and then cut into 4mm slices. Tissue sections were stained with hematoxylin-eosin (H&E) and periodic acid-schiff (PAS), examined with a Nikon 50i photomicroscope, and photographed with a microscope-connected camera system and APR 50 photos elementary program. Taking into account previous studies, the sections were

evaluated and scored for tubular dilatation (TD), interstitial inflammatory cell infiltration (IICI), intertubular hemorrhage and congestion (IHC), interstitial fibrosis (IF), and tubular cast (TC) (13). Tissue damage scores were no visible change [0], minimal or slight change [1], moderate change [2], and severe change [3]. After calculating the score for each of the histopathological changes, the total score was obtained by addition of all the scores from tissue damage markers.

Apoptosis evaluation (TUNEL assay)

Apoptotic cells were detected with terminal deoxynucleotidyl-transferase-mediated deoxy-UTP nick end labeling (TUNEL), using an in situ detection kit (ApopTag, Calbiochem, San Diego, CA, USA) according to the manufacturer's instructions. The preparations were investigated at 400 magnification and 6 different areas were screened for each subject. A total of 100 TUNEL--positive or -negative cells were counted in each case, in each different area. For each subject the mean percentage TUNEL-positive cells were taken and the apoptosis index calculated.

Dynamic renal scintigraphy

Before imaging, all rats had previously described anesthesia performed. The abdomen was opened along the previous incision line, and ~37MBq/0.2mL 99mTc-MAG3 injection administered intracaval. Immediately after the injection 40 minutes imaging was begun with a Hawkeye dual-head gamma camera (GE Infinia, Buckinghamshire, United Kingdom). In the first minute a total of 60 frames at one second intervals were taken for perfusion images, then a total of 39 frames at one minute intervals were taken for concentration and excretion images. Images were evaluated quantitatively and qualitatively by common consensus of two nuclear medicine experts. The contribution rates for kidneys to total renal function was calculated from regions of interest (ROI) drawn with the aid of a computer. Semi-quantitative evaluation in the Sham/S, UPUO/S and HBO groups assessed the contribution of each kidney to total function. Groups were compared in terms of the percentage contribution of each operated kidney.

Statistical analysis

Statistical analyses were performed using statistical software SPSS version 15.0 (SPSS Inc, Chicago, IL, USA). Variable distributions were assessed with the Kolmogorov-Smirnov normality test. The results are presented as mean±standard deviation. The significance of the differences between groups was determined using the Student unpaired t-test for normal distribution. Biochemical parameters with non-normal distribution, histopathological findings and scintigraphic results were evaluated with the Kruskal-Wallis test as they were nonparametric. The Mann-Whitney U test was performed to test the significance of pairwise differences using the Bonferroni correction to adjust for multiple comparisons. Values of $p<0.05$ were considered significant.

RESULTS

Biochemical Findings

Blood biochemical results for the experimental groups are given in Table-1. Between control and sham groups, only IMAR results were significantly different (p=0.045). There was no significant difference between HBO and sham groups in terms of plasma biochemical parameters. When compared with the sham group, the high plasma TNF-α, IMA, IMAR, and PTX3 values in the UPUO group were statistically significant (p=0.045, p=0.028, p=0.011, p=0.045, p=0.035, respectively). In the UPUO/HBO treated group, the plasma TNF-α, IMA, IMAR and PTX3 values were low compared to the UPUO group (p=0.032, p=0.042, p=0.011, p=0.023, respectively).

Tissue biochemical results for the groups are given in Table-2. According to tissue biochemistry results, there was no significant difference between the control and HBO groups with the sham group in terms of the parameters. Compared with the sham group, the UPUO group had high MDA, TOS and OSI values and low TAC value that were statistically significant (p=0.010, p=0.004, p<0.001, p=0.001, respectively). In the treatment group, the reduction in MDA, TOS and OSI values and increase in TAC values were observed to be statistically significant compared

Table 1 - Serum biochemical analysis.

	CONTROL	SHAM	HBO	UPUO	UPUO/HBO
Sodium	135.81±2.73	137.26±1.27	136.81±2.62	137.36±1.67	134.52±1.64
Potassium	4.81±0.66	4.65±0.71	4.72±0.79	4.89±0.46	4.92±0.62
Chloride	98.09±2.04	99.08±1.45	99.12±1.72	99.03±2.66	100.69±3.24
Urea	25.36±4.65	29.65±5.76	28.23±12.12	34.53±7.61	30.67±10.97
Creatinine	0.21±0.03	0.26±0.14	0.23±0.15	0.28±0.08	0.26±0.04
Pentraxin-3	1.48±0.34	1.67±0.27	1.66±0.31	2.04±0.30[a]	1.68±0.17[b]
TNF-α	3.52±0.53	4.30±2.12	3.87±0.91	10.38±6.86[a]	5.67±2.23[b]
IL-6	15.29±3.39	19.09±6.61	17.02±7.29	33.22±24.34	28.52±5.84[a]
IMA	0.64±0.04	0.69±0.05	0.67±0.02	0.82±0.12[a]	0.69±0.06[b]
IMAR	0.17±0.02[a]	0.21±0.03	0.19±0.03	0.32±0.09[a]	0.23±0.03[a,b]

Values are mean ± standard deviation. **HBO =** Hyperbaric Oxygen Group; **UPUO =** unilateral partial ureteral obstruction group; **UPUO/HBO =** UPUO and HBO treated group; **TNF-α =** Tumor necrosis factor- alpha; **IL-6 =** interleukin-6; **IMA =** Ischemia modified albumin; **IMAR =** IMA/albumin ratio.

[a] p< 0.05 compared with the SHAM group; [b] p< 0.05 compared with the UPUO group

Table 2 - Tissue biochemical analysis.

	CONTROL	SHAM	HBO	UPUO	UPUO/HBO
SOD	3.78±1.74	3.35±1.70	3.55±1.59	1.89±0.97	2.63±0.93
MDA	1.09±0.38	1.31±0.45	0.96±0.32	2.04±0.46[a]	1.06±0.30[b]
TAC	0.37±0.20	0.32±0.06	0.35±0.04	0.19±0.05[a]	0.31±0.03[b]
TOS	0.86±0.34	0.98±0.48	0.94±0.41	2.07±0.67[a]	1.01±0.54[b]
OSI	2.80±0.83	3.08±1.65	2.66±1.08	8.64±2.18[a]	3.79±1.95[b]

Values are mean ± standard deviation. **HBO =** Hyperbaric Oxygen Group; **UPUO =** Unilateral partial ureteral obstruction group; **UPUO/HBO =** UPUO and HBO treated group; **TNF-α** = Tumor necrosis factor- alpha; **IL-6 =** interleukin-6; **IMA =** Ischemia modified albumin; **IMAR =** IMA/albumin ratio; **SOD =** Superoxide dismutase (U/g wet tissue.); **MDA =** Malondialdehyde (μM/g wet tissue); **TAC =** Total antioxidant capacity (mmol Trolox Equiv./g wet tissue); **TOS =** Total oxidant status (μmol H_2O_2 Equiv./g wet tissue); **OSI =** Oxidative stress index (arbitrary unit).

[a] p< 0.05 compared with the SHAM group; [b] p< 0.05 compared with the UPUO group

to the UPUO group (p<0.001, p=0.007, p<0.001, p=0.001, respectively).

Histopathologic Findings

Histopathological analysis and apoptosis index results for the groups are given in Table-3. There was no significant difference in the parameters between the control and HBO groups and the sham group. The TD, IICI, IHC, IF and TC scores in the UPUO group were observed to be higher than the sham group (p=0.001, p=0.001, p=0.001, p=0.001, p=0.011, respectively). In the UPUO/HBO treatment group, the mean TD, IICI, IHC and IF pathological evaluation scores were identified to be low compared to the UPUO group (p=0.002, p=0.002, p=0.026, p=0.002). Obtained by summing all the scores from morphological renal damage markers, the total score was increased in the UPUO group when compared with the Sham group (11.14±2.55, 1.43±1.90, p=0.001). But, the total score significantly decreased after administration of HBO (4.14±1.77, p=0.001 compared with the UPUO group) (Figure-1).

Apoptosis Index observed using immunohistochemical staining was 2.87±0.98

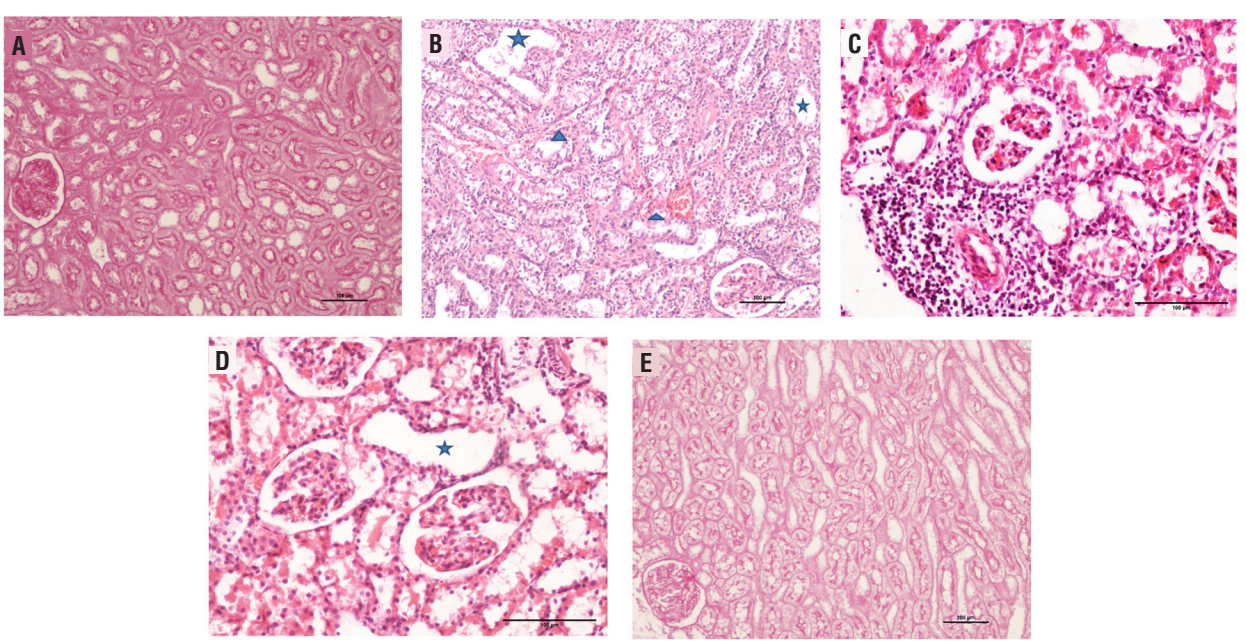
Table 3 - Histopathological Analysis and Apoptosis Index Results.

GROUPS	TD	IICI	IHC	IF	TC	TOTAL NUMBER	APOPTOSIS
CONTROL	0.29±0.49	0.14±0.38	0.14±0.38	0.14±0.38	0.14±0.38	0.86±0.69	2.31±0.38
SHAM	0.43±0.54	0.29±0.49	0.29±0.49	0.14±0.38	0.29±0.49	1.43±1.90	2.87±0.98
HBO	0.14±0.38	0.29±0.49	0.43±0.54	0.14±0.38	0.14±0.38	1.14±1.07	2.45±0.53
UPUO	2.43±0.54[a]	2.71±0.49[a]	2.29±0.76[a]	1.43±0.98[a]	1.29±0.76[a]	11.14±2.55[a]	27.85±7.78[a]
UPUO/HBO	1.00±0.58[b]	1.14±0.69[a,b]	1.14±0.69[a,b]	0.33±0.54[b]	0.43±0.54	4.14±1.77[b]	9.00±2.94[a,b]

Values are mean ± standard deviation. **TD =** Tubular dilatation; **IICI =** Interstitial inflammatory cells infiltration; **IHC =** Intertubular hemorrhage and congestion; **IF =** Interstitial fibrosis; **TC =** tubular cast; **HBO =** Hyperbaric Oxygen Group; **UPUO =** unilateral partial ureteral obstruction group; **UPUO/HBO =** UPUO and HBO treated group.

[a] $p < 0.05$ compared with Sham group; [b] $p < 0.05$ compared with UPUO group.

Figure 1 - a) Normal histological structure in the sham group, regular edges observed [Periodic acid-schiff (PASx100)]. b) Tubular dilatation (TD) (★), intertubular hemorrhage and congestion (IHC) (▲) and disrupted glomerular structures observed in the unilateral partial ureteral obstruction (UPUO) [Hematoxylin-eosin (H&Ex200)]. c) Clear infiltration by interstitial inflammatory cells in the UPUO group (H&Ex200). d) TD (★) and tubular cast (TC) observed in the UPUO group (H&Ex200) e: Close to normal histological structure, regular brush-like edges in the UPUO/HBO therapy group. (PASx100).



in the Sham group, 27.85 in the UPUO group (p=0.001 compared with the Sham group) and 9.0 in the UPUO/HBO group (p=0.001 compared with the UPUO group) (Figure-2).

Renal Scintigraphy Findings

Dynamic renal scintigraphy with 99mTc - MAG3 results for the groups are given in Table-4. The average of percentage contribution by the intervened kidney was 48.66±1.57 in the Sham group, 32.72±4.17 in the UPUO group (p<0.001 compared with the Sham group) and 41.73±3.00 in the UPUO/HBO group (p=0.001 compared with the UPUO group) (Figure-3). There was no significant difference between the Sham and HBO groups for dynamic renal scintigraphy results.

Figure 2 - Apoptotic cells were detected with the TUNEL method (400X). a) Low numbers of TUNEL (+) apoptotic cells in the sham group. b) Chronic obstructive tissue in UPUO group has dense apoptosis. c) Apoptotic cells are diminished in the UPUO/HBO therapy group.

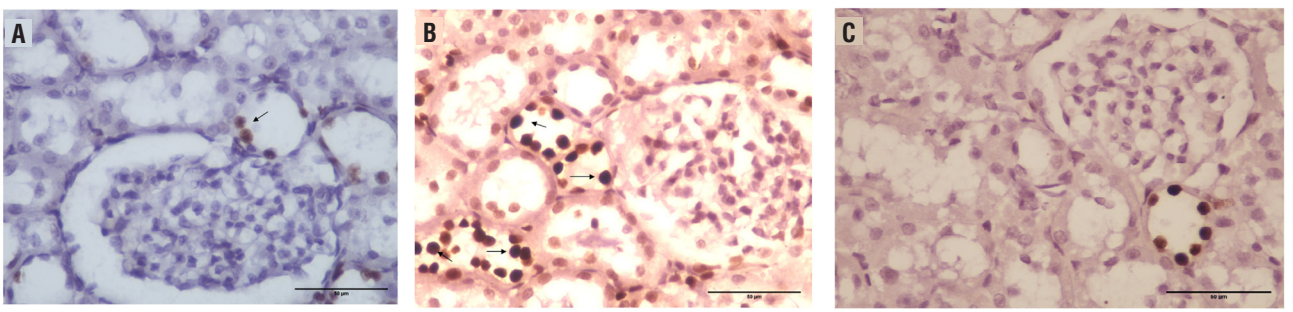


Table 4 - Dynamic renal scintigraphy with 99mTc-MAG3 showing residual functional capacity of injured kidney.

	SHAM	HBO	UPUO	UPUO/HBO
Mean %	48.66±1.57	49.80±2.34	32.72±4.17[a]	41.73±3.00[a,b]

Values are mean ± standard deviation. **HBO =** Hyperbaric Oxygen Group; **UPUO =** unilateral partial ureteral obstruction group; **UPUO/HBO =** UPUO and HBO treated group.

[a] $p < 0.05$ compared with Sham group; [b] $p < 0.05$ compared with UPUO group.

DISCUSSION

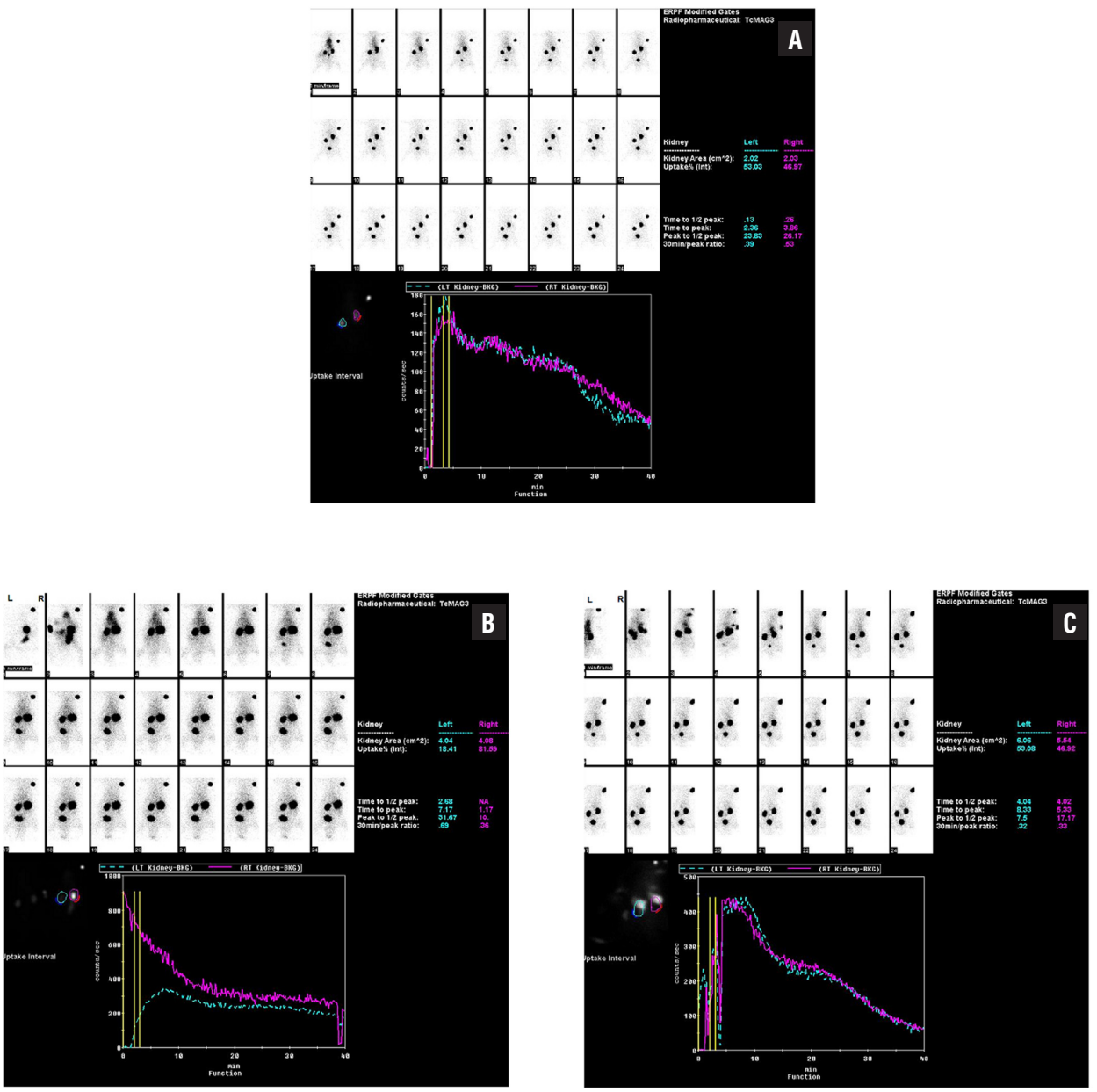
This is the first study that demonstrates the efficiency of HBO therapy on biochemical parameters, renal morphology and renal scintigraphy in rats undergoing UPUO. Our study demonstrated that HBO therapy had a reno-protective effect by reducing inflammation and oxidative stress, and preserving renal function in renal tissue injury after the induction of UPUO.

Obstructive uropathy is a common problem in daily clinical urology practice and can occur anywhere along the urinary tract (14). Upper urinary tract obstruction is most often secondary to calculi, strictures, tumors and ureteropelvic junction or ureterovesical junction obstruction and is usually a reversible and partial unilateral condition (4). Although ureteral obstructions may cause kidney parenchymal damage due to several mechanisms, the exact pathophysiological mechanism of the changes in UPUO has not been fully understood (3, 14). Intrarenal collecting system pressure elevation, renal blood flow impairment, vasoactive and inflammatory mediators are some of the known factors in pathophysiology of renal damage arising from UPUO (3, 4). As renal blood flow increases in the first 12 hour period after obstruction, hypoperfusion develops in advancing periods and is called secondary vascular injury. In current publications it is reported that ROS may lead to severe injury to the cell membrane by lipid peroxidation reactions and may have an important role in tubulointerstitial inflammation associated with obstructive nephropathy (3, 4, 14). Additionally, apoptosis has been reported to play an important role in pathophysiology of obstructive renal parenchymal injury (4).

Hyperbaric oxygen therapy is defined as respiration of 100% oxygen by patients at intervals in a pressurized treatment room with pressure higher than sea level (15). Currently HBO is used as alternative treatment for ischemic injury to renal, brain, pulmonary, liver, cardiac, skeletal muscle, testes and intestinal tissue (7). It has been shown to have anti-inflammatory and anti-oxidant effects on ischemic tissue, reducing neutrophil adhesion, free radical production and apoptosis and increasing nitric oxide production (16).

Some studies have shown that HBO therapy improved the glomerular filtration rate (GFR) in kidneys injured after renal ischemic reperfusion (17). Additionally, HBO therapy increases both vasoconstriction and tissue oxygenation, and is the only treatment modality causing

Figure 3 - Dynamic renal scintigraphy with 99mTc-MAG3. a) Functions of both kidneys appear normal in the sham group. b) Chronic partial obstructed left kidney in UPUO group has low percentage contribution. c) Close to normal percentage of uptake observed in the UPUO/HBO therapy group (For orientation during imaging, an external marker was placed on the right side of the rat's head).



hyperoxic vasoconstriction (18). With all these properties, HBO therapy is expected to provide positive contribution to both primary and secondary injury periods in renal tissue damage as a result of chronic obstruction.

The chain of inflammatory events caused by UPUO includes infiltration of the kidney by inflammatory cells involving monocytes, activation, and possible transformation of intrinsic renal cells, and interactions between infiltrating and resident cells (1). A study by Solmazgül et al. stated that HBO reduced neutrophil infiltration in rats with renal ischemia reperfusion (19). Another study reported that HBO had an anti-inflammatory effect with decreased neutrophil activation and downregulation of adhesion molecule expression on endothelial cells, precluding adherence between neutrophils and endothelial cells (1).

The long PTX3 protein is a member of a superfamily of conserved proteins, and is expressed in vascular endothelial cells and macrophages. Thus, its levels may more directly reflect the inflammatory condition of the vasculature (20). Recently, several clinical investigations have demonstrated that higher plasma PTX3 levels are associated with cardiovascular diseases and with lower GFR and independently predict incidence of chronic kidney diseases (20, 21). In our study, in accordance with the literature, plasma PTX3 levels were significantly higher in the chronic UPUO group than in the Sham group. In the UPUO/HBO treatment group, however, these parameters decreased compared to the UPUO group. Other parameters indicating inflammation, similar to TNF-**α**, IMA and IMAR values, were observed to be high in the chronic UPUO group and low in the UPUO/HBO treatment group.

There has been concern about the use of HBO, based on the hypothesis that providing extra oxygen would increase free radical production and tissue damage. However, HBO has been shown to decrease lipid peroxidation in a number of studies (8, 18, 22). A study by Ilhan et al. determined that HBO therapy attenuated MDA levels by increasing SOD and GPx activities in rats with renal ischemia reperfusion (6). In recent years, diverse oxidant species can be measured totally and lipid peroxidation activities have been analyzed by evaluating TOS (23). The protecting enzymes from oxidative stress of SOD, catalase (CAT), glutathione reductase (GR) and glutathione peroxidase (GPx) resist the destructive actions of ROS, and these enzymes engender the TAC. The advantage of TAC measurement is that it can measure the antioxidant capacity of all antioxidants in a biological sample. Even more importantly, the ratio of TOS to TAC is accepted as the OSI, which is a more valuable indicator to reflect oxidative status than TAC or TOS level alone (13, 23). In this study, we found that tissue MDA, TOS and OSI levels were significantly higher in the UPUO group than in the Sham group. After treatment with HBO, MDA, TOS and OSI levels were markedly decreased. Although TAC and SOD levels were lower in the UPUO group and higher in the UPUO/HBO group, there were no significant changes detected in SOD values between the groups. The reason for these results can be attributed as being due to the 14-day chronic process possibly reducing the endogenous SOD activity. According to blood and tissue biochemical findings, HBO was observed to have a renoprotective effect reducing inflammation and oxidative stress in chronic UPUO.

Histopathologic findings also showed the protective nature of HBO against kidney injury induced during chronic UPUO. Migita et al. demonstrated that HBO suppressed apoptosis, and promoted tubular cell regeneration after renal ischemia/reperfusion injury (IRI) in rats (9). Gurer et al. showed that HBO therapy attenuated renal IRI in rats by decreasing total histopathology scores (8). In accordance with the literature, in our study the apoptosis index decreased significantly in the UPUO/HBO group compared with the UPUO group. The total histopathologic score was higher in the UPUO group compared with the Sham group. It was observed that the total score significantly decreased in the group administered HBO therapy. Briefly, amelioration was detected in the UPUO/HBO treatment group in the form of a remarkable decline in histopathological changes caused by chronic UPUO. In addition, the components of nephrons, the glomeruli and tubules were observed to be apparently healthy.

In the study by Rubinstein et al. they demonstrated that HBO treatment has potential in

the treatment of GFR by improving the antioxidant/oxidant balance in the ischemic kidney (17). Accordingly, GFR was reduced by 94% in the untreated group compared with the untouched normal kidney. In contrast, in the HBO therapy group, GFR of the ischemic kidney was reduced only by 68%. In the literature we did not encounter any other study evaluating the effect of HBO with renal scintigraphy. In our study on dynamic renal scintigraphy with 99mTc-MAG3, the percentage contribution of each intervened kidney was calculated to be 48.66 in the sham group, 32.72 in the UPUO group and 41.73 in the UPUO/HBO group.

Factors limiting our study include the fact that though HBO therapy suppresses inflammation increasing NO formation, in our study NO levels were not examined. Again, enzymes with very short half lives like SOD and MDA were no evaluated during the study period.

CONCLUSIONS

The findings of this study indicate that HBO administration improves impairment of renal functions in rats experiencing UPUO. HBO therapy diminished the inflammation parameters in serum and oxidative stress parameters in tissue, and ameliorated histopathological alterations and apoptosis. Dynamic renal scintigraphy also showed convincing evidence regarding the protective nature of HBO against kidney injury. More studies should be conducted to provide a better understanding of the potential benefits and fully assess the effect of HBO on chronic obstructive kidney damage.

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Ethical standard

The experimental protocols were in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals protocols. Ethical approval for this experimental study was obtained from Çanakkale Onsekiz Mart University, Animal Experiments Local Ethics Committee (No. B.30.2.ÇAÜ.0.05.06-050.04-100).

CONFLICT OF INTEREST

None declared.

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The prostate after castration and hormone replacement in a rat model: structural and ultrastructural analysis

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ABSTRACT

Purpose: To evaluate if late hormonal replacement is able to recover the prostatic tissue modified by androgenic deprivation.

Materials and Methods: 24 rats were assigned into a Sham group; an androgen deficient group, submitted to bilateral orchiectomy (Orch); and a group submitted to bilateral orchiectomy followed by testosterone replacement therapy (Orch+T). After 60 days from surgery blood was collected for determination of testosterone levels and the ventral prostate was collected for quantitative and qualitative microscopic analysis. The acinar epithelium height, the number of mast cells per field, and the densities of collagen fibers and acinar lumen were analyzed by stereological methods under light microscopy. The muscle fibers and types of collagen fibers were qualitatively assessed by scanning electron microscopy and polarization microscopy.

Results: Hormone depletion (in group Orch) and return to normal levels (in group Orch+T) were effective as verified by serum testosterone analysis. The androgen deprivation promoted several alterations in the prostate: the acinar epithelium height diminished from 16.58±0.47 to 11.48±0.29µm; the number of mast cells per field presented increased from 0.45±0.07 to 2.83±0.25; collagen fibers density increased from 5.83±0.92 to 24.70±1.56%; and acinar lumen density decreased from 36.78±2.14 to 16.47±1.31%. Smooth muscle was also increased in Orch animals, and type I collagen fibers became more predominant in these animals. With the exception of the densities of collagen fibers and acinar lumen, in animals receiving testosterone replacement therapy all parameters became statistically similar to Sham. Collagen fibers density became lower and acinar lumen density became higher in Orch+T animals, when compared to Sham. This is the first study to demonstrate a relation between mast cells and testosterone levels in the prostate. This cells have been implicated in prostatic cancer and benign hyperplasia, although its specific role is not understood.

Conclusion: Testosterone deprivation promotes major changes in the prostate of rats. The hormonal replacement therapy was effective in reversing these alterations.

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Hormone Replacement Therapy; Prostate; Orchiectomy; Hypogonadism

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INTRODUCTION

Androgen deficiency of the aging male (ADAM) is a well described syndrome which affects 6% of 40 years old men and 12.3% of 69 years old men (1). Hormonal replacement therapy is efficacious in establishing normal testosterone serum levels and relieving clinical symptoms, im-

proving libido, sexual function, mood and reducing fat body mass (2).

Despite the beneficial aspects of testosterone replacement, the hormone replacement therapy is not completely accepted, due to its possible collateral effects and risks (3). Because of the fear of developing prostatic diseases, or because of poor medical assistance, many men do not begin replacement therapy until testosterone level is very low and clinical symptoms established (4).

The prostate is an androgen-dependent organ and as so, is influenced by the testosterone serum levels. Androgen ablation in adulthood promotes a fast and extensive involution of the prostate with arrest of secretory activity and elimination of epithelial cells by apoptosis (5). The prostate extracellular matrix is also modified by low testosterone levels. In an experimental model with chemically or surgically castrated gerbils, increase in collagen fibers and fibromuscular stroma was observed (6). The extracellular matrix is also altered in patients with benign prostatic hyperplasia, with increased densities of reticular fibers and fibronectin (7, 8). Although this information was not correlated with testosterone levels, it was shown that the prostatic stroma of old mice has also several modifications, with abundant and disorganized collagen fibers, and disordered smooth muscle orientation (9).

Mast cells are enrolled in many biologic responses through degranulation and secretion of its contents. It is well known that these cells plays a role in chronic inflammation, hemotopoiesis, hemostasis, angiogenesis, tissue remodeling, and fibrosis (10). Furthermore, mast cells control and induce the extracellular matrix production and deposition in certain fibroproliferative diseases (11). It was shown that the amount of mast cells increases from birth to youth adulthood in the human prostate (12), and these cells were implicated in benign prostatic hyperplasia (10, 13), as well as in prostate cancer, being even proposed as a prognostic marker (14, 15). A great amount of mast cells were also reported in the prostate of rats (16). Its density was highest during the pubertal period, declining significantly with age (17). However, the direct influence of testosterone levels on prostate mast cells was not previously investigated.

Several methods have been used for studying the human and animal prostate in different conditions. Although conventional light microscopy gives important information on the prostate epithelium and stromal characteristics, the quantification of these structures by morphometrical methods may translate the tissue characteristics into numbers, what allows statistical comparison among different groups (18, 19). Further, scanning electron microscopy and polarization microscopy can be used to distinguish collagen types (20) and its three-dimensional patterns (21-23). Scanning electron microscopy has been used both with cellular digestion pre-treatment, whereas the connective tissue is very well depicted (21, 22), and without this treatment for observation of cellular components (23). Sirius red stained sections observed under polarization microscopy shows a birefringent image that is highly specific for collagen, and allows the differentiation of collagen types. This characteristic has been used to investigate the collagen in the prostate (24, 25) as well as in other organs (26, 27).

Nevertheless, the influence of late hormonal replacement over the prostate of individuals with low testosterone levels is not known. Thus, the objective of the present study is to evaluate in a rat model if the late hormonal replacement is able to recover the prostatic tissue modified by androgenic deprivation.

MATERIAL AND METHODS

Animals

Twenty four Sprague-Dawley male rats aged 24 weeks were included in the present study. The rats were kept in a room with controlled temperature (24±1°C), artificial dark-light cycle (lights on from 7:00 am to 7:00 pm) and standard rat food and water ad libitum.

All experiments were performed in accordance with the Brazilian laws for scientific use of animals, and the project was approved by the ethical committee for the care and use of experimental animals, of the Institute of Biology Roberto Alcantara Gomes, State University of Rio de Janeiro (protocol number 231/2008).

Groups

The rats were randomly assigned into a Sham group (n=8), which was submitted only to anesthesia and a simulated operation, an androgen deficient group (Orch; n=8), submitted to bilateral orchiectomy, and a group with hormone replacement (Orch+T; n=8) which was submitted to bilateral orchiectomy followed by testosterone replacement therapy.

Surgical procedure

Under ketamine (80mg.Kg^{-1}) and xylazine (10mg.Kg^{-1}) anesthesia, bilateral orchiectomy was performed through a scrotal exposure. Testes were exposed and removed after spermatic cords ligature in groups Orch and Orch+T. Group Sham were submitted only to testes exposure and reinsertion into the scrotum. For all animals, scrotal incision was closed with 4-0 nylon in a simple interrupted pattern.

Hormone replacement

Animals from Orch+T group received a single-dose subcutaneous injection of testosterone 30 days after surgery. Replacement therapy was done according to a previously described protocol (28-30), using of testosterone undecanoate (Jenahexal Pharma, Jena, Germany) at 100mg/kg body weight.

Euthanasia and tissue collection

After 60 days from surgery, under deep anesthesia, blood was collected by heart puncture and the serum was separated by centrifugation and used to testosterone determination by radioimmunoassay. The rats were killed by anesthetic overdose and the prostate was en bloc removed. The ventral lobe, which better corresponds to human prostate (31, 32), was then dissected under magnification and divided in two fragments for different analysis.

Light microscopy analysis

Fragments used for light microscopy analysis were fixed in 4% formaldehyde and routinely processed for obtaining 3µm thickness sections. Images of conventional and polarized light microscopy were captured by a DP71 camera coupled to BX51 microscope (Olympus, Tokyo, Japan). Images of fluorescent microscopy were obtained in 400x magnification by a scanning laser confocal microscope (LSM 510 META, Zeiss, Jena, Germany)

Acinar epithelium height

The acinar epithelium height was measured in hematoxylin & eosin stained sections. The linear distance from the luminal surface of the glandular epithelium and its basement membrane was measured in micrometers. For this purpose, the ImageJ software version 1.43 (NIH, Bethesda, Maryland, USA) was used with previously calibration for the magnification of 600X. The mean of each animal was calculated after 250 measurements performed in at least 25 different fields.

Density of acinar lumen

The area density of acinar lumen (Sv[lum]) was calculated by the point-counting method in the same sections. A 100-point grid was superimposed over the images using the software ImageJ, and the acinar lumen touched by the points were counted (33). For each animal, Sv[lum] was determined by the mean of measurements in 25 fields with 100X magnification.

Mast cells quantification

The number of mast cells was accessed in toluidine blue stained sections, under a 600X magnification. For this analysis, at least 50 fields were analyzed in order to calculate each animal mean. Again, ImageJ software was used for this measurement. For this purpose, in each image (histological field) all mast cells were manually counted with aid of the "cell counter" plugin. This parameter was expressed as mast cells per field.

Qualitative analysis of muscle fibers

Muscle fibers were qualitatively analyzed in anti α-actin fluorescent immunolabeled sections under 400X magnification. Antigen retrieval was carried out prior to incubating the sections with the primary antibody by treating dewaxed sections with a ready-made pepsin solution (Digest-All Kit, Zymed Laboratories, San Francisco, California, USA), according to the manufacturer's

instructions. The primary antibody used was a monoclonal anti-α-smooth muscle-actin (08-0106, Zymed Laboratories, Carlsbad, California, USA). Secondary antibody was Alexa Fluor 488 (A-1100, Invitrogen, Camarillo, California, USA).

Density of collagen fibers

The area density of collagen fibers (Sv[col]) was measured in Sirius red stained sections, observed under polarized light at a magnification of 200X, in which only collagen appears birefringent over a dark field (20). Image pro plus was used for measuring Sv[col] by color segmentation. These same images were used to differentiate collagen types III (seen in green) and I (red/orange) (20).

Electron microscopy analysis

The differences of collagen fibers were also analyzed by scanning electron microscopy (SEM). For this purpose, samples were fixed by immersion in 2.5% glutaraldehyde and cellular content was chemically removed by alkali treatment (34). After this treatment, samples were dehydrated in ethanol, critical point-dried with CO_2 and sputter-coated with gold for observation in a LEO 435 (Carl Zeiss, Oberkochen, Germany) scanning electron microscope for differences on the thickness and arrangement of collagen fibers (21).

Statistical analysis

The one-way ANOVA, followed by Bonferroni's multiple comparison test were used for mean comparisons. In all cases, significance was considered when $p<0.05$. All analyzes were performed using GraphPad Prism software (GraphPad Software, San Diego, California, USA). All numerical data is present as mean±standard deviation.

RESULTS

Testosterone analysis

Hormone depletion and replacement were effective as verified by serum testosterone analysis. Animals from group Orch had undetectable levels of testosterone while Orch+T rats had statistically similar values of this hormone when compared to Sham (Table-1).

Quantitative morphological analysis

The acinar epithelium height of Orch animals was of 11.48±0.29µm, thus it was diminished ($p<0.0001$) in comparison to Sham animals which presented values of 16.58±0.47µm. This alteration was not present in Orch+T in which there was no statistical difference from Sham (Table-1).

Regarding Sv[lum], Orch animals presented a significant decrease ($p<0.001$) in comparison to Sham. Orch animals had values of 16.47±1.31%, while Sham animal's values were of 36.78±2.14%. Hormonal replacement therapy was effective in recovering of Sv[lum]. Actually, animals that received the therapy presented values of 43.18±4.46%, which was even higher than those of Sham animals (Table-1).

The number of mast cells per field in group Orch was 2.83±0.25, that was increased

Table 1 - Hormonal and morphometric data of prostate from rats of groups Sham (n=8), hypogonadal (Orch) (n=8), and hypogonadal with hormonal replacement (Orch+T) (n=8).

Groups	Sham	Orch	Orch+T	p value
Testosterone level (ng/mL)	1.28±0.28	0.00±0.00	0.99±0.23	<0.0001
Epithelium height (µm)	16.58±0.47	11.48±0.29 [a]	17.67±1.26 [b]	<0.0001
Sv[lum] (%)	36.78±2.14	16.47±1.31 [a]	43.18±4.46 [a,b]	<0.0001
Mast cells (cells/field)	0.45±0.07	2.83±0.25 [a]	0.52±0.14 [b]	0.0024
Sv[col] (%)	5.83±0.92	24.70±1.56 [a]	2.81±0.19 [a,b]	<0.0001

Sv[lum], area density of acinar lumen; **Sv[col],** area density of collagen fibers.
Post-test analysis: **a**≠from Sham group; **b**≠from Orch group.
Data is present as mean±standard deviation.

(p=0.0024) in comparison to Sham animals, that presented 0.45±0.07 mast cells per field (Figure-1). Between Sham and Orch+T groups no significant difference was found (Table-1).

Concerning Sv[col], Orch animals presented a significant increased stromal collagen in comparison to Sham animals (p<0.001). Orch animals had values of 24.7±1.56%, while Sham animal's values were of 5.83±0.92%. For this parameter, hormone therapy promoted a decrease of the collagen content, returning to 2.81±0.19% (Table-1).

Qualitative morphological analysis

The amount of periacinar smooth muscle fibers showed was marked increased in group Orch. This alteration was not noted in Orch+T animals (Figure-2).

When observed under polarized light, the Sirius red stained sections showed an equivalent amount of types I and III collagen in Sham, which has changed to a predominant red pattern in Orch sections, indicating a major presence of type I collagen. Sections of Orch+T presented a very similar pattern of those from Sham group.

Similar modifications of collagen fibers were also seen when observing acellular prostate preparations by scanning electron microscopy. With this method, it was observed both thin and thick collagen fibers in group Sham, compatible with types I and III, respectively. In group Orch, it was found a predominance of type I collagen fibers, while in group Orch+T it was observed an equivalent presence of both collagen types (Figure-3).

Figure 1 - Ventral prostate of rats stained with toluidine blue and observed 600X magnification. In image A) we observe normal quantity of mast cells (0.45±0.07) per field. In image B) (group Orch) we observe an increase on the number of mast cells per field (2.83±0.25), which returned to normal (0.52±0.14) in animals receiving hormonal replacement as seem in image C) (group Orch+T).

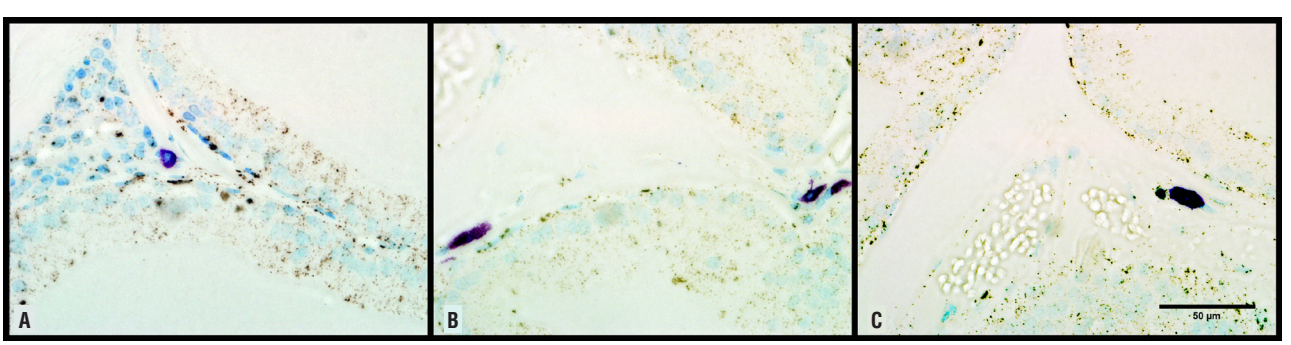


Figure 2 - Ventral prostate of rats immunolabeled with anti α-actin antibodies and observed under fluorescence microscopy under 400X magnification. In image A) we observe normal quantity of smooth muscle of Sham group. In image B) (group Orch) we observe an increase of muscle fibers, which returned to normal in image C) (group Orch+T).

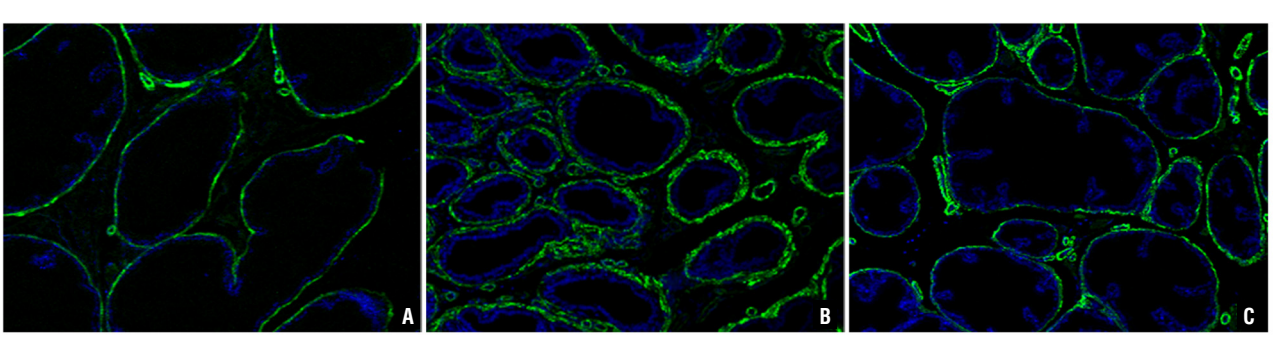
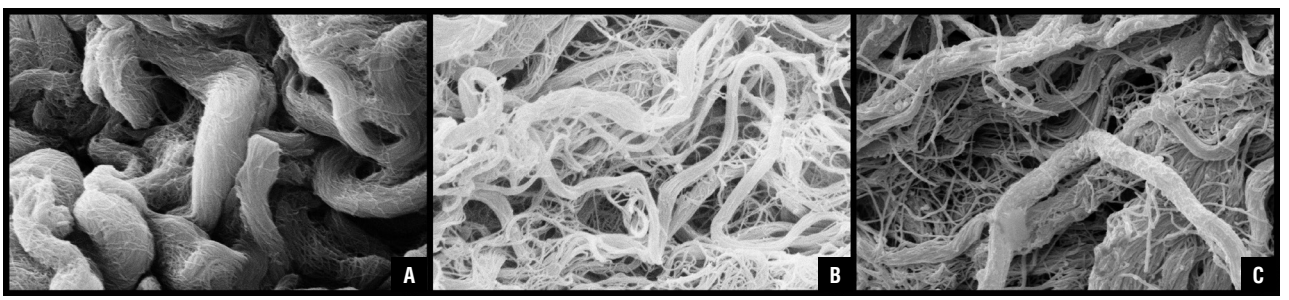


Figure 3 - Decellularized ventral prostate of rats observed under scanning transmission microscopy. In image A) (group Sham) we observe both thin and thick collagen fibers, compatible with types I and III, respectively. In image B) from group Orch, there is a predominance of type I collagen fibers, while image C) (group Orch+T) resembles what was observed in image A, with presence of both collagen types.



DISCUSSION

ADAM is a syndrome that should be not underestimated as it implicates in patient's life quality. Besides its genital and psychological effects, systemic diseases (such as obesity, diabetes and hypertension) are related to hypogonadism (35). Even so, more than 68% of physicians believe that hormonal therapy for ADAM implies in more risks than benefits (4). The concern that testosterone therapy may induce benign prostatic hyperplasia or prostate cancer was proven not to be true (4, 36). Actually, testosterone replacement improves mood and feelings of well-being, sexual function, muscle mass and strength, bone density, and reduction of body fat mass and waist circumference (37). Even so, 35% of patients with diagnosed ADAM do not receive treatment because of the risks of hormonal therapy (4).

Under low levels of testosterone, it is well recognized that the prostate suffers structural changes, with modifications in its acinar epithelium, basement membrane, elastic system fibers and collagen (5, 38-40). However, the effects of hormone replacement therapy are still fairly known. In the present study, late testosterone replacement (30 days after orchiectomy) was able to overturn most of the changes associated with hypogonadism, increasing the height of the acinar epithelium (which was reduced by 30% in castrated animals) and acinar lumen area density (reduced by 55% in castrated animals). Both these parameters are linked to prostate physiology since they indicate normal prostatic fluid production. Corroborating with these data, some clinical studies suggests that after testosterone therapy the prostate volume increases, usually to the normal volume seen in eugonadal individuals (2).

We should point out that the testosterone reposition therapy in men is still a controversial topic, especially in the men with a history of prostate cancer (41). The main concern is that testosterone may accelerate prostate growth not only in benign conditions but also in cancer. Although the current knowledge indicates that testosterone reposition does not appear to increase PSA levels or the risk of prostate cancer development, studies with longer follow-up are still being performed, and the topic is still on discussion (42).

The prostate gland should not be seen only as a site for diseases. Its secretion accounts for 30% of the seminal plasma (43) which actively participates on the sexual and reproductive process. The prostatic fluid not only carries the spermatozoa into the female reproductive tract, but its components participate in key events related to sperm function, fertilization and embryo development in the female reproductive tract (44, 45). A histologically normal prostate is necessary for normal prostatic production and thus may be desirable for normal sexual and reproductive function in ADAM patients.

Besides the glandular epithelial cells, other cell types are present on prostate. Numerous mast cells are observed in the stroma of the rat ventral prostate, and they are often observed close to

blood vessels and nerves in the prostate as well as in other organs (17). In the present study, we observed that castration induced a 528% increase in mast cells in the ventral prostate which was overturned by hormonal therapy. Little information is known about the influence of testosterone and mast-cells. It was shown that mast cells present in the Harderian gland of hamsters are "androgen--dependent" cells. These mast cells are induced to degranulate when testosterone links to its specific receptors (46). Other study demonstrated that mast cells from human foreskin and breast skin (from female subjects) express androgen receptor. These authors showed that male skin mast cells expresses (10.8-fold) higher levels of androgen receptor than those from females (47). It seems that testosterone may influence the mast cells of some regions, although this was not proven yet. The recent information correlating the mast cell density with the prognostic of prostate cancer (14) corroborates this hypothesis. Future studies that address the influences of testosterone on mast cells and its role in normal and pathological prostate conditions are warranted.

The testosterone depletion is also linked to increased collagen deposition and augmented smooth muscle fibers in the human (48) and animal prostate (5, 28, 38, 39, 49). An accumulation of collagen fibers and smooth muscle cells around the rat prostate epithelium after castration was previously reported (50), and confirmed in the present study. Collagen density was augmented by 323% in castrated rats. Also, it was shown that the collagen has different characteristics as seen by optical and electron microscopy what is indicative of a turnover of this structure. Most importantly, the hormonal replacement therapy was effective in reversing (partially or completely) these stromal alterations.

We should point out that this is an animal study and its results should not be directly transposed to humans. Although the rodent model has been very well accepted for these studies, this is still an experimental setting and different from the clinical setting. Further, these castrated animals were healthy individuals, without any other medical condition which, again, does not represents the majority of patients with hypogonadism.

CONCLUSIONS

The present study demonstrates that the prostate of castrated rats suffers major morphological modifications, with parenchymal reduction and increase of stromal structures, including a higher presence of mast cells. The testosterone replacement restores the original architecture of prostate, regarding both parenchyma and stromal structures.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Dipyridamole reduces penile apoptosis in a rat model of post-prostatectomy erectile dysfunction

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ABSTRACT

Purpose: Despite the nerve-sparing technique, many patients suffer from erectile dysfunction after radical prostatectomy (RP) due to cavernous nerve injury. The aim of this study was to evaluate dipyridamole as a potential treatment agent of post-radical prostatectomy erectile dysfunction.

Material and methods: A total of 18 male Sprague-Dawley rats were randomized into three experimental Groups (SHAM+DMSO, BCNI+DMSO and BCNI+DIP). An animal model of bilateral cavernous nerve crush injury (BCNI) was established to mimic the partial nerve damage during nerve-sparing RP. After creating of BCNI, dimethyl sulphoxide (DMSO) was administered transperitoneally as a vehicle to SHAM+DMSO and BCNI+DMSO Groups. BCNI+DIP Group received dipyiridamole (10mg/kg/day) as a solution in DMSO for 15 days. Afterwards, rats were evaluated for in vivo erectile response to cavernous nerve stimulation. Penile tissues were also analyzed biochemically for transforming growth factor-β1 (TGF-β1) level. Penile corporal apoptosis was determined by TUNEL method.

Results: Erectile response was decreased in rats with BCNI and there was no significant improvement with dipyridamole treatment. TGF-β1 levels were increased in rats with BCNI and decreased with dipyridamole treatment. Dipyridamole led to reduced penile apoptosis in rats with BCNI and there was no significant difference when compared to sham operated rats.

Conclusions: Although fifteen-day dipyridamole treatment has failed to improve erectile function in rats with BCNI, the decline in both TGF-β1 levels and apoptotic indices with treatment may be helpful in protecting penile morphology after cavernous nerve injury.

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INTRODUCTION

In spite of using the nerve-sparing technique, erectile dysfunction (ED) is a common complication after radical prostatectomy (RP) due to neuropraxia of the cavernous nerve (1). The main reasons which cause the cavernous nerve damage during surgery include compression, tensile and thermal damage of the nerve (2). The cavernous nerve regeneration may take several months after

surgery and such a lengthy absence of innervations may lead to structural changes within the corpus cavernousum including smooth muscle loss and fibrosis (3, 4). These changes have been attributed to apoptosis after RP (5, 6). It has been well documented that smooth muscle apoptosis occurs within 24 hours after cavernous nerve injury (7). To date, some treatment approaches such as phosphodiesterase type 5 (PDE5) inhibitors, erythropoietin, FK506 (tacrolimus) have been tested for preserving the penile vascular bed and functional integrity of the cavernous nerves following RP (3, 8-10). Although they have proven some benefits for the ability to have sexual intercourse, there is still a need for new treatment approaches to prevent the penile corporeal damage mediated cavernous nerve injury.

Dipyridamole is currently used clinically as an antithrombotic drug. It increases cAMP level by inhibiting phosphodiesterase in platelet. It blocks the re-uptake of adenosine and increases the intracellular adenosine concentration (11, 12). Dipyiridamole leads to vasodilatation by increasing the adenosine formation and improves tissue perfusion in combination with antiplatelet and vasodilatory effects (13). There are also some studies that demonstrated antioxidant, neuroprotective, antiapoptotic and antifibrotic effects of dipyridamole in different tissues (14-20). Based on these features, dipyridamole may show therapeutic effect on the restoration of penile corporeal tissue after nerve-sparing RP.

In this study, an animal model of cavernous nerve crush injury was chosen to mimic the partial nerve damage during nerve-sparing RP. We aimed to evaluate the effects of daily administration of dipyridamole on penile apoptosis and erectile function measured in vivo in rats with BCNI. We also investigated the expression of transforming growth factor-β1, a well-known profibrotic cytokine that activates penile fibrosis.

MATERIAL AND METHODS

Animals and drugs

This experimental study was carried out in accordance with Karadeniz Technical University Animal Care and Ethic Committee directives and was approved by that committee. A total of 18 male Sprague-Dawley rats (weighing between 150 and 200g) were randomized into three experimental Groups; i) sham operation with exposure of bilateral cavernous nerves and no manipulation of the nerves plus dimethyl sulphoxide (DMSO) (SHAM+DMSO, n: 6); and ii) exposure of bilateral cavernous nerves and associated nerve injury plus DMSO (BCNI+DMSO, n: 6) and iii) exposure of bilateral cavernous nerves and associated nerve injury plus dipyiridamole (BCNI+DIP, n: 6). To create bilateral cavernous injury, animals were anesthetized with an intraperitoneal injection of a mixture of ketamine/xylazine (100+10mg/kg). The prostate was exposed via a midline abdominal incision. The cavernous nerves were identified posterolateral to the prostate. Injury was induced by applying Dumont #5 forceps (Fine Science Tools, Foster City, California, USA) to the nerve 2-3mm distal to the major pelvic ganglion. The forceps were held to closure three times for 15 seconds each, causing a moderate injury (2, 21, 22).

Following the BCNI, treatments were given according to Groups. DMSO was administered transperitoneally as a vehicle to SHAM+DMSO and BCNI+DMSO Groups for 15 days. BCNI+DIP Group received dipyiridamole (Sigma-Aldrich, St. Louis, Missouri, USA; 10mg/kg/day) as a solution in DMSO for 15 days transperitoneally. Drug dose was determined based on a report that demonstrated a protective effect of dipyiridamole in haloperidol-induced orofacial dyskinesia (23). After a 24 hours washout period, erectile responses were measured and penile tissues collected on the fifteenth day following BCNI.

Measurement of Erectile Responses in Vivo

After the treatment period, rats were anesthetized with a transperitoneal injection of ketamine/xylazine (100+10mg/kg) and a standard in vivo experimental protocol was conducted for evaluation of in vivo erectile response to cavernous nerve stimulation (22, 24, 25). Researchers were not aware of whether rats received placebo or dipyridamole. The carotid artery was cannulated to measure mean arterial pressure (MAP). The right penile crura was exposed and a 25G needle, connected to PE-50 tubing with 250U/mL heparin,

was inserted to measure intracavernosal pressure (ICP). The cavernous nerve was identified and distal portion of nerve crushing area was stimulated with a square pulse stimulator (Grass Instruments, Quincy, Massachusetts, USA) at a frequency of 20Hz and pulse width of 50 seconds. The application of 2, 4, 6, and 8 volts was used to achieve a significant erectile response. The duration of stimulation was 1 minute with rest periods of 5 to 10 minutes between subsequent stimulations. MAP and ICP were measured with a pressure transducer (Deltran, Utah Medical Products Inc. Midvale, Utah, USA) connected to a data acquisition system (ADInstruments, Colorado Springs, California, USA). Total erectile response or total ICP was determined by the area under the erectile curve (AUC; mmHg·sec) from the beginning of cavernous nerve stimulation until the ICP pressure returned to baseline or pre-stimulation pressures. The ratio between the maximal ICP and MAP obtained at the peak of erectile response was calculated to normalize for variations in systemic blood pressure. These methods have been previously described (22, 24).

Measurement of Rat Transforming Growth Factor-β1 (TGF-β1) Levels

Levels of rat TGF-β1 levels were determined by enzyme-linked immunosorbent assay kit (eBioscience-Ref No: BMS623/3, Lot No: 83382003, San Diego, California, USA), according to the manufacturer's protocols. The absorbance of samples was measured at 450nm using VERSA max tunable microplate reader (Designed by Molecular Devices, California, USA). The results were expressed as pg TGF-β1 per mL.

TUNEL assay

Tissue samples from the mid-shaft of the penis were harvested (n=10/group), fixed in 10% formaldehyde, embedded in paraffin, and cut in 5μm sections. Terminal deoxynucleotidyl transferase (TdT) deoxyuridine triphosphate nick end labeling assay (TUNEL) method was applied to determine the number of apoptotic cells both in smooth muscle cells and collagen fibers. TUNEL staining of sections was performed using an in situ cell death detection kit (AP kit; Roche, Mannheim, Germany), in accordance with the manufacturer's instructions. Endogenous peroxidase activity was blocked in 3% hydrogen peroxide. Color was then developed with a 3,3′-diaminobenzidine including kit (DAB, Sigma, St Louis, Missouri, USA). Two independent observers, blinded to the treatment regimen, separately evaluated apoptotic cells. Collagen fiber and muscle cells with brown nuclei were evaluated as apoptotic. TUNEL-positive cells were counted in five different fields of connective tissue and smooth muscle cells separately with 400X magnification. Quantification of TUNEL--positive cells was performed using the Analysis 5 Research program (Olympus Soft Imaging Solutions, Munster, Germany). The ratio of apoptotic nuclei to total number of nuclei was presented as the apoptotic index (AI) (26, 27).

Statistical analysis

The statistical analyses were performed with a computer software package (GraphPad Prism™ software version 5.0, La Jolla, California, USA). Data were expressed as mean±standard error of the mean (SEM). Differences between multiple Groups were compared by Kruskal-Wallis analysis of variance. Post-Hoc analyses were done by Mann-Whitney test with Bonferroni adjustment. P value of less than 0.05 was considered statistically significant.

RESULTS

Following the BCNI, a total of 18 rats were treated with dipyridamole and placebo (DMSO) according to groups for 15 days. Mean body weights were 320.7±10.02g in SHAM+DMSO Group, 359.7±29.04g in BCNI+DMSO Group and 377.8±25.96g in BCNI+DIP Group. There were no differences in weight among the Groups at the end of the treatment ($p>0.05$).

There were no differences on baseline MAP and ICP levels among the Groups (respectively, $p>0.05$ and $p>0.05$). After right cavernous nerve was revealed, electrical stimulations were applied for 2, 4, 6 and 8 volts respectively to assess erection quality. Both Total ICP and ICP/MAP ratio decreased in rats with BCNI in both BCNI+DMSO and BCNI+DIP Groups as compared to sham operated rats

(p <0.05). The decreased response in both total ICP and ICP/MAP of nerve injured rats were correlated for all voltages (2, 4, 6 and 8v) stimulation. After 15-day treatment with dipyridamole, there was no significant improvement in erectile response of rats in BCNI+DIP Group compared to placebo treated rats (p >0.05). Total ICP and ICP/MAP ratio of Groups are shown in Table-1 and Figure-1.

Penile corporal tissues of rats were evaluated biochemically in terms of TGF-β1 levels (Table-2). Fifteen days after crush injury of cavernous nerves, there was an increase in TGF-β1 levels of BCNI+DMSO Group compared to SHAM+DMSO Group (p<0.05). Dipyridamole treatment led to decrease in TGF-β1 levels of rats in BCNI+DIP Group and there was no statistical difference between BCNI+DIP Group and SHAM+DMSO Group (p>0.05).

Penile apoptosis was evaluated by TUNEL method (Table-2 and Figure-2). A significant increased level of TUNEL positive cells in muscle cells and connective tissue of rats with BCNI was found compared to sham operated rats (p<0.05). The fifteen-day treatment with dipyridamole led to reduced penile apoptosis in rats with BCNI and there were no significant differences when compared to SHAM+DMSO Group (p>0.05).

DISCUSSION

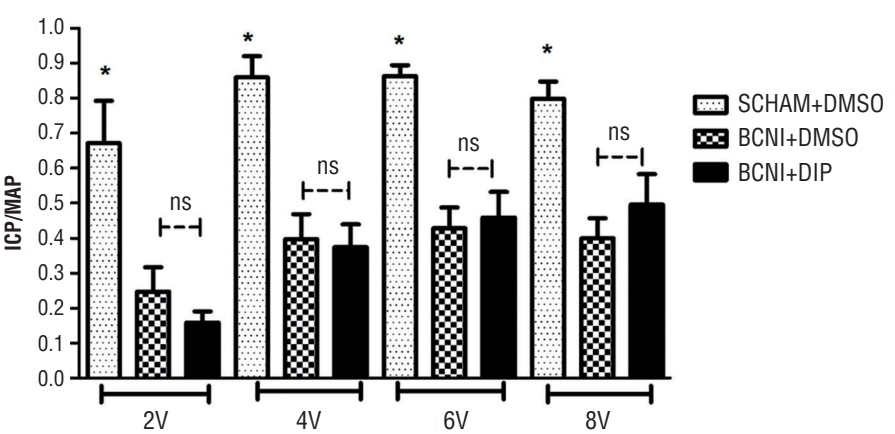
The purpose of the present study was to evaluate dipyridamole as a potential treatment agent of post-radical prostatectomy ED. A rat model of cavernous nerve crash injury was chosen to assess this hypothesis (8, 9, 28, 29).

Table 1 - Shows voltage-dependent erectile responses as measured by total ICP (area under the erectile curve [AUC; mmHg·sec]).

	SHAM+DMSO	BCNI+DMSO	BCNI+DIP	p
2v	2743±322.9	915.5±222.0	575.2±132.3	P<0.05*
4v	3318±273.8	1356±216.1	1247±196.1	P<0.05*
6v	3766±188.7	1409±202.4	1461±202.1	P<0.05*
8v	3485±191.3	1284±195.4	1606±253.2	P<0.05*

DMSO = dimethyl sulphoxide; **DIP =** dipyridamole; **BCNI =** bilateral cavernous nerves injury
***** = p<0.05 (SHAM+DMSO vs. BCNI+DMSO, SHAM+DMSO vs. BCNI+DIP)

Figure 1 - Bar graph shows voltage-dependent erectile responses as a ratio of the intracavernosal pressure (ICP) to mean arterial pressure (MAP).



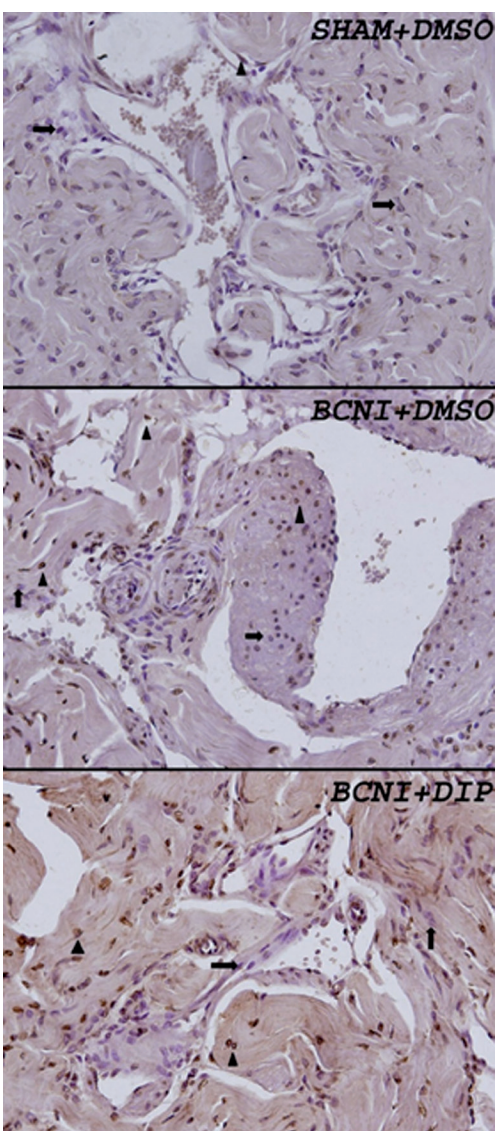
*** =** p<0.05 (SHAM+DMSO vs. BCNI+DMSO, SHAM+DMSO vs. BCNI+DIP)
ns = p>0.05 (BCNI+DMSO vs. BCNI+DIP)

Table 2 - Shows the findings of TGF-β1 and penile corporal apoptosis fifteen days after bilateral cavernous nerves injury.

	SHAM+DMSO	BCNI+DMSO	BCNI+DIP	p
TGF-β1 (pg/mL)	17950±129	21490±2035	19380±432	<0.05*
Apoptotic index in smooth muscle (%)	23.50±0.80	55.33±1.68	34.17±1.47	<0.05*
Apoptotic index in connective tissue (%)	55.40±1.327	70.67±1.229	68.33±1.45	<0.05*

TGF-β1 = transforming growth factor-β1; **DMSO =** dimethyl sulphoxide; **DIP =** dipyridamole; **BCNI =** bilateral cavernous nerves injury.
***** = SHAM+DMSO vs. BCNI+DMSO (p<0.05); SHAM+DMSO vs. BCNI+DIP (p>0.05); BCNI+DMSO vs. BCNI+DIP (p>0.05)

Figure 2 - Corpus cavernousum sections stained with the TUNEL technique (original magnification 400x).



Δ= Apoptotic cells; ↑ = Normal cells

Despite advances in nerve-sparing radical prostatectomy technique, many patients are experiencing the loss of erectile function during postoperative period (22, 30). Penile fibrosis as a result of cavernous nerve injury has been well determined in both experimental models and in patients (7, 31). Neuropraxia causes an increased apoptosis and fibrosis in both penile smooth muscle cells and endothelium (5, 6). Additionally, an increase in reactive oxygen species and TGF-β1 over expression has been reported (31-33). It has been also reported that BCNI causes a reduction in nitric oxide synthase (NOS) containing nerve fiber in animal models (34).

Even though nitric oxide (NO) is the principal relaxant of the penile smooth muscle cells, multiple other factors, either neuronal or vascular, have also been shown to modulate penile erection (35-37). Adenosine, like NO, is a potent vasodilator and its role in penile erection has been investigated in many studies which showed that intracavernous injection of adenosine resulted in tumescence and penile erection (38-41). Adenosine induced vasodilatation is mediated by increased intracellular cyclic adenosine mono phosphate (cAMP) levels in vascular smooth muscle cells via A_2 receptor signaling (42, 43). Along with normal penile erection, adenosine signaling has also been found to be critical in erectile disorders. Gur and Ozturk suggested a greater role for adenosine as a modulator in human corpus cavernousum than in the corporal tissue of rats (44). The impairment of nonadrenergic noncholinergic neurotransmission and endothelial dysfunction due to diabetes, chronic renal failure, and hypothyroidism, seem to contribute toward erectile dysfunction, but adenosine induced relaxation of

corpus cavernousum is preserved, indicating a potential therapeutic role for adenosine (45-47). Faria et al. observed partial resistance of corpus cavernousum in men with vasculogenic impotence to adenosine induced relaxation and showed that dysfunctional A_{2B} receptors, supposedly on the endothelium, are the cause for the signaling impairment (48). Similarly, Kilic et al. observed full erection and no side effect with high dosage of intracorporeal adenosine injection in vasculogenic impotence in human (49). Chiang et al. and Filipi et al. evaluated the effect of intracorporeal injection of adenosine in impotent men which caused increased cavernosal arterial flow and resulted in suboptimal erection (50, 51). Chiang et al. attributed the suboptimal erection upon adenosine injection to the rapid degradation of adenosine by adenosine deaminase (50).

Dipyridamole is an adenosine transport inhibitor which is currently in use clinically as an antithrombotic drug. There are also some studies that demonstrated antioxidant, neuroprotective, antiapoptotic and antifibrotic effects of dipyridamole in different tissues (14-20). In a study to investigate the antioxidant properties of dipyridamole, Vargas and colleagues have found that dipyridamole probably clears the reactive oxygen radicals released from human polymorphonuclear leukocytes (ROS) (15). Also, it has been reported that dipyridamole protects the erythrocyte membranes from oxidation (52). Another animal study showed that dipyridamole protects the liver cells from the damage of ischemia/reperfusion injury (16). In addition, Garcia-Bonilla et al. identified the neuroprotective effects of dipyridamole in experimental models of cerebral ischemia in rats (17).

Dipyridamole increases cAMP level by inhibiting phosphodiesterase in platelet. It blocs the re-uptake of adenosine and increases the intracellular adenosine concentration (11, 12). Dipyiridamole leads to vasodilatation by increasing the adenosine formation and improves tissue perfusion (13). According to this knowledge, in this study, we anticipated that phosphodiesterase inhibition and adenosine accumulation by dipyridamole might contribute penile erection. But we did not see any different among the Groups after fifteen-day dipyridamole treatment. This failure might be caused by a short time for the recovery of injured cavernous nerves.

Hung et al. reported that dipyridamole has antifibrotic effect and inhibits collagen gene expression induced by TGF-β in human peritoneal mesothelial cells (20). In previous reports of animal model of BCNI, penile corporeal fibrosis has been linked to over expression of TGF-β1 (53, 54). In present study, BCNI led to increase TGF-β1 levels and fifteen-day dipyridamole treatment reduced its expression. This effect might help to reduce penile fibrosis and preserve smooth muscle cells.

Some reports have shown that dipyridamole has an antiapoptotic effect. Schrier and Yang reported that dipyridamole significantly blocks the activity of caspases which play an important role in the mechanism during the apoptotic cell death (18, 19). In our study, although we did not investigate caspase pathway, dipyridamole reduced penile corporeal apoptosis determined by TUNEL technique.

There are certainly a few limitations that are worth noting with this study. The main limitation of our study is that we have only used one time point and pharmacological dose to evaluate the therapeutic effect of dipyridamole. There is a possibility to get various outcomes with longer duration of treatment and/or different pharmacological dose. Additionally, this study did not evaluate other possible effects of dipyridamole to contribute erectile function recovery such as the antioxidant and neuroprotective effects.

CONCLUSIONS

Although fifteen-day dipyridamole treatment has failed to improve erectile function in rats with BCNI, the decline in both TGF-β1 levels and apoptotic indices with treatment may be helpful in protecting penile morphology after cavernous nerve injury. Further studies are required to understand the effect of different pharmacological dose and long term treatment with dipyridamole especially in terms of penile hemodynamic response.

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CONFLICT OF INTEREST

None declared.

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Use of indocyanine green angiography in microsurgical subinguinal varicocelectomy – lessons learned from our initial experience

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ABSTRACT

Microsurgical subinguinal varicocelectomy (MSV) is generally considered the gold standard nowadays in view of the lower risk of complications and recurrence. To achieve complete ligation of veins while preserving testicular artery (TA) during the procedure remains challenging despite the application of high power optical magnification and micro-Doppler ultrasonography. The use of intraoperative indocyanine green angiography (ICGA) with infrared fluorescence operative micro-scope in MSV potentially lowers the incidence of TA injury and shortens the learning curve of novice surgeons. We present our initial experience in the application of the technique in nine patients and explore the potential of the new adjunct.

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INTRODUCTION

Subinguinal microsurgical varicocelectomy (MSV) became the gold standard technique for varicocelectomy nowadays in view of the lower rate of recurrence and complications compared with open or laparoscopic techniques (1, 2). On one hand, subinguinal approach allows exposure of external spermatic and gubernacular veins and the lack of fascial incision results in less pain postoperatively. On the other hand, the more difficult dissection with a greater number of internal spermatic arteries and veins subinguinally (3) poses challenges to the operating surgeons. Injury to the testicular artery (TA) is a major complication of the procedure and a potential cause of testicular atrophy, but the incidence is unclear (4). It is believed that accidental arterial injury may go unnoticed and underreported particularly in non--microscopic varicocelectomy with inadequate optical magnification (5). Inspection of the cord for presence of arterial pulsations under high power magnification with irrigation of papaverine solution and the use of micro-Doppler (6, 7) are the most commonly adopted and effective means to locate the testicular artery (TA). However, the techniques require a certain level of experience and the result can be operator dependent. The application of indocyanine green angiography (ICGA) in MSV has been recently reported in the literature

(8). The objective images provided by ICGA potentially simplify TA localization and decrease the incidence of inadvertent TA injury.

Surgical Technique

Between September 2016 and January 2017, nine patients had unilateral MSV and ICGA performed on left grade 2 to 3 varicoceles in our unit. Four of the nine patients suffered from infertility with abnormal semen parameters. Two patients who presented with incidental finding of grade 3 left varicocele and oligozoospermia preferred surgical intervention after counseling. One patient was operated on due to bothersome discomfort associated with left grade 3 varicocele. Two varicocelectomies in adolescents were performed in view of testicular size discrepancy.

The procedures were performed under general anaesthesia. The infrared fluorescence operative microscope (Zeiss OPMI Pentero 900, Oberkochen, Germany) was brought into the field after incision of skin and spermatic fasciae. The vas deferens and its vessels were protected. ICGA was performed when the possible TA was identified. A pack of 25mg of indocyanine green (ICG) (Diagnogreen, Tokyo, Japan) was dissolved in 10mL of water. Each angiography required 5mL (12.5mg) of ICG solution which was prepared and administered by the anaesthetist in a bolus via a peripheral line. The Infrared 800 mode of the microscope was activated and the fluorescence angiography was recorded and analyzed. ICGA was repeated if necessary and at the end of the procedure to confirm a successful TA preservation.

Testicular artery was clearly identified by ICGA in all patients (Figure-1). Two testicular arteries were visualized in one patient while a single TA was identified in the remaining eight cases. The maximal diameter of the TA identified was no more than 1mm. All TA were shown up within one minute upon injection of ICG with a mean time of 36.3 seconds. Cremasteric and deferential arteries were visualized during intraoperative ICGA in most of the patients (Figure-1). The real-time angiographic images could be recorded and analyzed with the assistance of the built-in computer program of the operating microscope (Figure-2). The data could

Figure 1 - Intraoperative images during microsurgical subinguinal varicocelectomy. A) Microscopic view before injection of indocyanine green. B) Indocyanine green angiography clearly demonstrated all the arterial supply to the testicle. The testicular artery was marked by arrows. Deferential artery and cremasteric arteries were denoted by arrow heads and stars respectively.

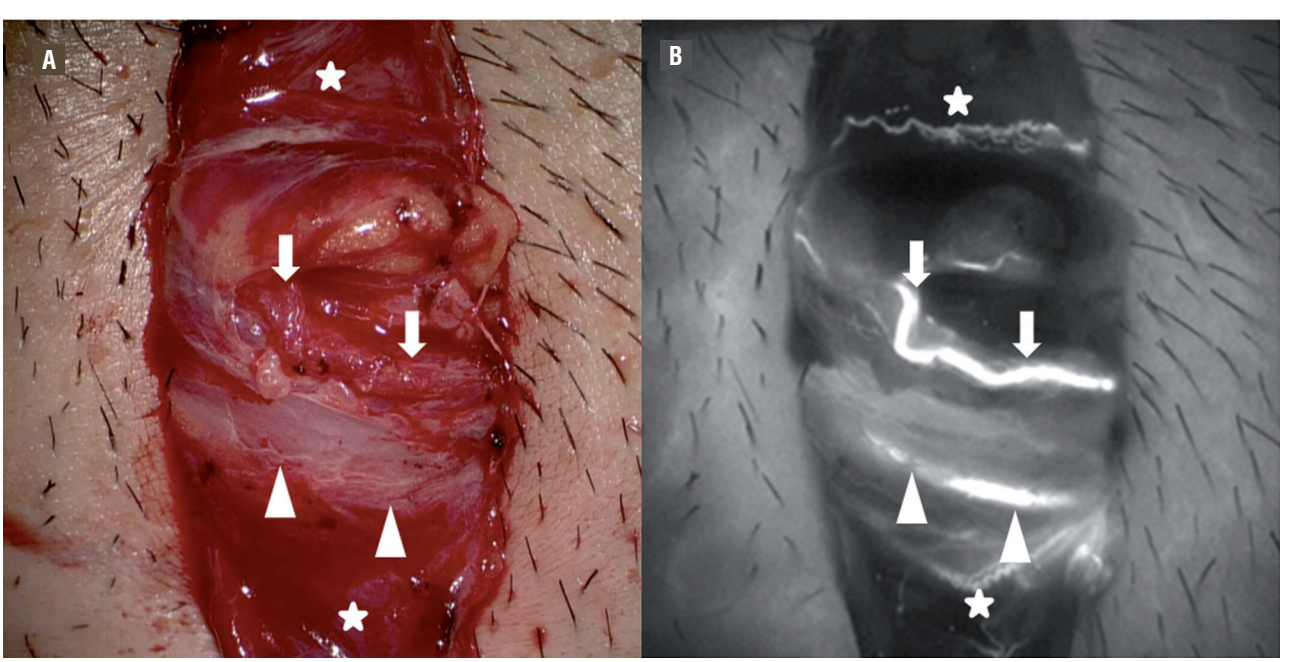
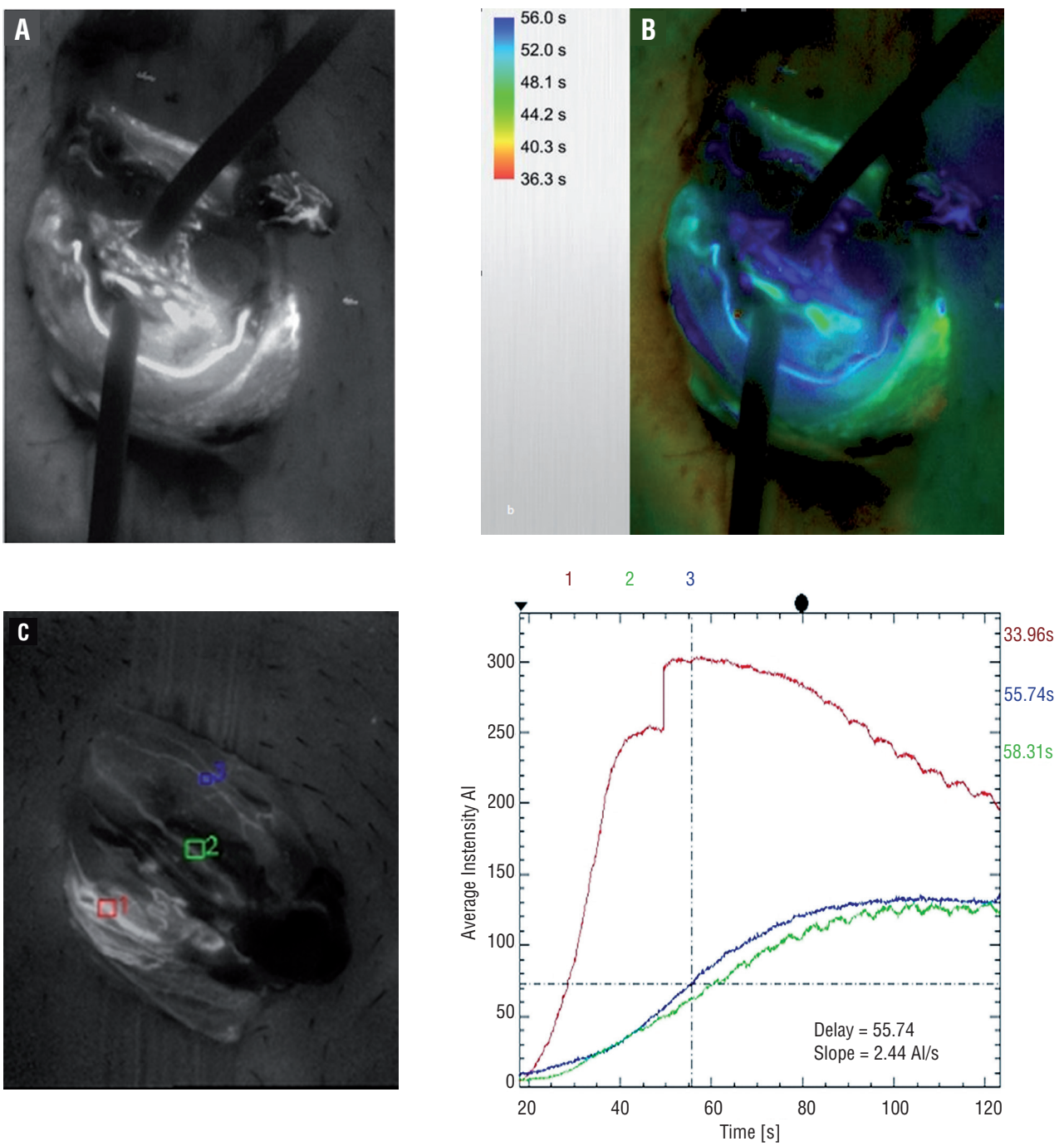


Figure 2 - Built-in fluorescence modules of the operating microscope provided analysis of the vascular dynamics. A) Infrared 800 module demonstrates the relative intensity of indocyanine green signal. B) Flow 800 module illustrates the sequences the flow dynamics into a visual map. C) Interpretation of specific area on the angiographic image can be marked and D) Flow dynamic of each region can be illustrated in the form of curves.



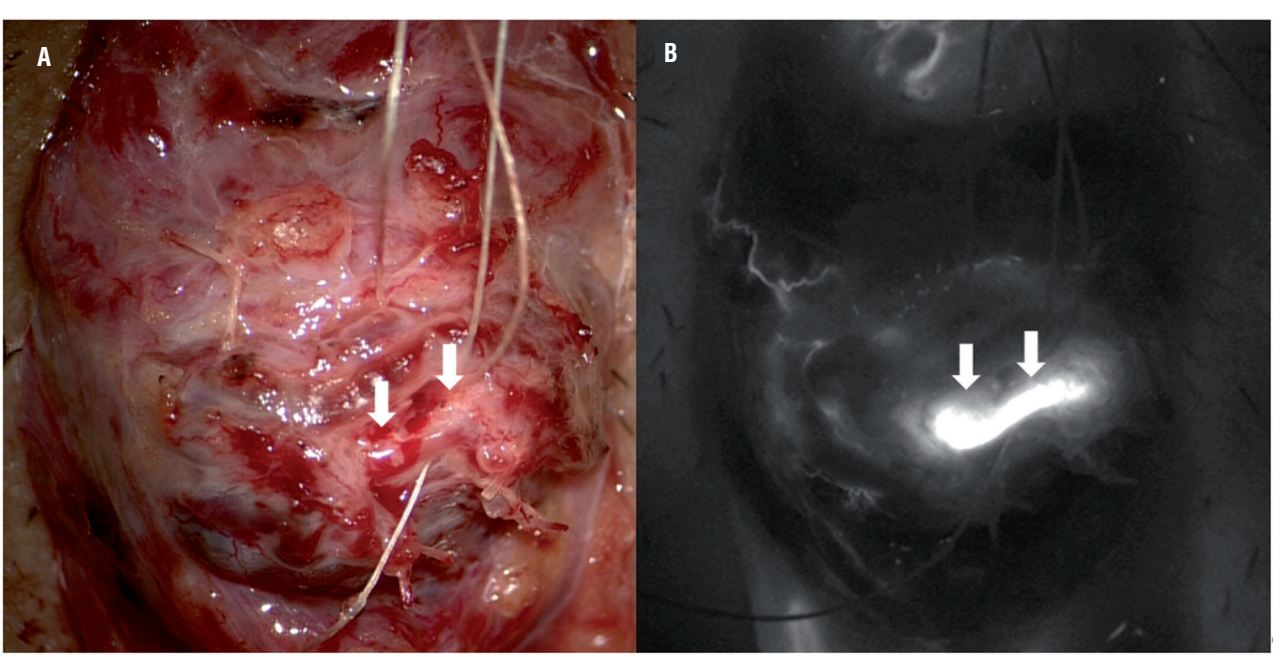
be presented in different formats by comparing the relative intensity and time to visualization of each vessel.

All patients were discharged the same day after the operation. No adverse reaction was observed after injection of ICG. No clinical recurrence and complication was recorded upon follow-up at 4 weeks after the operation.

COMMENTS

The use of ICGA as an adjunct to MSV seems a promising technique in our initial experience. Localization of TA was achieved in all patients. The technique repeatedly demonstrated its ability in clearly identifying small TA of less than 1mm diameter. It was applicable to both adults and adolescents. ICGA is unique in providing an objective real-time assessment and images of arterial flow in the cord compared to direct visualization of pulsation under high power magnification and micro-Doppler. The intraoperative pictures can be recorded and are particularly useful for training and documentation purposes. It may facilitate transfer of technique to training surgeons and potentially shorten the learning curve. The technique of ICGA is not operator dependent and easy to administer with minimal prior preparation. Each ICGA spent no more than a few minutes and did not significantly prolong the operating time. The high-contrast images provided by the angiography allow simple interpretation to most surgeons. ICG has low toxicity with LD_{50} of 50-80mg/kg in animals (9). Confinement to the vascular compartment through binding with plasma proteins and rapid excretion via bile explained the safe nature of ICG. The safety (10) and short plasma half-life of ICG allows repeated ICG administration without compromising the quality of images. Its use was particularly valuable in patients with dense adhesion among intermingled arteries and veins (Figure-3). The adhesion rendered the identification of TA difficult by damping the arterial pulsation. The pulsation may appear weak and the exact localization of a particular pulsating artery may be difficult before the vessels were freely separated. ICGA may be superior in this scenario since the

Figure 3 - Intraoperative indocyanine green angiography may facilitate early identification of testicular artery. A) Microscopic view showing dense adhesions among intermingled artery and dilated veins which render the identification of arterial pulsation extremely difficulty. B) Indocyanine green angiography showed a single testicular artery among the densely adhered vessels.



arterial flow is not obscured by adhesion among vessels. Small TA could be visualized before the adhesion was completely lysed. The whole course of TA across the operating field was shown up clearly most of the time. An earlier and more precise identification of TA during the procedure will reduce the risk of inadvertent arterial injury. Further comparative studies among the different strategies in TA preservation is required in delineating the potential advantages of ICGA in facilitating earlier TA identification and/or decreasing the risk of TA injury.

The recent advancement in fluorescence angiography lays in the analysis of ICG fluorescence dynamics. The built-in computer modules of the operating microscope provide data of flow dynamics of each vessel in the operating field. Although the significance of relative flow among testicular/deferential/cremasteric arteries in testicular blood supply is unknown, the demonstration of an intact collateral flow may be of importance in case of TA injury. An intact deferential and cremasteric supply may predict less probability of testicular atrophy and impairment of spermatogenesis after TA injury. In addition, ICGA may have a role in TA repair in case of accidental injury by localizing the abdominal end of the transected artery. The confirmation of intact deferential artery is preferred in the presence of prior groin or scrotal surgery when the status of the collateral supply is doubtful. The assessment of collateral arterial supply to the testes is not feasible with the technique of optical magnification and micro-Doppler.

The vascular anatomy and ICG dynamics illustrated by ICGA could be a research tool in better understanding the intraoperative microanatomy and physiology of varicocele. The information of microanatomy may further refine and decrease the complication of varicocelectomy.

ICGA may prove to be a more cost effective than the use of other adjunct such as micro-Doppler. Although the set-up of an infrared fluorescence operative microscope is more costly compared to a micro-Doppler machine (USD $283.000 versus $11.600), the microscope can be shared among different specialties in the setting of a multi-disciplinary hospital. The running cost of ICGA is much lower than micro-Doppler for each procedure. A pack of 25mg Diagnogreen costs around USD $43 in our locality and usually one to two packs were consumed for each procedure while a disposable micro-Doppler probe costs USD $386.

In conclusion, the use of intraoperative ICGA is safe and consistently provides objective assessment of testicular artery. The technique facilitates early identification and preservation of TA, and may decrease the incidence of TA injury during MSV. ICGA is potentially superior to and provides additional information compared to the current technique of TA identification with direct visualization of pulsation under high power magnification and micro-Doppler.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

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Editorial Comment: Use of indocyanine green angiography in microsurgical subinguinal varicocelectomy – lessons learned from our initial experience

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Use of indocyanine green angiography in microsurgical subinguinal varicocelectomy - lessons learned from our initial experience.

Dr. Chak-Lam et al., from China, produce an elegant manuscript that describe the use of intraoperative indocyanine green angiography with infrared fluorescence operative microscope in microsurgical subinguinal varicocelectomy that potentially allows an early identification as well as preservation of testicular artery (1).

The main goal of varicocelectomy is to preserve testicular function and initiate pregnancy in infertile couples (2). Although surgical repair of a varicocele can be performed using several methods, microsurgical repair appears to be associated with better outcomes and lower complication rates (3). The most common complications associated with conventional approaches include postoperative varicocele recurrence or persistence, hydrocele formation and testicular artery injury (4).

Most infertility experts prefer the subinguinal approach that is performed through an incision below the external inguinal ring obviating the need to open the aponeurosis of the external oblique which causes less pain (5). However, the number of spermatic arteries identified in the spermatic cord seems to be dependent on the level of the dissection. The augmented probability of encountering multiple spermatic arterial branches in the subinguinal region contributes to the technical difficulty of this approach (5). Therefore, the use of an operating microscope providing magnification up to 25x allows a better preservation of the testicular arteries and lymphatic vessels during subinguinal approach.

Previous studies reported that multiple spermatic arteries are identified in approximately 40% of the spermatic cords during microsurgical varicocelectomy at the subinguinal level (5, 6). Jarow et al., found numerous arterial branches in 81% of the spermatic cords upon histological analysis, which is higher than clinical observation studies (7). Therefore, it is possible that an inadvertent unrecognized ligation of a small (secondary) internal spermatic artery occurs more frequently than reported. Although there is not unanimity about the necessity to preserve all testicular arterial branches, this might be responsible for suboptimal spermatogenic recovery or failure to improve fertility in some cases (4). Data from our group published in 2010, showed that systematic use of intraoperative Doppler during subinguinal microsurgical varicocele repair allows a higher number of arterial branches preserved as well as a superior number of internal spermatic veins ligated (8). A solitary artery was identified in 45.5% of cords, while 2 arteries were identified in 43.5% and 3 or more arteries were identified in 11%. The identification of the main spermatic artery can be confirmed by visualization of clear pulsatile movement; however, the identification of tiny secondary arteries is not always so evident.

In the present study, the authors found a low average number of arteries using intraoperative indocyanine green angiography compared to published data mentioned above. These findings could be explained by an aggressive manipulation of the vessels during dissection that can lead to spasm, making it difficult to achieve the ideal indocyanine green perfusion especially in secondary tiny arteries. In addition, the present study has some limitations that must be addressed before we can conclude that

a combination of subinguinal microsurgical varicocelectomy and indocyanine green angiography may decrease the incidence of artery injury during varicocele repair. For example, the authors did not compare the benefits of this new technique with conventional microsurgical procedures. Also, the number of patients studied is too small to draw definite conclusions. However, the authors must keep in mind that current results highlight how the continued investigation appears worthwhile and additional research is needed to better clarify whether all these technological advances is likely to improve testicular function, seminal parameters or even fertility potential.

In conclusion, the testicular artery is the largest artery supplying the testicle and its ligation during varicocele repair may exert deleterious effects on testicular function. Thus, there is growing support for artery sparing techniques and accidental arterial injury during varicocelectomy should be avoided with all effort possible. Current available data indicates that preoperative parameters are not predictive of the number of testicular arteries identified at the time of surgery. As a result, the application of technological advances during varicocelectomy including optical magnification, microsurgery skills, vascular Doppler and indocyanine green angiography should be alternative options to achieve maximal preservation of the arterial blood supply to the testes.

CONFLICT OF INTEREST

None declared.

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Synthetic mesh repair of an anterior perineal hernia following robotic radical urethrocystectomy

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ABSTRACT

Introduction: Perineal hernia is a protrusion of intra-abdominal viscera through a defect in the pelvic floor and is a rare but challenging complication after extensive abdominoperineal surgery. There have been small series published after colorectal exenteration, but no cases have been reported after radical cystectomy and urethrectomy.
Case Presentation: A 68 years old woman developed an anterior perineal hernia, with no vaginal prolapse, after an anterior exenteration for bladder cancer. A perineal approach with the use of a synthetic polypropylene mesh was chosen to resolve the condition. After 6 months of follow-up, the patient has no symptoms or recurrence of the anterior perineal hernia.
Conclusion: To our knowledge, this case is the first report of perineal hernia after radical urethrocystectomy. Although being a case report, this article describes a potential and challenging complication after extensive anterior pelvic surgery, that could increase its incidence in the future. Literature review shows that whether perineal, abdominal or combined approach is chosen, surgery must respect hernia repair principles.

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Keywords:
Perineum; Pelvis; Cystectomy

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INTRODUCTION

Perineal hernia is a protrusion of intra-abdominal viscera through a defect in the pelvic floor. Symptomatic perineal herniation is a rare but challenging complication after extensive abdominoperineal surgery. A Mayo Clinic publication, reported a prevalence of 0.34% (8 of 2732) in patients operated on between 1990 and 2000 with a minimum 5-year follow-up (1). Risk factors for perineal hernia may include wound infection, coccygectomy, previous hysterectomy, pelvic irradiation, redundant small bowel mesentery, female pelvis, excision of or failure to reapproximate the elevators, perineal wounds left open postoperatively, placement of drains through the perineal wound itself instead of through separate stab incisions and tobacco use (2, 3).

To our knowledge, no cases have been published following radical cystectomy and urethrectomy. This article reports a perineal hernia after this surgery and its surgical management using a synthetic mesh through a perineal approach.

CASE PRESENTATION

A 68 years old female, with a history of smoking habit, was diagnosed with high-grade

muscle invasive urothelial bladder carcinoma after undergoing transurethral bladder resection for gross hematuria. The tumor involved the left lateral wall and the bladder neck. A positron emission tomography showed enlarged iliac lymph nodes and a neoadjuvant chemotherapy based on platinum (M-VAC: methotrexate, vinblastine, doxorubicin and cisplatin) was prescribed. No pelvic irradiation was necessary.

A robotic radical cystectomy, hysterectomy with bilateral adnexectomy, extended pelvic lymphadenectomy and urethrectomy with heterotopic Bricker urinary diversion was performed. Due to the locally advanced disease prior to chemotherapy a broad resection was performed including a complete urethrectomy.

The postoperative recovery was marked by a delayed vestibule healing and an inguinal hematoma that required surgical drainage. The pathologic examination retrieved a high-grade muscle-invasive bladder urothelial carcinoma, and a final TNM score of pT2 No M0 with negative surgical margins.

After one month of the surgery, an anterior perineal bulge appeared during efforts, increasing its volume during the following months. The patient had severe discomfort, despite not complaining of pain or digestive symptoms.

Upon physical examination, an anterior perineal hernia was observed between the ischiopubic rami, at the level of the vestibulum with labia majora bulging but without vaginal prolapse (Figures 1 A and B and Figure-2). The content of the hernia was reducible and the skin covering the hernia had a diminished thickness.

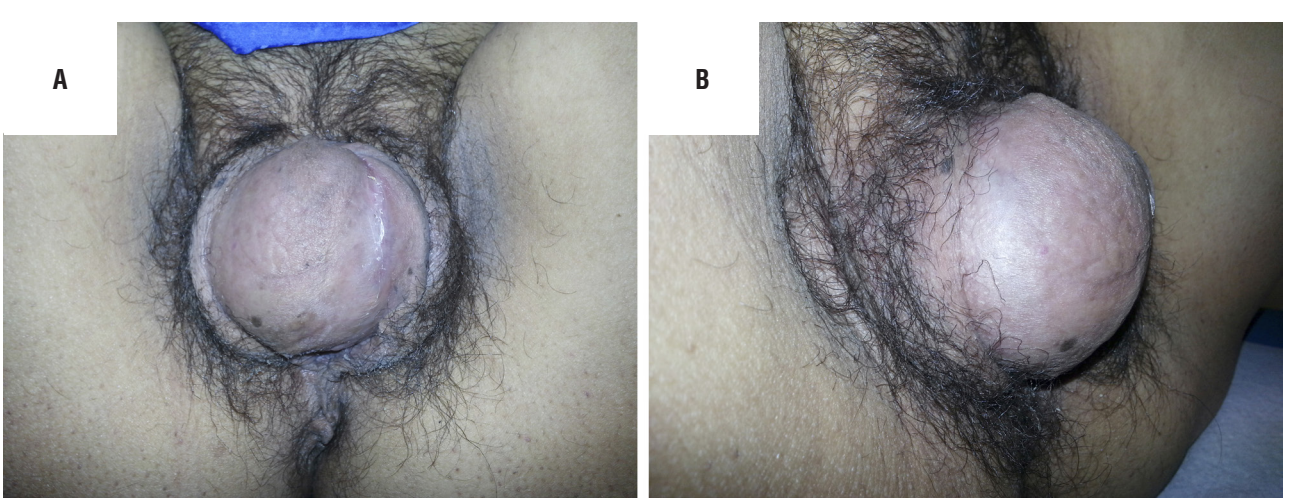
A magnetic resonance scan showed a small bowel content at the level of the perineal hernia, without vaginal prolapse (Figure-3A). No radiologic signs of cancer recurrence were observed.

A multidisciplinary meeting was held and, based on the patient's discomfort, possible complications, and after patient's consent, surgery was scheduled.

Under general anesthesia, with the patient placed in a lithotomy position with Allen stirrups, broad-spectrum antibiotic provided, an infiltration of the perineal skin with a solution of lidocaine and 1% adrenaline was performed. Sub - clitoridian vestibular and lower portion of the anterior vaginal wall incision. Dissection of the voluminous enterocele and opening of the peritoneum sac (Figure-3B).

Dissection was extended behind the fat tissue of the labia majora and to the level of the ilio-pubic rami, where two polypropylene 2/0 sutures were placed bilaterally on the inferior pubic ligaments. The peritoneum was closed with a purse-string polydioxanone 1 suture, and reinforcement of 2/0 poliglecaprone interrupted sutures. The urogenital diaphragm and bulbo-spongiosus muscles were then sutured in the midline using 2/0 poliglecaprone interrupted sutures to cover the peritoneum sac.

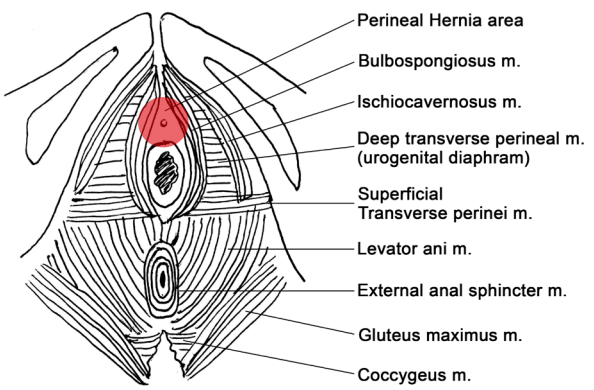
Figures 1A and B) Preoperative perineal hernia frontal and lateral appearance during Valsalva effort.



A transobturator light weight polypropylene mesh (Surgimesh®, Aspide Medical Laboratoire, La Talaudière, France) was placed, fixed to the ilio-pubic rami with the 2/0 polypropylene sutures and with one arm placed through the transobturator foramen on each side (Figures 3C and D). Finally, the mesh was attached to the anterior vaginal wall with polypropylene 2/0 interrupted sutures. This type of mesh and fixation was chosen since the vaginal vault was not accessible through this surgical approach. The mesh was partially covered medially by labia majora fat tissue using absorbable sutures. Finally, the skin and vestibular mucosa were closed with a 3/0 poliglecaprone running suture (Figure-3E).

After a follow-up of 6 months, there was no evidence of recurrent hernia and no scar defect (Figure-3F).

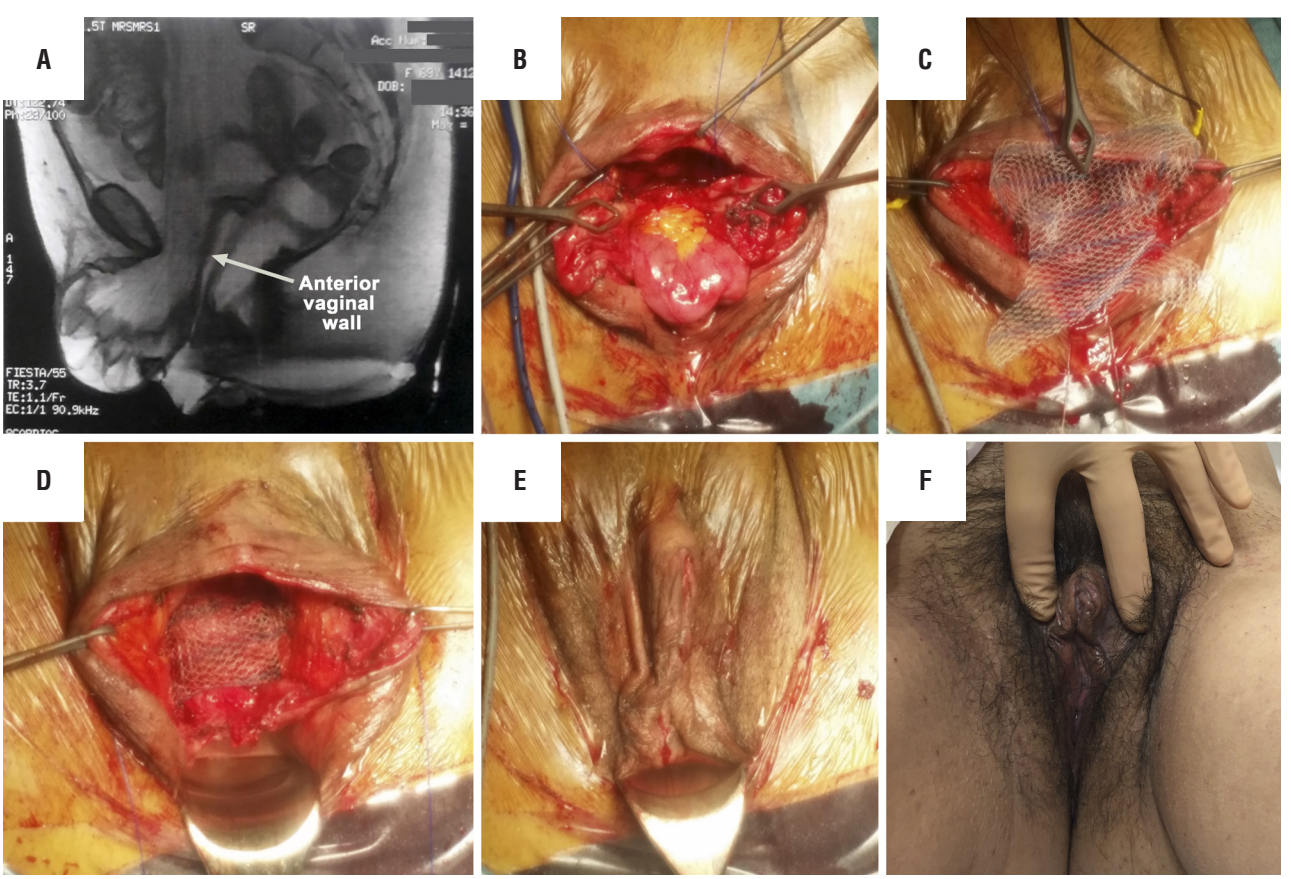
Figure 2 - Anatomy of perineum and location of this anterior perineal hernia.



DISCUSSION

Perineal hernia is an infrequent but challenging event after extensive abdominoperineal surgery, mainly in the posterior

Figure 3 - A) Sagital Magnetic resonance image. B) Intraoperative view of the opened sac of anterior enterocele. C) Four-arms polypropylene mesh. D) Intraoperative view of the fixed mesh. E) Intraoperative final result. F) Postoperative exam with Valsava effort after 6 months of surgery.



compartment. The publications on this subject are scarce and usually based on single or small case series. Incidence ranges between 0.6% and 7% (4-6). To our knowledge, there are no publications of anterior perineal hernia after radical cystectomy and urethrectomy.

Usual presentation is that of a soft, reducible mass, along with discomfort and bulging in the perineum, which was the case of our patient. Complications may include skin breakdown, bowel obstruction due to incarcerated small intestine, entero-cutaneous fistula or the extreme presentation of hernia rupture with small-bowel prolapse and/or evisceration (7).

As previously stated, risk factors for perineal hernia (1) may include wound infection, previous hysterectomy, pelvic irradiation, redundant small bowel mesentery, female pelvis, failure to reapproximate the elevators, perineal wounds left open postoperatively, placement of drains through the perineal wound itself instead of through separate stab incisions, and tobacco use (2, 3). In our case, the extensive resection in order to accomplish negative margins on the urethrectomy might have been the cause. Other reason could have been the lacking of force feed-back sensation in robotic approach.

Although diagnosis might be evident, the use of imaging studies, as computed tomography or magnetic resonance imaging may provide information on hernia content, soft tissue surroundings and exclude recurrent malignancy before deciding a reconstructive surgery.

Based in digestive surgery literature (2, 3, 8), a variety of methods for repair have been described, most as isolated case reports or small case series because of the relative infrequency of the condition.

The basic principles of hernia repair must be followed: exposure and mobilization of the hernia sac, reduction of its content, excision of the sac, and repair of the defect. There is no accepted consensus as to the preferred approach, perineal, abdominal or combined.

Regardless of chosen surgical approach, the main goal is to close the hernia defect, that can be achieved by reapproximation of the tissues with non-absorbable suture or in poor quality autologous tissues, by using a mesh support (9-11). When large anatomic defects are present or when the use of synthetic mesh implant is contraindicated, autologous fascia lata flaps or myocutaneous rotational flaps can be used (12). Whether the ideal material is an autologous graft or flap, synthetic mesh, or a bioprosthetic mesh has not been well established.

In our case, due to the urinary diversion, the perineal approach was chosen. Furthermore, since the patient had no previous radiotherapy, a polypropylene mesh was used in order to ensure a correct and permanent support of the pelvic floor defect, thus diminishing the risk of hernia recurrence.

Although being a rare condition, anterior perineal hernia should be suspected in patients who complain of perineal bulge after extensive abdominoperineal surgery. To our knowledge, this is the first case reported of anterior perineal hernia after radical cystectomy and urethrectomy.

INFORMED CONSENT

Informed consent was obtained from the patient for publication of this article and accompanying figures.

CONFLICT OF INTEREST

Brigitte Fatton is consultant for Boston Scientific, Astellas and Allergan. Renaud de Tayrac is consultant for Boston Scientific and has research partnership with Aspide Medical and Coloplast. Other authors declare that they have no conflict of interest.

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Anastomosing hemangioma simulating renal cell carcinoma

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ABSTRACT

The anastomosing hemangioma is a recent described rare variant, which histologically simulates an angiosarcoma and occurs primarily in the genitourinary tract. We present a case of renal anastomosing hemangioma from a radiologic perspective, describing its imaging features and reviewing its presentation and management.

Keywords: Radiology; Kidney; Magnetic Resonance Imaging

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CASE PRESENTATION

A 53-year-old man underwent computed tomography (CT) for renal stone evaluation. His physical examination was otherwise unremarkable. His creatinine level was 1.0mg/dL and his fasting glucose was 91mg/dL. An incidental left renal mass was identified (Figure-1), that was further evaluated with magnetic resonance imaging (MRI).

MRI showed a renal mass with thick septa and progressive enhancement after gadolinium injection. The lesion was interpreted as a complex renal cystic lesion, classified as Bosniak IV (Figures 2-5).

After MRI results, patient underwent videolaparoscopic resection of the lesion, later confirmed to be a renal anastomosing hemangioma by histopathological analysis (Figure-6).

DISCUSSION

Renal vascular tumors are extremely rare, with hemangiomas being the most frequent lesion in this subgroup (1).

The vast majority of renal hemangiomas are smaller than 2cm, asymptomatic and incidentally found on imaging exams. Symptomatic patients may have recurrent episodes of hematuria and abdominal pain (1, 2).

The anastomosing hemangioma is a rare variant, which histologically simulates an angiosarcoma (3). This histological subtype has been recently described as morphological variant of hemangioma that occurs primarily in the genitourinary tract. On non-enhanced CT, they are lobulated lesions, with soft-tissue attenuation. After contrast administration, they appear as

Figure 1 – Corticomedullary phase from the urotomography demonstrates the lesion (arrow) with wall and septa enhancement.

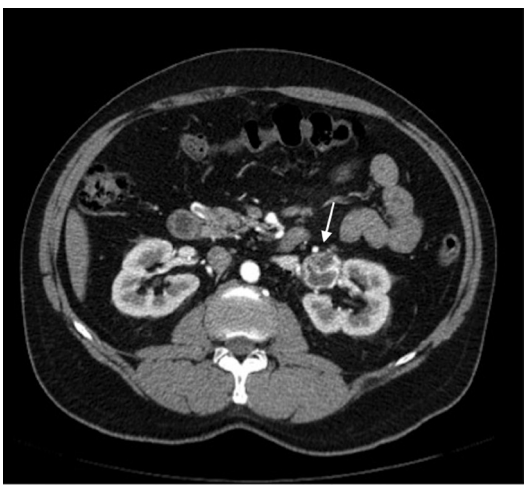


Figure 2 - Axial T2 imaging with fat saturation shows an expansive, exophytic lobulated mass with high signal, (arrow) in the upper pole left kidney.

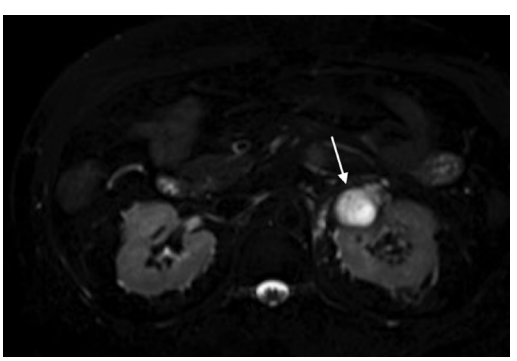


Figure 3 - Coronal T1 pre-contrast imaging – the lesion is hypointense to adjacent renal parenchyma (arrow).

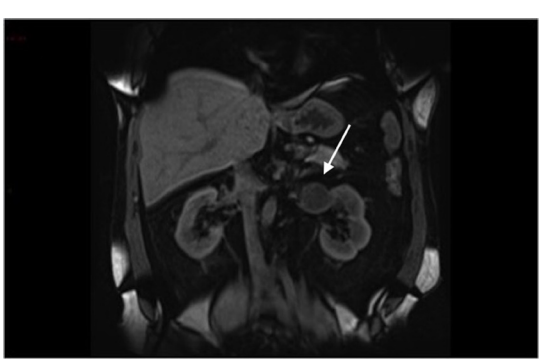


Figure 4 - Coronal T1 post-contrast arterial phase imaging showing peripheral enhancement (arrow).

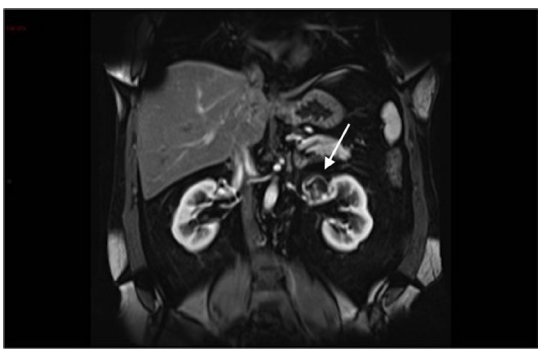


Figure 5 - Coronal T1 late post-contrast phase shows progressive enhancement of the lesion.

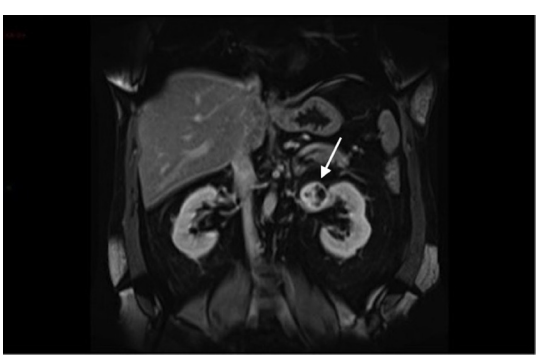
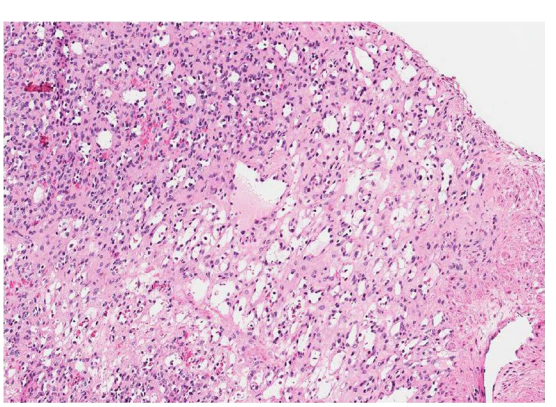


Figure 6 - Histologic sample of the ressected lesion shows anastomosing proliferation of capillary sized vessels, reminiscent of splenic sinusoids and scattered hobnailed endothelial cells, confirming the diagnosis of an anastomosing hemangioma



solid heterogeneous lesions, with intense and progressive enhancement (3).

On MRI, hemangiomas show hyperintensity on T2 and variable degrees of enhancement after contrast administration. Presentations may resemble cystic lesions with solid component, mimicking cystic renal cell carcinoma as the present case (1, 2, 4). When large, these lesions are indistinguishable from malignant lesions such as angiosarcomas and renal cell carcinomas with central necrosis.

Treatment is controversial since preoperative diagnosis is not possible based on imaging exams. When biopsy results are available, it may vary from expectation to partial nephrectomy, embolization and radical nephrectomy, depending on the lesion size, location and presence of symptoms.

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RADIOLOGY PAGE

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A solitary urothelial tumor arising from one of bilateral ureteroceles

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INTRODUCTION

A ureterocele is a congenital defect of the ureter. Based on available autopsy reports, the highest incidence of ureteroceles has been reported as 1 in 500, occurring four to six times more commonly in females than in males. It can occur in up to 95% of females with a duplex collecting system (1, 2).

Ureteroceles in adults usually arise within a single renal system with no or mild obstruction. They may present as recurrent urinary tract infections, flank pain or remain asymptomatic, only to be picked up incidentally via imaging. Stasis and infection may predispose to calculus formation in the ureterocele and upper urinary tract (3).

The association of a ureterocele with a tumor is very uncommon. In this paper, we report a unique case of a tumor arising within one of bilateral ureteroceles.

Case Presentation

A 67-year-old Chinese male presented with painless gross hematuria after sexual intercourse. He was a non-smoker, and had no previous contact with anilines or other chemicals. Urine cytology and serum prostate specific antigen were normal. Computed tomography (CT) urography revealed bilateral simple ureteroceles with the left containing a slightly enhancing soft tissue nodule (Figures 1A and B). Flexible cystoscopy revealed bilateral ureteroceles with no lesion seen. (Figures 2A and B).

Transurethral unroofing of the left ureterocele containing the tumor together with right ureterocele was performed. There was a papillary lesion on the inner surface sparing the proximal end of the ureterocele and the ureteric orifice (Figure-2C). This corresponded to the filling defect that was visualised on CT urography. The right ureteric orifice was normal (Figure-2D). The patient was elected for resection of both ureteroceles. This was to prevent the development of metachronous tumors and complications such as calculi formation and infection, as well as to simplify cystoscopy surveillance.

The pathology laboratory received multiple fragments of tissue, aggregating 1.5x1.5x0.3cm and weighing 0.5g. Histological examination of resected specimen revealed tumor cells displaying round to oval nuclei arranged to form a papillary architecture with fibrovascular cores, without stromal invasion. The tumor cells exhibited mild nuclear atypia and occasional mitoses, and there were no high grade nuclear features seen. These findings were consistent with a low-grade noninvasive papillary urothelial carcinoma (Figures 3A and B). Post-operatively, the patient was given 40mg intra-vesical mitomycin. To date, this patient is recurrent free 3-months post resection. His cystoscopy surveillance schedule will be as for low risk bladder transitional cell carcinoma following the American Urological Association guidelines (4).

Figure 1 - A and B): CT Urography revealed bilateral simple ureteroceles with the left containing a slightly enhancing soft tissue nodule measuring 0.4 x 0.7 x 0.9cm (red arrow).

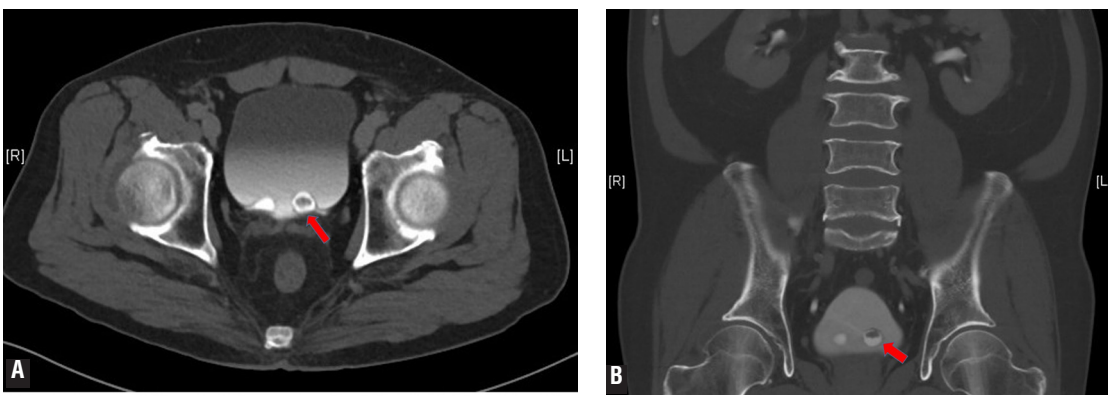
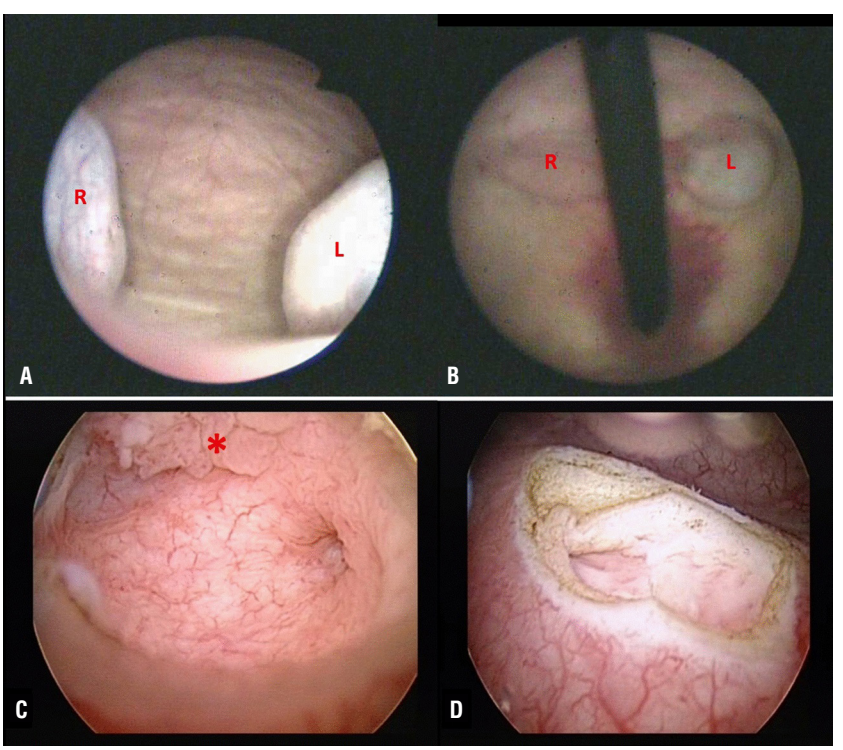


Figure 2 - A and B): Flexible cystoscopy was done and bilateral ureteroceles were seen but no suspicious lesion was seen as the lesion was enclosed within the left ureterocele (R- Right, L- Left). C) There is a papillary lesion on the inner surface sparing the proximal end of the ureterocele and the ureteric orifice (red asterisk). D) The right ureteric orifice was normal.

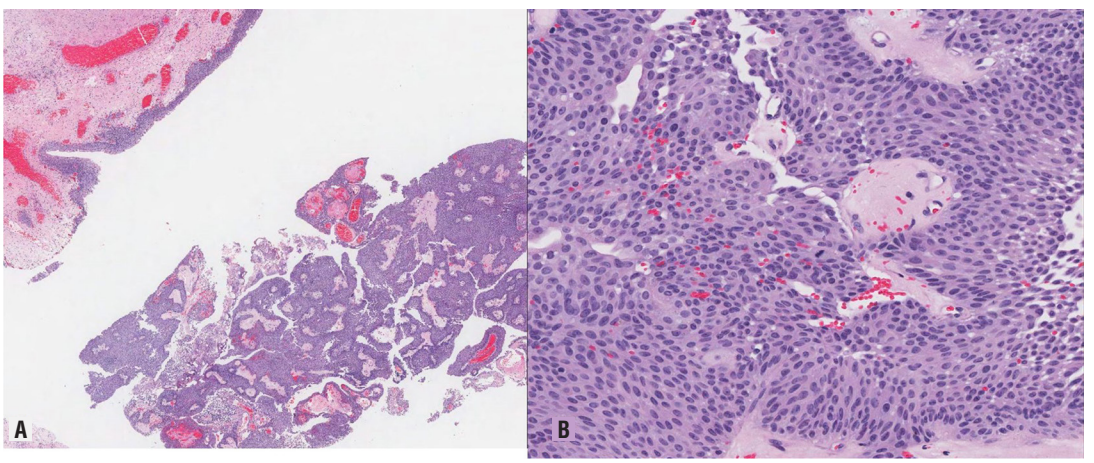


DISCUSSION

A combination of imaging techniques for ureteroceles has been employed in the past till present. Modalities include ultrasonography, intravenous pyelogram (IVP) and CT urography. Classical appearances of ureteroceles based on different imaging modalities are described below.

The sonographic finding of a well-defined cystic intra-vesical mass within the posterior

Figure 3 - A) Photomicrograph showing tumour cells which display round to oval nuclei in a papillary architecture with fibrovascular cores, no stromal invasion seen (H&E x 20). B) The tumour cells exhibit mild nuclear atypia and occasional mitosis, no high grade nuclear features present (H&E x 200).



bladder wall is suggestive of a ureterocele and a classic description is that of a cyst within a cyst. Tumors arising from the ureterocele may bear features of irregular echogenicity without acoustic shadowing (5). However, these may be missed if the patient's bladder is empty or fully distended, or if the ureteroceles were small.

The classic finding on IVP is a round radiopacity in the bladder surrounded by a radiolucent rim. The characteristic appearance of a ureterocele on CT urography is an intra-vesical defect that is radiolucent and globular in nature manifesting as the "cobra-head sign" (5). The CT urogram is useful in visualizing enhancing masses such as tumors. It also excludes extra-vesical disease. While CT urography has gradually replaced the use of IVP in more recent times, each of the three above mentioned techniques demonstrate some utility in the initial imaging of a ureterocele.

Magnetic resonance imaging (MRI) is usually not used, but it should be as effective as IVP and CT urogram for visualization of ureteroceles, especially when MR urography is performed with or without contrast (6). There is limited data on how MRI may be useful for imaging tumors which arise from these ureteroceles.

There are fifteen reports of tumors arising from true ureteroceles [5, 7-12], however this is the first report of transitional cell carcinomas (TCC) in a patient with bilateral ureteroceles. In a true ureterocele TCC represent the majority of tumors that may arise [5, 7, 8, 10-12], although one case of squamous cell carcinomas has been reported (9). This is because the urothelial tissue preserves its capacity to undergone malignant transformation (13). Regarding imaging findings, these 15 reports detail similar findings as described above. Although cystoscopy successfully demonstrated the presence of tumors encroaching on the outer surface of the ureterocele in 3 out of 15 of the cases (5, 10), cystoscopy in our case did not reveal any suspicious features arising from the left ureterocele as the tumor was enclosed within the inner surface of the ureterocele. Hence there was a need for transurethral unroofing of the ureterocele for visual confirmation and resection for clearance and histological diagnosis of the tumor.

This case highlights the need for upper tract imaging as an investigation for gross hematuria regardless of whether urine cytology reflects no evidence of malignancy. Common causes of gross hematuria include urinary tract infections, stones and malignancies. Whilst highly unusual, this patient was found to have bilateral ureteroceles, of which one harbored a tumor. There are no current guidelines on the management of uro-

thelial tumors arising from ureteroceles. However, there is general consensus that when the tumor does not encroach the ureteric orifice or distal ureter, adjuvant therapy and intensity of surveillance can be guided by the histological grade and stage of the tumor (4).

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Robotic assisted laparoscopic augmentation ileocystoplasty

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ABSTRACT

Introduction: Augmentation ileocystoplasty is a common treatment in adults with low capacity bladders due to neurogenic bladder dysfunction. We describe here our technique for robotic assisted laparoscopic augmentation ileocystoplasty in an adult with a low capacity bladder due to neurogenic bladder dysfunction.
Materials and Methods: The patient is a 35 years-old man with neurogenic bladder due to a C6 spinal cord injury in 2004. Cystometrogram shows a maximum capacity of 96cc and Pdet at maximum capacity of 97cmH_2O. He manages his bladder with intermittent catheterization and experiences multiple episodes of incontinence between catheterizations. He experiences severe autonomic dysreflexia symptoms with indwelling urethral catheter. He has previously failed non operative management options of his bladder dysfunction. Our surgical technique utilizes 6 trocars, of note a 12mm assistant trocar is placed 1cm superior to the pubic symphysis, and this trocar is solely used to pass a laparoscopic stapler to facilitate the excision of the ileal segment and the enteric anastomosis. Surgical steps include: development of the space of Retzius/dropping the bladder; opening the bladder from the anterior to posterior bladder neck; excision of a segment of ileum; enteric anastomosis; detubularizing the ileal segment; suturing the ileal segment to the incised bladder edge.
Results: The surgery had no intraoperative complications. Operative time was 286 minutes (4.8 hours). Estimated blood loss was 50cc. Length of hospital stay was 8 days. He did experience a postoperative complication on hospital day 3 of hematemesis, which did not require blood transfusion. Cystometrogram at 22 days post operatively showed a maximum bladder capacity of 165cc with a Pdet at maximum capacity of 10cmH_2O.
Conclusions: As surgeon comfort and experience with robotic assisted surgery grows, robotic surgery can successfully be applied to less frequently performed procedures. In this case we successfully performed a robotic assisted laparoscopic augmentation ileocystoplasty displaying improvement in measurable functional outcomes.

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VIDEO SECTION

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Focal cryotherapy: step by step technique description

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ABSTRACT

Introduction and objective: Focal cryotherapy emerged as an efficient option to treat favorable and localized prostate cancer (PCa). The purpose of this video is to describe the procedure step by step.
Materials and methods: We present the case of a 68 year-old man with localized PCa in the anterior aspect of the prostate.
Results: The procedure is performed under general anesthesia, with the patient in lithotomy position. Briefly, the equipment utilized includes the cryotherapy console coupled with an ultrasound system, argon and helium gas bottles, cryoprobes, temperature probes and an urethral warming catheter. The procedure starts with a real-time trans-rectal prostate ultrasound, which is used to outline the prostate, the urethra and the rectal wall. The cryoprobes are pretested and placed in to the prostate through the perineum, following a grid template, along with the temperature sensors under ultrasound guidance. A cystoscopy confirms the right positioning of the needles and the urethral warming catheter is installed. Thereafter, the freeze sequence with argon gas is started, achieving extremely low temperatures (-40ºC) to induce tumor cell lysis. Sequentially, the thawing cycle is performed using helium gas. This process is repeated one time. Results among several series showed a biochemical disease-free survival between 71-93% at 9-70 month- follow-up, incontinence rates between 0-3.6% and erectile dysfunction between 0-42% (1-5).
Conclusions: Focal cryotherapy is a feasible procedure to treat anterior PCa that may offer minimal morbidity, allowing good cancer control and better functional outcomes when compared to whole-gland treatment.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Robotic assisted laparoscopic excision of a retroperitoneal Ganglioneuroma

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ABSTRACT

Introduction: Ganglioneuromas are rare benign neoplasms of the sympathetic nervous system. We describe the case of an incidentally found ganglioneuroma in a woman. To our knowledge this is the first described case of robotic excision of a retroperitoneal ganglioneuroma.
Case: A 41-year-old female had an incidental retroperitoneal mass found during a routine US. CT scan and MRI showed an 8.3cm homogeneous mass, adjacent to left kidney upper pole, with peripheral contrast enhancement. Metabolic tests were normal. Patient was positioned in a left flank position and five ports were introduced transperitoneally. A 4-arm Da Vinci SI was docked at a 45º angle to the table. Lesion was dissected along with left adrenal gland, beginning at the left renal hilum and proceeding cephalad.
Results: Operating time was 325min and blood loss was 50ml. Patient was discharged after 72hours. There were no post-operative complications. Pathology showed ganglionic cells with neural tissue, and normal adrenal.
Discussion: Ganglioneuromas rare benign tumors originating from neural crest and typically affect young adults. Most frequent locations are posterior mediastinum, retroperitoneum and adrenal gland. As in this case, ganglioneuromas are usually silent, slow growing tumors discovered incidentally or by mass effect. US and CT imaging may suggest the diagnosis while MRI findings can be specific for ganglioneuroma. Percutaneous biopsy is an option. Although benign, usually requires surgical excision for treatment.
Conclusions: Our case shows that a robotic approach is feasible and allows for meticulous and safe dissection of vascular structures, facilitating adequate hemostasis while maintaining oncological principles.

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LETTER TO THE EDITOR

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Re: Insufficient conclusions regarding the association between overactive bladder symptoms and degree of dementia

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To the editor,

Recently, Jung et al. (1) reported a remarkable study on a possible association between the symptoms of overactive bladder (OAB) and the degree of dementia. Considering the paucity of relevant studies on this issue, this study has value. However, several issues could be upgraded by the authors to contribute to a better understanding of the subject.

First, there are several pitfalls in the authors' methodology, including the exclusion criteria used, covariates, and the questionnaire-related data acquisition method. The authors are not addressing whether or not patients were on medications for voiding dysfunction including alpha blockers and desmopressin. In Table-1, other covariates, including body mass index, menopausal state, and history of pelvic surgery, are needed to be added because those covariates could impact lower urinary tract symptoms (LUTS) regardless of age. The data acquisition method also must be documented more clearly because the method of data acquisition itself could affect the results of questionnaires, especially in older people with decreased cognitive functioning (2).

Second, there are several additional pitfalls regarding the reporting of the contents of the study, including not dividing the participants by gender and reporting the results of a 3-consecutive-day voiding diary or the Indevus Urgency Severity Scale (IUSS), which the authors clearly mention in the methods section. Considering the fact that pathophysiology of OAB is known to differ according to sex, covariates including prostate size and menopausal state are potent risk factors for aggravation of LUTS in male and female patients, respectively (3, 4), and the authors did not consider such covariates during data analysis.

Lastly, the authors must consider age during correlation analysis. As the authors state in Table-2, age impacts OAB symptoms quite seriously. Partial correlation after adjustment for age would be a far better analytic strategy.

Although the authors demonstrated remarkable results concerning the association between OAB symptom severity and degree of dementia, it is possible that such results are mere associations due to other potent confounding factors. Other potential covariates must be considered and sound statistical analyses using regression analysis after adjustment for age and other potential covariates must be carried out. Considering that the database of this study cohort is hospital-based, acquisition of information regarding other covariates should be possible, and obtaining that information would yield more scientific research on this issue.

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Re: Preliminary assessment of neck circumference in benign prostatic hyperplasia in patients with metabolic syndrome

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To the editor,

We read with great interest the current study written by Akin and colleagues (1) entitled 'Preliminary assessment of Neck Circumference in Benign Prostatic Hyperplasia in patients with Metabolic Syndrome'. BPH is one of the most common diseases in aging men and despite intense research the exact etiopathogenesis is still under debate. Age and androgen stimuli are the well-known factors for prostate enlargement but multiple partially overlapping and complementary systems (nerve, endocrine, immune, and vascular) as well as local factors are also likely to be involved (2). Scientific interest in the association between anthropometric measurements and prostate hyperplasia has mainly been focused on height, weight and measures of weight adjusted for height, such as body mass index (BMI) with less interest in waist circumference and its ratio to hip circumference. Although published epidemiological data demonstrate that obesity may increase the risks of BPH and LUTS, the quantitative evidence to certify this association is still lacking. Firstly, we congratulate the authors for their great effort in carrying out a study that provides some quantitative results on the potential association of the relatively little used anthropometric measurement, neck circumference, with BPH parameters. Nevertheless, there are some concerns that should be addressed and need further discussion. Contrary to many studies (3-5), the baseline parameters including IPSS, Q max value, and prostate volume were comparable between the two groups (with MtS vs. without MtS) in the current paper. According to the present study, although the baseline BPH parameters did not significantly differ, the patients with MetS had decreased benefit from alpha-blockade drugs. Being prospective, one of the strong attributes of the present study, these results are valuable but the statistical analysis could be misleading as few patients were included, so they should be tested with more data before being used in clinical applications.

We should also address some potential considerations: It is unclear whether waist circumference, BMI, neck circumference or waist-to-hip ratio constitute the best anthropometric parameters for correlating BPH parameters with central obesity. Additionally, these are only measurement tools indirectly suggestive of general body composition or central obesity and their accuracy can easily be affected by ethnical and racial changes. Thus, the outcomes from this study that comprised only Turkish men should not be generalized to those of other races or ethnicities if the effects of the disease processes that lead to the development of LUTS and BPH differ among these groups.

Consequently, this study provides important preliminary results for the potential unfavorable effect of metabolic syndrome in BPH patients treated with alpha blockade drugs. It is obvious that the clinical significance of these results should be tested with further well-designed studies including a larger cohort.

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LETTER TO THE EDITOR

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Re: Assessment of sexual functions in partners of women with complaints of urinary incontinence

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To the editor,

We have read the article by Keles et. al. (1) which was an interesting study evaluating the sexual function of partners of women with complaints of urinary incontinence (UI). In this study, they tried to assess the sexual function in men with female partners suffering stress or urge UI by International Index of Erectile Function (IIEF). They showed that erectile function in the partners of women with UI may be adversely affected by the UI of their partners.

Multifactorial nature of sexuality should be considered during the evaluation of the sexual function of men and women. The factors affecting male sexual dysfunction are depression, anxiety, stress, other mental health problems and physical causes including diabetes, obesity, metabolic syndrome, cardiovascular diseases, hypertension, treatments for prostate cancer, benign prostate hyperplasia, neurological diseases, hypogonadism, smoking, and pelvic surgeries (2). Although this study did not evaluate the sexual function of women, the UI has a negative impact of sexual function of the women (3). A significant correlation between female sexual function and male erectile function has been reported, based on scores from the Female Sexual Function Index (FSFI) and IIEF (4). In addition to these factors, several andrologic studies suggested that total testosterone plays an imperative role in erectile physiology in humans and its deficiency causes ED. The recent EMAS study found that total testosterone is significantly associated with ED (5).

Thus, we consider that these factors for male dysfunction, as mentioned above, are limitations of this study, because the authors did not evaluate these factors and female sexual function and they aimed to reach a conclusion that UI in women have adverse effect on male sexual function. In addition, the authors did not report the hormonal status of male partners and if they use were using any medical treatment including hormones, and phosphodiesterase inhibitors, because these medications can affect sexual function. As a result, we claim that these factors should be indicated as a limitation to strengthen the outcomes of the study.

CONFLICT OF INTEREST

None declared.

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LETTER TO THE EDITOR

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Re: Persistent Mullerian Duct Syndrome: a rare entity with a rare presentation in need of multidisciplinary management

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To the editor,

We would like to make some comments about the article "Persistent mullerian duct syndrome: a rare entity with a rare presentation in need of multidisciplinary management" (1).

The authors report a DSD case diagnosed as PMDS and review some clinical aspects of this exceedingly rare syndrome, but some unclear aspects are notable. The patient described seems to be a case of ambiguous genitalia (proximal hypospadias and bilateral cryptorchidism), classified as 46,XY DSD. No gonadal biopsy was done and only the right gonad was found/described. Anti-mullerian hormone dosages are not available.

In most PMDS cases the patient presents normal testes or testicles only secondarily affected by cryptorchidism. Primary testicular failure, as seen in this patient, has never been previously described. To the best of our knowledge no PMDS cases associated to streak gonads, dysplastic gonads or absent gonads have been described till this moment, despite anatomically complicated cases of cryptorchidism being common, including crossed testicular ectopy.

Also, in PMDS the external genitalia is of normal male (see Table-1). The only known exception to this moment is the patient described in reference 12, but in his case two normal cryptorchidic "peeping" testes were found.

From our point of view other DSD diagnoses are still possible, especially mixed gonadal dysgenesis, that may associate to a variety of karyotypes. Abnormal/absent gonads, primary and precocious testicular failure and the absence of a Fallopian tube at the left side are also compatible with this alternative diagnosis (in PMDS cases the uterus is anatomically normal, despite being atrophic).

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LETTER TO THE EDITOR

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REPLY BY THE AUTHORS: Re: Persistent Mullerian Duct Syndrome: a rare entity with a rare presentation in need of multidisciplinary management

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To the editor,

Dr. de Jesus in his elegant commentary on our recent published article in the Int Braz J Urol (1) dwelled on the diagnosis challenges about patients with disorders of sexual differentiation (DSD) (2). Indeed, we appreciate and agree with his comments that given the rarity of this condition the differential diagnosis between Persistent Mullerian Duct Syndrome (PMDS) and other DSD, including mixed gonadal dysgenesis (MGD), represents a challenge for clinicians (3). In particular, these patients usually present for evaluation at later stages of sexual development, and a comprehensive clinical and laboratory evaluation is not always possible, as discussed below. Notably, as reasoned in our paper (2) and highlighted here, a multi-disciplinary team approach is essential to handle such conditions.

The diagnosis of PMSD in our patient was based on the presence of Müllerian duct derivatives - a fallopian tube, a bicornuate uterus with a more prominent right horn, and an enlarged cervix possibly hydrocolpos -with the presence of normal 46,XY karyotyping. The patient's mother provided the history of undescended testes with an ambiguity of genitalia, with no clear documentation, as the medical records are no longer available for perusal. However, there was no substantial evidence to support the ambiguity of genitalia. As for the authors' remark that PMSD patients do not exhibit testicular failure, Claranette et al. suggested that such patients can be classified into three subgroups according to the position of reproductive organs: (i) Intra-abdominal Müllerian structures and testes in a position simulating that of the ovaries, (ii) one testis in a hernial sac or scrotum together with Müllerian, and (iii) both testes located in the same hernia sac along with the Fallopian tubes and uterus (4, 5). During laparoscopy, we identified two structures in the left pelvic region, one of which could represent an abdominal testis. We therefore believe the finding of a streak gonad might be compatible with the diagnosis of PMSD.

The typical features of PMDS include undescended testes and the presence of a small, underdeveloped uterus in an XY infant or adult, which both were found in our patient. This condition is usually caused by a deficiency of fetal anti-Müllerian hormone (AMH) effect due to mutations in the gene for AMH or the anti-Müllerian hormone receptor, however, may also be seen as a result of insensitivity to AMH of the target organ (6). Unfortunately, we were not able to investigate the AMH levels as the patient defaulted follow-up and treatment. The patient only recently sought treatment again for the problem of haematuria.

Although mixed gonadal dysgenesis (MGD) is similar in some ways to PMDS, the conditions can be distinguished histologically and by karyotyping. In our case, the chromosomal analysis was clearly 46,XY with no mosaicism. Unfortunately, a gonadal biopsy was not made as the diagnosis with karyotyping was thought to be sufficient in this case.

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