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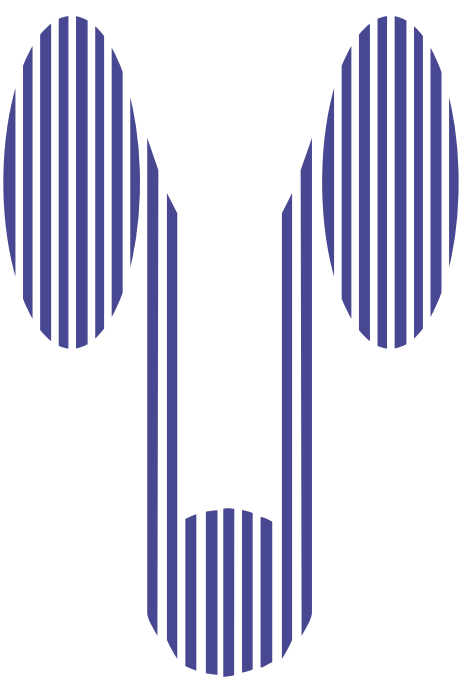

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EDITOR'S COMMENT

Ileal Neobladder for Women with Interstitial Cystitis

The July - August 2007 issue of the International Braz J Urol presents interesting contributions from different countries, and as usual, the editor's comment highlights some papers.

Doctor Kochakarn and co-workers, from Mahidol University, Bangkok, Thailand, reported on page 486 their experience with cystectomy and ileal neobladder for women suffering from interstitial cystitis (IC). The authors studied 35 patients with the mean age of 45.9 ± 4.4 years. All of them had experience of suprapubic pain with irritative voiding symptom and were diagnosed as having IC based on NIDDK criteria for at least 2 years. Conservative treatments had failed to relieve their symptoms; therefore, all of them agreed to undergo a bladder removal. All patients reached good treatment outcome with regard to both diurnal and nocturnal urinary control without any pain. Quality of life using SF-36 questionnaire showed significant improvement of both physical health and mental health. Spontaneous voiding with minimal residual urine was found in 33 cases (94.3%), and 2 cases (5.7%) had spontaneous voiding with residual urine and lived with clean intermittent catheterization. Twelve out of 30 cases with sexually active ability had a mild degree of dyspareunia but without disturbance to sexual life. The authors concluded that bladder substitution by ileal neobladder for women who suffer from IC could be a satisfactory option after failure of conservative treatment. Doctor Philip M. Hanno, from University of Pennsylvania, Philadelphia, USA, provided editorial comment on this paper.

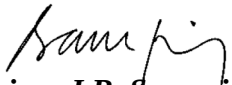
Doctor Paez and colleagues, from Fuenlabrada Hospital and other three centers at Madrid, Spain, assessed on page 502 the patient satisfaction and functional results at long term follow-up after surgical correction for Peyronie's disease (PD) and congenital penile curvature (CPC) with the technique of tunical plication. One hundred and two men operated for PD (n = 76) or CPC (n = 26) in four different departments of urology in public hospitals agreed to answer a six-question telephone questionnaire about treatment satisfaction. Tunica albuginea plication procedures represented the standard surgical approach. Significant differences between patients with CPC and PD were noticed in the prevalence of postoperative penile deformity, sensory changes, erectile dysfunction and ability to complete vaginal intromission, PD patients always showing a more pessimistic view. The authors concluded that long-term outcome after surgical correction for PD and CPC with the technique of tunical plication can be poor. Probably patient expectations are above the real performance of surgical techniques and therefore, preoperative information should be more exhaustive. Doctor Kimihiko Moriya, from Hokkaido University, Sapporo, Japan, Doctor Geng-Long Hsu, from Taiwan Adventist Hospital, Taipei, Taiwan, China and Doctor T. John, from Wayne State University, Detroit, MI, USA, well-known experts in the field, provided important editorial comments on this paper.

Doctor Foinquinos and co-workers, from State University of Pernambuco and Federal University of Sao Paulo, Brazil, developed an additional reconstructive option using tunica vaginalis grafts placed dorsally, for the treatment of anterior urethral strictures (page 523). A total of 11 patients with anterior urethral

strictures were treated with a tunica vaginalis graft urethroplasty. The authors described their surgical technique and presented that with a follow-up ranging from 7 weeks to 5 months, all patients were voiding well, showing a uroflowmetry greater 14 mL per second. It was concluded that this initial experience indicates that tunica vaginalis dorsal graft urethroplasty may be considered within the reconstructive armamentarium of genitourinary surgeons. Doctor Deepak Dubey, from Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India and Doctors Guido Barbagli & Massimo Lazzeri, from the Center for Reconstructive Urethral Surgery, Arezzo, Italy, experts in the field, provided balance and interesting comments on this paper.

Doctor El-Tantawy and colleagues, from National Organization for Drug Control and Research, Cairo, Egypt, investigated on page 554 the effect of Tribulus alatus extracts on free serum testosterone in male rats. All tested extracts showed significant increase in the level of free serum testosterone when compared to that of corresponding control, and, therefore, it was concluded that Tribulus alatus extract appears to possess aphrodisiac activity due to its androgen increasing property. Doctor Q. T. Yang, from Shantou University Medical College, Shantou, China and Doctor Nina Atanassova, from Institute of Experimental Morphology & Anthropology, Sofia, Bulgaria, provided editorial comments on this paper.

Doctor Kaygisiz and collaborators, from Ankara Numune Education and Research Hospital, Ankara, Turkey, investigated on page 470 predictor factors for prostate biopsy and probe insertion pain. Seventy-one patients who were undergoing prostate biopsy without anesthesia were included in the study retrospectively. Pain had been assessed with visual analogue scale (VAS 0-10). Digital rectal examination (DRE) pain was analyzed for biopsy and probe insertion pain. The authors found that DRE pain was related to both probe pain and biopsy pain, and concluded that although the level of pain during DRE determines patients in need of local anesthesia, since the number of patients with moderate-severe pain is rather big, it seems efficient in determining the patients in need of additional anesthesia due to probe pain. Doctor Joe Philip, from Leighton Hospital, Crewe, United Kingdom, and Doctor Mark S. Soloway, from University of Miami, Florida, USA, provided editorial comments.



Francisco J.B. Sampaio, M.D.
Editor-in-Chief

Review Article
International Braz J Urol Vol. 33 (4): 461-469, July - August, 2007

Surgical Treatment of Anterior Urethral Stricture Diseases: Brief Overview

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ABSTRACT

We performed an up-to-date review of the surgical techniques suggested for the treatment of anterior urethral strictures. References for this review were identified by searching PubMed and MEDLINE using the search terms "urethral stricture" or "urethroplasty" from 1995 to 2006. Descriptive statistics of the articles were provided. Meta-analyses or other multivariate designs were not employed. Out of 327 articles, 50 (15%) were determined to be germane to this review. Eight abstracts were referenced as the authors of this review attended the meetings where the abstract results were presented, thus it was possible to collect additional information on such abstracts. Urethrotomy continues to be the most commonly used technique, but it does have a high failure rate and many patients progress to surgical repair. Buccal mucosa has become the most popular substitute material in urethroplasty; however, the skin appears to have a longer follow-up. Free grafts have been making a comeback, with fewer surgeons using genital flaps. Short bulbar strictures are amenable using primary anastomosis, with a high success rate. Longer strictures are repaired using ventral or dorsal graft urethroplasty, with the same success rate. New tools such as fibrin glue or engineered material will become a standard in future treatment. In reconstructive urethral surgery, the superiority of one approach over another is not yet clearly defined. The surgeon must be competent in the use of various techniques to deal with any condition of the urethra presented at the time of surgery.

***Key words**: urethral stricture; surgical procedures, operative; graft; tissue engineering*
Int Braz J Urol. 2007; 33: 461-9

INTRODUCTION

Urethral strictures are a frequent source of lower urinary tract disorders in adults, such as urinary tract infection, acute urinary retention, high-pressure voiding leading to secondary bladder thickening and irritability and even bladder diverticula or perineal fistulas and abscess (1). Blunt perineal trauma, urethral catheterization or instrumentation, lichen sclerosus and sexually transmitted diseases are the most frequent causes of strictures (1). However, most causes of urethral strictures remain unknown, but they are probably the result of a remote unrecognized perineal trauma experienced during childhood (1).

Surgical treatment of urethral stricture diseases is a continually evolving process, and currently there is renewed controversy over the best means of reconstructing the urethra. Moreover, the superiority of one technique over another has not yet been clearly defined. Urologists must be familiar with the use of numerous and various surgical techniques to deal with any condition of the urethra during surgery. This re-

view aims to provide an update on the reconstructive techniques currently used to repair anterior urethral strictures and offer some insight on possible future strategies.

MATERIALS AND METHODS

Inclusion criteria for the literature review were operationalized before the initial literature search. The search incorporated original and review articles presenting data regarding all aspects of the surgical repair of anterior urethral strictures. The exclusion criteria included articles presenting opinions rather then evidence and articles that were not published in peer reviewed journals. The articles reviewed were limited to English language publications. A review of the world literature was performed via the MEDLINE/ PubMed databases using the search terms "urethral stricture" or "urethroplasty" from January 1995 through August 2006. The bibliographies of all relevant articles were reviewed for applicable citations that might not have appeared upon the database search. The authors independently reviewed each abstract identified by the database searches and relevance to the topic was ascertained.

RESULTS

A total of 327 articles were identified in our search and 50 of these (15%) were determined to be germane to the topic under review. The bibliographies of all 50 articles were scanned and references that were not hits in our initial database search were also reviewed. Four articles were included from the bibliography search in the literature review. Eight abstracts were referenced as the authors of this review were in attendance at the meetings where the abstract results were presented, thus it was possible to collect additional information on the presented abstracts. A meta-analysis or other multivariate designs could not be correctly employed due to the heterogeneous nature of the data in the articles reviewed. Reasons for this are that standard diagnosis, success and complication criteria vary among authors. Therefore, only descriptive statistics of the articles are provided in this review.

TREATMENT OF URETHRAL STRICTURES

Peterson and Webster suggested that treatment for urethral strictures include numerous options, such as dilation, urethrotomy, stent and reconstructive surgical techniques and emphasized that no one technique is appropriate for all stricture diseases (2).

Internal Urethrotomy vs. Open Urethroplasty

Dilation and urethrotomy continue to be the most commonly used techniques, but they have a high failure rate with recurrence in 47.6% of patients and many patients progress to surgical repair (2,3). Moreover, repeated dilation or urethrotomy exacerbates scar formation, thus adding to stricture length and predisposing to a more difficult definitive open repair and a lower success rate (1-3). Persistent use of dilation or urethrotomy for the treatment of urethral strictures may be the result of unfamiliarity with literature and inexperience with urethroplasty surgery (3). Surprisingly, a recent survey of stricture management involving 424 urologists from the USA showed that only 21% to 29% indicated that they would refer a patient with a recurrent urethral stricture to another urologist for urethroplasty, while 34% elected to continue endoscopic management despite predictable failure. Seventy-four percent of urologists believed that literature supports the use of urethroplasty only after repeated endoscopic failure (4). Greenwell et al. recently developed an algorithm for the management of urethral strictures based on cost-effectiveness and concluded that repeat urethrotomy or dilation are neither clinically effective nor cost-effective and can no longer be justified (3). Wright et al. determined, using decision analysis, the cost-effectiveness of different management strategies for short bulbar urethral strictures and concluded that the most cost-effective strategy for the management of short bulbar urethral stricture is to reserve urethroplasty for patients in whom a single endoscopic attempt has failed (5). Instead, for strictures for which the success rate of an urethrotomy is expected to be less than 35%, applying urethroplasty as the primary therapy is cost-effective (5).

Open urethroplasty is regarded as the gold standard treatment for urethral strictures (1,2). Nevertheless, urethroplasty is not a routine operation and a lack of the necessary skills should prompt a referral to a specialist skilled in urethroplasty (3). Unfortunately, most urologists have little experience with urethroplasty surgery and erroneously believe that the use of these complex reconstructive urethral procedures are justified only in young, healthy patients, since these treatments are associated to a high rate of complications requiring longer patient hospitalization and higher hospital costs. Internal urethrotomy is a less-invasive outpatient procedure, providing the obvious benefits of surgeon/patient convenience and cost control. Recent literature, however, shows that urethroplasty can also be considered a "minimally" invasive technique and a more efficient therapy than internal urethrotomy. Santucci et al. reviewed 70 open urethroplasties performed on males older than 64 years old and concluded that urethroplasty should not be withheld solely on the basis of age, as older men tolerate urethroplasty well and complication rates are low (6). MacDonald et al. presented the review of 54 patients who underwent anterior urethroplasty to evaluate the safety and feasibility of decreasing the impact of urethroplasty by minimizing operative time, maximizing adjuvant pain therapy and using anesthetic agents that decrease the incidence and severity of side effects (7). The authors showed that urethroplasty could be safely performed with less than 24-hours hospital stay and concluded that anterior urethroplasty performed as a same-day procedure appeared to be safe and well tolerated, without compromising functional outcome, and it costs 40% to 60% less than the same procedure performed on in-patients. Finally, Rourke & Jordan suggested that treatment for a 2 cm bulbar urethral stricture with primary open urethroplasty is less costly than endoscopic treatment with internal urethrotomy (8).

Urethral Tissue Transferred Material: Penile Skin vs. Buccal Mucosa

Buccal mucosa has become the most popular substitute material in the treatment of urethral strictures, as it is readily available and easily harvested from the cheek or lip, allowing for a concealed donor site scar and low oral morbidity (9). Buccal mucosa is hairless, has a thick elastin-rich epithelium, which makes it tough yet easy to handle and a thin and highly vascular lamina propria, which facilitates inosculation and imbibition (9). Moreover, the use of buccal mucosa avoids cosmetic disadvantages and consequences caused by the use of genital skin. Prior to the use of buccal mucosa, penile skin was the preferred tissue transferred material used for urethroplasty. The question remains: is buccal mucosa really superior to penile skin? Alsikafi et al. in an effort to answer whether buccal mucosa is really the best, compared the outcome of 95 buccal mucosa urethroplasty and 24 penile skin graft urethroplasties (10). The overall success rate of penile skin urethroplasty was 84% (mean follow-up 201 months), while the success rate of buccal urethroplasty was 87% (mean follow-up 48 months) and no statistically significant difference was found between the two groups (10). Gozzi et al. retrospectively evaluated the results on 194 patients with glanular (20.6%), penile (16%), bulbar (20.1%), membranous (29.4%) and post-hypospadias repair (13.9%) urethral strictures (11). All patients were treated by dorsal onlay techniques with genital and extra-genital skin grafts and reported excellent results with a 2% restenosis rate and a mean follow-up of 31 months (11). We retrospectively reviewed the outcome of 95 patients who underwent bulbar substitution urethroplasty, 45 receiving penile skin grafts (12) and 50 buccal mucosa grafts (13). Thirty-three of the 45 penile skin urethroplasties were successful (73%) and 12 (27%) were failures (12). Forty-two of the 50 buccal mucosal urethroplasty were successful (84%) and 8 (16%) were failures (13). The skin graft urethroplasty showed a higher failure rate (27%) compared to the buccal mucosa graft (16%), with the penile skin grafts having a longer follow-up (mean 71 months) compared to the buccal mucosa grafts (mean 42 months) (12,13). In conclusion, skin and buccal mucosa are both excellent materials for urethroplasty with a comparable success rate, though the use of skin appears to have a longer follow-up than buccal mucosa.

Penile Urethral Reconstruction

Basically, the surgical technique for penile urethral reconstruction is selected according to the etiology of the urethral stricture disease and must also

be based on the proper anatomic characteristics of the penile tissues to ensure flap or graft take and survival (14). Furthermore, sexual function can be placed at risk by any surgery on the genitalia and dissection must avoid interference with the neurovascular supply to the penis. The use of flaps or grafts, in single or multi-stage repair, should not compromise penile length or cause penile chordee, and certainly should not untowardly affect penile appearance. Penile urethroplasty could be a simple procedure in patients with a normal penis, but it can be a difficult challenge in men with strictures associated to genital lichen sclerosus or following failed hypospadias repair. Regardless, penile urethroplasty, be it a single or multi-stage repair, is intrinsically prone to complications such as edema, hematoma or infection, which in turn can lead to secondary complications, such as fistula or tissue necrosis, and it is the procedure most likely to produce alterations in sexual functions.

Flaps vs. Grafts

The controversy over the best means of reconstructing the penile urethra has been renewed and in recent years, free grafts have been making a comeback, with fewer surgeons using genital flaps (15-17). Rarely, has the current literature provided us with prospective studies comparing the grafts with the flaps, making it hard to declare a clear favorite (16). At present, we are uncertain in which patients the use of a pedicled flap will have better chances of success than a free graft, as the thin penile corpus spongiosum and the dartos fascia do not ensure sufficient graft support in all patients (15,16). Identification and use of criteria to more carefully select the appropriate procedure for the patient might clarify whether the use of a graft is preferable to the use of a flap according to the characteristics of the vascular and mechanical tissues used to support the original urethral plate. Different authors recently described a new one-stage penile urethroplasty that involves a deeply longitudinal midline incision of the urethral plate and the suturing of buccal mucosal tissue as an inlay graft into the bed obtained within the urethral plate (15,18,19). Unfortunately, the long-term results in a large series of patients treated with this new one-stage penile graft urethroplasty are, at the moment, not available in the current literature.

One-Stage vs. Two-Stage Repair

Penile urethroplasty should be performed in a single-stage whenever possible to avoid patient discomfort and disability that can be caused by the use of multi-stage procedures. In patients with urethral strictures caused by trauma, infection, instrumentation or catheter, the penis is generally normal and the penile skin, urethral plate, corpus spongiosum and dartos fascia are suitable for urethral reconstruction. In such cases, one-stage urethroplasty is the surgery of choice. Instead, in patients who have experienced failed hypospadias repair or in whom the penile skin, urethral plate and dartos fascia are not suitable for urethral reconstruction, two-staged urethroplasty is recommended (20,21). In addition, in patients suffering from genital lichen sclerosus, the use of buccal mucosa is mandatory since, as a skin disease, any skin that would be used as graft material is already or may become diseased (22,23). When used in a multistage procedure, the buccal mucosa or skin grafts do not heal in the same way in all patients and numerous revisions of the graft-bed may be necessary to obtain a satisfactory mucosal bed before the urethral closure (21). Unfortunately, these repeated surgical revisions of the scars could have a tremendous psychological impact on the patient (21).

Bulbar Urethral Reconstruction

Basically, the surgical technique used in the repair of the bulbar urethral stricture is selected according to stricture length (14). Strictures ranging from 1 to 2 cm are treated by using end-to-end anastomosis; strictures ranging from 2 to 3 cm are managed using augmented roof-strip anastomosis; strictures longer than 3 cm are treated using substitution urethroplasty. Finally, in patients with strictures associated to local adverse conditions (fistula, abscess, tumor, stent, or previous failed urethroplasty) multi-stage urethroplasty is mandatory.

End-to-End Anastomosis

Short strictures in the bulbar urethra are generally amenable to complete excision with primary anastomosis via a perineal incision, affording a high success rate of 95%, as reported by Santucci et al. (24). The surgical technique of end-to-end anastomosis was recently illustrated step by step by Mundy

with the use of nicely executed color drawings and excellent commentary (25). Recently, the stricture length ideal for the application of end-to-end anastomosis has become a contentious issue. Guralnick & Webster suggested that end-to-end anastomosis is appropriate only for a bulbar stricture of 1 cm or less as excision of a 1 cm urethral segment with opposing 1 cm proximal and distal spatulation results in a 2 cm urethral shortening, which may be adequately accommodated by the elasticity of the mobilized bulbar urethra without chordee (26). The authors emphasized that excision of a longer urethral segment risks penile shortening or chordee, even if lengthening maneuvers are applied (26). On the contrary, Morey & Kizer reported 22 patients with proximal bulbar urethral strictures greater that 2.5 cm long (range 2.6 to 5 cm) that were managed using an extended anastomotic approach, suggesting that the possibility of reconstructing the urethra is proportional to the length and elasticity of the distal urethral segment (27). They reported a 91% success rate with a mean follow-up of 22.1 months, and with no increase in erectile complaints compared to shorter strictures (27). Finally, Al-Qudah & Santucci suggested that the use of end-to-end anastomosis is also controversial in the treatment of short and medium length urethral strictures (range 0.5 to 3.0 cm) (28). They presented 47 short urethral strictures treated with end-to-end anastomosis or buccal mucosal onlay graft urethroplasty and compared early and intermediate outcomes to determine which was the best technique (28). The recurrence rate was 7% in those patients who underwent end-to-end anastomosis and 0% in patients who underwent buccal mucosal graft urethroplasty. Early and late major complications occurred in 18% of the patients after anastomotic repair, including penile chordee and erectile dysfunction (28). In conclusion, buccal mucosal onlay graft urethroplasty is suggested as the operation of choice even for short urethral strictures (28).

Augmented Roof Strip Anastomosis

In 1998, Iselin and Webster modified our original technique of dorsal onlay urethroplasty (29). In this procedure, the worst section of the stricture is removed and the urethra is re-anastomosed and dorsally augmented with a free graft (29). The surgical technique of augmented roof-strip anastomosis was recently illustrated step by step by Mundy, who also included an excellent commentary (29). In 2004, Delvecchio et al. suggested that the use of augmented roof-strip anastomotic urethroplasty incorporating the graft onlay into the receiving urethral plate is less successful, either because of the inherent deterioration of transferred tissues exposed to urine or to the fact that the onlay is performed in an area of dense spongiofibrosis, generally at the site the stricture disease originated, which is unsuitable for simple onlay grafting (30). These authors proposed always excising this area, followed by direct reanastomosis of the floor strip and onlay of the adjacent "better" stricture, whatever its length (30). The authors showed that this technique had only a 5.2% failure rate in 38 patients, compared with a 9% failure rate in 11 patients who underwent a simple augmented graft urethroplasty without excision of the strictured tract. They concluded that excision of the worst stricture segment avoids a long onlay in a poor urethral bed where failure often occurs at the location of even the smallest stricture caliber (30). Augmented roof strip anastomotic repair may be arranged using ventral or dorsal graft location. In 2005, Abouassaly & Angermeier reported the results of 36 patients undergoing augmented anastomotic repair with ventral onlay grafts and 4 patients undergoing augmented anastomotic repair with dorsal onlay grafts and concluded that ventral or dorsal onlay seems to offer comparable results (31). In 2006, Abouassaly and Angermeier recommended complete excision of the stricture and use of an augmented roof-strip anastomotic repair for strictures that cover a particularly narrow area of 1-2 cm in length (32). Out of 69 patients, 63 were successful (91%) with a mean follow-up of 34 months (32).

Substitution Urethroplasty Using Buccal Mucosal Graft

Buccal mucosal urethroplasty represents the most widespread method for the repair of strictures in the bulbar urethra, due to its highly vascular tissue. Location of the graft on the urethra surface has become a contentious issue (33), dating from the time we described dorsal onlay graft urethroplasty techniques (34). Wessells & Armenakas suggested a list of the technical advantages of ventral onlay urethroplasty: complete circumferential mobilization of the

urethra is not necessary, thus preserving arterial and venous connections to the corpora cavernosa; stricture is easily seen; performance of a urethrotomy allows the lumen to be clearly delineated, thus allowing the surgeon to identify mucosal edges, measure the size of the plate, carry out a watertight anastomosis and, if necessary, excise portion of the stricture and perform dorsal re-anastomosis (35,36).

Success with bulbar buccal mucosal grafts has been high with dorsal (13,33) or ventral graft location (35,36) and the different graft positions have shown no difference in success rate (13,31). Recently, Abouassaly and Angermeier reported the intermediate term results on 100 patients with penile (21%), bulbar (82%) and bulbomembranous (17%) urethral strictures undergoing anterior and posterior buccal mucosal graft urethroplasty using different graft locations (ventral or dorsal) (31). These patients had a final success rate of 92% (mean follow-up 29.5 months) (31). In our experience, the placement of the grafts on the ventral, dorsal or lateral surface of the bulbar urethra provided the same success rates (83% to 85%) and stricture recurrence was uniformly distributed in all patients (13). Recently, we reviewed the patterns of failure following bulbar substitution urethroplasty and investigated the prevalence and location of anastomotic fibrous ring strictures occurring at the apical anastomosis between the graft and urethral plate (37). Out of 107 patients, 85 (80%) were successful and 22 (20%) failured. Failure in 12 patients (11%) involved the entire grafted area and in 10 patients (9%) it involved the anastomotic site (5 distal, 5 proximal). The prevalence and location of these anastomotic ring strictures were uniformly distributed among the three different surgical techniques, using either skin or buccal mucosal grafts (37). Others authors found these anastomotic fibrous ring strictures after substitution onlay urethroplasty (37).

Use of Fibrin Glue in Urethral Reconstruction

Fibrin glue contains fibrinogen, Factor XII, plasmafibronectina and plasminogen dissolved in an aprotin solution (bovine) with an activate thrombin component (human) mixed with a calcium chloride solution. When combined, a dense gelatinous clot is quickly formed at the point of application. Because this fibrin sealant is non-synthetic and, therefore biocompatible with the natural fibrinolytic mechanism, healing is promoted without inflammation and fibrosis formation (38). Several studies emphasized the use of fibrin glue in tissue-engineered procedures (39,40). The use of fibrin sealant is widely published in the literature. Since this sealant is composed of human products, the plasma is screened, tested and thermally treated to ensure viral safety (41).

The application of fibrin glue in surgery mainly relates to its sealing power. It has been shown to be a beneficial adjunct to sutures for closing wounds and promoting healing since it increases tissue plane adherence, accelerates revascularization, reduces hemorrhage, prevents seroma formation and decreases inflammation. The published urological literature has recently contained an increasing number of studies suggesting the use of fibrin glue in reconstructive genital and urethral procedures. In 2002, DeCastro & Morey described the use of fibrin tissue adhesive in genital skin loss due to Fournier's gangrene (42). In 2003, Evans et al. reported the use of fibrin sealant to manage iatrogenic urinary tract injuries, urinary fistulas and surgical complications (38). In 2004, Hick and Morey assessed whether fibrin sealant promotes early catheter removal after urethral reconstruction (43). In 2006, Morris et al. reported the use of fibrin glue in the reconstruction of genital skin loss (44). We recently reported our experience with the use of fibrin glue in bulbar urethral reconstruction in a series of patients who underwent augmented anastomotic repair (45) or dorsal onlay graft urethroplasty (46). However, further comparative studies are necessary to confirm that the use of fibrin glue is really beneficial and to evaluate whether its use reduces restenosis rate following substitution urethroplasty (45,46).

Tissue Engineering Urethroplasty

McAninch recently emphasized that urethral reconstruction can require some of the most challenging techniques in urological surgery and excellent results can be obtained with today's techniques, but it would be a significant advantage to have tissue-engineered products for urethroplasty (47). Carson suggested that urethroplasty represents a model of international progress in urology and the field of urethral stricture

repair has matured greatly with a growing number of single-stage repairs being performed with continued improvements in patient outcome (48). Moreover, the use of tissue engineering to optimize graft material may allow us to combine the most refined surgical techniques with the best graft material, to archive even more reliable results (48).

Ribero-Filho et al. recently presented a new urethroplasty technique that uses human cadaveric urethral acellular matrix (49). After having been harvested from a cadaveric donor the urethral mucosa and spongiosum tissue were enzymatically converted into a urethral acellular matrix graft (49). The graft was applied onto the urethra as a ventral onlay patch. No immunosuppressors were necessary, there were no postoperative complications and the final outcome was satisfactory (49). Could it be that we have reached the limit of this veteran workhorse of substitution urethroplasty? (50). The time has arrived to look beyond buccal mucosa to the development of other forms of substitution material, incorporating tissue engineered materials or stem cells into our quest for the Holy Grail of urethral substitution (50).

CONCLUSION

Reconstructive urethral surgery must better adapt to the characteristics of the disease if the features defining its professionalism are to be strengthened: control over setting standards, improvement of minimally invasive procedures, research and translation of the basic scientific results into daily clinical practice, and imposing the responsibility for organizing, appraising and maintaining quality patient care.

CONFLICT OF INTEREST

None declared.

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Can Pain During Digital Rectal Examination Help us to Decide the Necessity and the Method of Anesthesia for Transrectal Ultrasound Guided Prostate Needle Biopsy?

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ABSTRACT

Objective: Transrectal ultrasound (TRUS) guided prostate biopsy is well tolerated by patients but the lack of an effective marker to predict pain prevents us from determining pre-procedurally which patient group needs local anesthesia for biopsy and probe pain. Thus in this study, we investigated predictor factors for prostate biopsy and probe insertion pain.
Materials and Methods: 71 patients who were undergoing prostate biopsy without anesthesia were included in the study retrospectively. Pain had been assessed with visual analogue scale (VAS 0-10). Digital rectal examination (DRE) pain was analyzed for biopsy and probe insertion pain.
Results: DRE pain was related to both probe pain and biopsy pain.
Conclusion: Although level of pain during DRE determines patients in need of local anesthesia, since the number of patients with moderate-severe pain is rather big, it seems efficient in determining the patients in need of additional anesthesia due to probe pain.

***Key words**: prostate biopsy; pain; predictive factors; digital rectal examination*
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INTRODUCTION

Transrectal ultrasound (TRUS) guided needle biopsy is a standard method used in the diagnosis of prostate cancer. Generally, only 15 to 25% of the patients feel severe pain during this procedure applied in outpatient clinic conditions (1-4). Also, lack of an effective marker for the prediction of pain prevents us from determining pre-procedurally which patient group needs local anesthesia (3).

The pain felt during biopsy has been attributed to probe insertion and needle punctures into the prostate. Twenty seven percent of the patients felt pain due to probe insertion as bad as or worse than needle biopsies themselves in literature (5). Therefore, prevention of probe pain together with needle pain is required in many patients. However, since the periprostatic nerve blockade is ineffective on probe insertion pain (6), the determination of patients in need of additional anesthesia becomes important. Unfortunately, there is no effective marker in literature for predicting in which patients' severe probe insertion pain will occur.

Pain score during digital rectal examination (DRE) can be used in determining rectal sensitivity and pain sensitivity. While DRE increases the

magnitude of pain and unpleasantness due to rectal volume and pressure (7), we expected more rectal pain with probe insertion than with digital rectal examination. In addition, since the decision for prostate biopsy is made based on DRE, performing a query during DRE to predict the biopsy pain does not cause extra morbidity.

In this study, we evaluated correlation between probe, biopsy pain to digital rectal examination pain. Furthermore, we investigated the predictive value of the pain during DRE to determine patients in need of additional anesthesia due to probe insertion pain.

MATERIALS AND METHODS

This retrospective study was designed using our 71 patients who were undergoing prostate biopsy without anesthesia because of abnormal DRE or > 4 ng/mL PSA level. The same doctor performed digital rectal examination before the biopsy with the accompaniment of TRUS as the standard, and pain score was evaluated with visual analogue scale (VAS 0-10).

The experienced urologist evaluated with TRUS, and at least six core biopsies were taken simultaneously. It was first biopsy for all patients. A Hitachi EUB-400 ultrasonography device and 6.5 MHz transrectal probe were used in TRUS. The biopsy procedure was performed with the patient lying in left lateral decubitus position. Pain was assessed with VAS for probe and biopsy. Antibiotics prophylaxis was performed with ciprofloxacin 500 mg twice a day for 5 days starting from the day before the biopsy. After the biopsy, patients were asked whether they would accept the biopsy under the same conditions or not.

All statistical evaluations were done by SSPS 10.0 package program. All the data are given as mean ± standard deviation. Spearman correlation was used to show the relation of pain with parameters. We used the chi square test and Fischer's Exact Test, student-t test for parameter's analysis. In our statistics $p < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics are summarized in Table-1. Prostate cancer was determined in 10 patients (14.8%). Pain was moderate-severe (VAS > 4) for 23 patients (32.4%) at probe insertion and 41 patients (57.75%) at prostate needle biopsy. Because of severe pain at biopsy, we paused it for 9 patients (12.7%). While 96.8% of patients (1/23) without moderate-severe pain (VAS ≤ 4) accepted biopsy under same conditions, 51.2% of the patients (21/41) with moderate-severe pain stated that they would not accept repeat biopsy without additional anesthesia. Complications requiring hospitalization developed in none of the patients.

Digital rectal examination pain has correlation with probe and biopsy pain ($p < 0.001$). While mean VAS value was 2.46 ± 1.7 for probe insertion and 3.67 ± 2.17 for biopsy when DRE VAS value was

Table 1 – *Characteristics of 71 patients.*

	Mean ± SD	Median	Range
Age	65.9 ± 7.64	67	42 - 84
Volume	53.15 ± 24.67	47	21 - 32
Total PSA	13.9 ± 13.29	9.15	1.66 - 68.6
PSA density	0.31 ± 0.19	0.19	0.05 - 2.77
VAS DRE	2.59 ± 1.84	2	0 - 7
VAS probe	3.66 ± 2.39	3	0 - 9
VAS biopsy	4.96 ± 2.56	5	0 - 10

VAS = visual analogue scale; DRE = digital rectal examination; SD = standard deviation.

less than 3, it was 4.97 ± 2.35 and 6.36 ± 2.2 for DRE VAS value 3 and over. Statistically significant differences were found in DRE pain for probe and biopsy pain ($p < 0.001$).

While moderate-severe biopsy pain was two-fold in patients that DRE pain was greater than 2 as compared to those with DRE pain was 2 or less, moderate-severe probe pain was about four-fold greater (statistically significant, $p < 0.01$), Table-2.

COMMENTS

Local anesthesia during biopsy has been widely used together with developing techniques in recent years. It has not also been very clear which patients should receive local anesthesia. In addition, the periprostatic blockade used widely in biopsy is not useful in preventing the pain arising from probe insertion, and this makes it important to determine the patients in need of local anesthesia for probe insertion (6). Therefore, we investigated the relation of digital rectal examination pain with the pain during biopsy.

Anesthesia is being routinely performed for patients in our clinic during biopsy, since the benefits of needle biopsy accompanied by periprostatic anesthesia has been shown in various placebo-controlled, randomized prospective studies (6,8,9). Therefore, we included in this study patients that previously constituted the control group.

Since 51.2% of the patients with VAS ≥ 5, and 3.2% of the patients with < 5 stated that they would not accept repeat biopsy without additional anesthesia we took the threshold value of VAS for patients requiring additional anesthesia as 5. We found the number of patients in need of anesthesia greater than that found by Bastide et al. in our study (%31-%15) (3). Such fact can be related to different patient groups.

The severe pain level during biopsy in patients who did not receive anesthesia is reported of approximately 20% in literature (1,2). Also, the number of patients with VAS ≥ 5 is controversial in studies on pain scoring. Irani et al. reported 16% before local anesthesia was introduced to clinical use, while Bastide et al. reported this ratio 54% after (1,4). Our study was consistent with the study of Bastide et al.

To the best of our knowledge, we investigated the role of DRE pain in the prediction of biopsy pain for the first time in literature.

It was found that pain during DRE was related to probe insertion and biopsy pain in univariate analysis. While moderate-severe pain in biopsy was 37.8% when DRE VAS value was less than 3, it was 79.4% when it was 3 and over. Being the ratio of moderate-severe pain 57.7% in this study, it reduces the clinical use of DRE pain for the prediction of biopsy pain. More significant results can be obtained from different patient populations. However, according to our results, moderate-severe pain occurs in about 40 % of the patients even when DRE pain is less than 3, therefore, applying local anesthesia to all the patients before biopsy seems to be a good alternative.

Together with this, a more distinctive clinical relationship between DRE and probe insertion pain has been noted. When the DRE VAS value is less than 3, 13.5% of patients feel moderate-severe probe

Table 2 – *Relation between pain on digital rectal examination (DRE) and probe and biopsy.*

	VAS Probe 0-4	**VAS Probe 5-10**	**VAS Biopsy 0-4**	**VAS Biopsy 5-10**	
VAS DRE 0-2	32 (45.1%)	5 (7%)	23 (32.4%)	14 (19.7%)	37
VAS DRE 3-10	16 (22.5%)	18 (25.4%)	7 (23.3%)	27 (38%)	34
	48	23	30	41	71

VAS = visual analogue scale; N% = percentage of the total of patients.

pain, while 52.94% of patients feel moderate-severe pain for values 3 and over. Feeling moderate-severe probe insertion pain of about 4 times for values 3 and over allowed us to determine the patients in need of anesthesia for probe insertion pain.

As a result, the level of pain during DRE appears to be effective in determining the patients in need of additional anesthesia for probe insertion pain, rather than determining patients in need of local anesthesia. Applying pudendal nerve blockade, 40% DMSO with lidocaine intrarectal gel or topical anesthesia with prilocaine-lidocaine cream to prevent probe insertion pain in such patients seems to be a good approach (10-12).

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Kaygisiz et al. have retrospectively analyzed the accuracy of pain on digital rectal examination (DRE) in predicting prostate biopsy / probe introduction pain. They use an 11-point visual analogue pain scale. The retrospective nature of this study is a significant flaw. However, it is a well-written paper.

The use of peri-prostatic nerve block (PPNB) had been introduced as early as 1996 (1) for minimizing prostatic biopsy pain with lignocaine local anesthesia. Many studies have evaluated and conclusively proved the benefit of PPNB (2-4). I dispute the necessity to assess whether patients require anesthesia for prostatic biopsy. The authors do concur that in modern urological practice, most urologists would offer patients some form of analgesia prior to prostatic biopsy. In fact, I think most urologists would be hard pressed to offer patients prostatic biopsy without anesthesia. I feel that most of us do not appreciate the extent of pain that patients have during biopsy.

Recent studies have found that older men had a lower perception of pain on biopsy (5). This could be because they may have a decreased anal tone enabling easier probe introduction and lesser pain perception (6). The authors have not explained the reasons why they think patients with more DRE pain perceive more probe pain.

The authors report of 34% of their study group considering refusing to undergo a repeat biopsy. This is especially poignant as the cancer detection rate is only 18.5%. More than 80% of the patients would have to be considered for a repeat biopsy. Initial analgesia would have made the experience tolerable and a patient population more conducive to urological advice. The authors may need to reassess their biopsy protocol, as the cancer detection rate is low.

This article has raised an important point in identifying a sub-group of patients who are at higher risk of significant procedure pain. These patients should be offered analgesia in addition to the PPNB such as perianal analgesia and maybe even sedation (7).

Overall, the authors have reported on the need for analgesia in prostate biopsy; a subject that I feel may already be a foregone conclusion (8).

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EDITORIAL COMMENT

The authors suggest that the discomfort related to a digital rectal examination (DRE) is an indicator of which men will have more severe pain during transrectal ultrasound (TRUS) probe insertion and thus raise the question as to whether they should have additional analgesia or even sedation in order to minimize the discomfort or pain during the entire procedure. I would certainly agree with the authors that we should strive to minimize pain associated with any procedure we perform. A prostate biopsy session ranks at or near the top of procedures which urologists perform in the office and which can cause pain. Some of the others are urethral dilatation, fulguration of bladder tumors, and vasectomy. In each case we weigh patient discomfort against patient inconvenience, cost, and safety. In the US the cost of a procedure rises dramatically when we move from the office to a surgical facility. Thus the introduction of an anesthesiologist to administer sedation increases the cost appreciably. Even the process of intravenous sedation in the office adds additional requirements such as monitoring duration. This would likely also prohibit the patient from driving home alone after the procedure. Oral surgeons and some dentists have mastered the use of sedation, urologists have not. Most urology offices are simply not equipped for this. A brief history of the periprostatic nerve block specifically associated with a TRUS prostate biopsy session might be useful. K. Shinohara is a member of the faculty in the Department of Urology at University of California, San Francisco. He adapted the technique of anesthetizing the prostate described by Reddy (1) in 1990 to another type of prostate procedure, TRUS biopsy. Nash et al. published their results outlining for the first time the procedure of prostatic nerve blockade for prostate biopsies under TRUS guidance in 1996 (2). Evidently not many urologists read the article or realized that there was a better way of performing TRUS biopsies. Men were certainly being subjected to at best an uncomfortable procedure and at worst a very painful one in which many became diaphoretic and begged the urologist to limit the number of biopsies. I was among the uninitiated until one day in 1999 I mentioned to Can Obek, a fellow in our department in Miami, that there must be a way to reduce the amount of pain from this procedure. He recalled a presentation he heard in Turkey that was virtually identical to what Shinohara had reported (3). I immediately obtained the spinal needles and modified the technique to target 3 locations along each side of the prostate. There was no doubt the amount of pain was much reduced. We submitted our findings to the Journal of Urology and thanks to the then Editor, Jay Gillenwater, the manuscript was published in January 2000 (4). This time the technique did not go unrecognized. We followed with the results of a prospective randomized trial comparing our initial observations with a peri-prostatic nerve block (PPNB) to control group (5). There have been several accounts summarizing the results of many randomized trials and they indicate the efficacy and safety of the PPNB (6-7). This should be offered to every one of the estimated 1 million men who undergo a prostate biopsy each year in the US alone.

There are means to further allay patient anxiety and discomfort associated with this procedure. This is particularly important as we no longer perform 6 or even 8 biopsies but often 10 or even 12. Recent papers have outlined these methods (8) and we should find the ones that in addition to the PPNB reduce the discomfort associated with this procedure.

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Preoperative Determination of Prostate Cancer Tumor Volume: Analysis through Biopsy Fragments

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ABSTRACT

Objective: Preoperative determination of prostate cancer (PCa) tumor volume (TV) is still a big challenge. We have assessed variables obtained in prostatic biopsy aiming at determining which is the best method to predict the TV in radical prostatectomy (RP) specimens.
Materials and Methods: Biopsy findings of 162 men with PCa submitted to radical prostatectomy were revised. Preoperative characteristics, such as PSA, the percentage of positive fragments (PPF), the total percentage of cancer in the biopsy (TPC), the maximum percentage of cancer in a fragment (MPC), the presence of perineural invasion (PNI) and the Gleason score were correlated with postoperative surgical findings through an univariate analysis of a linear regression model.
Results: The TV correlated significantly to the PPF, TPC, MPC, PSA and to the presence of PNI ($p < 0.001$). However, the Pearson correlation analysis test showed an R^2 of only 24%, 12%, 17% and 9% for the PPF, TPC, MPC, and PSA respectively. The combination of the PPF with the PSA and the PNI analysis showed to be a better model to predict the TV (R^2 of 32.3%). The TV could be determined through the formula: Volume = 1.108 + 0.203 x PSA + 0.066 x PPF + 2.193 x PNI.
Conclusions: The PPF seems to be better than the TPC and the MPC to predict the TV in the surgical specimen. Due to the weak correlation between those variables and the TV, the PSA and the presence of PNI should be used together.

***Key words**: prostatic neoplasms; needle biopsy; volume, tumor; prognosis*
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INTRODUCTION

Except for skin cancers, prostate cancer (PCa) is the most common tumor in men. In the United States, the number of new cases increased from 198,000 in 2001 to approximately 232,090 in 2005 (1). This tumor is also responsible for the second leading cause of death due to cancer and in 2005, 30,000 deaths due to this disease are expected (1).

One of the most important factors associated to the PCa tumor biology is the tumor volume (TV) in radical prostatectomy (RP) specimens (2-5). An increased TV has been associated to high levels of preoperative prostatic specific antigen (PSA), and to many unfavorable pathological findings (6). Stamey et al. (4) demonstrated that biochemical recurrence rates after the RP are of 14%, 39%, 67% and 97% for patients with a TV of 0.5 to 2.0 cm^3, 2.1 to 6.0 cm^3, 6.1 to 12.0 cm^3, and bigger than 12 cm^3 respectively.

Various studies have tried to analyze that preoperative variables are significantly related to the TV (7,8) or are capable of identifying patients with

"clinically insignificant" tumors (inferior to 0.5 cm^3 and presenting a Gleason score of less than 7) (9,10). While image exams have demonstrated limitations (11,12), data supplied by USG guided prostate biopsy have been widely studied (13,14). Some of the most frequent measures of PCa tumor extension in biopsy include the percentage of positive fragments (PPF), the total percentage of cancer (TPC) and the maximum percentage of cancer in a fragment (MPC). However, it is still not clear which ones relate better to the TV. While some believe that the PPF is the most important variable (7,13,15), others use the TPC (8,14,16) or the MPC (10).

In the present study, the authors analyze which is the best method to preoperative determination of TV in RP specimens based in tumor extension measures obtained in prostate biopsy.

MATERIALS AND METHODS

The study comprised the revision of prostate biopsy samples of 168 patients with clinically localized prostate tumor submitted to RP between 2001 and 2003. Pertinent clinical information such as age, clinical stage and initial PSA were documented. Six patients with insufficient pathological data were excluded from the study.

All the biopsy specimens were analyzed by the same pathologist (KRL). Data obtained in the biopsy were the tumor degree, the presence of perineural invasion (PNI), the PPF, TPC and the MPC. The PPF was defined by the formula number of positive fragments/total number of fragments removed X 100. The percentage of cancer in each fragment of the biopsy was obtained by the measure of tumor quantity in millimeters (mm) divided by the total length of the fragment in mm. X 100. The MPC was documented. This method helped to reduce the possibility of error caused by the variability of lengths among the fragments.

All patients were submitted to RP. To measure the TV in cubic centimeters (cm^3), the RP specimens were introduced in a graded glass with water. The displacement of the liquid corresponds to the volume occupied by the gland. Mean and median prostate volume was 47.4 cm^3 and 36.3 cm^3 (12.8 to 32.8 cm^3) respectively. Each gland was submitted to histological analysis according to previously described recommendations (17). The Gleason score was used to assess histological differentiation (18), and the TNM staging system from 1992 was used (19).

Tumor extension in the surgical specimen was defined with the use of Grid as described by Humphrey & Vollmer (20). The mean cancer percentage in the surgical specimen was of 15%, mean 11.5% (1 to 55). Finally, the TV in cm^3 was obtained based on the volume of the whole gland and the tumor extension defined by Grid. The extra-prostatic disease was defined as the invasion of adipose tissue and/or of the periprostatic neurovascular plexus. It was considered as "clinically insignificant" tumors those with < 0.5 cm^3 of volume and Gleason score < 7 (9,10).

Associations between the measures of tumor extensions in the biopsy and the pathological characteristics were analyzed through the Kruskal Wallis and Mann-Withney tests. A linear regression model was used to correlate the TV in the RP specimens with preoperative variables. To analyze the biopsy and the PNI Gleason score as categorical variables, the ANOVA and student's T tests were performed. The statistical significance was defined as a $p \leq 0.05$, and the statistical calculations were performed in the software SPSS 12.0 for Windows.

RESULTS

The mean age was 61.9 years (39 to 79). Mean PSA was 7.9 ng/mL, median 6.6 ng/mL (0.8 to 26.4). The mean Gleason score was 6.7, median 7 (4 to 9). PNI was present in 18% of the cases. The mean number of fragments removed in the biopsy was 12.5, with a median 13. The mean value of the PPF, TPC, MPC was 32.7% (6 to 100), 15.6% (0.4 to 100) and 60% (5 to 100) respectively. The final pathological stage was pT2 in 117 (72.1%) and pT3 in 45 (27.9%) patients. The postoperative Gleason score was 2 to 6, 7 and 8 to 10 in 49 (30.9%), 64 (40.1%) and 49 (29%) patients respectively. The presence of extra-prostatic extension, involvement of seminal vesicles and PNI in the surgical specimen

was observed in 41 (25.5%), 18 (11.2%) and 144 (89.4%) patients respectively.

The PPF, TPC and the MPC were significantly related to the pathological stage ($p = 0.001$, $p < 0.001$ and $p < 0.001$), extra-prostatic extension ($p < 0.001$, $p < 0.001$, $p < 0.001$), PNI ($p = 0.001$, $p = 0.003$, $p = 0.005$) and with the involvement of seminal vesicles ($p = 0.013$, $p = 0.005$, $p < 0.001$) respectively. The postoperative Gleason score significantly related to the TPC ($p = 0.007$) and the MPC ($p = 0.007$), but not to the PPF ($p = 0.181$).

The mean TV in the RP specimens was 5.6 cm^3, with a mean value 4.4 cm^3 (0.4 to 20). The Pearson correlation analysis showed that the age of the patients was not related to the TV ($r = -3.3\%$; 95% CI [-18.6%; 12.2%]). The TV significantly related to the PPF, TPC, MPC and to the preoperative PSA. When we add a percentage unit (1%) to the PPF, there was a significant increase of the 0.0872 cm^3 in the TV ($p < 0.001$). The adding of one percentage unit in the TPC and in the MPC resulted in an increase of the 0.076 cm^3 and 0.054 cm^3 in the TV respectively ($p < 0.001$). The adding of one unit to the PSA (1 ng/mL), increased 0.257 cm^3 in the TV ($p < 0.001$). The presence of PNI, analyzed as a categorical variable showed a significant association with the TV. The mean TV between the patients with or without the PNI was 8.3 cm^3 (median 8.0; 0.6 to 16.5) and 4.6 cm^3 (median 3.7; 2 to 20) respectively ($p < 0.001$), Figure-1. The Gleason score of the biopsy also analyzed as categorical variable did not show a relation with the TV ($p = 0.462$).

However, despite the significant association among the majority of the preoperative variables and the TV, the linear regression model demonstrated that these variables were weak. The multiple determination coefficient (R^2) for PPF was 24%, i.e., only 24% of the observations in the x-axis had a linear relation with the y-axis (Figure-2). The values of the R^2 for the TPC, MPC and for the PSA were yet inferior (12%, 17% and 9% respectively) (Figure-2).

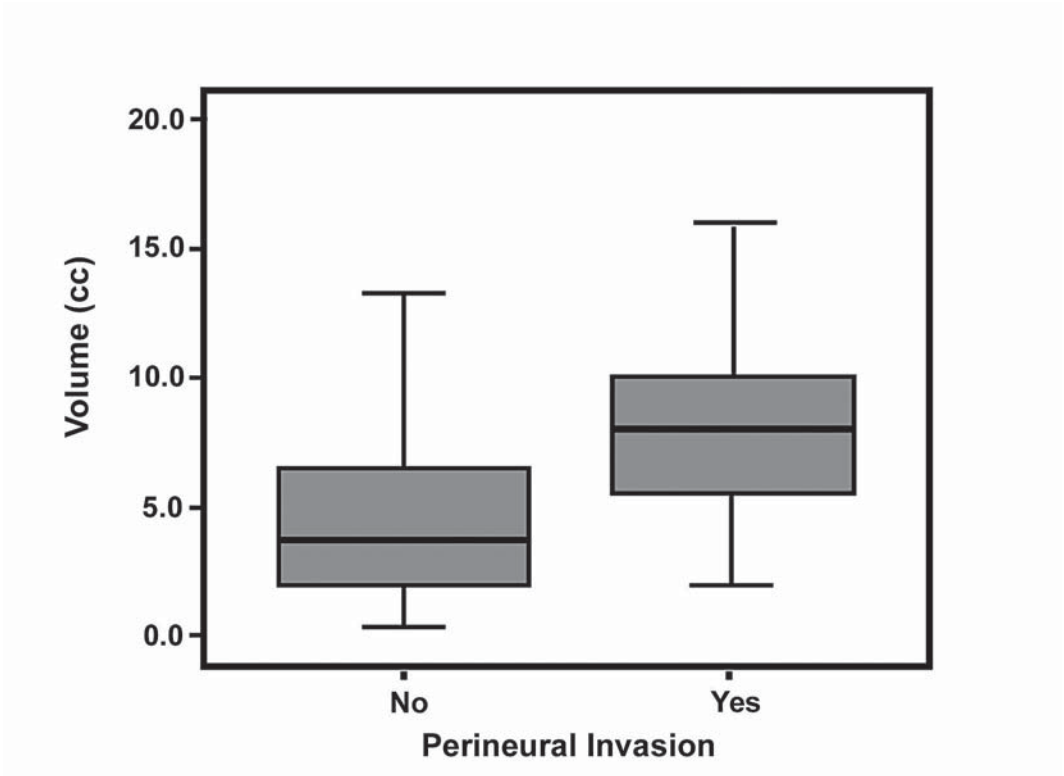

Figure 1 – *Tumor volume box-plot according to the presence of perineural invasion.*

After testing all the variables, the regression model that provided a better estimation of the TV in the surgical specimen included the PPF, the PSA and the PNI: Volume = 1.108 + 0.203 x PSA + 0.066 x PFP + 2.193 x PNI. The R^2 for this model was of 32.3% that means that together, these variables can explain 32.3% of the variables in the TV.

COMMENTS

The present study analyzed in 162 patients the predictive factors of the TV in prostatic variables recently performed (between 2001 and 2003) and with a large number of fragments (mean 12.5 per patient). Except for the lack of association between the PPF

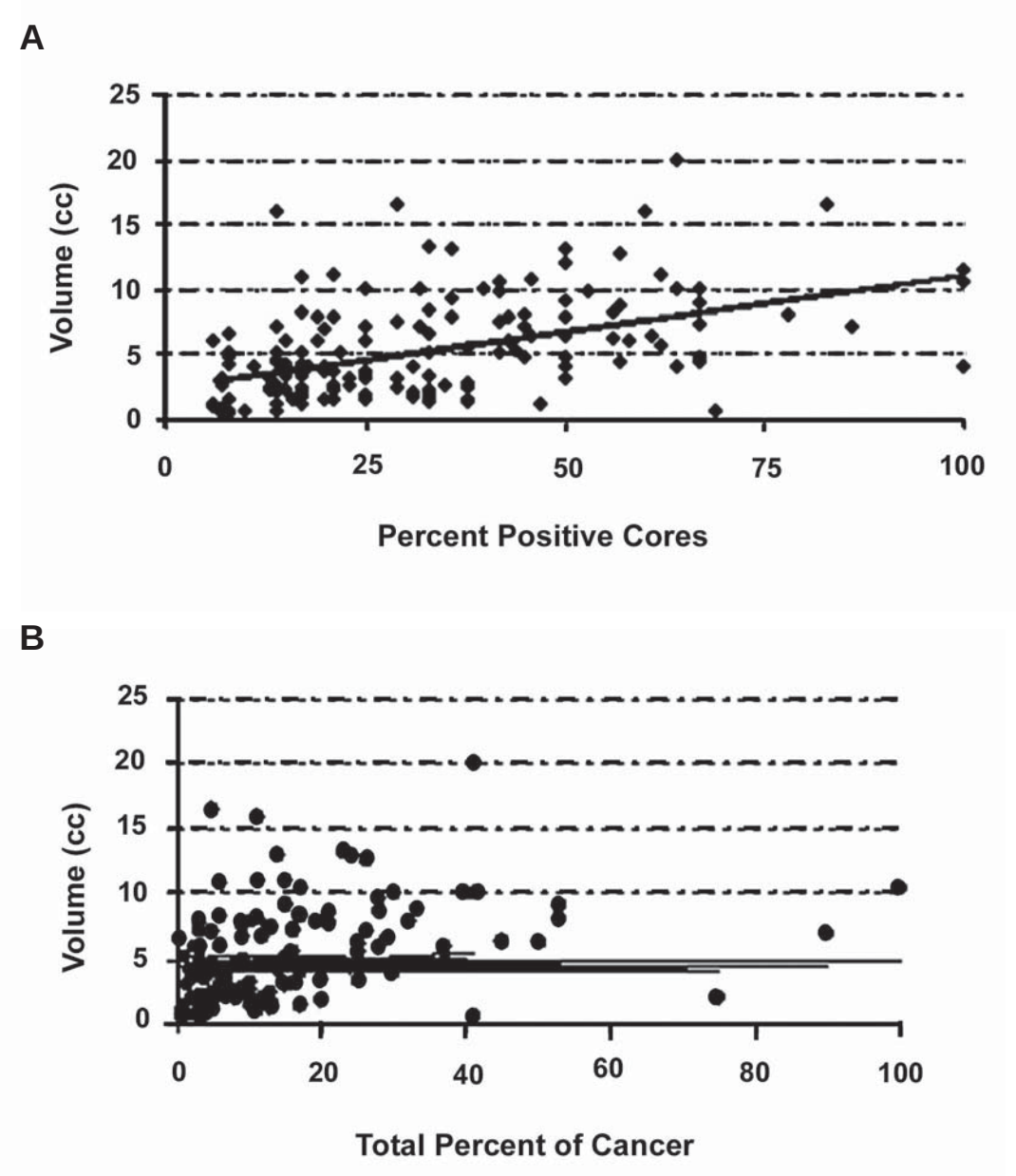

Figure 2 – *A) Tumor volume scatter plot according to the percentage of positive fragments (r = 48.9% - 95% IC [35.3% - 60.5%]). B) Tumor volume scatter plot according to the total percentage of cancer (r = 34.4% - 95% IC [18.2% - 48.8%]).*

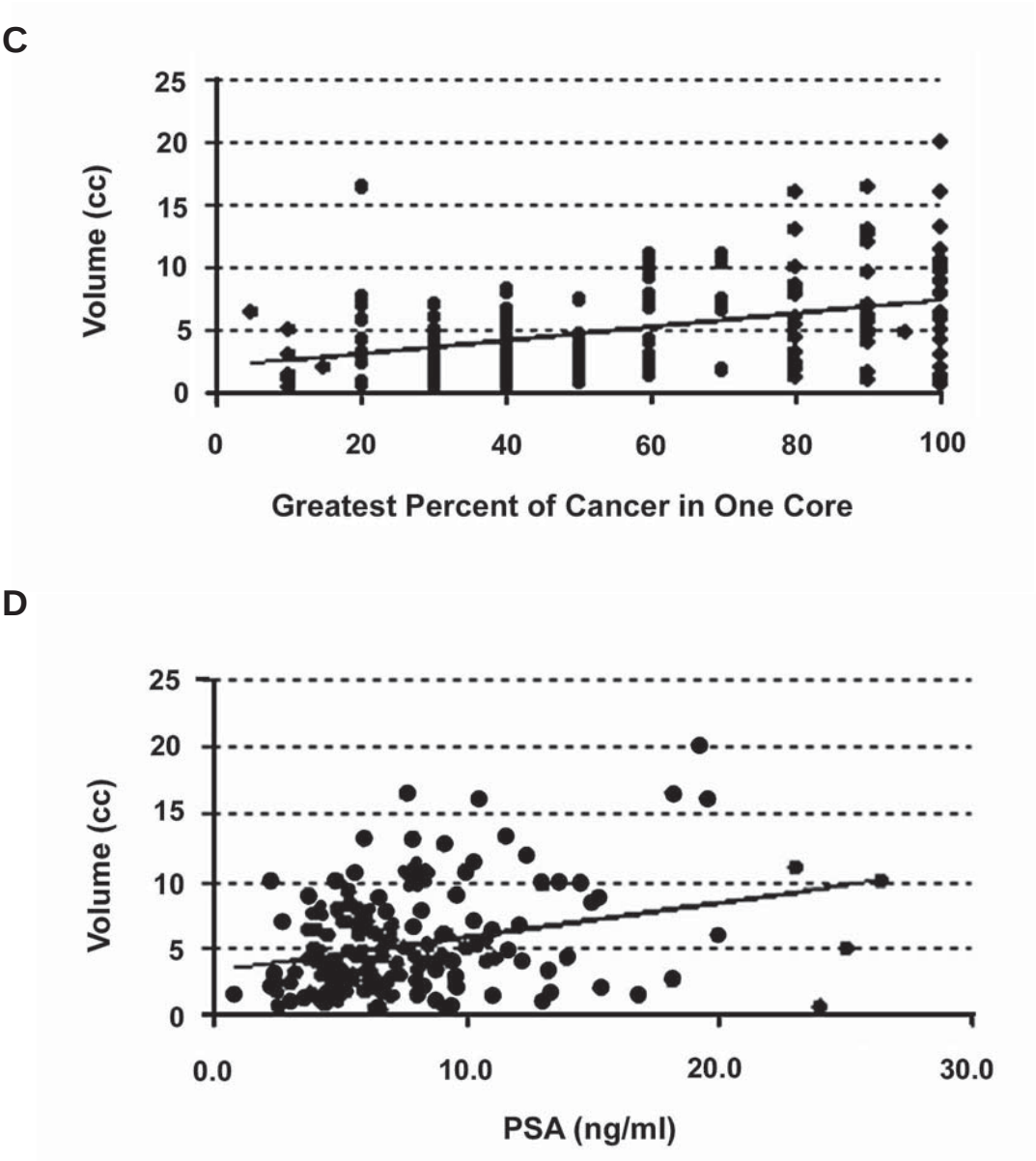

Figure 2 – *C) Tumor volume scatter plot according to the maximum percentage of cancer in a fragment (r = 41.4% - 95% IC [27.6% - 53.6%]). D) Tumor volume scatter plot according to the prostate specific antigen (r = 30.7% - 95% IC [16.0% - 44.0%]).*

and the final Gleason score, all the measures of tumor extension in the biopsy significantly related to postoperative pathological findings. The PPF, TPC and the MPC have also significantly related to the TV, but the linear regression model demonstrated only a weak relation. The PPF related better to the TV when compared to the TPC and the MPC. The addition of the PSA and of the PNI analysis improved the sensibility of the final model to predict the postoperative TV.

There is no consensus in literature regarding the best model to predict the TV in RP specimens. In a 207 patient study, Sebo et al. (7) reported in a

multivariate model including the PSA and the Gleason score, that the PPF and the TPC are the most important predictive factors of the TV pathological stage, however, the PPF constituted a more practical and reproducible variable. Gancarczyk et al. (15) defined that the PPF, together with the PSA and the Gleason score of the biopsy were the most important variables to define the pathological stage, and based in these variables have developed a nomogram to predict the evolution of the patients after an RP.

Some authors prefer the use of the TPC to predict the TV in RP specimens. Bostwick et al. (16) showed that the combination of the PSA, Gleason score and the TPC provide the best sensibility to predict the chance of capsular penetration and invasion of seminal vesicles. Grossklaus et al. (14), stated that the TPC together with the PSA and the presence of positive fragments bilaterally are independent predictors of TV and suggest its routine use to predict the PCa pathological characteristics in the surgical specimen. However, none of these studies assessed the PPF. Cupp et al. (8), comparing the PPF, the TPC and the extension of the cancer in millimeters (total millimeters of cancer divided by the number of fragments in the biopsy), defined that the best variable to predict the TV as the TPC. The linear regression model used found r = 0.51, almost the same value found by us when we analyzed in a similar way the PPF (r = 0.49), and as in our study they have also found a great variation of TV for a given percentage of cancer in the biopsy.

Other authors have also found a weak relationship between the measures of tumor extension in the biopsy and the TV in the RP specimens. Noguchi et al. (13), determined that even though the TV is significantly related to the number of positive fragments, PPF, total length of the cancer in the biopsy and the percentage of Gleason score 4 and 5, each of those variables demonstrated an R^2 inferior to 10%. A possible explanation for this weak relation is due to the fact that 84% of the biopsies have been performed with only 6 fragments. In the present study, 19 (12%) patients were submitted to biopsies with 6 fragments or less. Due to the PCa multifocality maybe if more fragments were routinely removed, stronger correlations could have been found.

Other models, also based on TV tried to identify patients with "clinically insignificant" tumors. Epstein et al. (9), studying 157 patients treated with RP, defined that the best model to identify those tumors include patients with a PSA density inferior to 0.1 ng/mL/g, less than 3 positive fragments, absence of Gleason 4/5 and MPC of 50%. Sensitivity and specificity of this method were 56% and 95% respectively. Carter et al. (21), using the same model in 72 patients, found a sensitivity and specificity of 27% and 96% respectively. Anast et al. (10) defined that the best model would include patients with a MPC inferior to 10% and a Gleason score inferior to 7. Sensitivity and specificity of this model were 77% and 75% respectively.

However, investigation of insignificant tumors was not possible since only one patient presented this type of tumor. Some considerations can explain this fact. Firstly, identification of tumors with small volume is difficult due to the prostate biopsy imprecision, and secondly, it seems to really exist a low incidence of these tumors in patients candidates to RP. In the Cupp et al. (8) series, only 3 (2.3%) of the 130 patients studied presented such tumors. Our model needs to be applied to a population with a larger number of insignificant tumors in order for us to develop a model aiming at identifying these tumors.

Finally, with the present study we observed that for a given percentage of cancer in the biopsy, there is a great variability in the TV. These findings show that the measures of tumor extension in the biopsy are insufficient to precisely predict the TV and, thus other variables should be used jointly to try to improve the method's sensitivity. The use of the PPF together with the PSA and the assessment of the presence of PNI has constituted the best method to predict the TV in the surgical specimen.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The amount of tumor in prostate needle cores is an extremely important pathologic parameter and a predictor of lethal phenotype of prostate cancer that must be reported in needle biopsies, as the extent of involvement of needle cores by prostatic adenocarcinoma has been shown to correlate (albeit not perfectly) with the Gleason score, tumor volume, surgical margins and pathologic stage in radical prostatectomy specimens (1-8). The extent of needle core involvement including bilateral involvement has also been shown to predict biochemical recurrence, post-prostatectomy progression and radiation therapy failure in univariate and often in multivariate analysis. It is a parameter included in some recent nomograms created to predict pathologic stage and seminal vesicle invasion after radical prostatectomy and radiation therapy failure. While the correlation for high tumor burden in needle biopsies is directly proportional to the likelihood of an adverse outcome, low tumor burden in needle biopsies is not necessarily an indicator of low volume and low-stage cancer in the prostatectomy specimen. As with the other parameters, combination of the extent of involvement of needle cores with the Gleason score, location of the tumor and serum PSA levels increases the prognostic and predictive power of this parameter.

There is lack of consensus in the literature and, hence, to some extent in clinical practice as to the best method of reporting the extent of tumor involvement. It is recommended that the report should provide the number of involved of cores. In addition, one or both of the following more detailed methods of tumor extent should be performed. One method is to report the linear length of cancer. The other method is to provide a percentage estimate of involvement of each of the cores derived by visual estimation. Typically, small foci (depending on the individual case) are reported as less than 1% or less than 5%, etc., of needle core biopsies and linear length in increments of 0.5 mm. The correlation, as alluded to before with prognosis, is with greater involvement of the cores, and studies have shown cut-offs of ≤ 33%, 34-50% and 51-100% or ≤ 20%, 21-55% and > 56%, etc., to be of significance. The method of calculation in different studies has varied from visual estimation to linear measurement of each core calculated as a percentage length or percentage estimation for an entire case and not individual biopsies. Since literal translation of these findings to clinical cases would be difficult and not really necessary, reporting the percentage of cancer involvement in increments of 5 or 10% is appropriate. One problem encountered with this otherwise straightforward method is when there is extreme fragmentation of the needle biopsy specimen, making assessment of the number of cores and the percentage of cancer within each core difficult. This problem needs to be resolved on an individual case basis using best medical judgment. In case of highly fragmented tissue, this may be overcome by providing a composite (global) percentage of involvement of cancer in all needle biopsy tissue, and this may be a slightly more accurate correlate of the amount of cancer in the prostate gland itself. Bilateral cancer, which indicates multifocality, is indirectly partially suggestive of greater tumor volume, is most often not specified by pathologists in the report, but this parameter is directly and easily deduced from the pathology report findings of each of the cores submitted. In patients not subsequently treated by radical prostatectomy, this forms a critical factor in assigning “pathologic stage”.

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Bladder Substitution by Ileal Neobladder for Women with Interstitial Cystitis

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ABSTRACT

Objective: To report our experience with cystectomy and ileal neobladder for women with interstitial cystitis (IC).
Materials and Methods: Thirty-five female patients treated during 2000-2005 with the mean age of 45.9 ± 4.4 years were included in this study. All of them had experience suprapubic pain with irritative voiding symptoms and were diagnosed as having IC based on NIDDK criteria for at least 2 years. Conservative treatments had failed to relieve their symptoms; and therefore all of them agreed to undergo a bladder removal. For cystectomy, the urethra was cut 0.5 cm below the bladder neck, proximal to the pubourethral ligament, leaving the endopelvic fascia intact. An ileal segment of 65 cm was used to create the neobladder with the Studer's technique.
Results: All patients presented good treatment outcome with regard to both diurnal and nocturnal urinary control without any pain. Quality of life using the SF-36 questionnaire showed significant improvement of both physical health and mental health. Spontaneous voiding with minimal residual urine was found in 33 cases (94.3%), and the remaining 2 cases (5.7%) had spontaneous voiding with residual urine and were placed on clean intermittent catheterization (CIC). Twelve out of 30 cases with sexually active ability had a mild degree of dyspareunia but without disturbance to sexual life.
Conclusion: Bladder substitution by ileal neobladder for women who suffer from IC can be a satisfactory option after failure of conservative treatment. Resection of the urethra distal to the bladder neck can preserve continence and allow spontaneous voiding in almost all patients.

Key words: *interstitial cystitis; surgery; ileum; bladder*
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INTRODUCTION

Interstitial cystitis (IC) is a chronic inflammatory disease of the bladder with unknown etiology. It is characterized by suprapubic pain, urinary frequency and urgency (1). Due to severity of symptoms, the patient with IC becomes socially incapacitated (2). Treatment is mostly non-curative because of its yet unknown etiology. Therefore, oral medications, many kinds of intravesical instillations, neuromodulation, hydrodistention of bladder and acupuncture are introduced as means of treatments (3). Moreover, surgery is recommended as the treatment of choice in the intractable cases that do not respond to conservative treatment (4). Because of little knowledge about the female continence mechanism, supratrigonal cystectomy and replacement using intestinal segment are introduced. Preservation of the trigone makes patients continent because there is no damage to the autonomic nerve system. On the

other hand, preservation of trigone prevents spontaneous voiding in this group of patients (5). Benjary & Politano in 1995 advised to cut the urethra distal to the bladder neck and reported spontaneous voiding and patients completely dry (6).

In the present paper, we reported our experience with this technique with long-term follow up.

MATERIALS AND METHODS

From January 2000 to December 2005, a total of 35 women aged from 35-53 years (mean = 45.9 ± 4.4 years) who underwent total cystectomy and bladder replacement due to intractable IC were included in this study. The follow-up time was 15 to 68 months (mean 28 months). All patients presented symptoms of frequency, urgency to urinate and suprapubic pain relief by voiding. All of them were proven as IC according to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria. Cystoscopy revealed glomerulation in all cases and no Hunner's ulcer was noted in any case. Awake cystometric bladder capacity was done and the results are shown in Table-1. Unresponsive to conservative treatment including medical, intravesical and bladder hydrodistention were noted for at least 2 years. All patients suffered from severe intractable symptoms and had agreed to bladder removal.

Hysterectomy was performed in 32 patients who had enough children or were postmenopausal. The bladder was removed and the urethra was sectioned proximal to the pubourethral ligaments and 0.5 cm distal to the bladder neck, leaving the endopelvic fascia intact as described by Benjary & Politano (6) and shown in Figure-1. Bladder substitution was then carried out by using a 65 cm ileal segment as described by Studer et al. (7). In the case of hysterectomy, the vaginal wall was closed with a double row of 2-0 polyglycolic sutures (Figure-2). The omentum was harvested to keep vascular supply intact and over sewn with vaginal stump keeping as back support of neobladder. Kinking between the urethra and the neobladder as well as fistula formation is prevented by omentum covering (Figure-3 and 4).

Intraoperative complications, as well as immediate and late consequences were studied. Voiding pattern and continence were determined by expert nurse personal interviews during regular follow-up. The patients were classified as spontaneous voiding with minimal residual urine, spontaneous voiding with significant residual urine (more than 100 mL) and unable to void. Daytime continence was defined as completely dry without any pad. Nighttime continence was defined when the patient was dry without need for pads and uncontrolled urinary leakage. Pain was evaluated by using visual analog scale (VAS) with scoring from 1-10. Quality of life (QoL) was evaluated at 3 months and 6 months by using SF-36 questionnaire that was translated into Thai. Questionnaire reliability as well as validity was assessed following previous studies (8). The SF-36 questionnaire is a generic instrument assessing eight domains: physical functioning, role physical health, body pain, general health, vitality, social functioning, role emotion and mental health. We analyzed into two groups: physical health and mental health, scores range from 0-100 for each dimension, with 100 indicating optimum QoL.

Table 1 – *Baseline and follow up data on bladder capacity, pain score and SF36 score, mean (SD).*

Outcome	Baseline	3 Months	6 Months	12 Months	p Value
Bladder capacity (mL)	170.6 (61.5)	-	462.3 (54.9)	-	< 0.001*
Pain score (VAS) SF-36	9.8 (0.43)	3.9 (1.0)	1.7 (0.70)	1.8 (0.55)	< 0.001**
Physical health score SF-36	55.7 (2.3)	-	-	82.6 (1.8)	< 0.001*
Mental health score	50.7 (1.7)	-	-	75.7 (2.7)	< 0.001*

** = paired t-test; ** = repeated measures ANOVA.*

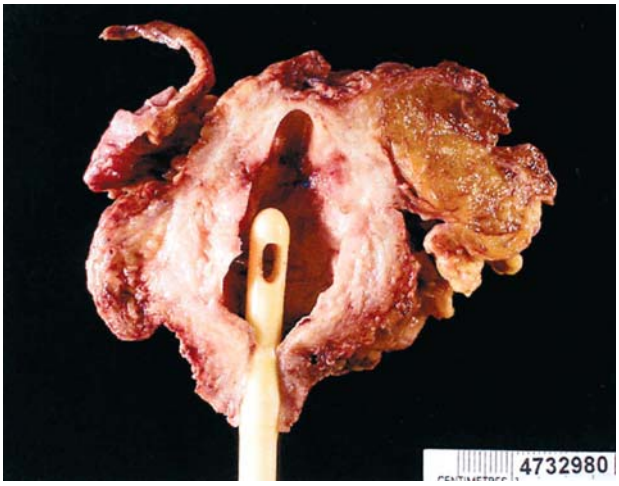

Figure 1 – *Bladder specimen.*

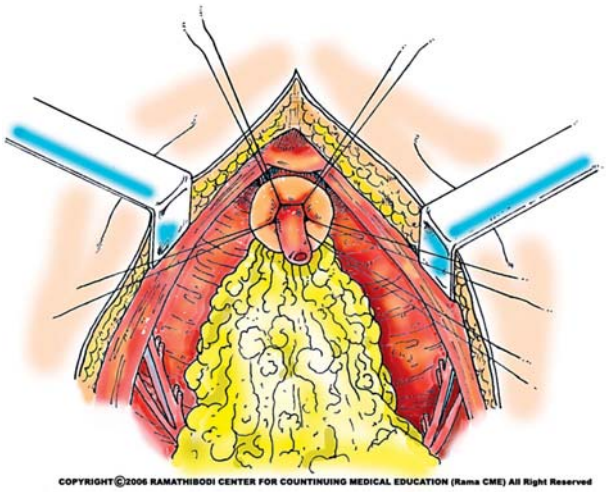

Figure 3 – *Omentum is used over sewn with vaginal stump. Dead space of pelvis is obliterated and omentum act as back support for neobladder.*

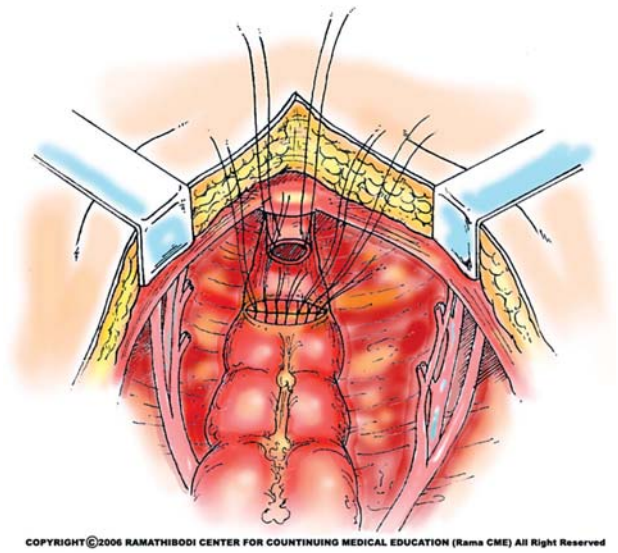

Figure 2 – *View of the pelvis from above with urethral suture placement as well as vaginal stump suture, leave sutured end for over sewn with omentum.*

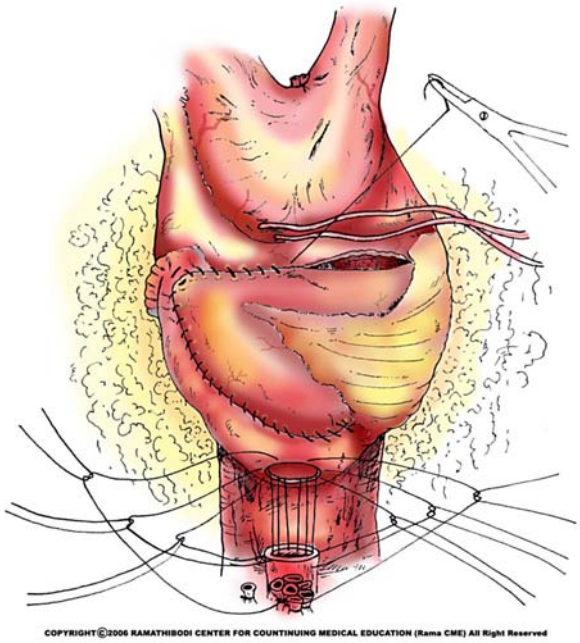

Figure 4 – *Studer's ileal neobladder is placed using 5 stitches of polyglycolic acid seromuscular sutures.*

All of the patients came to follow up at 2 weeks, 3 months, and 6 months after operation. If no major side effects were noted, yearly check up was done. Ultrasonography, urea, creatinine and routine blood chemistry were performed at 3 months, 6 months and yearly. When indicated, intravenous pyelography, renal scan and endoscopic examination were performed.

Statistical methods were used to analyze continuous and ordinal data and summarized as mean

± SD. Statistical comparison of continuous or ordinal outcomes before and after an operation was performed using paired t-test or, in the case of pain score, by repeated measures ANOVA. Statistical significance was defined as a p-value of 0.05 or less. Stata v.7 (Stata Corp, College Station, TX, USA) was used for all statistical analyses.

RESULTS

On reviewing the medical records, no intraoperative complications were noted. One case developed intestinal obstruction in the second week after operation and improved with conservative treatment. Postoperatively, all of the patients had pain improvement through visual analog scale and all of them returned to normal life within 2 months. The average pain score is plotted against the follow-up time as shown in Figure-5, where the spread of the data at each time point is also shown.

There was a highly significant increase in bladder capacity 6 months after operation. The pain score significantly and consistently decreases after operation reaching a minimum from 6 to 12 months after operation. The quality of life as measured by the SF-36 v. 2 scale showed a significant increase in the scales of both physical and mental health components (Figure-5).

At the follow up of 6 months, diurnal and nocturnal continence were achieved in all of them (100%). Spontaneous voiding was noted in 33 cases and the other 2 cases were spontaneous voiding with significant residual urine. Residual urine was recorded around 100-250 mL and clean intermittent catheterization was used. Three patients experienced acute pyelonephritis in one month, 4 months and 6 months, respectively. All were cured after conventional treatment and had no recurrent infection since the last follow up. On the late follow up, bilateral hydronephrosis was found in one case but renal scan

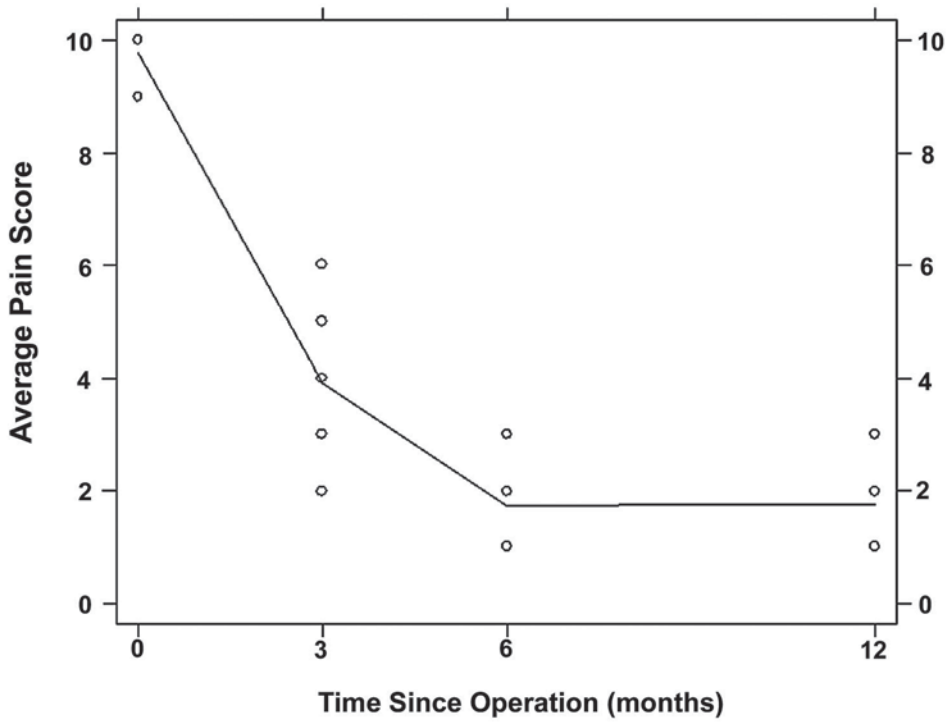

Figure 5 – *Plot of average pain score versus follow-up time in months, showing data spread at each time point.*

showed no anatomical obstruction. Mucous plug was found in almost all of the cases but intermittent bladder irrigation in the early postoperative period was enough to get rid of this problem. No mucous plug was reported after 6 months of surgery. Neobladder stone developed in one case and treated endoscopically. No stress incontinence was found in all cases. Among 30 cases of sexually active patients, 12 cases had mild degree of dyspareunia during the first year and no patient had disturbance in sexuality after 1 year of follow up.

COMMENTS

Interstitial cystitis (IC) encompasses a major portion of the chronic painful bladder syndrome. It is characterized by suprapubic pain, irritative voiding symptoms including frequency, urgency and dysuria (1). Interstitial cystitis predominantly affects middle-aged women but it is occasionally found in men. On a surveying study, IC affects 10.6 per 100,000 people with male to female ratio of 1 to 12 (9). Criteria for diagnosis of IC are chronic irritative voiding symptoms, sterile urine and characteristic cystoscopic findings (10). Potassium test was mentioned as one modality for diagnosis but it was found to be not specific for IC (11). The diagnosis of this condition is usually delayed due to the lack of knowledge of diagnosis criteria. Treatment is mostly palliative and non-curative because its etiology is still obscure (3). Only chronic inflammatory cells infiltrate in the bladder wall, particularly mast cells without infective agents were mentioned in pathological examinations (12). Many reported series have suggested that IC may be a cell-mediated autoimmune disorder. Familial history is also found, so genetic predisposing may be another factor determining the etiology of IC (13).

Many types of treatment have been used for the management of IC including oral medications, hydrodistention, intravesical instillation of DMSO, heparin and BCG. Also, immunosuppressive drugs with corticosteroid and azathioprine are mentioned as treatment of IC (14). After treatment failure, neuromodulation, acupuncture or even urinary diversions were used (15). In cases of failure of all conservative treatments, cystectomy with enterocystoplasty is used in many institutes. At the beginning of bladder substitution in women, supratrigonal cystectomy was done to avoid urinary incontinence, nevertheless, hypercontinence was the result and patients were unable to urinate and, therefore, clean intermittent catheterization was needed for urinary drainage (16). Even leaving only vestigial bladder muscle, persistent painful bladder was still present (17). Webster & Maggio reported complete painful relief after additional removal of the trigone in patients submitted to supratrigonal cystectomy and enterocystoplasty for treating IC (18).

Urinary incontinence after a neobladder operation depends on creating adequate storage reservoir and preserving the sphincteric mechanism. Sectioning the urethra below bladder neck in female patients can maintain the continence mechanism with better emptying than in the case of bladder neck preservation (19). In cases where the sphincteric mechanism is not functional enough to prevent urinary leakage, Kegel exercises is recommended (20). In the postoperative period, daily use of saline irrigations into bladder can get rid of mucous plug that usually obstructs voiding (21). Nerve sparing cystectomy is another factor believed to provide early continence in female patients. Sparing of autonomic nerve fibers supply beneath the urethra was found to provide early urinary control in derived patients. Keeping endopelvic fascia intact not only preserves the nerve but also keeps urethropelvic ligament, enhancing urinary control (22).

The use of cystectomy with ileal neobladder for treatment of patients with bladder carcinoma has been reported with long-term follow up, demonstrating that this operation is safe for female patients (23). After gaining more experience in treatment of bladder malignancy, we were more confident to perform this operation in a benign bladder disease as IC. There is a small risk of developing malignancy in the neobladder and it usually occurs after 15 years postoperatively (24). Metabolic and nutritional complications may result with the use of B12 and fat-soluble vitamins, chronic metabolic acidosis, intestinal osteopathy and diarrhea. Although periodical follow up for any metabolic or nutritional disorder is suggested, bladder reconstruction with ileum is safer that reconstruction with colon (25). Our study confirmed that this operation

is safe with minimal complication and allow our patients with IC to enjoy a better quality of life after bladder removal.

We concluded that bladder substitution with ileal neobladder may be an appropriate option in intractable symptomatic interstitial cystitis patients. Urethral resection distal to bladder neck, nerve preservation, and leaving endopelvic fascia intact can preserve continence and spontaneous voiding.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The authors report one of the largest series of cystectomy and orthotopic neobladder formation for bladder pain syndrome/interstitial cystitis in the literature. Their results are outstanding, though follow-up is relatively brief. Urologists should be aware that long-term results of cystectomy and continent diversion for this disease are mixed, that pain can become centralized and persist despite cystectomy, and that pain can develop in the urinary reservoir years after the initial procedure. For patients with severe, longstanding disease unresponsive to standard therapies, urinary diversion with or without cystectomy is certainly a reasonable option. I have preferred conduit diversion because it avoids the possibility of pouch or neobladder pain in the future. As is obvious after reading this report, these procedures are best done in centers by surgeons with extensive experience in reconstructive surgery.

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Double-Blind Randomized Placebo-Controlled Study of Bixa Orellana in Patients with Lower Urinary Tract Symptoms Associated To Benign Prostatic Hyperplasia

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ABSTRACT

Objective: To determine the efficacy of Bixa Orellana (BO) in patients with benign prostatic hyperplasia (BPH) presenting moderate lower urinary tract symptoms (LUTS).
Materials and Methods: It is a prospective double-blind randomized placebo-controlled study. One thousand four hundred and seventy eight patients presenting moderate LUTS associated to BPH were interviewed, from whom we selected 136 to fulfill the criteria of inclusion and exclusion. Assignation was performed at random in blocks of four to receive B0 at a dose of 250 mg 3 times a day or placebo (Pbo) for 12 months, 68 patients were assigned to each group. From the patients in the study we obtained data of demographic, epidemiologic, symptom score, uroflowmetry and post void residual urine variables.
Results: Basically both groups were compared clinically, demographically and biochemically. Throughout the study variations of symptom score, mean delta symptom score during each visit and the final average delta were similar for both groups (BO - 0.79 ± 1.87 and Pbo - 1.07 ± 1.49) (p = 0.33). Similarly variations of Qmax mean, Qmax average delta and final average delta were similar (BO 0.44 ± 1.07 and Pbo 0.47 ± 1.32) (p = 0.88). Variations of post void residual urine mean, post void residual urine average delta in each visit and the final average delta were similar for both groups (BO 4.24 ± 11.69 and Pbo 9.01 ± 18.66) (p = 0.07). No differences were found in the answers of clinically significant improvement assessed with relative risk and risk differences, even though the proportion of adverse effects was similar for both groups.
Conclusion: Patients with BPH that present moderate LUTS did not show any benefit receiving BO when compared to placebo.

***Key words**: prostatic hyperplasia; bladder outlet obstruction; phytotherapy; Bixa orellana*
Int Braz J Urol. 2007; 33: 493-501

INTRODUCTION

The term benign prostatic hyperplasia (BPH) indicates the growth of the gland without the presence of urinary obstruction. The increase in the size of the prostate only occur in men older than 40 years old, existing a well established association between prostatic growth and urinary obstruction in older men

(1). More than half of men are affected by this condition throughout their lives and from those at least 25% seek medical assistance. Investigations performed in countries such as the United States and Scotland show a significant increase in the prevalence according to age differently from what was found in Japan and China where prevalence is low (2). Currently many such patients are initially treated with alpha blockers or 5 alpha-reductase inhibitors, who have demonstrated that they improve the symptoms and objective parameters associated to BPH (3-5); the inconvenience of these drugs is that they should be used permanently, for if they are suspended the symptoms recur (6). At the same time, phytotherapy as an alternative therapy, has been used since ancient times being very popular all over the world, especially in Europe, China and Japan. It is estimated that today phytotherapeutic agents constitute approximately 50% of all medicines prescribed for BPH in Italy (7) and almost 90% in Germany and Austria (8). This popularity is based on the fact that they are advertised as natural elements, therefore not harmful, even though they are not free from adverse effects. Their popularity is also due to the fact that they can be acquired without any medical prescription (9). Many plant extracts have been used in the treatment of patients with BPH that present LUTS, some of them derive from roots, seeds, cork and plant fruits such as alfalfa, fodder cereal, Saw Palmetto berry, African plum, pollen extract, aspen leaves, African potato, Urcubia pepo seed and purple coneflower root (9,10).

Currently we count on studies performed with pollen extract, Saw Palmetto berry (SPB), Rye pollen and African plum, however the results are not conclusive (11-15). These evidences show the need of conducting studies, such as double-blind placebo-controlled, with phytotherapeutic agents in the long term, in order to determine their efficacy and safety (12,16).

In Peru, the use of medicinal plants is known since the Incas. An important proof of the contribution that Peruvian traditional medicine brought to the world is the discovery of Peruvian bark or quinine to the treatment of malaria (17). Traditionally in Peru, plants with therapeutic properties are used and in the specific case of LUTS caused by the "prostate", it is popular all over the country the consumption of achiote (Bixa orellana - BO) in preparations, extracts or spray of achiote leaf, presentations that are sold without medical prescription under the name of Achiotec and Achiote. There are no clinical tests that demonstrate the efficacy and safety of BO in patients with BPH that present LUTS, a fact that led us to conduct the present study.

MATERIALS AND METHODS

A double-blind randomized placebo-controlled study was conducted from November 2002 to August 2004 in the Urology Service of the National Hospital Cayetano Heredia, Lima - Peru, to evaluate the efficacy and safety of BO in patients with BPH that presented moderate LUTS. The study counted on the approval of the Peruvian University Cayetano Heredia (UPCH) ethics committee, and a written informed consent was signed. The study was designed to have duration of 12 months with a temporary cut, at the time the last patient enrolled ended 6 months of treatment. To be able to enroll the study the patients should fulfill the following inclusion criteria: to have between 50 and 70 years of age, good physical and mental condition judging by his clinical history, physical exams and laboratory data. Experience at least 2 obstructive urinary symptoms, have a maximum urinary flow (Qmax) in average from 5 to 15 mL/sec, a post void residual urine inferior to 250 mL, an increased volume of the prostatic gland according to digital rectal examination, as well as prostatic specific antigen (PSA) less than 10 ng/mL. They should also fulfill the following criteria of exclusion: presence of dysuria or hematuria, abnormalities in laboratory determinations, have a maximum urinary flow > 15 mL/sec, a prostatic gland with reduced volume at digital rectal examination, PSA > 10 ng/mL, allergies, drug abuse, chronic use of medicine with antiandrogenic properties, history of diseases that predispose to urethral stenosis, urinary infection, invasive interventions for BPH treatment, evidence of prostate cancer, history of intermittent catheterization and neurogenic bladder. We have interviewed 1,478 patients presenting moderate LUTS associated to BPH, from who we selected 136 patients to fulfill the criteria for inclusion and exclusion. Together with the reading of the informed consent, we explained about the study and

after they accepted the conditions, they signed in. A routine clinical history and physical exam was performed and they all answered the symptom score questionnaire in writing. Basic hematologic, renal function, hepatic function, biochemistry and urine analysis were performed. In addition, a transrectal echography of the prostate, uroflowmetry and post void residual urine measurement were performed. Selected patients were assigned randomly in groups of four and for such effect, 17 groups were chosen (17 x 4), each group was randomly chosen exchanging for four assignations, 2 for placebo and 2 for Bixa orellana. This procedure allowed balancing the groups, in a way that 68 patients received Bixa orellana and 68 placebo. According to the randomization it was administered orally, Bixa orellana one capsule of 250 mg or placebo, 3 times a day. The capsules of Bixa orellana were prepared in the following way; one ton of leaves of the plant of BO was gathered, the leaves were dried at environment temperature for 30 days, the BO leaves were lyophilized obtaining 10 bags of 1 Kg, they were further encapsulated by a pharmaceutical laboratory, 250 mg for each capsule. The capsules of placebo were carefully prepared by the same laboratory so that they have the similar form, color, smell and flavor of Bixa orellana. Evaluations started with patient selection visits (V0), followed by a treatment visit one month after (V1) and the following ones were every two months until they reached visit 7 (V7) to the 12 months of study. In every visit, the patient answered the AUA symptom score questionnaire. A Qmax measure was also performed with the Uro Flor Monitor 6030 as well as the post void residual urine with the Bladder Scan 3000. After 6 and 12 months of treatment an echographic control of the prostatic volume was repeated, performed with a 6.5 MH transducer. The physical exam was performed and it included measurement of vital signs and digital rectal examination of the prostate. The effects reported spontaneously were considered as adverse such as those reported by the patient when he was asked if he had presented any health problem since his last visit The results of the LUTS, Qmax and post void residual urine tests were compared by 2-way ANOVA, aiming at demonstrating the variations between means of each visit within each group and among groups. In the same way the measurements deltas within each group and between both groups in each visit by t-test were compared. Calculation of such deltas were performed aiming at evaluating more precisely if there was an improve or deterioration of the variables studied. Afterwards, the mean delta of all the visits for each group was estimated and compared to the means between both by the t-test. Positive deltas meant an increase in the values of the data of the variables and negative delta a decrease in the values of the data of the variables. The improvement of the patients was defined as the patients that presented an improvement $\geq 30\%$ or ≥ 3 mL/sec in relation to the initial Qmax, decrease $\geq 30\%$ in the total score of symptoms and decrease $\leq$ 30% of the initial post void residual urine (18,19). The relative risk (RR) was calculated as well as the risk differences (RD) to evaluate the clinical response, assessing the improvement of the symptoms, of the Qmax and of the post void residual urine. The size of the sample was calculated to determine advantages in the order of 30% of improvement in the symptoms score, for such effect both proportions were compared, bearing in mind the probability to make a mistake type I (α) of 0.05 and mistake type II (β) of 20%, with a power of 80% resulting in a sample size of 136. It was considered as statistically significant a $p \leq 0.05$. Data were analyzed in SPSS vs. 7.5 y STATA v.7.

RESULTS

From the 136 patients studied, with 68 in each group of treatment, we found that clinical, demographic and biochemical characteristics, prostate volume Qmax and post void residual urine in both groups were comparable (Table-1). A total of 30 patients left the study due to the fact that they did not come back to control visits. From those patients 14 (20.6%) were from the BO group and 16 (23.5%) from the Placebo group ($p = 0.4$). In the Analysis, in the best and worst scenarios (the intention-to-treat analysis), losses modify the results in favor of the placebo. In this study there was a rate of 22% of losses in follow-up, those losses may have affected the results. Throughout the study, variations in the measures of symptom scores were similar for both groups showing a trend to decrease (Figure-1). When we evaluated the delta variation of

Table 1 – *Bixa orellana vs. placebo in BPH. Characteristics of the studied population.*

	Bixa Orellana (n = 68)	**Placebo** (n = 68)	**p Value**
Age	61.4 ± 7.1	62.4 ± 7.3	0.42
Time of disease (years)	2.0 ± 1.6	2.4 ± 2.1	0.21
Family background of PCa	3	5	0.47
SAP_r	124.1 ± 13.1	121.9 ± 13.3	0.33
DAP_r	70.2 ± 13.7	67.9 ± 9.1	0.25
SAP_s	125.0 ± 12.3	122.8 ± 13.3	0.31
DAP_s	69.6 ± 8.3	67.6 ± 9	0.18
Body weight	69.5 ± 10.3	70.1 ± 13.1	0.76
Cardiac frequency	72.4 ± 7.2	72.3 ± 7.3	0.93
Hemoglobin (mg/dL)	133.4 ± 23	137.3 ± 9.4	0.23
Creatinine (umol/L)	81.0 ± 11.9	83.0 ± 13.6	0.31
Bilirrubins (umol/L)	23.6 ± 73.8	16.3 ± 15.1	0.42
AST (U/L)	31.4 ± 8.4	31.4 ± 9.2	0.99
ALT (U/L)	30.9 ± 13.6	30.1 ± 12.0	0.71
Urine pH (U/L)	6.3 ± 0.7	6.4 ± 0.6	0.37
PSA (ng/mL)	2.1 ± 1.8	2.2 ± 1.7	0.74
Prostatic volume (cc)	31.9 ± 20.3	35.0 ± 17.5	0.34
Post void residual urine (cc)	121.5 ± 62	113.9 ± 58.2	0.46
Qmax (cc)	10.6 ± 2.7	9.6 ± 3.2	0.052

SAP_r = systolic arterial pressure, resting; DAP_r = diastolic arterial pressure, resting; SAP_s = systolic arterial pressure, standing; DAP_s = diastolic arterial pressure, standing; AST = aspartate aminotransaminase; ALT = alanin aminotransaminase; PSA = prostatic specific antigen; Qmax = maximum urinary flow.

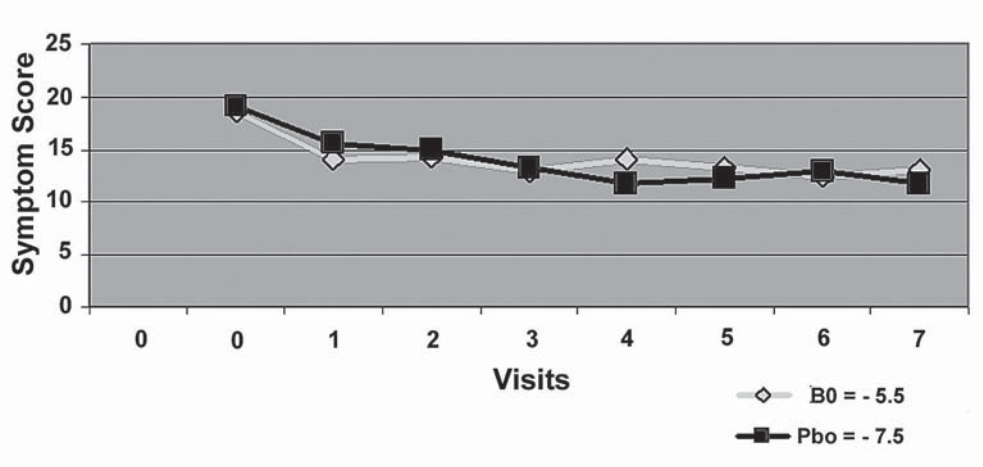

Figure 1 – *The variation of symptom score measurements during treatment shows the trend to decrease, for Bixa orellana (BO) = - 5.5 and placebo (Pbo) = - 7.5 scores, but without statistically significant differences. * p > 0.05 (in each visit); p > 0.05 (2 way ANOVA between groups).*

the means of symptom scores during each visit, we observed a trend to decrease and the final mean delta was similar for both groups (BO 0.79 ± 1.87 and Pbo 1.07 ± 1.49) (p = 0.33). Qmax mean variations were similar showing a trend to increase (Figure-2). In each visit the variations of the Qmax mean delta showed a trend to increase and the final mean delta was similar for both groups (BO 0.44 ± 1.07 and Pbo 0.47 ± 1.32) (p = 0.88). Even though post void residual urine mean variations was also similar in both groups with a trend to increase (Figure-3) and post void residual urine mean delta variations in each visit showed a trend to increase, the final mean delta was similar for both (BO 4.24 ± 11.69 and Pbo 9.01 ± 18.66) (p = 0.07). The answers of clinically significant improvements evaluated with RR and RD were similar for both groups. For symptom scores; BO vs. Pbo: RR: 0.97, RD: - 0.015 (- 0.18 – 0.15). For Qmax improvement; BO vs. Pbo: RR: 0.85, RD: - 0.059 (- 0.21 – 0.10). For post void residual urine improvement; BO vs. Pbo: RR: 1.14, RD: 0.044 (- 0.11 – 0.20) (Table-2).

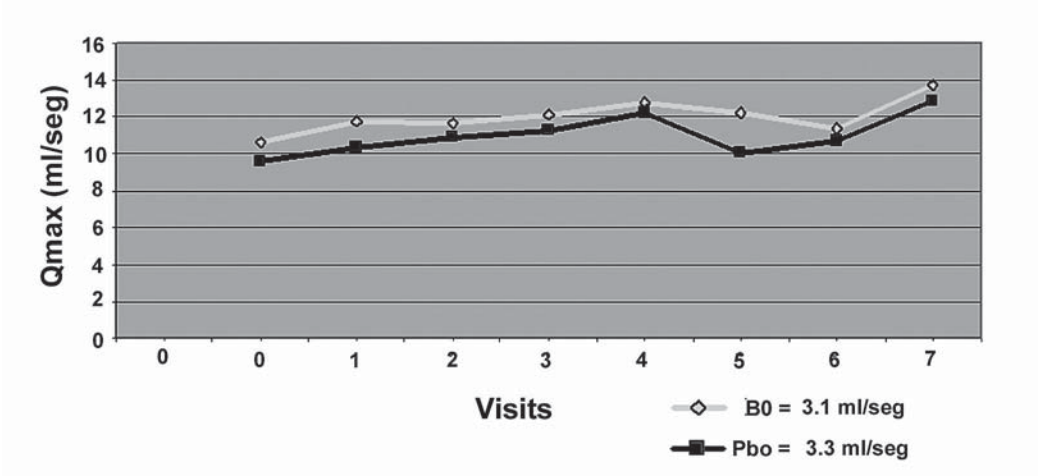

Figure 2 – *The variation of the Qmax means during treatment shows the trend to increase observed for Bixa orellana (BO) = + 3.1 mL/sec and placebo (Pbo) = + 3.3 mL/sec, but without statistically significant differences. * p > 0.05 (in each visit); p > 0.05 (2 way ANOVA between groups).*

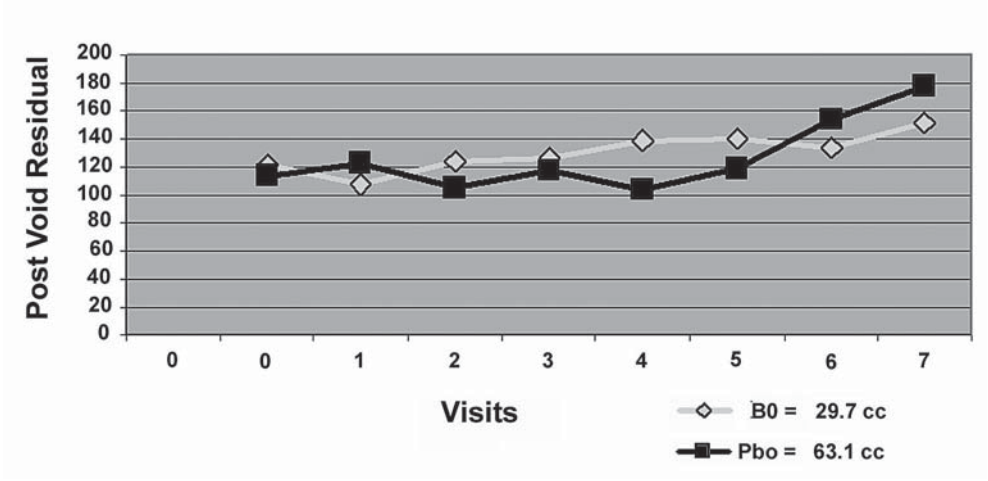

Figure 3 – *The variation of the post void residual urine means during treatment shows the trend to increase observed for Bixa orellana (BO) = + 29.7 cc and placebo (Pbo) = + 63.1 cc., but without statistically significant differences. * p > 0.05 (in each visit); p > 0.05 (2 way ANOVA between groups).*

Table 2 – *Bixa orellana (BO) vs. placebo (Pbo) in BPH. Evaluation of clinically significant answers.*

		Improvement	No Improvement	Total	RR	RD	IC 95%
Score-symptoms*	BO	37	31	68	0.97	- 0.015	(- 0.18 - 0.15)
	Pbo	38	30	68			
Qmax (mL/sec)**	BO	22	46	68	0.85	- 0.059	(- 0.21 - 0.10)
	Pbo	26	42	68			
Post void residual urine (mL)***	BO	24	44	68	1.14	0.044	(- 0.11 - 0.20)
	Pbo	21	47	68			

** decrease ≥ of 30% of symptom score; ** increase ≥ 30% or ≥ 3 mL/sec over the initial Qmax.; *** decrease ≤ 30% of the initial post void residual urine; RR = relative risk; RD = risk difference.*

Regarding adverse effects, we found that the patients of the BO group presented constipation (2.94%) and one form the Pbo group presented light gastritis (1.47%). This fact did not impede those patients from continuing in the study. When the last patient to enter the study completed 6 months of treatment, an external revising committee performed a temporary cut and when the results were disclosed the study was retained due to the fact that it demonstrated that the effect of BO was similar to that of the Pbo.

COMMENTS

There is not enough evidence to accept phytotherapy as an alternative to the urologist to treat patients presenting LUTS associated to BPH. The US National Institute of Health (NIH) has been conducting studies to determine the role of these agents even though in Germany and France some plant extracts have been registered to treat those patients (20). The WHO does not recommend phytotherapy as an appropriate treatment, mainly because there is little information available on well designed clinical trials utilizing placebo as a control. There are no studies with adequate sample size and segments to define the efficacy and tolerability in the long term of those plant extracts (21,22). Even though the US Department of Health and Human Services manifests that phytotherapeutic agents and other dietetic supplements are used in the whole world as treatment for patients with LUTS associated to BPH, the mechanism of action, effectiveness and security of such agents have not been well documented in multicentric clinical trials (6). One of the last publications shows the efficacy of a plant extract in the treatment of patients presenting LUTS associated to BPH, as equivalent to tamsulosin. This clinical trial was performed in 704 patients, from who 354 received Tamsulosin 0.4 mg/day and 350 Saw Palmetto berry (SPBE) 320 mg/day for a period of 12 months. The results show a decrease in the symptom score of 4.4 scores for both groups and an increase in the Qmax of 1.8mL/sec for those that received SPBE and 1.9 mL/sec for the ones that received Tamsulosin. The conclusions of this study show that SPBE and Tamsulosin are equivalent. In our opinion and coinciding with the editorial comments this conclusion is controversial, due to the fact that there is not a previous study with the same design that compares SPBE with Pbo. Under this circumstance it is not possible to differentiate the results of this study with that of Pbo (23). In relation to the mean symptom score, the patients from the BO had a decrease of 5.5 scores and those from the Pbo group of 7.5 scores, with a mean delta variation of symptom score for BO of - 0.79 ± 1.87 and Pbo - 1.07 ± 1.49 ($p = 0.33$) reaffirming the trend to decrease the symptom score in both groups (Figure-1). The decrease of the score in percentage showed an effect for BO equivalent to 54.4% and for the Pbo group to 55.9% ($p = 0.89$). The other variables showed the same trend and we could not find a coherent relation in the results; for example, the Qmax increased in both groups showing some benefit, but the post void residual urine had also increased showing a deleterious obstructive effect, those contradictory results reflect the absence

of significant differences between interventions. Various clinical trials have demonstrated that adrenergic alpha blockers such as terazosin, doxazosin and tamsulosin improve LUTS associated to BPH (24-29). Those evidences document the effect of the efficacy of alpha-adrenergic blocking agents in the treatment of patients presenting LUTS associated to BPH, information that is reinforced with the publications where it is revealed that surgeries related to BPH have decreased (30). We hope that BO has the same effects, as a product of our observation in the daily clinical practice, but in the light of these results, it is shown that there is no evidence that BO offers any therapeutic advantage to those patients. Thus, we emphasize that this product should not be used as phytotherapeutic in patients presenting moderate LUTS associated to BPH.

CONCLUSION

Bixa orellana compared with placebo in patients presenting moderate LUTS associated to BPH showed similar results in relation to symptom score, Qmax and post void residual urine.

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CONFLICT OF INTEREST

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EDITORIAL COMMENT

This is a randomized trial to study the effect of phytotherapy with Bixa orellana (BO) in patients with lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH). The study was sponsored by a pharmaceutical industry. This is a negative study, that is, the reported results did not show that BO is better than placebo in the studied population. The drug is used largely in Peru and probably the interest in the study is restricted to the populations in that area. But there is no other randomized clinical trial addressing this clinical question on pertinent literature, which justifies the publication of the article.

I have not heard about BO before this report. The message, after reading this paper, is that we should not use it in patients with LUTS and BPH. The conclusion of the authors is correct, that is, BO is not different from placebo in these patients. Therefore, urologists should not have this drug as an option for treating the condition.

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EDITORIAL COMMENT

The authors evaluated prospectively the use of the phytotherapeutic agent Bixa orellana and placebo in the treatment of lower urinary tract symptoms associated to benign prostatic hyperplasia. The study was well designed, with defined objectives and precise inclusion and exclusion criteria. The topic in general is contemporary, mainly due to the marketing relevance of phytotherapeutic agent in this segment of urologic practice. Nevertheless, Bixa orellana is a phytotherapeutic agent that is not well known worldwide, therefore its relevance is regional. The negative results found by the authors, present low impact in the urological literature.

However, because its well-designed methodology and seriousness of its development, this study would serve as a model for future similar publications, and therefore, its publications in a Journal of great circulation is justified.

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Long-Term Patient Satisfaction after Surgical Correction of Penile Curvature via Tunical Plication

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ABSTRACT

Objective: To assess patient satisfaction and functional results at long term follow-up after surgical correction for Peyronie's disease (PD) and congenital penile curvature (CPC) with the technique of tunical plication.
Materials and Methods: One hundred and two men operated for PD (n = 76) or CPC (n = 26) in four different departments of urology in public hospitals agreed to answer a six-question telephone questionnaire about treatment satisfaction. Tunica albuginea plication procedures represented the standard surgical approach. Subjects under investigation were correction of the deformity, feeling of bumps under the skin, pain during erection, penile sensory changes, development of erectile dysfunction (ED) and postoperative ability for complete vaginal intromission. Subjective response rates were compared using the chi square test on the basis of the etiology of the disease (CPC or PD).
Results: Significant differences ($p < 0.05$) between patients with CPC and PD were noticed in the prevalence of postoperative penile deformity, sensory changes, ED and ability to complete vaginal intromission, PD patients always showing a more pessimistic view. No significant differences (p = ns) were detected in terms of unpleasant nodes under the penile skin or pain during erection.
Conclusions: Long-term outcome after surgical correction for PD and CPC with the technique of tunical plication can be poor. Probably patient expectations are above the real performance of surgical techniques. Preoperative information should be more exhaustive.

***Key words**: penis; Peyronie's disease; surgery; erectile dysfunction*
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INTRODUCTION

Peyronie's disease (PD) and congenital penile curvature (CPC) are the most frequent causes of penile deformity. PD is an acquired disorder of the tunica albuginea of the penis characterized by the formation of a plaque of fibrotic tissue, which may be associated to penile deformity, pain on erection and erectile dysfunction (ED). PD affects up to 9% of men (1,2). CPC is caused by asymmetry in compliance of tunica albuginea of the corpora cavernosa due to developmental arrest during embryogenesis (3). Mostly, ventral and/or lateral deviation of erected penis occurs. The reported prevalence of this condition is 0.04 - 0.6% (4,5).

Pharmacologic therapy has limited efficacy in both entities. Surgical treatment is necessary when significant curvature does not allow coitus. Rarely, penile deformity is also associated with psychological problems in adults with PD disease, but this is a frequent concern in younger patients.

While postoperative satisfaction is the rule, a number of patients find some side effects of surgical procedures unacceptable; apart of residual curvature, frequent reasons for dissatisfaction are unpleasant feeling of bumps under the skin (6), penile sensory changes and penile shortening (7), among others.

The aim of our questionnaire-based study was to assess patient satisfaction and functional results at long-term follow-up after surgical correction for PD and CPC using tunical plication procedures.

MATERIALS AND METHODS

Two hundred and forty men operated for PD or CPC throughout a 16-year period (January 1990-December 2005) using tunical plication techniques were contacted by telephone and invited to answer a six questions questionnaire about treatment satisfaction.

For different reasons (wrong telephone numbers, patient or spousal reluctancy) telephone contact was impossible in 124 cases. Eventually contact was substantiated in 118 cases. One hundred and two patients (102/240, 42.5%) agreed to participate.

Difficulty with intercourse was the most frequent preoperative complaint (82/102, 80.4%). Poor self-image accounted for the rest of consultations (20/102, 19.6%). At the time of surgery, the disease was stable for at least 1 year, and there was no pain.

The diagnosis of PD was based on a palpable penile plaque or acquired penile curvature. Preoperatively the deformity was assessed from self-photographs. Degree of angulation was not recorded. No reliable records on preoperative potency were available. Nevertheless, it is not our policy to use plication procedures in PD or CPC patients also diagnosed with ED; it could be indirectly induced that patients in our study were potent before surgery.

Thirty-one different urologists in four different public hospitals participated in operations. Circumcision was performed to avoid postoperative edema and paraphimosis. After penile degloving, a tourniquet was applied at the base of the penis to facilitate artificial erection injecting saline into the corpora cavernosa through small gauge butterfly needles. Tunica albuginea plication procedures represented the standard surgical approach; briefly, Buck's fascia opposite to the point(s) of maximal curvature was incised to expose the tunica albuginea. No major differences between PD and CPC cases in terms of tissue dissection could be accounted. Care was taken to avoid injury to neurovascular structures. Transversal or longitudinal (Yachia's modification for treatment of CPC) plication sutures of unabsorbable materials (mainly polyester) were placed through the full-thickness of the tunica albuginea. A new artificial erection was created at the end of the procedure to confirm that penile straightening was adequate. Once correction was achieved, the penis was closed in layers and a light compression dressing applied.

A specialized clerk assistant contacted all patients. Subjects under investigation were postoperative correction of the deformity (yes/no), feeling of bumps or lumps under the skin (yes/no), pain during erection (yes/no), penile sensory changes (yes/no), diminished erection (yes/no) and inability to complete vaginal intromission due to penile deformity (yes/no).

Subjective response rates were compared using the chi square test on the basis of the etiology of the disease (congenital or acquired). A commercial software (SPSS v.11.5) was used for statistical treatment. Confidence intervals (CI) of 95% were used for all comparisons.

RESULTS

Median time from the intervention to the interview was 56 months (min 1, max 194). Mean age at surgery was 48.6 years (SD 15.4, min. 12, max. 69). Table-1 shows the principal patients' characteristics at diagnosis.

According to the patient answers, correction of the curvature was only achieved in 50% of the cases (51/102). Similarly, 41 patients (41/102, 40.2%)

Table 1 – *Patient characteristics.*

	Peyronie's Disease (n = 76)	**Congenital Penile Deformity** (n = 26)	**p Value**
Age at surgery (mean, SD)	54.5 yrs, 10.7	31 yrs, 14.5	Students' t test < 0.001
Follow-up (mean, SD)	70.5 months, 46.5	55.9 months, 39.8	Students' t test = 0.16
Preoperative inability for penetration (%)	65/76 (85.5)	17/26 (65.4)	chi square test < 0.001

SD = standard deviation.

complained of suture-related complications as unpleasant feeling of bumps under the skin; in 24.5% of the cases (25/102), pain was present during erection while 56% (57/102) suffered penile sensory changes. Forty-eight patients (48/102, 47.1%) declared some degree of postoperative ED while 46 out of 82 (46/82, 56.1%) preoperatively unable to have vaginal penetration due to penile deformity were eventually able to complete sexual intercourse.

A significant difference (chi square = 0.006) was noticed in terms of subjective improvement in penile deformity between patients with CPC (19/26, 73.1%) and PD patients (32/76, 42.1%). Also, postoperative sensory changes were significantly more prevalent (chi square = 0.001) among PD patients (50/76, 65.8%) compared to patients with CPC (7/26, 26.9%). Different degrees of postoperative ED were significantly more prevalent among PD patients (60.5% and 7.7% for PD and CPC patients, respectively). The proportion of men with CPC able to complete vaginal intromission after surgery (15/17, 88.2%) was significantly higher (chi square = 0.003) compared to the results in PD patients (31/65, 47.7%). No significant differences (p = 0.21) were detected in terms of unpleasant nodes under the penile skin or pain during erection. Table-2 summarizes this phase of the study.

COMMENTS

Treatment end points after surgical correction for penile curvature include erection that is pain-free, coitus comfortable for patient and partner, and deformity that does not interfere with vaginal intromission.

Overall, the reported success rate with tunica albuginea plication procedures is 85-100% (8-11); in our experience, patient dissatisfaction was the rule. Why such discrepancy? Most studies dealing with postoperative outcome rely on non-validated questionnaires thus making comparisons pointless

Table 2 – *Postoperative results according to patient interview. Denominator used for the analysis of question #6 was different since only patients complaining of difficulties for preoperative vaginal intromission were taken into account for calculations.*

		Peyronie's Disease (n = 76)	**Congenital Penile Deformity** (n = 26)	**p Value**
Question #1	Deformity corrected (%)	32/76 (42.1)	19/26 (73.1)	chi = 0.006
Question #2	Bumps under the skin (%)	27/76 (35.5)	14/26 (53.8)	chi = 0.10
Question #3	Pain during the erection (%)	21/76 (27.6)	4/26 (15.4)	chi = 0.21
Question #4	Penile sensory changes (%)	50/76 (65.8)	7/26 (26)	chi = 0.001
Question #5	Postoperative erectile dysfunction (%)	46/76 (60.5)	2/26 (7.7)	chi < 0.001
Question #6	Postoperative ability for penetration (%)	31/65 (47.7)	15/17 (88.2)	chi = 0.003

(12,13). It is generally agreed that self-applied validated questionnaires should be used when possible. Nevertheless, there is no well-structured questionnaire for penile curvature correction. The present study was based in a telephone interview using a 6-questions questionnaire elaborated ad hoc. It is difficult to disclose to what extent it really reflects the domain of patient post-operative satisfaction; it might well be mirroring dissatisfaction with the medical establishment or translating couple frustration. In our four centers, tunical plication procedures are considered "low complexity" surgical interventions; this is why mainly general urologists participated in surgical interventions. It remains a matter of speculation if technical aspects were responsible for the current results. In spite of this limitation, a clear difference in outcomes was detected between patients with congenital and acquired disease. It has been suggested that after tunica albuginea plication procedures the force of penile erection might allow the sutures to cut through the albuginea layers thus partially explaining a number of failures. This hypothesis does not explain the differences detected in the present study between PD and CPC patients. Actually, our results are in contradiction with already published material, using absorbable sutures where younger patients (< 24 yr) had a higher chance of suture failure than elder patients (14).

Long-term results of plication techniques in the pediatric setting are rarely reported, but success seems to be the rule (8,9,15,16). In our experience, the long-term degree of subjective satisfaction among patients with CPC was remarkable and supports the philosophy of corporoplasty in this setting.

In our study, more than half of the PD patients declared unresolved difficulties for complete vaginal intromission after surgery; again, the degree of satisfaction of patients with CPC in this topic was higher, perhaps reflecting a better long-term anatomical result.

Some authors have raised concerns about the possibility of postoperative loss of glanular sensation (7,10,11). In our study, penile sensory changes were more prevalent in PD patients. While the surgical principles were identical for both PD patients and patients with CPC, it is unlikely that technical aspects could explain those differences. Indeed, most of CPC were ventral thus deserving dorsal plicatures, which theoretically could result in a higher rate of damage to the dorsal sensory nerves. Anyway, diminished postoperative penile sensitivity due to irritation and/or damage of the dorsal neurovascular bundles can be avoided by careful attention to spare the penile dorsal nerves.

A common problem after plication procedures is the formation of granulomas around the sutures at the plication sites. Palpable induration and irregularity have been noted by patients in previous studies (6,12,15). In this study, postoperative induration was highly prevalent. Probably this was one of the most objective questions in our questionnaire thus ending in similar results both for patients with congenital and acquired (PD) penile curvature.

Postoperative de novo pain during erection is a frequent complaint after plication procedures (17-19). It can act against full sexual activity in up to 60% of the patients (17,19). In this experience, while highly prevalent, no major differences between patients with CPC and PD were noticed. It is also remarkable the prevalence of different degrees of subjective impotence among PD patients. Due to the nature of the study -questionnaire-based and focused in overall results of plication procedures- it cannot be clarified if the reported incidence of different degrees of ED really translates late side-effects of curvature correction or it simply mirrors naturally occurring events. What is evident is that CPC patients' answers to question #6 were significantly more optimistic.

In general, comparisons between men operated for CPC and PD yield interesting findings. In previous studies, satisfaction results were almost identical in both settings (16,20). In our experience, the differences affected all aspects including those related to the curvature correction, perhaps reflecting a better performance of plication techniques in the management of totally stable deformity, as in congenital curvatures; in other words, it might be that patients with PD presumed stable were still in progression. Otherwise, it is difficult to explain why plication techniques were more successful in patients with CPC in terms of mere curvature correction. Given most of them presented with ventral deformities, it could be argued that Nesbit procedures are more effective in this particular type of curvature. This has

not been proven yet. Another hypothesis to explain the differences detected in this study is that younger patients could have a more optimistic approach to the postoperative outcome. It has been reported elsewhere that quality of life issues heavily depend on age (21,22).

Anyway, achieving a good correction at the end of the case (as shown in all cases in our study by creating an artificial erection) represents a subjective criterion for clinical success that does not necessarily means that patients will be satisfied in the long run (11). Quality of life is multifactorial and aspects related with sexual life can be even more complicated. Subjectivity could be playing a very important role in this study. A more elaborated approach to the performance of tunical plication procedures in the field of penile deformity correction is needed.

CONCLUSIONS

Long-term results of surgical correction for penile deformity, via tunica plication, in the hands of general urologists - irrespectively of patient's age at surgery and etiology - can be poor. Patient expectations are above the real performance of surgical techniques. Probably, preoperative information should be more exhaustive.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Long term outcome of surgery for penile curvature is quite important to evaluate the durability of the procedure and treatment strategies. Authors presented a poor long term outcome of tunical plication surgery especially in cases with Peyronie's disease (PD).

One crucial point is timing of the surgery. In cases with congenital penile curvature, the direction of curvature is usually ventral and the surgery is usually performed at diagnosis. On the other hand, in cases with PD, their presenting symptoms are plaque, painful erection and penile deformity at erection, and the surgery should be performed once the disease has stabilized. There are some differences in treatment strategies between both groups though tunical placation was performed for penile curvature.

Another point is a surgical procedure. Surgical approaches for the correction of PD can be divided into three basic categories; tunical plication, plaque excision (incision) and grafting procedures, and penile prosthesis implantation (1). In addition, new insights of penile anatomy (2,3) plication technique (4) have been reported. Timing of surgery, understanding of the penile anatomy, selection of surgical method and the meticulous surgical procedures to preserve neurovascular bundles may be important to improve the long term outcome and to reduce the complications.

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EDITORIAL COMMENT

It is unexceptionally advisable on penile curvature correction surgeries regardless of using Nesbit procedure, tunical plication or a grafting surgery in the literature. These procedures might, subsequently, be regarded as easy uro-surgical works. Among them, the plication surgery seems to be recently popular because of its simplicity and reproducibility. Should their outcomes be consistently reliable since all methods are based on a traditional description of the tunica albuginea in which a single layer with uniform thickness and strength circumferentially is unequivocally depicted (1)?

After the efforts of chronological studies have been made we find that the three dimensional ultra-architecture of tunica albuginea is, however, a bi-layered structure with inner circular and outer longitudinal collagen bundles which account for the variable thickness and strength circumferentially and can be clearly seen even under naked eye with an os-equivalent structure - distal ligament extending into glans penis (2-4). The outer longitudinal layer is the determinant tissue of establishing penile morphology as well as functional integrity since it is essential in making the most ideal environment in the entire human body to apply Pascal's law which depicts that pressure applied to any part of the enclosed fluid at rest is transmitted undiminished to every portion of the fluid and to the walls of the containing vessel (5). It is the tissue being operated during penile morphological reconstruction surgery because it acts as the wall. Therefore, it is not surprise to see this unfavorable report on the tunical placation surgery since this determinant layer is consistently overlooked in urology literature.

Some adverse complications are not indispensable since the surgical tissue is the tunica albuginea where neither significant vascular or lymphatic vessels nor nominate nerve is distributed. After degloving of the tissues superficial to the Colle's fascia is made, we consistently use a hydro-pressure technique in which normal saline solution is injected into the expected surgical region between the tunica albuginea and its overlying tissue in order to expand and separate them before immobilization attempt. This is very helpful in facilitating the completeness of dissection at minimal expense of damaging the neurovascular bundle otherwise (6). A postoperative penile sensory change is no more observed as usual. Similarly, the prevalence of penile lump can be minimized while using finer 6-0 nylon suture to replace a coarser-unabsorble ones. Besides from these interesting observational factors in this study in order to avoid the penile shortage which was frequently complained postoperatively by patients who underwent either a modified Nesbit procedure or a tunical plication surgery despite it is not remarkable from surgeon's view, a grafting surgery was, therefore, meticulously developed and recommended despite it is challenging and might be away from consensus (7,8). Accordingly, on penile morphological surgery all procedures seem intriguing rather than easygoing uro-surgical entities, which should be more exhaustive preoperatively as advised by authors in this study. Overall, it appears that neither surgical methodology nor surgical outcome for penile curvature correction, including tunical plication method, has been elucidated already. Further scientific study is warranted.

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EDITORIAL COMMENT

This paper tries to compare the outcome of tunical plication surgery for congenital curvature of the penis and Peyronie's disease (PD). This is a retrospective study based on cases done over a 16-year period.

The cases were done by 31 urologists, which does not reflect uniformity in surgical technique. One drawback of this study is the fact that there is no documentation of preoperative erectile dysfunction. Peyronie's disease is frequently associated with erectile dysfunction. Inability for penetration could be due to penile deformity, erectile dysfunction (ED) or a combination of both.

The congenital curvature group has a lower mean age (31 years). This group is more likely to have good erectile function and be satisfied with the results of surgery, even if there is some amount of residual curvature.

On the other hand, the mean age of the PD group is significantly higher (54.5 years). The incidence of preoperative erectile dysfunction will be higher and very likely to contribute to patient dissatisfaction with surgery. Surgery could lead to worsening of ED.

The apparent difference between the two groups in ability to have penetration may be a reflection of the difference in erectile function and may not be a difference in surgical outcome.

The authors are correct in stating that preoperative information should be more extensive in Peyronie's disease surgeries.

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Relation between the Area Affected by Fournier's Gangrene and the Type of Reconstructive Surgery Used. A Study with 80 Patients

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ABSTRACT

Objective: To assess the affected skin area and the reconstructive techniques used in 80 patients affected by Fournier's gangrene.
Materials and Methods: Eighty patients ranging in age from 19 to 85 years (mean = 51) affected by Fournier's gangrene were studied. When admitted to the emergency room the patients were submitted to clinical and laboratory examinations to analyze the gravity of the case. All patients were submitted to an extensive debridement of the lesion, urinary derivation by cystostomy and colostomy whenever necessary.
Results: Only 13 patients (16.25%) died. From the 67 remaining patients, in 44 (65.6%) debridement was restricted to the scrotum, in 10 (14.9%) there has been scrotum and penile lesions and in 13 (19.3%) there has been a debridement of the scrotum and the perineal region. In 11 cases (16.4%) there was no need for reconstructive surgery with wound closing by second intention, in 16 cases (23.8%) reconstructive surgery was performed with mobilization of local skin, in 19 (28.3%) we have used skin grafts, 20 patients (29.8%) needed reconstructive surgery with the use of skin flaps and in 1 case (1.4%) there has been the use of skin flaps and grafts simultaneously.
Conclusions: Fournier's gangrene is a serious pathology and should be treated aggressively with an extensive debridement of the area with necrosis. The use of precocious reconstructive surgery of the genitals present good results and tends to greatly reduce the length of hospital stay and improve the psychological conditions of these patients.

***Key words**: scrotum; genitalia; infection; Fournier´s gangrene; reconstructive surgical procedures*
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INTRODUCTION

The occurrence of gangrene in the genitals is rare but potentially lethal (1). The Fournier's gangrene is characterized by an acute necrotizing fasciitis of an infectious origin that affects the genital, perineal and perianal regions. The infectious process leads to a thrombosis of the subcutaneous vessels resulting in skin gangrene (2). The Fournier's gangrene is an urologic urgency that needs a precocious diagnosis and aggressive treatment with the use of wide spectrum antibiotics and surgical debridement (1,3).

In spite of the development of new treatment techniques, the rate of mortality of Fournier's gangrene is close to 50% (2,4). Many conditions are associated to this pathology, the main ones are diabetes, alcoholism, immunosupression, local trauma and genitourinary infections (2). Patients presenting with acquired immunodeficiency syndrome also present a higher predisposition to the disease (2). The clinical

condition presents evolution from 2 to 7 days and is characterized by uneasiness, fever, gangrene of the genitals and leukocytosis (5). Generally, the infection is caused by 3 or more germs, being the most common the E. coli, Proteus, Enterococcus and anaerobes (2,6).

The treatment of choice for the Fournier's gangrene is aggressive surgical debridement. The use of hyperbaric therapy with oxygen is an adjuvant treatment to this pathology, recently described and with satisfactory results (7). The surgical wound can heal by second intention or need further flaps or grafts for a better evolution (8).

The aim of this work is to correlate the extension of the genital area affected by the Fournier's gangrene with the type of treatment used to reconstruct the genitals.

MATERIALS AND METHODS

From January 1996 to January 2006, 80 patients ranging in age from 19 to 85 years (mean = 51.18) affected with Fournier's gangrene were studied. When admitted in the emergency room the patients were submitted to clinical and laboratory exams to analyze the gravity of the case. The typical aspect of the genitals of a patient with Fournier's gangrene is demonstrated in Figure-1. After assessment of pulse, respiratory frequency, arterial blood pressure and temperature and the presence of associated pathologies, they were submitted to blood analyses, including electrolytes, creatinine, leukocytes, hematocrit, glucose and serum bicarbonate.

***Figure 1** – Patient presenting Fournier's gangrene affecting the scrotum.*

All patients had the gangrene area quantified according to the classification mentioned by Laor et al. (9) and divided in the following groups: A) Isolated gangrene of the scrotum, B) gangrene of the penis and scrotum, C) gangrene of the scrotum with extension into the perineum and D) Gangrene with extension up to the abdominal wall. After classification, the patients were submitted to an extensive debridement of the lesion, urinary derivation with cystostomy and colostomy whenever necessary.

RESULTS

Only 13 patients (16.25%) died due to septic shock, from those three died during debridement and 10 in the immediate postoperative period. Laboratorial exams of the dead patients presented important alterations in the full blood count, glucose and renal function. Because they were submitted to a reconstructive treatment of the genitalia, these patients were excluded from the study. The division of the 67 remaining patients according to the area of necrosis can be seen in Table-1. From the 67 patients, 44 (65.6%) were from group A, with a lesion restricted to the scrotum, 10 (14.9%) were from group B, presenting a lesion of the scrotum and penis (Figure-2),

***Table 1** – Distribution of the 67 patients divided in 4 groups according to the area affected by Fournier's gangrene. A) Isolated gangrene of the scrotum, B) Gangrene of the penis and scrotum, C) Gangrene of the scrotum with extension into the perineum, D) Gangrene with extension up to abdominal wall.*

Groups	Cases (%)
A	44 (65.6 %)
B	10 (14.9 %)
C	12 (17.9 %)
D	01 (1.4 %)
Total	67 (100%)

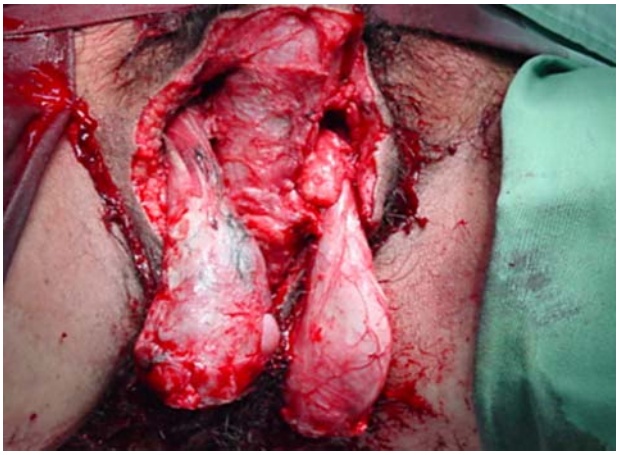

Figure 2 – *Patient presenting Fournier's gangrene after debridement. The lesion affected the scrotum and the penis. Note bilateral exposure of the testes.*

12 (17.9%) were from group C, being necessary the debridement of the scrotum and perineal region and 1 patient (1.4%) was from group D, presenting necrosis extending into the abdominal wall.

In 27 cases (30.2%), all from group A, there was no need for plastic surgery with rotation flaps or grafts; in 11 cases the wound closure was by second intention and in 16 cases reconstructive surgery was performed with local skin mobilization. In 19 cases (28.3%); 9 from the group A and 10 from the group B, we have used skin graft (Figure-3); 20 patients (29.8%) need a reconstructive surgery with the use of skin flap (8 from group A and 12 from group C) and in 1 case (1.4%) there has been a use of flap and graft simultaneously, in a patient from Group D (Table-2).

Complications of reconstructive surgery occurred in 7 cases (9.8%), being infection in 5 cases (3 patients submitted to grafts and 2 submitted to flap) and loss of flap in 2 cases.

Figure 3 – *Postoperative aspect of the reconstructive surgery of the scrotum with thigh skin graft.*

COMMENTS

Aggressive treatment with extensive debridement of the lesion and the use of broad-spectrum antibiotics is the best chance of cure for Fournier's gangrene (6,10). Previous studies demonstrated that 100% of the patients that were not submitted to debridement died (11), while only 6% of the patients submitted to debridement died. Some authors commend debridement for both the tissue with apparent necrosis and the tissue with doubtful viability and extension to health areas (5); however, this more aggressive treatment can be challenged because it leads to larger tissue loss making it more difficult the healing and extending the patient's recovery period (5).

One of the most important prognostic factors in gangrene of the genitals is the extension of the necrosis (9). Patients with gangrene area between 0 and 3% rarely die (12), while patients that present with an area affected by the gangrene larger that 5% have a poor prognostic (12).

The scrotum was the area most commonly affected by the gangrene. In our study in most of the cases, it was restricted to the scrotum (65.6%) and in 14.9%, it was associated to penile lesions. In a previous study by Benizri et al. (5), there is evidence that

Table 2 – *Type of treatment used in the 67 patients affected with Fournier's gangrene.*

Type of Reconstruction	Cases (%)
Closure by second intention	11 (16.4%)
Local skin mobilization	16 (23.8%)
Skin graft	19 (28.3%)
Skin flap	20 (29.8%)
Flap + graft	01 (1.4%)
Total	67 (100%)

in most of the cases the Fournier's gangrene affects the scrotum or the penis isolatedly (5). In this study, there were a significant number of cases presenting extension to the abdominal wall (54%) (5), which were rare in our series, occurring in only 3 of 80 patients studied (3.75%).

Surgical debridement can lead to extensive skin defects of the genitalia, perineum and anterior abdominal wall. Even though these defects present a satisfactory healing by second intention, this process can be slow and reconstructive surgery might be necessary (13).

Reconstructive surgery of the genitalia in Fournier's gangrene can be considered only after an improvement of the patient's clinical condition (13). The main objective of the genitalia reconstruction in Fournier's gangrene is efficient coverage of skin loss with maintenance of penile functions (erection, ejaculation and voiding) (13-15).

The extension of the disease and the mortality rate are controversial themes in literature. Some studies report that the extension of the disease is related to a higher death rate (16), while other studies report that the extension of the gangrene do not relate to a poorer prognosis (4). The extension of the gangrene should be analyzed together with the clinical condition of the patient and the Fournier's gangrene severity index, recently described, is a good prognostic value to the patient's evolution (17). In our study from the 13 patients that died 6 were from group A, 5 from group B and only 2 presented with the gangrene affecting the abdominal wall (group D).

The skin defects of the external genitalia and of the perineum lead to a significant morbidity and the reconstructive surgery with coverage of the lesion leads to a fast and good improvement of the patient (8). Many authors use the remaining prepuce or the scrotal skin to cover skin defects (13), however free grafts are easy to be done, are versatile and present good cosmetic aspects. The flaps present superior cosmetic aspects, even though the donating sites are limited and present a higher morbidity (8). The grafts are frequently used in the treatment of traumas, burns, avulsions and suppurative hidradenitis**,** presenting better results in contaminated areas.

From the 40 patients that needed reconstructive surgery in only 7 (9.8%) we observe complications, without statistical significant difference between the graft and the flap. In the other 33 patients (90.2%), the reconstructive surgery did not present complications and the esthetic aspect was satisfactory.

CONCLUSION

The Fournier's gangrene is a serious pathology with a high mortality rate and should be treated aggressively with antibiotic therapy and extensive debridement of the area presenting necrosis. The use of precocious reconstructive surgery of the genitalia present satisfactory results and tends to reduce the period of hospital stay and improve the psychological conditions of these patients.

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Scrotal Neoplasia: Would Truck Drivers Be At Greater Risk?

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ABSTRACT

Objective: To analyze how scrotal neoplasias have been managed during the past decade and to question possible factors or professions associated to its presence.
Materials and Methods: We retrospectively evaluated every case reported from 1995 to 2005 at our hospital. We described the clinical scenario, complementary exams, treatments and outcomes. We also tried to verify if there was any risk, predisposing factors or professions that would explain the cancer origin.
Results: Six cases were reviewed. Out of these, three patients were truck drivers. Five of them showed restricted lesions without inguinal lymph nodes enlargement. Histologically, six patients presented squamous carcinoma, with two of them having the verrucous type. The median age of patients was 52 years old (31 to 89). The five patients who are still alive had their lesions completely removed with safety margin and primary closure.
Conclusions: We have noticed that the scrotal carcinoma behavior is similar to that of the penis, where removal of the lesion and study of the regional lymph nodes help to increase the patient survival rate. The outstanding fact was that three out of six patients were truck drivers, raising the hypothesis that such profession, maybe due to the contact or attrition with the diesel exhaust expelled by the engine or to sexual promiscuity, would imply in a larger risk of developing this rare neoplasia.

Key words*: urogenital neoplasms; scrotum; squamous cell carcinoma*
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INTRODUCTION

Scrotum malignant neoplasia is a rare disease and it has been occasionally reported. Its historical context is always remembered as it was initially described by Bassius, in 1731, and soon after that by Treyling, in 1740. However, in 1775, in the famous report "Cancer Scroti", Sir Percival Pott was the first one to link these tumors to chimney sweepers and, since then, this disease has been considered the first occupational neoplasia described in the medical literature. Noticing that these professionals had precarious hygiene, he advised them to take a daily bath. Soon after, the Danish association of chimney sweepers requested daily hygiene from their members, which reduced the incidence of the disease (1,2). This incident was considered one of the first and the most effective interventions in Public Health. Nowadays, scrotal cancer corresponds to 0.1/100,000 cases a year in the USA. Even in America, the largest oncological hospitals have, at the most, a few dozen cases in their files (3). In Brazil, it has been reported in a ship's engine operator (4). Scrotal cancer is extremely similar to penis tumors, and its management has been based on the protocols adopted for the latter. We reported the six cases seen at our hospital during

the last decade and reviewed the literature on the subject.

We retrospectively analyzed the cases of malignant scrotal neoplasia seen in our service from 1995 to 2005. Six cases were reported. Even if briefly, we took the time to describe the clinical scenario, diagnostic and therapeutic strategies adopted, and the evolution of every specific case. Besides, we also tried to verify if there was some risk, predisposing factor or profession that would explain the origin of this neoplasia.

CASE REPORTS

Case #1 - B.S., 45 year-old black male, truck driver. Nine months before the initial visit, he noticed the appearance of a lesion in the scrotum, which had developed into a urethro-scrotal fistula. The patient was submitted to incisional biopsy, which demonstrated a squamous cell carcinoma. The lesion was considered irresectable and, during staging exams, the presence of bilateral inguinal lymph node and pulmonary metastasis was noticed. In July 1995, the patient was submitted to systemic radio and chemotherapy with BEP - bleomycin, etoposide, and cisplatin. The overall clinical status of the patient worsened and he died of sepsis in November 1995.

Case #2 - J.C.S., 49 year-old black male, farmer. Ten years before the initial visit, he was submitted to perineal cutaneous urethrostomy in another hospital due to complex and recurrent stenosis of the urethra. Three months prior to coming to our hospital, he noticed a scrotal nodule, close to the urethrostomy. The patient was submitted to incisional biopsy, which was diagnosed as squamous cell carcinoma. Staging exams did not show any metastasis. In August 1998, the patient was submitted to a complete removal of the lesion, with a safety margin of 2.0 cm. The lesion dimensions were 6.0 x 4.0 x 2.5 cm. The result was compatible with the biopsy, with free margins. He progressed with stenosis of the perineal urethrostomy, which was solved with urethral dilations. The patient is still alive and well.

Case #3 - J.A., 52 year-old white male, truck driver. Five years ago, the patient noticed a vegetative tumor mass of slow growth in the scrotum, which ulcerated and did not heal. In May 2004, the patient was submitted to excisional biopsy of the lesion, which measured 4.0 x 2.5 x 2.5 cm. The result demonstrated a well-differentiated infiltrating squamous cell carcinoma (grade-I) with verrucous pattern. The staging exams did not show any metastasis. The patient is doing well, without signs of recurrence or dissemination.

Case #4 - C.F.B., 89 year-old white male, retired farmer. Eighteen months prior to his first visit, the patient noticed a 3.0 cm ulcerated lesion in the left hemiscrotum, presenting tumoral aspect. The patient was submitted to incisional biopsy, and the result showed squamous cell carcinoma (grade-II). In April 2004, the patient was submitted to wide resection of the lesion (4.5 x 3.5 x 2.9 cm), with a 1.0 cm safety margin. The result was similar to that of the biopsy, with free margins. The patient missed the follow-up and returned only in August 2005, presenting left inguinal tumoral lymph nodes, 8.0 cm wide, without mobility, with possible deep invasion, and considered irresectable. The scrotal scar had a good aspect. The patient was referred to radiotherapy and chemotherapy. Since then he is seen on an outpatient basis.

Case #5 - J.C.A., 51 year-old brown male, truck driver. Ten years prior to the initial visit, the patient noticed the beginning of verrucous lesions in the pubic and scrotal areas. The patient sought medical aid and was treated for condylomatosis with topical application of podophyllin for countless times. Most of the lesions disappeared, except for a scrotal lesion that continued progressing and, three months before evaluation, it had reached 8.0 cm and was ulcerated. In December 2004, the patient was submitted to resection of the left hemiscrotum and study of the inguinal sentinel lymph node through the dynamic lymphoscintigraphy technique by use of ^{99m}Tc and patent blue dye. The result was grade-I verrucous carcinoma with free margins and the removed lymph node was negative. The patient is doing well, without signs of recurrence.

Case #6 - A.A.S., 31 year-old male, clerk, HIV positive. Two years prior to the initial visit, he noticed a red flat lesion, somewhat squamous, in the right hemiscrotum. He sought medical aid and was treated with topical cortical therapy without success.

The lesion developed, increased in size, and ulcerated. In July 2005, the patient was submitted to excisional biopsy that evidenced a low grade squamous cell carcinoma. The patient did not present evidences of inguinal lymph nodes enlargement and is seen on an outpatient basis.

COMMENTS

Being initially described over 250 years ago and soon after, associated to the contact with the soot regarding chimney cleaners, scrotal neoplasia is considered the first occupational neoplasia recorded in medical literature (1,2). Today, it is a known fact that the responsible agent for these cases of neoplasia is the carcinogen 3:4-benzpyrene, a hydrocarbon found in coal (5). The disease has some defined iatrogenic causes in its genesis: the Fowler's solution, an arsenic composition which has been used to treat psoriasis in the past; the association with psoralene and ultraviolet A radiation (PUVA) also employed in the treatment of this disease, causing solar keratosis and epidermoid dysplasia (6,7); and the radiotherapy used in the treatment of scrotal eczema or groin lymphoma (8). Besides the role of hygiene as a probable cause, mechanical or chemical irritation is also questioned because there have already been cases reported in carriers of hypospadia, the scar of Fournier's gangrene, and spinal cord injury with urinary incontinence and chronic use of rubber urinals (9-11). From the total of patients, three were truck drivers, professionals who do not always practice the ideal type of hygiene, besides being exposed to diesel exhaust and having mechanical attrition of the scrotal area. In these workers, there are significant positive trends in lung cancer risk with increasing cumulative exposure to diesel exhaust (12). High risks have also been reported for other sites: skin, larynx, bladder, and kidney (12). There has been recorded a little higher incidence of scrotal carcinoma in the Iranian nomad (old Persia) population, who used to carry bags containing embers of coal underneath their clothes to keep them warm in the winter. Another issue to be raised is the role of HPV viruses, especially HPV16 and HPV18, in the genesis of a less aggressive variant, the verrucous carcinoma. These viruses are the same ones related to penis cancer (8). Likewise, truck drivers are traditionally considered one of the most sexual promiscuous groups in Brazil (13).

In the genesis of basal cell carcinoma, which corresponds to 5% of scrotal neoplasia, the etiology in question is immunosuppression due to aging, UV rays used in other sites, and the previous use of radiotherapy.

The natural history of scrotum cancer seems to be very similar to that of the penis and the protocols applied to the latter can be applied to the former (1).

Clinically, the lesion is usually presented isolatedly in the 6th decade of life, with slow growth, ulcerating after six months. Since it takes patients from eight to twelve months to seek medical help, a biopsy of the scrotum should be performed whenever suspicious growth is present (1).

The differential diagnosis should be chosen between squamous cell carcinoma, which is the most common lesion, and other neoplasias, such as malignant melanoma, reticular cell sarcoma, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, basal cell carcinoma, extra mammary Paget's disease, Bowen's disease (in situ carcinoma), epithelial dysplasia and epithelioid sarcoma (14); benign lesions should also be taken into account: sebaceous cyst, acanthoma, hemangioma, leiomyoma, lymphangioma, fibroma, lipoma, myxoma, pigmented nevus, syphilis, psoriasis, eczema, periurethral abscess, tuberculous epididymitis and cutaneous schistosomiasis (15). Scrotal metastatic neoplasias are also uncommon and they have already been recorded as originating from the lungs, kidneys, ureter, bladder, appendix, and colon (16-20).

The preferred diagnostic method is the excisional or incisional biopsy, depending on the extension of the neoplasia.

The staging follows the basic principles of penis neoplasia staging: physical exam describing the extension and depth of the lesion, palpation of inguinal lymph nodes, pelvis imaging exams (CT or MRI) to evaluate pelvic lymph nodes and thorax X-ray to evaluate the lungs. There are records of dynamic scintigraphy (study of the sentinel lymph node) with use of ^{99m}Tc and the patent blue dye, similar to the method described for penis cancer (21). In cases #5 and #6 described here, we used this technique, and it

was possible to remove one inguinal lymph node ipsilateral to the scrotal lesion.

When treating the primary lesion, the intervention must be fast, just like it happens in penis cancer. The reason is that the survival rate is low if the disease progresses, with 30% of deaths happening soon after the progression (22). This is what has happened in case #1 of the present series.

The excision with a surgical margin of 2 cm is recommended, followed by primary closing of the incision or use of grafts or flaps if the wound is large. Testicles should be preserved whenever possible by maintaining them in its own hemiscrotum, or transferring them to the contralateral hemiscrotum (23). Whenever this procedure is not feasible, testicles should be buried in the thigh subcutaneous tissue or protected with musculoskeletal flaps. If there the testis is affected, inguinal radical orchiectomy should be performed, similar to the treatment given to primary testicular tumor (1).

Inguinal lymphadenectomy or prophylactic inguinal iliac lymphadenectomy, for non-palpable lymph nodes, is controversial and it should be kept for palpable tumors after the use of antibiotic therapy, a protocol that is also similar to that of penis carcinoma (1). Lymphadenectomy should be bilateral, since the superficial lymph vessels of the scrotum communicate freely. In the presence of pelvic invasion, the prognosis has been poor. Simplified inguinal lymphadenectomy, with the preservation of the saphena vein, should be the method of choice (1).

Radiotherapy can also be applied, especially for verrucous carcinoma or for patients who do not accept surgery. In one case report, a 6200 cGy dose, in 31 fractions, allowed local control and significant reduction of symptoms (24). In another report, radiotherapy was given as initial treatment to 9 of 65 cases and showed no increment to survival rate after adjustment for other variables (22).

Reports on the treatment of systemic disease are scarce. BEP is the scheme that is applied most often, being also similar to what happens on penis cancer (22,25).

The most important predictors of survival are stage and age at diagnosis. Survival rates varies progressively with combinations of these two variables regarding subjects younger than 65 years old and seen at diagnosis presenting a 5 years survival rate of 75% or more, compared with 17% for subjects who are 65 years old and older with regional or distant spread (22).

Contrary to what happens to most neoplasias, scrotal carcinoma seems to be heading for extinction. Most cases have been reported during the first half of the last century, and, nowadays, they are reported in an anecdotal way (2). If such forecast does not come true, it should be established, among other things, if the HPV virus has any relationship in the genesis of such neoplasia, in addition to accomplishing genomic study in the few described cases, and to confirming the role of the sentinel lymph node study with the use of the dynamic lymphoscintigraphy technique.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Primary malignant lesions of the scrotum are rare albeit they pose a particular concern for the urologist in terms of both diagnosis and management. There is a wide range of differential diagnosis and predisposing factors. In the present study, the authors raise the question of increased tendency of truck drivers towards developing these lesions, which is attributable to chemical exposure and risk of HPV infection. As indicated in this paper, the patients were admit at various stages of the disease and generally there is a long interval between the onset of the lesion and primary admission. Correct diagnosis with the aid of immunohistochemical studies and sufficient clinical staging followed by prompt management is of utmost importance. Radical resection is the mainstay of the treatment, and although the prognosis is generally poor, a subset of patients with advanced disease may achieve potential cure with systemic chemotherapy and/or radiotherapy.

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EDITORIAL COMMENT

The authors have presented a retrospective review of six cases of scrotal carcinoma over a decade. While the increased risk of scrotal cancer in chimney sweepers is well established, it is not specifically linked to a particular occupation in the modern era.

The health hazards of diesel exhaust have been highlighted before, but mostly in relation to lung cancer. Diesel exhaust is considered a probable human carcinogen by the International Agency for Research on Cancer. This was based on the occurrence of lung cancer among truck drivers, bus drivers and railroad workers, who are exposed to diesel exhaust.

The authors have raised an interesting question, regarding increased risk of scrotal cancer in truck drivers. The number of cases in this series is small. As scrotal cancer is rare now, it will require multi-center analysis of a large number of cases, to gain more information on this hypothesis.

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Case Report
International Braz J Urol Vol. 33 (4): 521-522, July - August, 2007

Urgent Penectomy in a Patient Presenting with Epidermoid Carcinoma of the Penis Associated to Myiasis

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ABSTRACT

The objective of this study is to describe the case of a patient presenting advanced epidermoid carcinoma of the penis associated to myiasis. A 41-year-old patient presenting with a necrotic lesion of the distal third of the penis infested with myiasis was attended in the emergency room of our hospital and was submitted to an urgent penectomy. This is the first case of penile cancer associated to myiasis described in the literature. This case reinforces the need for educative campaigns to reduce the incidence of this disease in developing countries.

***Key words**: penis; penile cancer; myiasis; amputation*
Int Braz J Urol. 2007; 33: 521-2

INTRODUCTION

Penile cancer is a rare neoplasia with low incidence in developed countries (0.1 - 0.9/100.000 in Europe and 0.7 - 0.9/100.000 in the United States). In developing countries, the incidence of this neoplasia is alarming with indexes that reach 2.9 - 6.8/100.000 in Brazil and 2 - 10.5/100.000 in India (1). Myiasis is defined as a disease caused by the infestation by larvae or maggots, of numerous species of flies (2). The occurrence of myiasis in the genitalia is rare. The objective of this article is to describe a case of myiasis in a patient presenting carcinoma epidermoid of the penis.

CASE REPORT

A 41 year-old patient came to the emergency room of our hospital presenting with dehydration, fever, paleness and claiming of strong pain in the genital region. On physical examination, we noticed an extensive necrotic lesion affecting the distal third of the penis (Figure-1A). We have also observed the presence of gross keratinizations in the lesion and an intense infestation due to myiasis (Figure-1B). The patient was previously healthy and had been hospitalized 2 years before to be submitted to a postectomy in another hospital. At the time of postectomy, a suspicious lesion in the gland was biopsied; however, the patient abandoned the treatment without knowing the result of the biopsy.

The patient was admitted, receiving hydration and venous antibiotic therapy, being immediately sent to the surgical unit, after the laboratorial exams were assessed. An urgent partial penectomy was performed with a safety margin of 2 cm and preservation of approximately 4 cm of the penile stump. The result of the pathology examination revealed a high-grade epidermoid carcinoma of the penis. The patient presented good evolution and is now in an outpatient follow up.

Figure 1 – *Patient affected by carcinoma epidermoid of the penis associated to myiasis. A) Note the extension of the necrosis, affecting the distal third of the penis. B) Magnification highlighting the myiasis that affected almost the totality of the necrosed area of the penis.*

COMMENTS

Myiasis is the infestation of the organs or tissues of host animals by the larval stages of dipterous flies, usually known as maggots or grubs. The fly larvae feed directly on the host's necrotic or living tissue, or in ulcerated mucosa and cavities (2). The most common form in men is in the skin, where the species Dermatobia hominis is the most common. The severity of the condition depends on the location and the degree of tissue destruction (2).

Penile cancer is very common in Brazil and the main risk factors of this neoplasia is phimosis, local chronic irritation, lack of personal hygiene and HPV types 16 and 18, that are present in around 50% of the patients with penile cancer. Neonatal postectomy is a significant protection factor for the occurrence of penile cancer (3).

In the present case, we observed a typical example of a misinformed individual, with precarious hygiene habits, leading to the aggravation of a condition that could have a less aggressive treatment in the initial phase. This is the first case of myiasis in a penile carcinoma described in the literature and serves as a warning, reinforcing the need to implement educating campaigns on penile cancer in developing countries.

CONFLICT OF INTEREST

None declared.

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Surgical Technique
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The Tunica Vaginalis Dorsal Graft Urethroplasty: Initial Experience

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ABSTRACT

Introduction: Nowadays, buccal mucosa grafts are the most successful method to reconstruct bulbar urethral strictures. Dorsal placement of the graft has been recently proposed, allowing the graft to be spread fixed on the tunica albuginea of the corporal bodies overlying the stricture. The dorsal graft is ingenious and represents a useful addition to the surgical armamentarium, since it offers a better chance for graft take than does the spongiosum when the urethra is diseased and poorly vascularized. We developed an additional reconstructive option using tunica vaginalis grafts, placed dorsally, for the treatment of anterior urethral strictures.
Surgical Technique: A total of 11 patients with anterior urethral strictures were treated with a tunica vaginalis graft urethroplasty. The surgical technique was done as described by Barbagli. The urethra was dissected from the corpora cavernosa and rotated 180 degrees. The dorsal urethral surface was exposed and fully opened. Both the distal and proximal lumina were calibrated. The tunica vaginalis graft was sutured, splayed and quilted over the corpora cavernosa using 6-0 PDS running stitches. The left side of the urethral mucosa was sutured to the graft using 6-0 PDS sutures. A 18F silicone Foley catheter was inserted at this point. The urethra was rotated back to its original position and sutured laterally to the right side of the graft. At the end of the procedure, the graft was completely covered by the urethra. With a follow-up ranging from 7 weeks to 5 months, all patients were voiding well (uroflowmetry > 14 mL per second).
Conclusion: This initial experience in 11 patients indicates that tunica vaginalis dorsal graft urethroplasty may be considered within the reconstructive armamentarium of genitourinary surgeons.

***Key words**: urethra; urethral stricture; urethroplasty; tunica vaginalis*
Int Braz J Urol. 2007; 33: 523-31

INTRODUCTION

Urethral reconstruction for trauma or stricture can require some of the most challenging techniques in urological surgery. Now that the role of urethrotomy has been drastically reduced, due to high long-term recurrence rates, urethroplasty is currently the best option to obtain a definitive cure for most urethral strictures (1).

Although an end-to-end anastomosis following resection of the diseased tissue is feasible for short localized strictures, additional tissue is often necessary for longer segments. Autologous nonurethral tissue grafts or flaps from genital and

extragenital skin, bladder, rectal and buccal mucosa have been used.

Two major topics have been introduced in the past decade in urethral surgery in adults: the use of buccal mucosa and the dorsal approach for urethroplasty. The dorsal approach proposed by Barbagli has proven to be an effective and successful treatment of urethral stricture disease with little morbidity (2). On the other hand buccal mucosa grafting for urethroplasty of both urethral stricture and hypospadias repair has gained widespread acceptance during the past 10 years.

To explore the possibility of urethral reconstruction with a graft of tunica vaginalis to treat long strictures we previously reported the use of tunica vaginalis graft as a novel substitute for urethral reconstruction in rabbits before performing the operation in patients.

We present our short-term experience with tunica vaginalis grafts, placed dorsally, for the treatment of anterior urethral strictures. To our knowledge we report the first use of tunica vaginalis graft in urethroplasty.

SURGICAL TECHNIQUE

Preoperative evaluation included clinical history, physical examination, urine culture, uroflowmetry, and retrograde and voiding cystourethrography in all patients.

The surgical procedure was performed with the patient under epidural anesthesia. With the patient in the lithotomy position, through a perineal midline incision, the bulbocavernosus muscle was divided and the bulbar urethra exposed.

The urethra is freed from the bulbocavernous muscles for its entire length and the muscles are fixed to a retractor using four stitches. The bulbar urethra is dissected from the corpora cavernosa (Figure-1). The urethra is rotated 180º and the distal extent of the stenosis is identified by gently inserting a 18F catheter with a soft round tip until it meets resistance.

The dorsal urethral surface is incised in the midline until the catheter tip and urethral lumen are exposed (Figure-2). The stricture is then incised along its entire length by extending the urethrotomy both distally and proximally. Once the entire stricture has been incised, the length and width of the remaining urethral plate is measured.

The tunica vaginalis graft is trimmed to an appropriate size according to the length and width of the urethral defect (Figure-3). All harvests were performed using our standard technique. The graft was then defatted and kept in saline until it was ready to be placed on the recipient site.

The opened urethra is rotated onto the right side and the graft is sutured, splayed and quilted over the corpora cavernosa using 6-zero running stitches (Figure-4). The right urethral margin is sutured on the right side of the graft. The urethra is rotated over the graft and the left side of the graft is sutured to the left side of the urethra. At the end of the procedure the graft is completely covered by the urethra (Figure-5). A 18 Fr silicone catheter was inserted in the reconstructed urethra and urinary diversion was performed using a suprapubic catheter for 2 weeks. A nonadhesive compressive dressing was used and left in place for 3 days. Patients were mobilized on the first postoperative day and were discharged home 3 days after surgery. Transurethral micturition started after 2 weeks, when voiding cystography showed a patent urethra without extravasation.

This technique has so far been used in 11 patients. The etiology of the stricture was infective in 6 patients, iatrogenic in 3 and not known in 2 patients. The clinical details of the patients are given in the Table-1.

The mean age was 53.1 years (range 21 to 77 years). The median length of the stricture was 3.9 cm (range 2.3 to 8). No blood transfusion was required.

No periurethral leakage at voiding cystourethrogram was observed (Figure-6). None of the patients complained of postoperative testicular discomfort.

Early postoperative complication occurred in 1 patient undergoing tunica vaginalis urethroplasty. This patient had a small scrotal hematoma that resolved with drainage. We follow the patients using a standardized protocol, including a questionnaire on patient satisfaction and determination of flow rate.

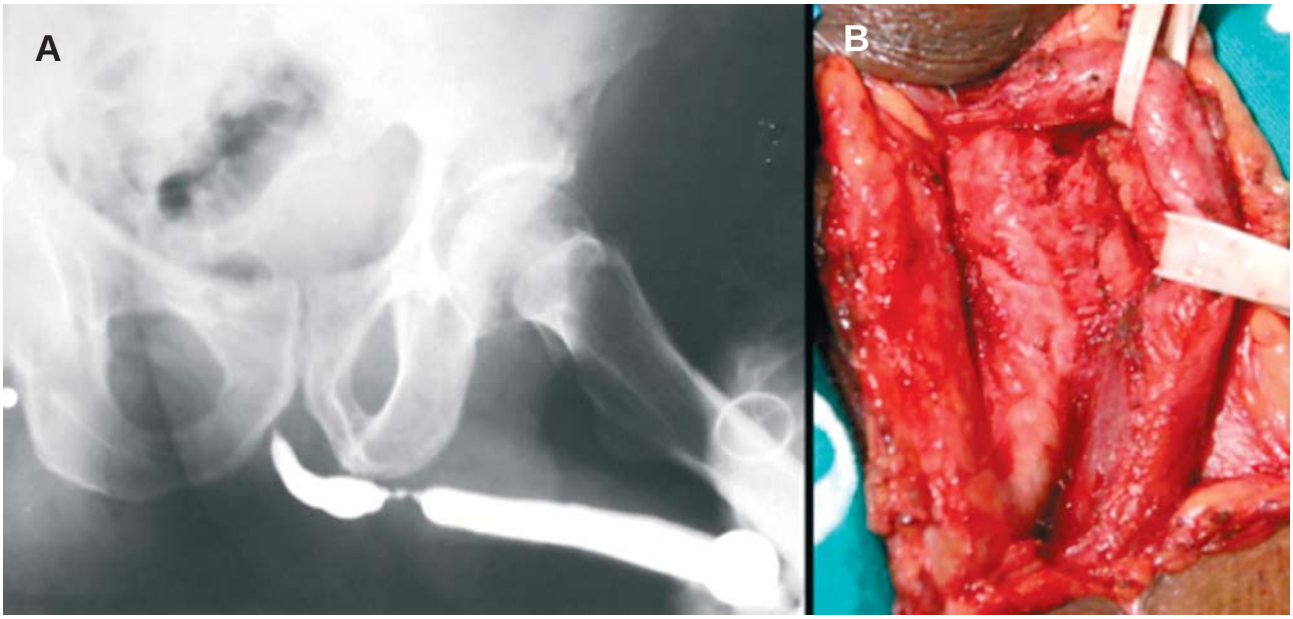

Figure 1 – *A) Retrograde urethrography showing the urethral stricture. B) The bulbar urethra is completely mobilized from the corpora cavernosa.*

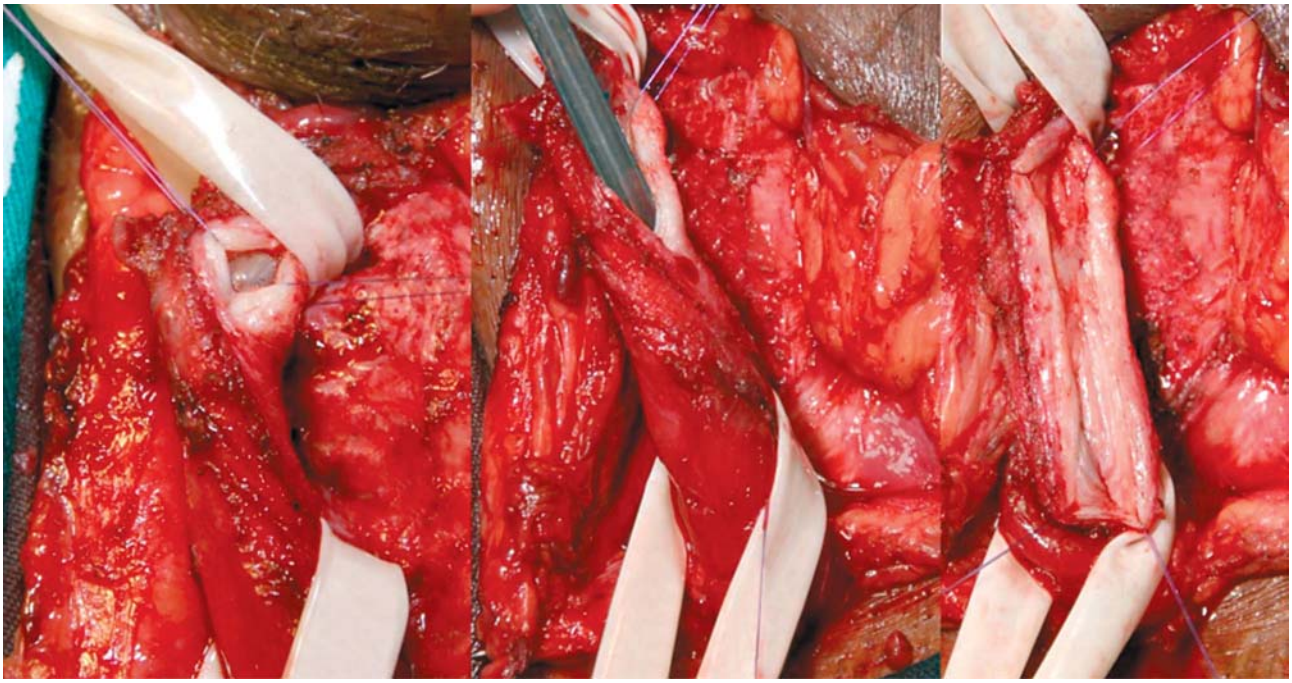

Figure 2 – *The urethra is rotated 180 degrees, and the stricture is incised along its dorsal surface.*

With follow-up ranging from 7 weeks to 5 months (mean follow-up 2.8 months), all patients were voiding well (uroflowmetry was more than 14 mL per second).

This study was approved by the Local Research Ethical Committee, reference number 025/2006. Informed consent was obtained from all patients.

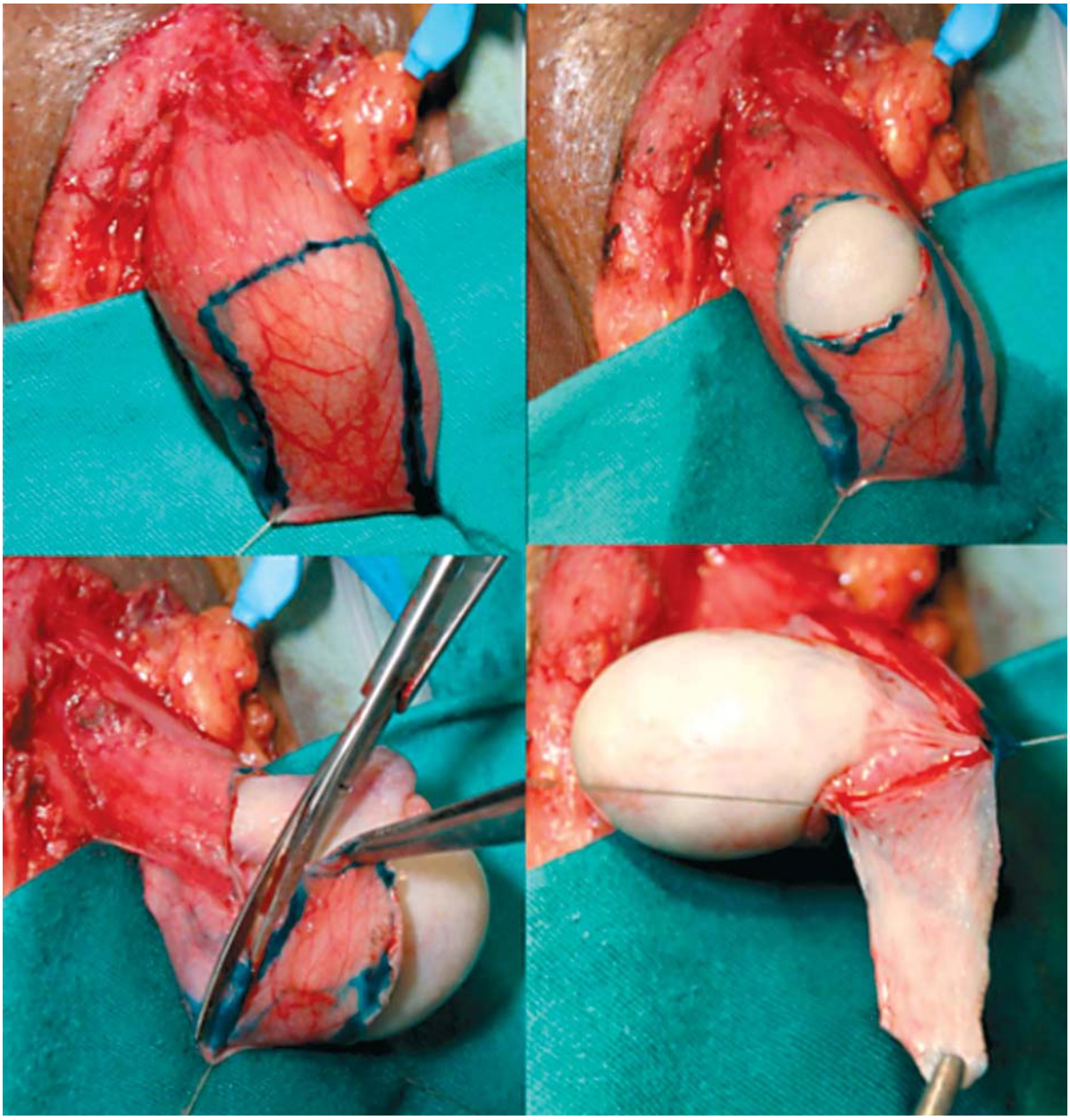

Figure 3 – *The tunica vaginalis graft was obtained by sharp dissection with fine scissors.*

COMMENTS

Surgery of the urethra for stricture disease is expanding because of the discouraging long-term high failure rate after urethrotomy. The use of new techniques and new urethral substitutes is challenging for the urologist.

In recurrent urethral strictures with failed prior internal urethrotomies, the indication is for an open approach. Similarly, urethroplasty may be the first option in long or multiple penile strictures, taking into account the high recurrence rates after internal urethrotomy. Although end-to-end anastomosis remains the method of choice in short uncomplicated

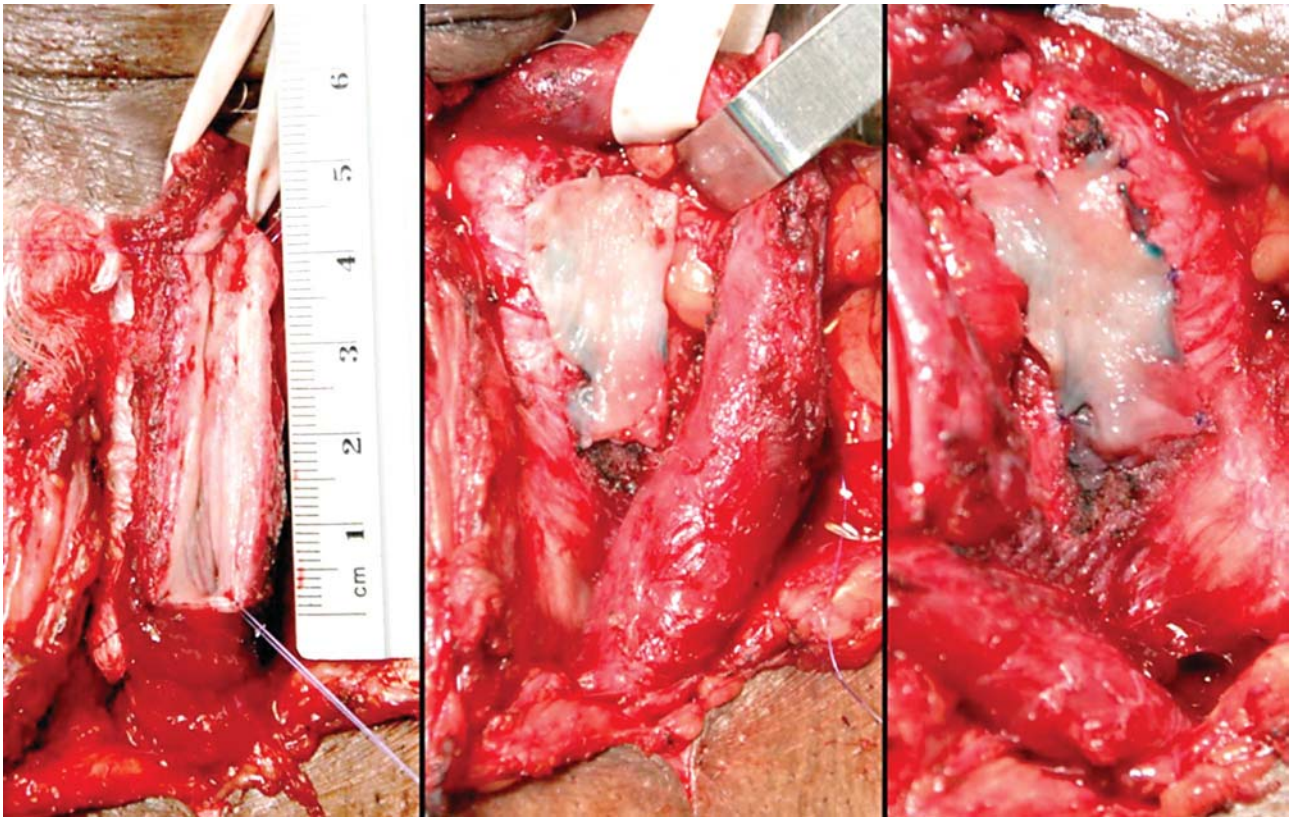

Figure 4 *– The tunica vaginalis graft was placed dorsally over the corpora cavernosa and tied with 6 running polydioxanone 6-0 sutures.*

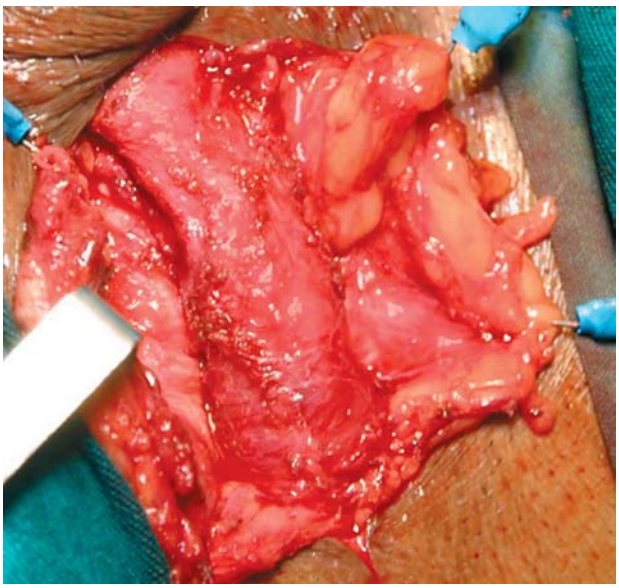

Figure 5 *– Final aspect of the tunica vaginalis urethroplasty. The graft is completely covered by the urethra.*

strictures, patients with a stricture length exceeding 1 to 2 cm or with complex strictures, particularly in the penile area, require urethroplasty with either genital or extragenital graft material (1).

During the last 10 years buccal mucosal grafts have secured an important place in the armamentarium of substitution urethroplasties for the treatment of congenital and acquired anterior urethral disease (3). Advantages of buccal mucosal as a free graft are that it is hairless, and has a thick elastin rich epithelium making it tough and easy to handle, with a thin and highly vascular lamina propria that facilitates inosculation and imbibitions. Buccal mucosa is relatively easily harvested from the inner cheeks or lower lip with reputed minimal morbidity but oral complications have been reported in 0% to 8.3% of patients (4). Buccal mucosal grafts are currently the procedure of choice in treating bulbar urethral strictures not amenable to excision and primary end-to-end anastomosis.

Table 1 – *Clinical data of the patients.*

Patient	Age (years)	Stricture Length (cm)	Etiology	Localization	Previous Treatments
1	77	5.0	Iatrogenic	Bulbar	No
2	50	3.4	Inflammatory	Bulbar	2 UT, 1 D
3	61	8.0	Iatrogenic	Bulbar	1 UT
4	65	3.4	Inflammatory	Penile	2 UT
5	66	2.3	Inflammatory	Penile	No
6	21	3.0	Inflammatory	Bulbar	No
7	64	3.2	Unknown	Bulbar	1 UT, 1 D
8	49	3.4	Inflammatory	Bulbar	1 UT
9	25	3.0	Inflammatory	Bulbar	No
10	37	4.0	Unknown	Penile	No
11	69	4.8	Iatrogenic	Penile	No

UT = urethrotomies; D = dilatations.

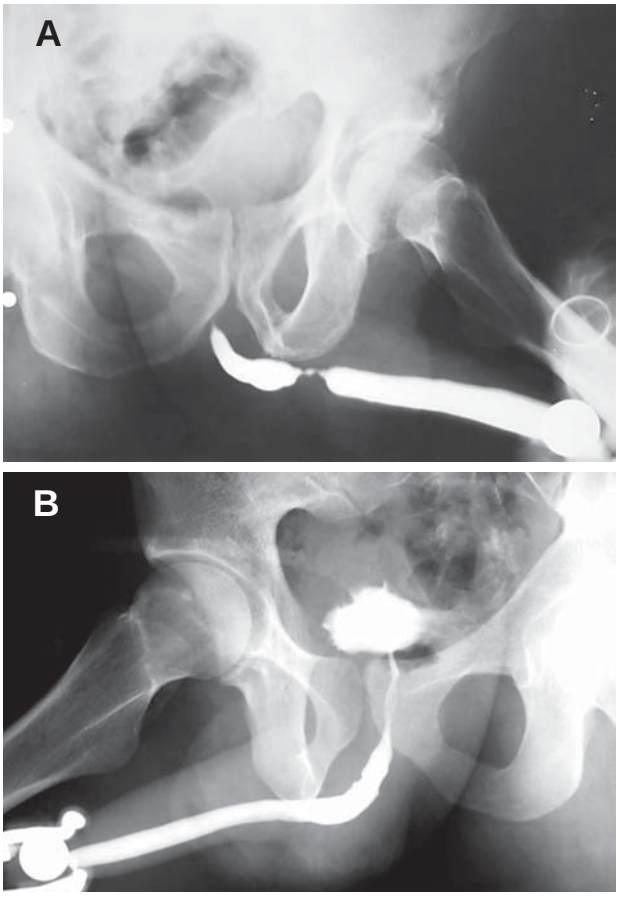

Figure 6 – *A) Voiding cystourethrogram showing a stricture. B) Voiding cystourethrogram after tunica vaginalis urethroplasty.*

Barbagli et al. (2) popularized the concept of dorsal grafts anchored directly to the corpora, which has possible advantages compared to ventral graft urethroplasty that include better mechanical support, a better blood supply to the graft, and prevention of urethral diverticula. The Barbagli technique also has another advantage. The incision through the corpus spongiosum is through the thinnest and, therefore, least vascular part of the urethra, making bleeding substantially less than after ventral incision of the stricture.

Using an animal model we evaluated tunica vaginalis graft as a substitute for buccal mucosa in dorsal urethroplasty. All animals demonstrated a patent and functional urethra, as evidenced by radiographic and histological analyses. There was no evidence of infection or fistula (5).

Tunica vaginalis graft is much easier to harvest than other materials and their application is faster. In addition, the donor site is near and the tissue is abundant. Use of the tunica vaginalis graft has the potential to significantly decrease operative time. The reduced operative time has remarkable advantages and helps prevent troublesome complications from prolonged high lithotomy position.

We realize that the study have some weaknesses. The main one is that the study has a short follow-up. The aim of this study was not the com-

parison of outcomes between penile skin, buccal mucosa and tunica vaginalis as substitute materials for urethroplasty. The present study only describes a new alternative in reconstructive urethral surgery and suggests the tunica vaginalis as the substitute material.

In our initial experience all patients had anatomically and functionally patent urethras as demonstrated by retrograde urethrography and uroflowmetry, but we know that the follow-up in this single study was brief. A wide series of patients with adequate follow-up are necessary to confirm our preliminary results obtained in this series.

CONCLUSION

This initial experience in 11 patients indicates that tunica vaginalis dorsal graft urethroplasty may be considered within the reconstructive armamentarium of genitourinary surgeons.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The search for an ideal urethral substitute carries on as investigators continue to evaluate various materials for substitution urethroplasty. Buccal mucosa has proven to be a versatile substitute for strictures involving the meatus and the entire anterior urethra. The morbidity following buccal mucosa harvesting is mild and not cumbersome for patients. With increasing reports of the success of buccal mucosa in urethroplasty, penile skin flaps are used more sparingly and the focus has shifted towards the use of free grafts. Newer urethral substitutes like colonic and tongue mucosa have been investigated as alternatives. The authors present results of a small study using the tunica vaginalis as a free graft on the urethra. There is experimental evidence to suggest that tunica vaginalis can be used successfully as a free graft for

urethral strictures. It also appears to be a less morbid procedure than buccal mucosa urethroplasty. As the follow-up is short and number of patients limited, no firm conclusions can be drawn regarding the long term durability of this technique. However, the authors provide a strong case for comparison of this technique along with other substitution methods of urethroplasty in a larger number of patients.

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EDITORIAL COMMENT

The use of tunica vaginalis in reconstructive urethral surgery was mainly suggested by pediatric urologists in hypospadias repair. The objective was to provide vascular and mechanical support to the reconstructed urethra in order to avoid fistula formation. For our best knowledge, the authors of this manuscript reported, by the first, the use of tunica vaginalis graft in adult bulbar urethroplasty. The authors honestly emphasized the weaknesses and the drawbacks of their study, including a very short follow-up. It can be speculated that the success rate of this new kind of urethroplasty will probably decrease with extended follow-up; it is a "natural evolution" of any kind of urethroplasty apart from the substitute graft material. History of reconstructive urethral surgery is full of new and different substitute materials for urethral reconstruction, but, unfortunately, the final, long term follow-up outcome of any kind of urethroplasty is probably influenced more by the original urethral pathology than by the substitute material used for the repair.

Surgical treatment of urethral stricture diseases is a continually evolving process, and urologists have changed over time the substitute material. In the '90s, skin grafts were the preferred substitute material for urethroplasty, but at present, many of us have left the use of skins graft. Up-to-date, buccal mucosa has become the most preferred substitute material in the treatment of urethral strictures as it is readily available in all patients and easily harvested from the inner cheek or lower lip and guarantees a concealed donor site scar and low oral morbidity. Buccal mucosa is hairless and has a thick elastin-rich epithelium, which makes it tough yet easy to handle, and a thin and highly vascular lamina propria, which facilitates inosculation and imbibition. These statements are now supported by literature evidence (1). In our experience, when we convey this message to the patients, they always appreciate it. Patients do not like to be considered as an experimental animal. For this reason, we are publishing all the results of our urethroplasties in an open and no-profit dedicate website (www.urethralcenter.it), to convey to the patients that the surgical technique we have selected for him is worldwide used in the urological community and the results of this technique are fully at his disposal. In the near future, every patient with a urethral stricture will be able to manage dedicated nomograms, which will predict his success and complication rate after surgery accurately on the basis of his age, of the site, of the length and the etiology of stricture.

This article is important for another reason. One of the basic principles in urethral reconstruction consists in the formation of an epithelialized tube from a buried strip of skin. In 1880, Duplay described a method for urethral construction in hypospadias, which was based on that principle, and reported the method that is usually associated with his name (2). In 1949, Denis Browne described a similar method for construction of the urethra in hypospadias (3). His method differs from Duplay's in a few essential respects. Over time, the Duplay's and Denis Browne's

principles, according to which the buried strip of intact epithelium becomes an epithelialized tube, is widely exploited in reconstructive urology. In 1980, Monseur described the first dorsal urethroplasty and fully quoted the Duplay's principle: "…En premier lieu, l'urètre c'est un tube natural. Si une bandelette de peu ou de muqueuse enfouie, selon le principe de Duplay, tend spontanément à se tubuliser, combine plus facilement le tube urètral transfromé en bandelette par une incision longitudinal reprendera-t-il sa forme préalabe! Elargir le canal ne suffit pas, il faut en fixer les bords" (4). In 1996 (reference 2 in the text), we have fully exploited the Duplay's-Denis Browne's-Monseur's principles. The authors of this article showed in the experimental model and in humans that a buried strip of tunica vaginalis becomes an epithelialized tube. One hundred-twenty-seven years later, these authors confirm and expand the ingenious Duplay's principle: each strip of autologus epithelial tissue has the potential to be used for urethral regeneration. This is an important message for people involved in tissue engineering studies.

This new surgical technique should be now included in the armamentarium of the reconstructive urethral surgeon. The reconstruction of urethral channel is a challenging problem, for instance, sometimes, in our daily surgical practice, we might ask ourselves what kind of repair we are going to do in a particularly unusual and complex case. The replay should be "let us use the tunica vaginalis graft as suggested in the International Braz J Urol in 2007!"

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Infantile Bladder Rupture during Voiding Cystourethrography

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ABSTRACT

Bladder rupture is rare during infancy and most of reported cases had urethral obstruction or neurogenic bladder. We report two cases of infantile bladder rupture during voiding cystourethrography (VCUG). This report reinforces the criteria for proper VCUG imaging procedure. Consideration of expected bladder volume for body weight, and close monitoring of bladder pressure and injection speed could prevent such complications.

***Key words**: bladder; children; diagnostic imaging; rupture; iatrogenic*
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INTRODUCTION

Voiding cystourethrography (VCUG) is widely applied for the radiological evaluation of the bladder and urethra in children. Bladder rupture during VCUG is exceedingly rare (1). We present two infants with iatrogenic bladder rupture during VCUG performed by radiology staffs in two district hospitals. These infants were referred to our center for further management.

CASE REPORTS

Case #1 - A 10-day-old boy, weighing 3.2 kg, was referred to nephrologists with history of prenatal hydronephrosis. On day 7 after birth, ultrasonographic exam confirmed bilateral hydroureteronephrosis, which was severe on the left side and mild on the right side. VCUG was requested to evaluate a possible vesicoureteral reflux (VUR). A 6F feeding tube was inserted into the urethra and contrast media was injected using a 50-mL syringe, under fluoroscopic guide. During the first filling cycle, severe left side VUR appeared following injection of 15 mL of contrast media (Figure-1) and the right VUR appeared in volume of 35 mL. However, the radiographer continued the instillation until the intraperitoneal bladder rupture occurred in volume of 60 mL (Figure-1). The baby was referred to urologist and immediately underwent abdominal exploration through a Pfannenstiel incision. The bladder dome was the site of a 2 cm long rupture. The peritoneal cavity was washed with saline and the bladder was closed in two layers using 4-0 polyglactin suture. A Malecot catheter was inserted in the bladder as suprapubic tube. A mini-vacuum closed drain was left in the perivesical space. The post-operative course was complicated by

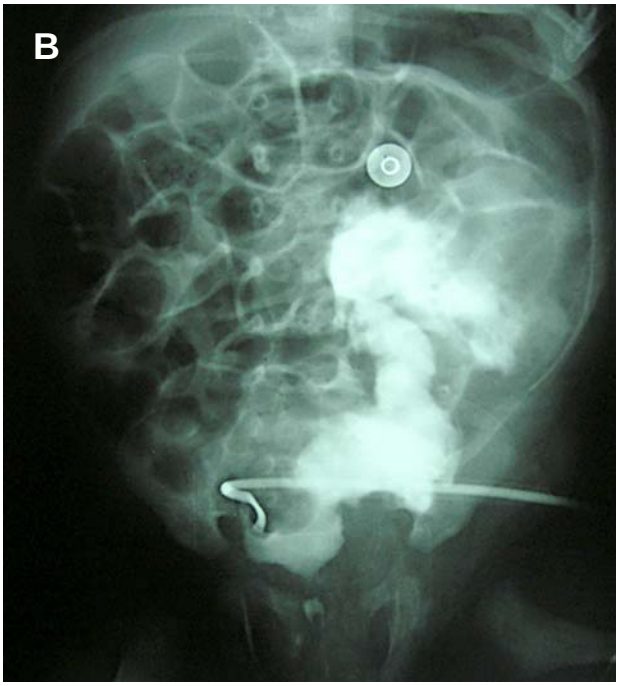

Figure 1 *– Voiding cystourethrography of case #1. A) High-grade vesicoureteral reflux on the left side. B) Intraperitoneal bladder rupture.*

prolonged urine leakage from the site of suprapubic catheter extracted on the 14th postoperative day. The child was referred to our institution for further management. A 6F Foley urethral catheter was inserted. After 7 days, the leakage was stopped and the catheter was removed on the 24th postoperative day. The patient was discharged 3 days later with good condition and prescription of prophylactic antibiotic (Figure-1).

Case #2 - A 9-month old female infant, weighing 7 kg, was referred to a radiologist for VCUG at a district hospital from a different province. Medical problems included urinary tract infection and failure to thrive. Contrast media was injected through an 8F urethral feeding tube under fluoroscopic guide. The radiographer instilled 100 mL of contrast media using a 50-mL syringe, during the first filling cycle. Speed of injection, bladder pressure and volume were not recorded. While reviewing the images, the radiologist discovered bladder perforation. She was taken to the operating room and underwent abdominal exploration. The bladder was exploded at dome with a 3 cm length. The site of perforation was closed in two layers using absorbable 4-0 polygalactin suture. A small Penrose drain was left in perivesical space and a 10F catheter was left per urethra. Post-operative course of the patient was uneventful and she was discharged one week later and referred to our clinic for further evaluation. Follow-up VCUG showed no leakage or reflux.

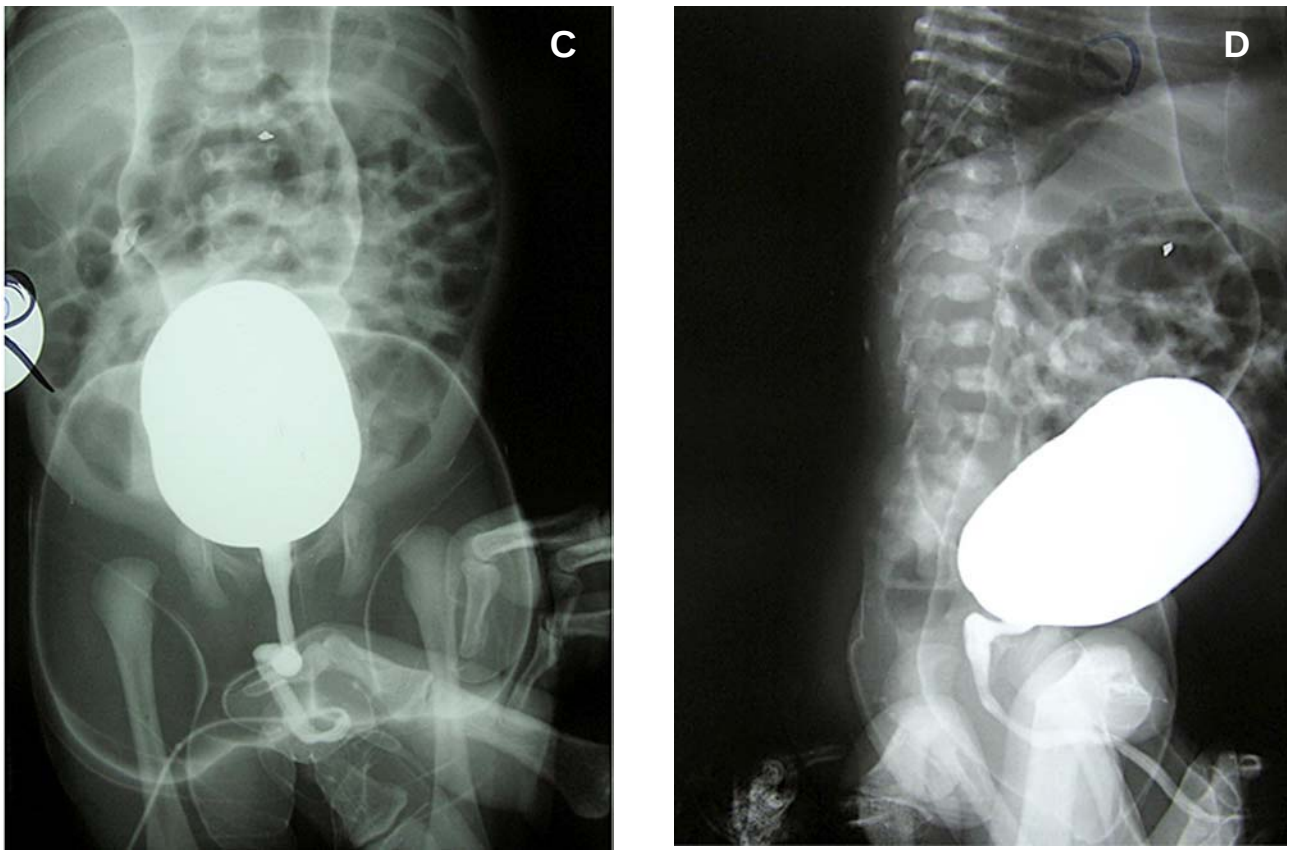

Figure1 – Voiding cystourethrography of case #1. C) and D) Frontal and lateral voiding cystourethrography views of the same patient after surgical repair.

COMMENTS

Infantile bladder rupture is rare (2) and only 17 cases have been reported between 1956 and 1985 (3). The main predisposing factors include posterior urethral valves and neurogenic bladder followed by bladder outlet obstruction from other etiologies and trauma (3). Few cases of iatrogenic bladder perforation have been reported in children following diagnostic and therapeutic procedures (3,4). To our knowledge this is the second report of infantile bladder rupture during VCUG (2).

There was none of the above-mentioned risk factors in our cases; however, inaccurate imaging procedure seems to be the main cause of perforation. In order to perform a safe and perfect VCUG, radiologists must pay attention to some factors such as bladder volume, style of contrast media instillation and patient conditions (underlying urinary disease) (1). Two formulae have been proposed for bladder volume estimation in children with regards to their weight and age (4,5); age < 2 years - bladder volume (mL) = weight (kg) × 7, age > 2 years - bladder volume (mL) = [age (years) + 2] × 30.

Proper catheter insertion, fluoroscopic guide, pressure and number of filling cycle should be considered in styles of instillation (1). To avoid pressure overload, hand injection of contrast material must not be used and the contrast container should not be placed higher than 60 cm from the patient. More than two cycles of filling does not appear to be necessary (1,6). The underlying urinary system disease is another important factor. In our cases, the bladder volume and pressure were not considered and the contrast media was instilled directly by syringe.

Management of infantile bladder rupture should be individualized. In the review by Trulock et al. (3), the majority of reported neonates were treated

with abdominal exploration and repair of the bladder leakage site; however some of the patients would be managed by the use of vesicostomy or urethral catheter alone.

In conclusion, during VCUG, it is important to consider the patient underlying disorder and expected bladder volume for age as well as to avoid hand injection of contrast material and placing the contrast container more than 60 cm higher than the patient. Moreover, in order to prevent high-pressure voiding in premature infants, it has been recommended to use small caliber and balloon-less feeding catheters that would not occlude the bladder neck during voiding.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

The authors of this manuscript present two cases of iatrogenic bladder rupture in infants undergoing voiding cystourethrograms. This radiographic study is one of the most common imaging studies ordered in children and needs to be performed safely and reliably. Those of us who work in dedicated children's hospitals take this for granted. However, the cases reported in this series were performed by radiologists clearly unfamiliar with proper technique as nicely outlined by the authors. It is important to remember that the peritoneum drapes quite anteriorly in small children thus making a rupture very likely to be intraperitoneal, as in these two cases, and therefore surgical exploration is required.

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Retroperitoneoscopic Renal Biopsy in Children

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ABSTRACT

Objective: We present our experience in a series of 17 consecutive pediatric patients submitted to retroperitoneal laparoscopic renal biopsy.
Materials and Methods: Retroperitoneal laparoscopic renal biopsy (LRB) was performed in 5 boys and 12 girls. Mean age was 8.1 years and age range from 2 to 12. Two or three trocars were used to expose the inferior pole of the kidney, remove enough cortical parenchymal specimen and fulgurate the biopsy site. Assessment included surgical time, estimated blood loss, hospitalization period, analgesia requirements, complications and number of glomeruli present in the specimen.
Results: LRB was successfully performed in all 15 patients (88%). In two cases, LRB was not possible to be performed. One patient was converted to a transperitoneal laparoscopy due to tear in the peritoneum. The other patient had had previous abdominal surgery and, during retroperitoneal balloon dilation, the peritoneum was opened and the open biopsy was performed. A third patient had postoperatively a perirenal hematoma, which was solved spontaneously. Complication rate was 17.6% (3/17 cases). Mean operative time was 65 minutes, while mean estimated blood loss was 52 mL, mean hospital stay was 2.2 days and mean analgesic requirement was 100 mg of tramadol. The mean number of glomeruli present in the specimen was 60.
Conclusion: Retroperitoneal laparoscopic renal biopsy in children is a simple, safe. Bleeding is still the most common complication. However, direct vision usually allows a safe control of this drawback. In our institution, laparoscopic approach is the chosen procedure in pediatric patients older than one - year - old.

***Key words**: renal biopsy; children; laparoscopy; complications*
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INTRODUCTION

Renal biopsy is an important procedure for renal disease investigation. Percutaneous needle renal biopsy (PNRB) is the most common technique to obtain renal tissue. However, there are absolute and relative contraindications such as solitary kidney, uncontrolled arterial hypertension, hemostasis disorders, renal artery aneurysm, Jehovah witness, percutaneous needle renal biopsy failure, morbid obesity and non-collaborative patients (1-4). In these situations, open renal biopsy (ORB) is the option through flank or posterior incision (5,6).

As an alternative to ORB in selected cases, some authors propose transperitoneal (7) or retroperitoneal laparoscopic approach (8-12). Laparoscopy allows potential advantages such as less postoperative pain, better cosmetic results, short hospitalization and convalescence (13,14).

Open renal biopsy was performed to obtain renal tissue samples in children before the laparoscopic

approach. We believe this procedure is safer than PNRB. In 2002, with the advent of laparoscopy and considering its potential benefits, we standardized the renal tissue sample through retroperitoneal route in children.

MATERIALS AND METHODS

Twenty renal biopsies were performed from April 2002 to February 2006 in children younger than 12-year old to different renal conditions. Seventeen children were submitted to retroperitoneal laparoscopic renal biopsy (LRB) and three were submitted to ORB. Large ascites in one patient, severe trombocitopenia in the second (fewer than 30,000 platelets) and low age (two-months-old) in the third child determined the choice for ORB.

The children's parents were informed about the procedure and the probability of choosing open surgery conversion. The study was evaluated and accepted by the ethics committee of the institution.

The procedure was performed under general anesthesia placing the Foley catheter in bladder and nasogastric tube. The patient was put in flank position in the renal side to be operated. The kidney bridge was elevated underneath the last ribs to increase the space between the costal margins and the iliac crest in order to create a larger retroperitoneal working area. Before the surgery, prophylactic antibiotics (cefalotin 50 mg/kg/24h) were administered.

A 1.0 to 1.5 cm incision was made in the tip of the 12th rib in the retroperitoneum. Through this incision, the retroperitoneal area was dissected and the peritoneum pushed forward. An additional retroperitoneal space was completed using balloon dissection whose function was to increase the working space and promote the hemostasis after the digital dissection.

Afterwards, a 10 mm trocar was placed and retroperitoneal area was created with CO_2 and a 10 to 12 mm Hg. Then, lower kidney pole was observed. A 5 mm trocar was placed in posterior lower axillary line, under laparoscopic view. Through the 5 mm trocar, scissors or biopsy grasper were used to perform 0.5 cm ellipsoid incision in lower renal pole or with a biopsy grasper. If necessary, a third 5 mm trocar was placed, behind the first one to facilitate renal surface exposition (Figure-1).

The biopsy bed was fulgurated with argon beam coagulator or pressed with gauze for 5 minutes. As a next step, oxidized cellulose could be used in biopsy bed. If there was no bleeding, retroperitoneum pressure was reduced to 5 mmHg and now, a new hemostasia revision was done. No drain was left. The nasogastric tube and Foley catheter were withdrawn after surgery. Analgesia was endovenous with tramadol (0.25 mg/kg/bolus) for every patient requirement by endovenous infusion pump plus dipirona (50 mg/kg/dose every 8 hours). The post-operative follow-up evaluated operation time, blood loss, intra and post-operative complications, hospital stay, cumulative

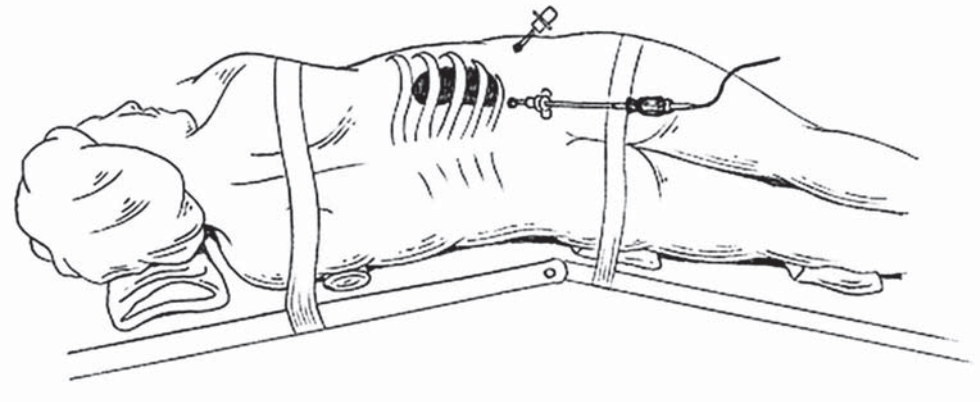

Figure 1 – *Patient position in operative table for retroperitoneoscopic renal biopsy.*

analgesia measure, histopathological diagnosis and glomeruli number.

RESULTS

LRB was performed in 5 boys and 12 girls. Patient data are listed in Table-1. Age ranges from 2 to 12 years old (mean 8.1 years) and mean operative time was 65 minutes (40 - 180 minutes). Hospital stay was 2.2 days. Three patients had complications. The first one, a 2-year old boy had peritoneum rupture during digital maneuver to create retroperitoneal area, which did not allow the completion of the retroperitoneal procedure. This surgery was performed by transperitoneal laparoscopic approach, using an additional trocar in left side in abdomen. The second patient had a huge peritoneum rupture, in the beginning of the surgery, thus not allowing laparoscopic procedure. This patient had been submitted to a previous open surgery (left hemicolectomy) due to inflammatory bowel disease. In both cases the hole in peritoneum is not repaired with sutures. The third patient had morbid obesity, which made it difficult to find the kidney in surgery. He lost blood in the first postoperative day and a 300 mL - perirenal hematoma was observed by ultrasound, and it was solved spontaneously. Mean analgesic doses were 100 mg of tramadol. All the samples presented renal cortex. Glomeruli mean per fragment was 60 (average 37 and 128).

COMMENTS

Renal biopsy is an important key in the diagnosis and treatment of some renal diseases. In some cases, flank incisions could lead to morbidity. Renal biopsy was reinforced after the report by Iversen & Braun showing PNRB as a safe, easy and less morbid method (15).

Table 1 – *Clinical features of patients submitted to retroperitoneal renal biopsy.*

Patient	**Age**	**Gender**	**Clinical Diagnosis**	**BMI**	**Operative Time** (min)	**Trocars**	**Stay Time**	**Analgesia** (tramadol)	**Operative Bleeding** (mL)	**Glomeruli Number**	**Complications**
1	7	M	NS	32	40	2	2	120	0	52	-
2	2	F	NS	23.6	85	3	2	60	25	37	transperitoneal conversion
3	7	F	ARF	24.5	50	2	2	200	0	46	-
4	9	F	LE	23.6	40	2	2	70	0	55	-
5	12	F	LE	55.6	180	3	2	150	100	150	perirenal hematoma
6	11	M	ARF	21.8	80	2	2	0	20	55	
7	10	F	HSP	18.5	75	2	2	0	0	128	
8	9	F	ARF	24	60	2	2	200	100	55	
9	6	M	ARF	24	60	2	2	140	0	80	
10	4	F	NS	25.7	73	2	3	0	100	100	
11	7	F	NS	13	52	2	2	200	0	28	
12	9	M	HSP	15	55	2	2	70	50	35	
13	10	F	NS	13.8	60	2	*	*	*	38	open conversion
14	11	F	HSP	14.7	40	2	2	0	0	50	
15	12	F	ARF	14.4	60	2	2	70	0	30	
16	9	F	NS	17.1	30	2	2	120	10	60	
17	6	M	NS	16.1	75	2	2	125	40	30	

M = male;F = female; NS = nephrotic syndrome; ARF = acute renal failure; LE = lupus erythematosus; HSP= Henoch-Schönlein purpura; BMI = body mass index.

Although PNRB is the standard procedure to obtain renal tissue samples nowadays, it is not indicated in different situations such as non-collaborative patients, failure to obtain samples for pathology tests, solitary kidney, morbid obesity and hematological disorders (1-4). In these cases, some authors suggest laparoscopic approach as an alternative to ORB (7-12,16).

PNRB could be done in children, but there are some drawbacks. They need some kind of sedation or general anesthesia for renal biopsy to be done under computerized tomography or ultrasound. In addition, PNRB presents some risks, which could lead to renal bleeding, arterio-venous fistulas and renal aneurysms (4,17,18). In laparoscopic approach, blood loss is minimized because biopsy bed is controlled quickly under direct view, which is not possible in PNRB. Another advantage of LRB is the high positivity about the renal samples (almost 100%) different from the needle method, which is around 90% of renal fragments (12,16-18). We believe LRB eliminates the necessity of another procedure.

In our study, two complications could be avoided. In order to avoid peritoneum tears during digital maneuver to create retroperitoneal space, this procedure must be carried out carefully because children have a thin peritoneum. However, not all peritoneal incidental lesions need to convert to open or laparoscopic transperitoneal approach because there could be CO_2 equivalence pressure between the intraperitoneal cavity and the retroperitoneum. Only in cases where there are big holes in the peritoneum, this maneuver could not be done, allowing the lowering of the peritoneal envelope on the retroperitoneal area, preventing the normal development of the procedure.

Caione et al. analyzed LRB in 22 children with the same parameters used by us (12). Data such as sample success and age were similar to our series. On the other hand, their operative time and hospital stay were shorter than ours according to Table-2.

As to the trocar numbers, we believe two are enough in most cases. In the beginning of our experience, we used three trocars. Usually, we only use the third trocar in hard cases, e.g. morbid obesity.

Obesity could complicate retroperitoneal access (16,19,20). It occurred in an obese patient, leaving a perirenal hematoma. It is not clear if the bleeding site was the biopsy bed or the perinephretic fat. It is hard to reach the renal lower pole in these

Table 2 – *Pre and postoperative clinical features and complications of patients submitted to laparoscopic renal biopsy.*

Author	**Study**	**Sample Success** (%)	**Age** (years)	**BMI**	**Operative Time** (min)	**Trocars**	**Stay Time** (days)	**Operative Bleeding** (mL)	**Complications**
Current series	17	100	8	21	65	2 (88%) 3 (12%)	2.2	52 (0-500)	2 peritoneum tears 1perirenal hematoma (17.6%)
Caione et al. (12)	20	100	9.2	-	40	2	1.2	0	1 peritoneum tear 1 conversion (obese patient)
Shetye et al. (16)	74	96	45	47.4	123	2	58% discharge in 1 day 18% discharge in 2 days	67 (5 - 2000)	3 hemorrhage episodes (25%) 2 inadverted biopsies 2 unsuccessful samples 1 bowel loop lesion 6 clinical complications (14.8%)

cases. Caione et al. performed the only open surgery conversion in an obese child, due to the difficulty of finding the operation landmarks (12). Yap et al. suggested the intra-operative ultrasound use in morbid obese to make kidney location easier for biopsy taking (20). Shetye et al. reported unexpected spleen biopsy in two cases in LRB in obese patients, showing that, in these cases, it was harder to set anatomic landmarks, due to excessive retroperitoneal fat. In a similar way, these complications were minimized with intraoperative ultrasound. Complication rate in this series of 74 patients (aged 3 to 74 years old) was 20%. The most frequent type of complication was hemorrhage, comprising 20% of all (16).

In our study, little analgesic was used and two children did not use it post - operatively. Cumulative analgesic average dose during hospital stay was 100 mg of tramadol and 500g of dipirone, which we believe to be very low. LRB complication rate ranges from 0.7 to 11% in adults (4,17,18). LRB can be an alternative procedure, as it is minimally invasive, with low complication rate and high successful sampling rate (Table-2).

As far as we know, this is the only series that uses LRB solely in children under 12 - years - old, because we believe that only this age range can benefit from this procedure. Caione et al. performed the laparoscopic approach just where PNRB could not be applied, because of uncontrolled hypertension, hematological disorders, anti-platelet medications and anatomic abnormalities (12). In teenagers, PNRB is regarded as a better, less invasive method, which does not require either sedation or general anesthesia, since most patients are collaborative.

CONCLUSION

LRB in children is a safe and effective procedure. At present this approach is used in our institution in children older than one year-old and younger than 12 years-old, as well as in patients with contraindication to PNRB.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Retroperitoneal endoscopic approach has gained popularity both worldwide and in our country including indications in pediatric cases (1-3).

Regarding the access, in general most comparative studies show no advantage for retroperitoneal to transperitoneal approach to kidney indications. In my opinion for kidney biopsy, retroperitoneoscopy offer advantage due to be a faster and direct procedure without violation of peritoneal cavity.

We reported the first series of this procedure in Brazil 5 years ago as an option for cases with high risk for bleeding, previous insufficient sample or when the technical conditions for ultrasound guided biopsy were not available(4,5).

At learning curve, our team had one conversion because the kidney was small and difficult to locate. Peritoneal tears are relatively frequent and innocuous, but in our experience, there are no conversions due to this "complication". Some maneuvers as place an anterior trocar to displace peritoneum medially, puncture with intracath in the peritoneum or to do a big opening in anterior peritoneum can solve the peritoneal compression to the working space.

Another important issue is to check the hemostasis before removing the trocars. Pressure of CO_2 need to be reduced to 5 mmHg and an inspection was done accurately. Additional cautery or a resin as surgicel or gelfoam can achieve a good hemostasis when necessary.

I agree with the authors that show that the samples are excellent for pathological analysis. This fact and an iterative anesthesia in children to do this procedure are the most important arguments to prefer the retroperitoneoscopic to needle biopsy in this age.

This report clearly confirms the growing indication of retroperitoneoscopic surgery in the modern urological armamentarium.

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EDITORIAL COMMENT

The authors are to be commended for their interesting and original series of 17 patients aged from 2 to 12 years-old undergoing retroperitoneoscopic renal biopsy (LRB) as an alternative to open renal biopsy (ORB). Three patients were contraindicated to the retroperitoneoscopic approach due to ascites, severe thrombocitopenia, and low age (two-month old).

There are some points however that should be discussed with the reader. Although the authors state that there are some drawbacks of percutaneous renal biopsy (PNRB) in children, and that LRB is the preferred method in their institution for renal sampling in children between 1 and 12 years, PNRB under ultrasound guidance continues to be the standard approach to allow histological diagnosis in children with evidence of renal disease.

While LRB requires general anesthesia, in a recent study Sinha et al. suggests that children older than five years of age may be selected on an individual basis for the biopsy to be performed under sedation as a day care procedure (1).

Although both ORB and LRB have the potential to minimize blood loss by quickly controlling the biopsy bed under direct vision, PNRB has achieved acceptable complication and bleeding rates of less than 5% (1,2), similar to the rates reported in LRB series (3,4).

Failure to obtain adequate tissue for diagnosis may occur with both PNRB and LRB. A recent study has proposed that a success rate over 95% in obtaining adequate tissue for diagnosis is an acceptable standard for PNRB (2). The success rate in two series of LRB by Shetye et al. (3) and Caione et al. (4) were respectively 96% and 95%. Even though LRB allows for biopsy of the kidney under direct vision, failure to obtain adequate tissue for diagnosis may occur mainly in obese patients due to excessive retroperitoneal fat and bleeding, with poor visualization of the laparoscopic field (3,4). These patients may require open conversion or additional procedures.

It should be emphasized that PNRB is the preferred method for obtaining renal biopsy in chil-

dren as long as there are no contraindications. LRB should be indicated as an alternative to ORB when there are contraindications to PNRB.

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Influence of Ovarian Hormones Deprivation on Gene Expression in the Lower Urinary Tract of Rats

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ABSTRACT

Objective: Identify the influence of ovarian hormone deprivation in expression genes on the lower urinary tract of rats.
Materials and Methods: This study deals with gene screening on lower urinary tract of rats. Fifty isogenic rats divided in two groups of twenty-five animals have their lower urinary tract surgically removed: group I, ovariectomized rats 30 days prior to surgery; group II, non-ovariectomized rats. Total RNA was isolated from bladder and urethra, and differential expression of genes was analyzed quantitative, qualitative and comparatively by array technology and RT-PCR.
Results: A total of 76 candidate genes were identified as differentially expressed between the groups, 26 being lower expressed in group II, and 50 in group I. Among them, differential expression validation was confirmed by RT-PCR for three lower expressed genes in group I: Vascular Endothelial Growth Factor (VEGF), Beta-2 Microglobulin (B2M) and Cytochrome c Oxidase subunit I (COX I).
Conclusion: Ovarian hormone deprivation influences the expression genes on lower urinary tract. We demonstrated that a 30-day period of castration down regulate the expression of VEGF, B2M and COX I in adult rats which are involved in activities of angiogenesis, immune responses and cellular metabolism respectively.

***Key words**: ovary; hormone; urinary tract; microarray analysis; gene*
Int Braz J Urol. 2007; 33: 544-53

INTRODUCTION

The climacterium, a period of decline in ovarian activity, is characterized by a variety of symptoms, in particular urogenital ones (1). Studies demonstrated a high incidence of urogenital symptoms in the climacterium and postmenopausal period, associating them to estrogen deficiency as the etiologic factor. Iosif & Bekassy (1), on studying 902 patients, observed approximately 29% urinary incontinence, 27% urge incontinence, 13% repeated infections of the urinary tract and 48% other symptoms due to urogenital atrophy, such as dysuria, dyspareunia, nocturia, micturition urgency.

It was believed sexual hormones deprivation would cause, among other modifications, urinary mucosa and muscle layer atrophy, increase in collagen/smooth muscle ratio in the urinary tract, decrease in pelvic vascularization, decrease in the protecting glycosaminoglycan layer in the vesical wall, modifications of the vaginal flora and pH, alterations in the cellular and humoral immunologic responses (2-10).

These findings had supported estrogen deprivation as the origin of urinary disorders on postmenopausal women. In fact, for many years, estrogen preparations have been used to treat urinary symptoms and they are no longer a treatment option for urinary incontinence (11,12).

Presently, the identification of some medicines starts by recognizing the genes that might be involved in pathological processes that, therefore, could be qualified as targets for future pharmacological interventions (13,14). In order to understand the way genes regulate cell function, the best procedure is by monitoring the set of gene activities in the cells (15). Microarray technology appeared in the last decade and constitutes an instrument able to quantitatively, qualitatively and simultaneously monitor hundreds or even thousands of genes (16,17). The use of arrays allows the global statistical analysis of the behavior of the different genes in certain evaluated situations and permits a dynamic analysis of the target tissue, since it compares expressions of the several genes among themselves (18,19).

We studied the influence of ovarian hormones deprivation on gene expression in the lower urinary tract, attempting to correlate biomolecular findings with mechanisms involved in urogynecologic diseases.

MATERIALS AND METHODS

Specimens - Rattus novergicus albinus (Rodentia Mammalia - Wistar EPM-1) from the animal house of the Federal University of São Paulo/EPM were kept in environmentally controlled, clean-air rooms with a 12-h light/dark cycle. They were fed Labina-Purina-SP-BR pellets and tap water ad libitum. Fifty virgin rats, 2-3 months old, were divided into 2 groups of twenty-five animals: Group I, rats that had their bladder and urethra removed 30 days after ovariectomy; Group II, non-ovariectomized rats that had their lower urinary tract removed 30 days afterwards. At the above indicated time, the corresponding animals were anesthetized; lower urinary tracts were rapidly frozen in liquid nitrogen for RNA extraction. This study received full Institutional Review Board approval.

RNA Extraction and Reverse Transcription - Total RNA was extracted from samples using TRIZOL (InVitrogen, São Paulo) according to the manufacture's instructions. The total RNA quality was checked by formaldehyde/agarose gel electrophoresis. Prior to reverse transcriptions, two pools of RNA were obtained by mixing 2 μg of total RNA from each individual case in two tubes representing Group I and II. In order to obtain radiolabeled cDNA probes, the two RNA pools, containing 50 μg RNA each, were reverse transcribed in the presence of oligodT primers and α-[^{33}P] dATP (2000 Ci/mmoL) by using kit Superscript II (InVitrogen) following the manufacture's instructions. Probes were purified by Probe Quant G50 microcolumns (Amersham Pharmacia Biotech).

cDNA Arrays and Hybridization Conditions - To analyze different gene expressions between group I and II, two Atlas rat cDNA expression array membranes (Clontech, Palo Alto, CA, USA) containing 1176 genes were used (two times). Hybridization took place at 42^{o}C in an overnight reaction containing 20X standard saline citrate (SSC), 50X Denhardt's solution, 50% formamide, 10x sodium dodecyl sulphate (SDS) and 100 μg/mL salmon-sperm DNA. The filters were washed at 50^{o}C in 1x SSC/0, 1% SDS for 15 minutes. Images were obtained by scanning the membrane in a storage phosphor system (Cyclone™ - Packard BioScience Company, Meriden, CT, USA). DNA targets on the arrays were located using grid overlays and spot intensities were subsequently measured (Diracom Bioinformática - São Paulo/Brazil).

Statistical Usage - Signs generated by hybridization of radioactive probes were processed and normalized using the digital software ArrayLab (Diracom Bioinformática - São Paulo, Brazil), by means of a superposing digital grid instrument on the cDNA spots marked on the nylon membranes. Thus, the expression of each gene was quantified by the calculation of the radiation volume (three-dimensional) emitted by the previously known spots of the membranes, consequently obtaining the numeric value corresponding to the images, on a logarithmic basis. We obtained the difference (DIF) of the expression of the same gene in the two groups (I and II) by the formula: DIF = $\log_2$(II-I). Values of DIF > 1 or < 1 were considered differentially expressed, that is, twice the difference in expression between the genes. The housekeeping

genes of the membranes, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), cytoplasmic beta actin (ACTB) and ubiquitin C had values of expression difference between the groups within the interval -1 < DIF < 1.

RT-PCR - Validation of array data by semi-quantitative RT-PCR was performed by pooling equal amounts of total RNA from each group; pools were then submitted to reverse transcription by using Superscript II RNAse H reverse transcriptase (InVitrogen) in a final volume of 20 µL according to the manufacture's instructions. Primers were designed by Prime3 program-http://www-genome.wi.mit.edu/cgi-bin/primer/primer3.cgi/primer3_www.cgi). Cytoplasmic beta actin (ACTB) gene was used to normalize the reactions. Two microliters of the reverse transcribed cDNA was amplified in a final volume of 100 µL by PCR under standard conditions: 1.5 mM $MgCl_{2,}$ 125 µM dNTP and 2.5 U Taq polymerase using specific primers at 10 µM concentration.

Cytoplasmatic beta actin: 375 bp; 32 cycles (94ºC, 1 min / 55ºC, 30 sec / 72ºC, 30 sec) S: 5'-CGTGACATTAAGGAGAAGCTG -3'; AS: 3'-CTCAGGAGGAGCAATGATCTTGA -5'

Beta-2 microglobulin: 225 bp; 25 cycles (94ºC, 1 min / 55ºC, 30 sec / 72ºC, 30 sec) S: 5'-GAATTCACACCCACCGAGAC -3'; AS: 3'-CCGGATCTGGAGTAAACTGG -5'

Cytochrome oxidase subunit I: 238 bp; 32 cycles (94ºC, 1 min / 55ºC, 30 sec / 72ºC, 30 sec) S: 5'- TCGCATCAAAACGAGAAGTG -3'; AS: 5'-GGGTTCGAATCCTTCCTTTC -3'

Vascular endothelial growth factor: 370 / 450 / 500 / 600 bp; 35 cycles (94ºC, 1 min / 58ºC, 30 sec / 72ºC, 30 sec) S: 5'- TGCACCCACGACAGAAGGC -3'; AS: 3'- TCACCCCCTTGGCTTGTCACAT -5'

The amplified PCR products were separated on 2% agarose gel containing 0.1 µg/mL ethidium bromide. The visualized bands were analyzed semi-quantitatively using image-scanning densitometry (Kodak EDAS 120).

RESULTS

Using the genetic cDNA screening microarray method with membranes of 1176 gene we observed that 76 presented a differential expression of at least two times between the two groups, of which 50 genes with lower expression in the group of castrated rats (I) and 26 in the group of non-castrated rats (II). These genes are involved in several steps of biomolecular and cellular processes (Tables-1 and 2).

The analyses of the images of agarose gel electrophoresis of the RT-PCR products confirm the data of differential gene expression in the two groups observed with microarrays for beta-2 microglobulin (β2M) and cytochrome c oxidase subunit I (COX I) genes (Figure-1). The two genes were less expressed in group I, the differences (DIF) between the groups being 1.54 and 1.65, respectively.

The difference in expression (DIF) in the arrays for the cytoplasmic beta actin housekeeping gene (ACTB), used in RT-PCR, was 0.12, proving membrane normalization.

We performed RT-PCR for amplification of the vascular endothelial growth factor (VEGF) in both groups and observed a lower expression of this gene in group I rats (Figure-1).

COMMENTS

We believe that depth in study of genes, biomolecular and cellular control mechanisms, as well as interaction of endogenous and exogenous factors with the genetic material of the cells would help our understanding of the pathophysiological processes that give rise to urogynecological diseases.

After screening 1176 genes with the help of the cDNA microarray technology, we identified 76 differential expression genes between the groups. In practice, it is not easy to distinguish the real differences in gene expression where there is a difference due to artifacts of technical variations. We considered differentially expressed genes with a difference in expression of at least two times between the groups, a value recommended by the statistical literature on array analysis, whose estimated error rate is 1% (20-22).

Gene screening allowed us to prove the influence of thirty-day castration of rats on gene expression in the organs of the lower urinary tract. The identified genes are involved in different cell activities:

Table 1 – *Genes lower expressed in Group II.*

GenBank	Genes	DIF
D84550	LEPTIN RECEPTOR PRECURSOR (LEPR); OB RECEPTOR (OBR); FA	-6.41
Z27118	HEAT SHOCK 70-KDA PROTEIN (HSP70)	-5.17
X54793	HEAT SHOCK 60-KDA PROTEIN (HSP60); 60-KDA CHAPERONIN (CPN60); GROEL HOMOLOG	-3.73
M36317	THYROLIBERIN PRECURSOR; THYROTROPIN-RELEASING HORMONE PRECURSOR (TRH)	-3.44
M31838	SUBSTANCE K RECEPTOR (SKR); NEUROKININ A RECEPTOR; NK-2 RECEPTOR	-2.95
X13412	FLK TYROSINE-PROTEIN KINASE; FPS/FES-RELATED	-2.82
U67958	URATE TRANSPORTER/CHANNEL	-2.42
U15098	GLUT AND GLUT-R GLUTAMATE TRANSPORTER	-2.19
Z14119	PLATELET-DERIVED GROWTH FACTOR RECEPTOR. ALPHA	-1.89
M86240	FRUCTOSE-16-BISPHOSPHATASE, LIVER	-1.86
J03572; M1	ALKALINE PHOSPHATASE	-1.82
L08493	GAMMA-AMINOBUTYRIC ACID RECEPTOR ALPHA 4 SUBUNIT PRECURSOR (GABA(A) RECEPTOR	-1.52
M59980	VOLTAGE-GATED K+ CHANNEL PROTEIN; RK5; POTASSIUM CHANNEL PROTEIN	-1.48
M58370	COLIPASE PRECURSOR (CLPS)	-1.45
U96920 + U	INOSITOL POLYPHOSPHATE 4-PHOSPHATASE TYPE II ALPHA +BETA	-1.34
X16054	BILE-SALT-ACTIVATED LIPASE PRECURSOR (BAL); BILE-SALT-STIMULATED LIPASE (BSSL)	-1.27
U59809	MANNOSE-6-PHOSPHATE/INSULIN-LIKE GROWTH FACTOR II RECEPTOR (M6P/IGFR2)	-1.21
J02998	RAS-RELATED PROTEIN RAB1A	-1.20
D32249	NEURODEGENERATION ASSOCIATED PROTEIN 1; DOWNREGULATED BY AXOTOMY	-1.20
M63837	PLATELET-DERIVED GROWTH FACTOR ALPHA RECEPTOR (PDGFRA)	-1.15
J05189	NEUROMEDIN K RECEPTOR (NKR); NEUROKININ B RECEPTOR; NK-3 RECEPTOR (NK-3R)	-1.12
U10097	SODIUM/CHLORIDE COTRANSPORTER, THIAZIDE SENSITIVE	-1.06
L15453	VOLTAGE-ACTIVATED CALCIUM CHANNEL ALPHA-1 SUBUNIT (RBE-II)	-1.04
M31178	CALBINDIN D28; AVIAN- TYPE VITAMIN D-DEPENDENT CALCIUM-BINDING PROTEIN (CABP)	-1.02
M32801 + J	3-KETOACYL-COA THIOLASE A + 3-KETOACYL-COA THIOLASE B	-1.02
M30705	SEROTONIN 5HT2 RECEPTOR	-1.00

DIF = difference in expression.

regulation of the cell cycle, turnover and translation of proteins and extracellular signaling, growth and cell metabolism, neurotransmission.

Among the genes identified as differentially expressed, we chose two genes, COX I and β2M, to be confirmed by RT-PCR, in view of the complexity of the used methodology.

We also analyze the expression of VEGF gene by RT-PCR, faced to the importance of the vascularization in the maintenance of urinary continence (2) and the demonstration of serum VEGF level decrease after menopause with the loss of ovarian function (23).

The VEGF gene is involved in the process of tissular angiogenesis (24) and thus, as with other growth factors, has its expression modulated by sexual steroids (25).

The VEGF protein is a polypeptide with a specific effect on cells of the vascular endothelium and vascular permeability and is the most potent mitogenic and proliferation factor of endothelial cells (26).

Experiments demonstrated serum levels of VEGF decreased after menopause with loss of ovarian function (23) and some authors described quantitative variations in VEGF according to the hormonal status. Andrade et al. (17) observed a significant decrease in levels of messenger RNA for VEGF in the endometrium of castrated adult rats when compared to the group of rats with estrogen replacement.

Table 2 – *Genes lower expressed in Group I.*

GenBank	Genes	DIF
J05029	LONG CHAIN-SPECIFIC ACYL-COA DEHYDROGENASE PRECURSOR	1.04
L22022	NEUROTRANSMITTER TRANSPORTER, SODIUM DEPENDENT	1.06
M64092	PKI-BETA; CAMP-DEPENDENT PROTEIN KINASE INHIBITOR (TESTIS FORM)	1.08
D30041	RAC-BETA SERINE/THREONINE KINASE (RAC-PK-BETA); AKT2	1.11
M15427	C-RAF PROTO-ONCOGENE; RAF-1	1.12
U02983	SECRETOGRANIN 3 (SG3)	1.12
M27716	DOPA DECARBOXYLASE ; AROMATIC-L-AMINO-ACID DECARBOXYLASE	1.12
M85301	SODIUM/HYDROGEN EXCHANGE PROTEIN 4	1.13
L33869; J0	CERULOPLASMIN PRECURSOR (CP); FERROXIDASE	1.14
L07925	RALGDSB; GTP/GDP DISSOCIATION STIMULATOR FOR A RAS-RELATED GTPASE	1.17
U27767	RGS4; REGULATOR OF G-PROTEIN SIGNALING 4 (RGP4).	1.17
U35174	SODIUM CHANNEL SHRSPHD, BETA SUBUNIT, EPITHELIAL	1.17
X59601	PLECTIN	1.18
M91466	ADENOSINE A2B RECEPTOR (ADORA2B)	1.18
M17526	GUANINE NUCLEOTIDE-BINDING PROTEIN G(O) ALPHA SUBUNIT (GNAO; GNA0)	1.18
M22413	CARBONIC ANHYDRASE III (CA3); CARBONATE DEHYDRATASE III	1.24
U62897	CARBOXYPEPTIDASE D PRECURSOR (CPD)	1.26
M95780	G PROTEIN, GAMMA 5 SUBUNIT	1.27
M37394	EPIDERMAL GROWTH FACTOR RECEPTOR (EGF RECEPTOR; EGFR)	1.28
S83440	14-3-3 PROTEIN BETA/ALPHA; PREPRONERVE GROWTH FACTOR RNH-1	1.34
X59949	NITRIC OXIDE SYNTHASE 1	1.37
X55446	CYTOCHROME P-450 2C23, ARACHIDONIC ACID EPOXYGENASE	1.43
L24907+L2	CALCIUM/CALMODULIN-DEPENDENT PROTEIN KINASE TYPE 1	1.44
L42810	C CALCIUM/CALMODULIN-DEPENDENT PROTEIN KINASE; PHOSPHORYLASE B KINASE KINASE	1.48
M32167	GLIOMA-DERIVED VASCULAR ENDOTHELIAL CELL GROWTH FACTOR	1.50
Z14117	PLATELET-DERIVED GROWTH FACTOR B-CHAIN (PDGFB); C-SIS	1.54
X16956 + U	MICROGLOBULIN; BETA-2-MICROGLOBULIN + PROSTAGLANDIN RECEPTOR F2A	1.54
J02852	CYTOCHROME P450 2A3 (CYP2A3); COUMARIN 7-HYDROXYLASE	1.59
M33962	PROTEIN TYROSINE PHOSPHATASE PTPASE	1.61
X70062	ATPASE, SODIUM/POTASSIUM, GAMMA SUBUNIT	1.62
S79304	CYTOCHROME OXIDASE, SUBUNIT I, SERTOLI CELLS	1.65
M34728	NONSPECIFIC LIPID-TRANSFER PROTEIN PRECURSOR; STEROL CARRIER PROTEIN 2 AND X	1.65
X63675	PIM1 PROTO-ONCOGENE	1.66
M18331	PROTEIN KINASE C EPSILON TYPE (PKC-EPSILON)	1.71
L38247	SYNAPTOTAGMIN IV (SYT4)	1.72
L29090	GUANINE NUCLEOTIDE-BINDING PROTEIN G(I)/G(S)/G(T) BETA SUBUNIT 3 (GNB3)	1.75
D38260	PROTEIN PHOSPHATASE 2A 55-KDA REGULATORY SUBUNIT BETA (PP2ABRB; PPP2R2B)	1.79
L35771	G PROTEIN-ACTIVATED INWARD RECTIFIER POTASSIUM CHANNEL 4 (GIRK4)	1.87
L38615	GLUTATHIONE SYNTHETASE (GSH SYNTHETASE; GSH-S; GSS); GLUTATHIONE SYNTHASE	1.91
AB000507	AQUAPORIN 7 (AQP7)	2.01
U90556	PHOSPHATIDATE PHOSPHOHYDROLASE TYPE 2	2.06
D83598	SULFONYLUREA RECEPTOR	2.12
U48246	PROTEIN KINASE C-BINDING PROTEIN NEL HOMOLOG 2	2.16
X62146; S3	RIBOSOMAL PROTEIN L11	2.21
X13817	CALMODULIN (CALM; CAM)	2.23
Z25868	BONE MORPHOGENETIC PROTEIN 2	2.27
L08227	NEURONAL ACETYLCHOLINE RECEPTOR PROTEIN ALPHA 6 SUBUNIT PRECURSOR	2.44
U10096	SODIUM-POTASSIUM-CHLORIDE COTRANSPORTER, BUMETANIDE-SENSITIVE	2.79
D10831	L-SELECTIN PRECURSOR;LYMPHNODE HOMING RECEPTOR;LEUKOCYTE ADHESION MOLECULE1	2.86

DIF = difference in expression.

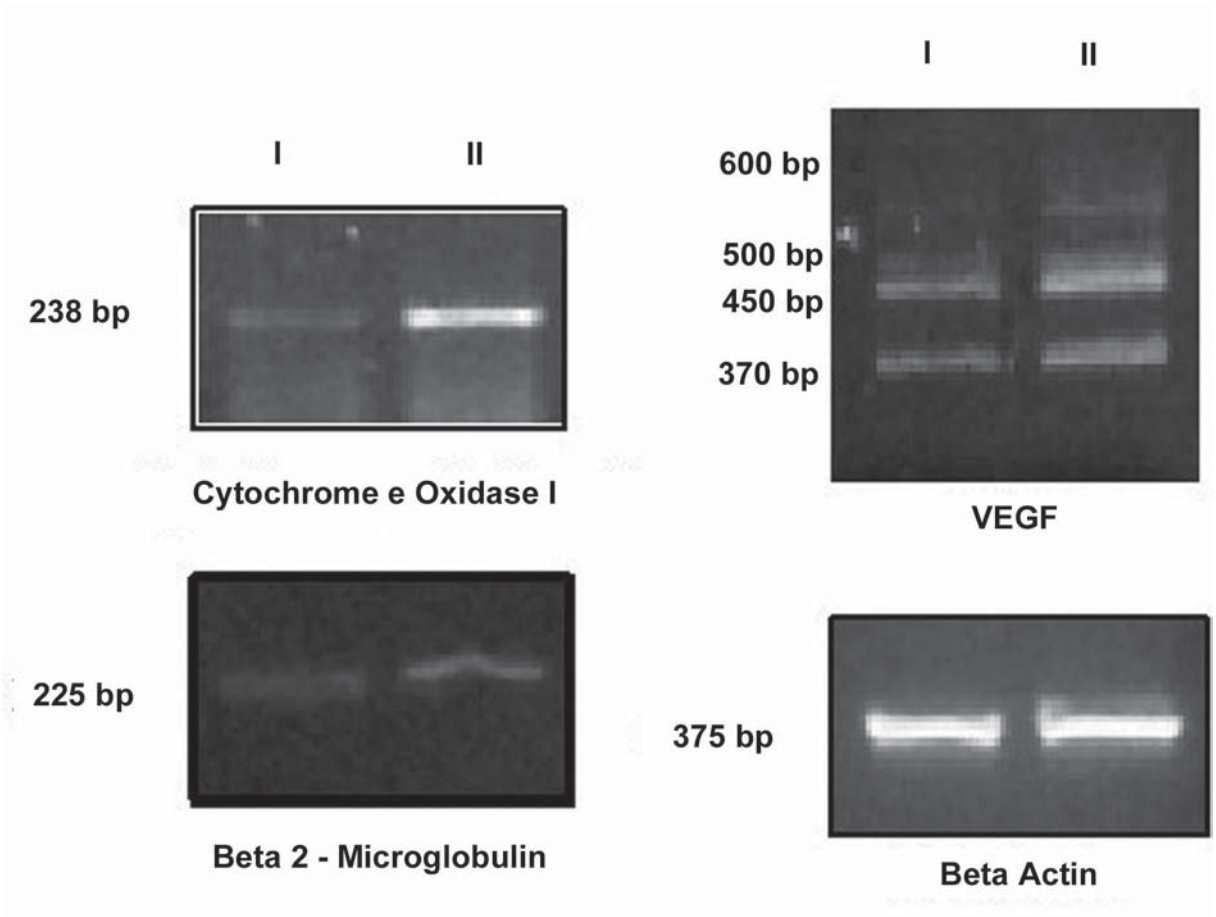

Figure 1 – *Validation of array data by semi-quantitative RT-PCR. Beta Actin was housekeeping gene.*

Agrawal et al. (27), using Doppler velocimetry in postmenopausal women, showed an increase in pulsatility indexes in carotid and uterine arteries, reflecting a higher vascular resistance in this phase, a process that was reversed after estrogen therapy with a subsequent increase in serum VEGF concentrations.

Zucchi et al. (28) observed protein expression of VEGF gene in the bladder, vesical-urethral junction and urethra of castrated and non-castrated rats had been verified significantly decrease of VEGF in castrated rat bladders compared to another group. There was also protein decrease in vesical-urethral junction even though not as accentuated as in the bladder.

Our observation of lower VEGF gene expression in urinary tract in castrated rats with ovarian hormones deficient could be associated to local blood vessel formation decrease. It would possibly contribute to the appearance of undesirable urinary symptoms such as irritating bladder and urethral symptoms, urinary incontinence and urinary infection, too common in postmenopausal women, by decreasing local circulation, oxygen offer and immunological defense.

COX I is a gene of mitochondrial DNA which encodes for cytochrome c oxidase subunit I that belongs to the respiratory complex IV and involved in the process of oxidative phosphorylation of cell (29).

It was suggested postmenopausal would have reduced capacity to perform prolonged intensive exercises after evidence of decrease of cytochrome oxidase activity by 40%, consequently, decrease of oxidase phosphorilation to obtain energy in muscles of ovariectomized rats exposed into stimulation (30).

Abelenda & Puerta (31) suggested ovarian sex hormones regulate oxidative capacity by studying ovariectomized animals. They concluded estrogen deprivation analyzed with ovariectomized rats exposed

to low temperature increases cytochrome oxidase activity in whole body thermogenic tissues, such as adipose tissue, soleus muscle, hearth, striated muscles, liver and kidneys. In the same study, authors did not observe alteration in enzyme complex activity in uterus after ovariectomy.

Tong-Long Lin et al. (32) studied the effect of age on mitochondrial enzyme activity in rat bladders while evaluating the following enzyme activities: citrate synthetase, malate dehydrogenase, NADH-cytochrome c reductase, succinate-cytochrome c reductase and cytochrome c oxidase, in addition to phosphocreatine and ATP concentrations in bladders of 24-month-old female rats. The authors observed significantly lower phosphocreatine and ATP levels and significantly lower enzyme activities, mainly of citrate synthetase, in bladders of old rats. They concluded that age reduced the activity of mitochondrial enzymes of rat bladders, resulting in less ability of energy production that could explain some micturition disorders frequent in elderly patients.

Adequate energy supply is a prerequisite for good vesical functioning, muscle contraction and vesical emptying. Cell energy, in the form of ATP originating from mitochondrial oxidative phosphorylation is the immediate energy used for contraction of detrusor muscles and other cell activities (32). Levin et al. (33) demonstrated that interruption of the oxidative metabolism abolished the plateau component of detrusor muscle contraction, resulting in decrease in the ability of vesical empting.

Our result demonstrated reduced expression of Cytochrome c oxidase subunit I gene in castrated rats. Thus, decrease in expression of genes of cell respiration may be one of the mechanisms by which ovarian sex hormones deficiency promote alteration in urinary tract metabolism and alterations in energy acquisition by cells needed for physiological activities such detrusor contraction.

The â2M gene encodes for the protein of the same designation that is a component of HLA antigens (histocompatibility antigens), being essential for their expression. It is structurally similar to the amino acid sequences of immunoglobulins and is implied in immunologic functions (34,35).

β2M function has not been completely clarified yet. However, it is postulated that β2M would be a link between antibodies or IgG and histocompatibility antigens. Therefore, it would have the function of cellular recognition of antigens and interaction of the cellular and humoral immune systems, by interaction between T and B lymphpocytes (35).

Several evidences support the hypotheses of regulation of immunologic functions by gonadal steroids: different behavior of immune system between men and women, alterations in immune response after gonadectomy, estrogen replacement and in women during pregnancy. Even so, hormone steroids receptors are identified in immune system organs (36).

Most scientific evidence demonstrates that particularly estrogens act as stimulators of the humoral immune response and as inhibitors of the cellular immune response (37).

Some authors studied different system immune compounds under ovarian hormones deficit. Kamada et al. (38) on studying T cell function in menopausal women observed lower quantity of Th1 cytokines, inducers of the cellular immune response, and imbalance in the relationship between the latter and Th2 cytokines, inducers of the humoral immune response.

Giglio et al. (39) detected reduced number of T CD4+ and B lymphocytes in postmenopausal period compared to young women. The same result for T lymphocytes weren't observed by Yang et al. (40), that also related NK cells toxicity were decreased in postmenopause, situation reverted by estrogen therapy.

Flory et al. (41) analyzed some parameters of immunological response as toxicity number and mitogenic response of NK cells in women treated with GnRH agonist and estrogen replacement thereafter. Temporary suppression of ovarian function in addition to estrogen therapy did not alter those parameters. Authors postulated immunological suppression findings are temporarily stable and possibly related to age, life style, associated diseases.

In our study 30 days period of castration were enough to reduce β2M gene expression. Maybe, system immune alterations after menopause observed by some authors can be at least partially mediated by β2M expression. It is possible that decreased expression of β2M in lower urinary tract is associated to increase of urinary infection.

However, the real function of β2M protein in immune responses, its association with infectious processes and the participation of the immune system specifically in the genesis of urinary infections in the postmenopausal period have to be better elucidated.

In our experience, cDNA microarray technology is a good screening method of genes of the lower urinary tract and is also efficient in the studies on molecular alterations induced by estrogen deficiency.

The high prevalence of urinary disorders in postmenopausal women justifies all efforts for their better understanding, treatment and prophylaxis, in the insisting attempt for a better quality of life.

This study deals with gene screening, and innumerable genes and protein still have to be evaluated and confirmed. Thus, on the basis of knowledge on genomics and pharmacogenomics, perhaps in the future we may identify new targets for drug action and make available therapeutic options for urinary disorders.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

This is an experimental study in rats, which has Institutional Review Board approval, examining the influence of estrogens deprivation on genes expression in the lower urinary tract. They identified 76 differential expression genes between ovarian hormone deprivation group and non-deprivation group using the genetic cDNA screening microarray methodology. So they analyze the difference of the expression of the same gene in the two groups and validation was confirmed for three lower expressed genes, i.e., vascular Endothelial growth factor (VEGF), Beta-2 Microglobulin (B2M) and Cytochrome c Oxidase subunit I (COX I). These genes are related to angiogenesis, immune responses and cellular metabolism respectively.

After all, they try to correlate biomolecular findings with urinary disorders usually seen on postmenopausal women by reviewing the literature. The authors hypothesized that lack of gene expression could be responsible for urinary disorders in postmenopausal women.

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Free Serum Testosterone Level in Male Rats Treated with Tribulus Alatus Extracts

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ABSTRACT

Objective: The present study was undertaken to investigate the effect of Tribulus alatus extracts on free serum testosterone in male rats.
Materials and Methods: Free serum testosterone level was measured in male rats treated with alcoholic extracts of the aerial part without fruits, fruits of Tribulus alatus and their fractions.
Results: All tested extracts showed significant increase in the level of free serum testosterone when compared to that of corresponding control, $p < 0.05$. Statistical comparison of all groups revealed that the maximum level was found in groups treated with chloroformic and ethanolic fractions of fruits extract.
Conclusion: Tribulus alatus extract appears to possess aphrodisiac activity due to its androgen increasing property.

***Key words**: Tribulus; testosterone; aphrodisiacs; rats*
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INTRODUCTION

In traditional medicine a variety of plants have been used as sex stimulants (1). For centuries, Arabs have made use of herbal drugs to improve sexual performance and increase libido (2). In African traditional medicine, especially in Cameroon, Zingiber officinale and Pentadiplan-dra brazzeana are used as aphrodisiac and male sexual stimulation (3). In Egypt, the pollen grains of dates (Phoenix dactylifera) and seeds of hermala (Peganum harmala) are used to restore sexual potency (4).

The genus Tribulus of the Zygophyllaceae comprises ca 20 species that grow as shrubs or herbs in subtropical areas around the world (5).Among the Tribulus species T. terrestris, T. cistoides and T. alatus have been phytochemically investigated and isolation of steroidal saponins from these plants was reported (6-8).

The present study was undertaken to investigate the effect of Tribulus alatus extracts on free serum testosterone in male rats.

MATERIALS AND METHODS

Plant Material and Preparation of Extracts

Samples of Tribulus alatus were collected from Al Azhar University, Nasr-city, Cairo and were kindly identified by Department of Botany, Faculty of science, Cairo University. A voucher specimen (number 3978/1) was deposited at Herbarium Horti Botanici Pisani (Flora Aegyptiaca), Pisa, Italy.

The dried aerial parts and fruits (400g and 100g, respectively) of Tribulus alatus were finely powdered and were macerated separately in 70% methanol. The alcoholic extract was evaporated to dryness under vacuum. The residues were combined, weighted (90g and 20g, respectively) suspended in distilled water and successively extracted with chloroform, ethylacetate and n-butanol saturated with water. Each extract was collected and evaporated to dryness under vacuum to give chloroformic extract (4g and 2.1g, respectively) ethylacetate extract (3.2g and 1.5g, respectively) and n-butanolic extract (8g and 3.8g, respectively) then the water was evaporated to dryness and the residue was macerated in absolute ethanol several times. The alcoholic extracts were combined and evaporated to dryness under vacuum to give ethanolic extract (30g and 8g, respectively)

Animals

Healthy, adult male Wistar albino rats weighing 200-250g, aged 4-5 months were used in this study. The animals had free access to a standard commercial diet, water and were kept in rooms maintained at 25 ± 1°C. The animals were divided randomly into different groups; each group consisted of six rats. Control groups treated with distilled water (2 mL/kg p.o.) only.

Toxicity Study

On the basis of the toxicity study, the LD50 value of the extract of the aerial part without fruits in mice was 812 and was 868 mg/kg body weight for the extract of fruits. On the other hand, LD50 value for extract of different fractions ranged from 155-200 mg/kg body weight. The experiment was carried out on three steps.

First Step

Control group: treated with distilled water (2 mL/kg p.o.). Group 1: received 70% alcoholic extract of aerial part without fruits (n = 6). Group 2: received 70% alcoholic extract of fruits (n = 6). Group 3: received 70% alcoholic extract of total herb (n = 6). Reference group: treated with 0.45 mg mestrolone (n = 6).

In the first step, groups received extracts (suspended in water using Tween 20 as a surfactant) at a dose of 50 mg / kg body weight orally by orogastric catheter once a day for 40 days. A reference group was treated with 0.45 mg mestrolone once a day for 40 days orally by orogastric catheter. After 40 days, blood samples were collected from the tail veins of the rats at the same time of the day and serum was separated.

Second Step

Control group: treated with distilled water (2 mL/kg p.o.). Group 4: received chloroformic fraction of aerial part without fruits (n = 6). Group 5: received ethylacetate fraction of aerial part without fruits (n = 6). Group 6: received butanolic fraction of aerial part without fruits (n = 6). Group 7: received ethanolic fraction of aerial part without fruits (n = 6). Reference group: treated with 0.45 mg mestrolone (n = 6).

Third Step

Control group: treated with distilled water (2 mL/kg p.o.). Group 8: received chloroformic fraction of fruits (n = 6). Group 9: received ethylacetate fraction of fruits (n = 6). Group 10: received butanolic fraction of fruits (n = 6). Group 11: received ethanolic fraction of fruits (n = 6). Reference group: treated with 0.45 mg mestrolone (n = 6).

On the other hand, in the second and third steps the groups received dose 12.5 mg / kg body weight orally by orogastric catheter once a day for 40 days. A reference group was treated with 0.45 mg mestrolone once a day for 40 days orally by orogastric catheter. After 40 days, blood samples were collected from the tail veins of the rats at the same time of the day and serum was separated.

Determination of Free Serum Testosterone

The level of free serum testosterone was measured by Enzyme-linked immunosorbant assay (ELISA) according to (9), KAPD29:040318/ 2KAPD2924 IN VITRO DIAGNOSTIC USEenBioSource Europe SA - Nivelles, Belgium.

Statistical Analysis

Data were presented as the mean ± SE (n = 6). Statistical analysis used Student's t-test to compare differences between groups and the control. One-way analysis of variance (ANOVA) was applied for

comparison between different treatments. Differences were considered statistically significant at $P < 0.05$.

RESULTS

Table-1 represents mean free serum testosterone level (pg/ mL) among group of rats treated with 70 % alcoholic extracts of Tribulus alatus. Testosterone level was significantly increased among all groups, when compared to that of their corresponding control, $P < 0.05$. The highest level was found in the group treated with the reference drug followed by the group treated with fruits extract, followed by the one treated with the aerial part without fruits and the lowest level was found in the group treated with total herb.

Table-2 illustrates mean free serum testosterone level (pg/mL) among groups of rats treated with different fractions of 70% alcoholic extracts of the aerial part without fruits of T. alatus. Testosterone level showed significant increase among all groups, when compared to that of their corresponding control, $p < 0.05$.

The level of testosterone in the group treated with the reference drug showed a significant increase when compared to that of all other groups. The level of testosterone in-group (5) showed a significant increase when compared to that of other groups including that treated by total aerial parts extract, group (1).

Table-3 illustrates mean free serum testosterone level (pg/mL) among groups of rats treated with different fractions of 70 % alcoholic

Table 1 – *Mean free serum testosterone level (pg/ mL) among groups of rats treated with 70% alcoholic extracts of Tribulus alatus.*

Tested Parameter	**Control Group**	**Group 1**	**Group 2**	**Group 3**	**Reference Group**
Mean ± SE	0.75 ± 0.024	2.96 ± 0.088	3.9 ± 0.14	1.85 ± 0.076	6.5 ± 0.98
		a	b	c	d
p Value		< 0.05	< 0.05	< 0.05	< 0.05

Values expressed as mean ± standard error of 6 animals/group. P < 0.05 in relation to control group (Student's t-test). Different letters mean significance.

Table 2 – *Mean free serum testosterone level (pg/mL) among groups of rats treated with different fractions of 70% alcoholic extract of aerial part without fruits of Tribulus alatus.*

Tested Parameter	**Control Group**	**Group 4**	**Group 5**	**Group 6**	**Group 7**	**Reference Group**
Mean ± SE	0.8 ± 0.06	3.88 ± 0.76	5.7 ± 1.02	2.93 ± 0.41	3.38 ± 0.55	8 ± 0.86
		a	b	a	a	d
p Value		< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

Values expressed as mean ± standard error of 6 animals/group. P < 0.05 in relation to control group (Student's t-test). Different letters mean significance.

Table 3 – *Mean free serum testosterone level (pg/mL) among groups of rats treated with different fractions of 70% alcoholic extract of fruits of Tribulus alatus.*

Tested Parameter	**Control Group**	**Group 8**	**Group 9**	**Group 10**	**Group 11**	**Reference Group**
Mean ± SE	0.72 ± 0.048	21.3 ± 0.882	8 ± 0.577	8.81 ± 0.079	18.75 ± 1.88	7 ± 1.0
		a	b	b	c	b
p Value		< 0.05	< 0.05	< 0.05	< 0.05	< 0.05

Values expressed as mean ± standard error of 6 animals/group. P < 0.05 in relation to control group (Student's t-test). Different letters mean significance.

extracts of the fruits of T. alatus. Testosterone level showed significant increase among all groups, when compared to that of their corresponding control, $p < 0.05$.

Testosterone level showed significant increase in groups 8 and 11. As compared with that of other fractions, total fruits extract and the group treated with the reference drug.

COMMENTS

Some causes that are responsible for low testosterone levels, include congenital problems such as deficiencies of male hormones and rare malformation syndromes, and acquired problems such as aging, chronic illness, drugs, starvation, stress, head trauma, infections, cancers, surgeries, alcoholism, removal or trauma to the testicles, and infection or twisting of the testicles in their sack.

The use of testosterone is widespread in the treatment of many problems including infertility, athletic enhancement, erectile dysfunction and libido problems. Its application can have grave consequences if not used properly. Androgen, or more specifically testosterone, is widely utilized to treat erectile dysfunction (10).

Various neurotransmitters and their inter/intracellular signaling are responsible for the relaxation of corpus cavernosal smooth muscle. Androgens influence these neurotransmitters and contribute to the regulation of penile erection. The classic theory about testosterone treatment is that it stimulates the sex drive and, by doing so, restores erectile functioning (11).

Once a man is diagnosed as hypogonadic, or having a low testosterone level, the next step is to choose which form of treatment to utilize. As with all medications, benefits should be evaluated against potential risk. Age is one important factor in making this decision.

In men less than fifty years old, the goal is to restore libido and erections. Testosterone also improves strength, physical stamina, and health status (10). Many people are now relying on herbal medicines for health care (12). Since other treatments applied are becoming more expensive and often carry serious side effects, there should be scientific dissemination of information on the therapeutic efficacy of these plants. Aphrodisiacs are substances that enhance sex drive and/or sexual pleasure or can arise sexual desire or libido (13). They are also agents that can be used to modify impaired sexual functions.

Studies have implicated the saponin component of plants in enhancing aphrodisiac properties due to their stimulatory effect of androgen production (11).

A survey concerning the secondary metabolites of genus Tribulus showed that steroidal saponins are the typical constituents of the genus, and in particular of T. terrestris (14). Saponins have been implicated as possible bioactive agent responsible for the aphrodisiac effect in Tribulus terrestris extract (11). These saponins were found to increase the levels of testosterone and luteinizing hormone (15).

It was reported that Tribulus alatus contained steroidal saponins (8), which might contribute to increasing endogenous testosterone levels by raising the level of luteinizing hormones (LH) as reported for saponins isolated from T. terrestris (15).

In the present study, the significant increase in the level of free serum testosterone is an indication of the aphrodisiac potential of Tribulus alatus extract.

CONCLUSION

The alcoholic extracts of both parts of Tribulus alatus produced a significant increase in the level of free serum testosterone at dose 50 mg/Kg body weight. Also different fractions of both parts of the plant revealed significant increase in the level of free serum testosterone at dose 12.5 mg/Kg body weight when compared to their corresponding controls. It is concluded that Tribulus alatus extract appears to possess aphrodisiac activity due to its androgen increasing property.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

In this manuscript, the authors evaluated the effect of Tribulus alatus extracts on free serum testosterone in male rats. The authors found that the alcoholic extracts of both parts of Tribulus alatus produced a significant increase in the level of free serum testosterone at dose 50 mg/kg body weight. Also different fractions of both parts of the plant revealed significant increase in the level of free serum testosterone at dose 12.5 mg/kg body weight. From these studies, the authors concluded that the alcoholic ex-

tract of the Tribulus alatus might thus be used to modify impaired sexual functions, especially those arising from hypotestosteronemia. The paper is very original and most part is carefully carried out. It presents some interesting observations.

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EDITORIAL COMMENT

Male reproductive disorders and sexual dysfunction is a serious problem of recent society. In this respect the current paper deal with topical question of increasing incidences of male sexual dysfunction and potential risk of application of synthetic hormonal drugs. There is limited understanding in the literature on aphrodisiac effect of plants, namely, Tribulus on man and primates. The study is interesting and informative and adds to our knowledge about aphrodisiac properties of species belonging to genus Tribulus. The authors develop a proper experimental model on rat and provide useful data on the ways for stimulation of androgen production by natural sources. The article contains new facts about isolation of different organic fractions from fruits and aerial part of Tribulus and their comparative effect on testosterone production. The data are useful for clinical practice and treatment of male sexual dysfunction. They will encourage further studies on finding natural products for stimulation of testicular endocrine function that would be of interest for pharmacology.

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Letter to the Editor

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Re: Surgical Technique Using AdVance™ Sling Placement in the Treatment of Post-Prostatectomy Urinary Incontinence

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Int Braz J Urol, 33: 231-237, 2007

To the Editor:

I am responding to the AdVance™ surgical technique paper that was recently published (1). The technique was first described by Rehder & Gozzi and the early results recently published (2). We want to draw attention to a few points of technique that seem very important built on our experience. The authors have performed more than 80 cases of AdVance™ since February 2006 in a wide range of patients.

The positioning of the patient is critical, as it should not be in extended dorsal lithotomy. Placing and tensioning the sling in this position might cause it to be loose once the legs are back in the supine position. This operative technique is based on providing dorsal support to the sphincteric urethra, which is not given when the sling is loose. The dissection on the urethral bulb is such as to mobilize it, and it is not continued for 4 cm beyond the perineal body as is stated in the article. This means that the bulb should be mobilized until a proximal movement of the proximal bulb becomes possible. When fixing the central portion of the mesh to the mobilized bulb, the distal sutures are most important, necessitating up to three sutures with a 2-0 resorbable suture. The idea is to proximally move and rotate the dorsal surface of the proximal bulb proximally utilizing a broad surface on the bulb. By doing this, the prolapsed dorsal surface of the sphincteric urethra is indirectly supported without causing direct compression on the urethral lumen. A cystourethroscopy during the procedure is not necessary, as the level of dissection and operation is below the pelvic floor and urethra. However, it is of critical importance to make the diagnosis preoperatively, to be able to determine the correct operative indication.

During examination of the stress incontinent patient, the following findings are helpful. The urethroscopy should be carried out in neutral dorsal lithotomy under local anesthesia of the urethra (lidocain gel). With gentle pressure of the pointed index finger directly to the midperineum well dorsal of the level of the membranous urethra the dorsal surface of the proximal bulb should be proximally displaced. A concentric coaptation (occlusion) of the urethral lumen should be appreciated indicating towards possible success with the AdVance™ sling. When this concentric coaptation cannot be obtained because of large sector defects to the sphincter or severe fibrosis limiting urethral mobility, then this patient should rather be indicated for a compressive device.

Postoperative care should include instruction to limit physical activity especially leg spreading, as this may loosen the sling leading to urinary incontinence again. The AdVance™ sling is the only product on the market focusing on restoring normal anatomy in male stress urinary incontinence (SUI). In October 2005 Gozzi & Rehder were the first to report on the possibility that urethral prolapse and dorsal sphincteric urethral descent may play a role in male SUI, and restoring this prolapse leads to the restoration of continence (Abstract at the SIU Meeting on Prostatic Disease: Recent Advances and New Technologies. Bariloche, Patagonia, Argentina).

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Re: Adverse Events and Readmissions after Day-Case Urological Surgery

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Int Braz J Urol, 33: 330-338, 2007

To the Editor:

This valuable retrospective study looks at the complication rate and frequency of re-admission following day case (ambulatory urological surgery), under both local and general anaesthesia. The authors have reviewed all day case surgery over a 16 month period at a single institution accumulating data on 1189 patients from a possible 1420.

The importance of this paper is two fold. Firstly, it highlights the ever increasing trend toward day case surgery throughout the world with an inevitable parallel rise in the degree of surgical complexity that can be accomplished in such a setting. Not too long ago, day case ureteroscopy with stent placement was unheard of, now it is common place with excellent results and acceptable rates of complication and re-admission.

The second important issue is that of re-admission and complications following day case surgery and the distribution of these issues amongst the various procedures with identification of risk factors where possible. It is no surprise that more complex procedures are inextricably linked to a higher rate of both complication and re-admission. One would accept this as the first cousin of change and progress and it is this facet that offers the greatest opportunity for improvement and further progress.

The re-admission figures are very impressive in this series – overall 0.5 %. This compares very favourably with figures from other studies[1] and is well below the recommended re-admission rate of 3% (1). There are minor omissions from this paper, the re admission rate following GA day case procedures,

whilst having a risk ration in excess of 7 in comparison to the rate following local anaesthesia is not calculated. It would also have been of use to include the actual re-admission rates for each procedure classification. In our own multi-centre study (2), ureteroscopy yielded a re-admission rate of over 13% which may be loosely compared to the 18% complication rate following ureteroscopy in this series despite an unknown rate of re-admission.

There is no doubt that there is a huge drive, both from a patient acceptability view and from a health economic stand, for day case surgery to continually evolve. As it does so, there is a vital need for perpetual audit and analysis of results to ensure that patient interests are not overlooked or indeed sacrificed in the name of such progress.

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Re: The Role of Squamous Differentiation in Patients with Transitional Cell Carcinoma of the Bladder Treated with Radical Cystectomy

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Int Braz J Urol, 33: 339-346, 2007

To the Editor:

Antunes et al., provide an interesting insight into the adverse prognostic role of squamous differentiation of transitional cell carcinoma (TCC) of the bladder. In their retrospective study, both disease recurrence and mortality were statistically higher in those patients with squamous differentiation, with the adverse prognosis being confirmed on a multivariate analysis. Some deficiencies were noted in the study, most importantly the small number of patients, and the lack of information about the presence and extent

of lymph node metastases, which may have affected results. Certainly these results have not been demonstrated by other investigators that have found no statistically significant difference between squamous differentiation and pure TCC, although many have shown mortality reductions with other subtypes such as adenocarinoma, carcinosarcoma and small cell carcinoma of the bladder (1-3). Nonetheless, it remains crucial that further, preferably randomized or well conducted retrospective studies are performed, to confirm which TCC subtypes truly portend a poorer prognosis. This data could then be used to assist in the integration of chemotherapy or radiotherapy, together with surgery in the management of these aggressive cancers in order to improve clinical outcomes.

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Re: The Role of Squamous Differentiation in Patients with Transitional Cell Carcinoma of the Bladder Treated with Radical Cystectomy

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Int Braz J Urol, 33: 339-346, 2007

To the Editor:

Squamous differentiation is well known to occur in the bladder urothelial carcinoma and represents the most common form of mixed differentiation (1-5). When defined by the presence of intercellular bridges and/or keratinization in urothelial carcinoma, it occurs in 21% of urothelial carcinomas of the bladder, and in 44% of tumors of the renal pelvis (2-3). Its frequency increases with grade and stage

(2-3). The diagnosis of squamous cell carcinoma is reserved for pure lesions without any associated urothelial component, including urothelial carcinoma in situ (5). Tumors with any identifiable urothelial element are classified as urothelial carcinoma with squamous differentiation and an estimate of the percentage of squamous component should be provided (3-5).

The clinical significance of squamous differentiation remains uncertain, but seems to be an unfavorable prognostic feature in such patients undergoing radical cystectomy, possibly, because of its association with high-grade tumors (1-5). This is supported by Antunes et al. (1). These authors have conducted an interesting study related to clinical implications of squamous differentiation in urothelial carcinoma treated by radical surgery. In their study, 22% of tumors had squamous differentiation, but most importantly, they observed a higher disease recurrence and mortality in patients having squamous differentiation as compared with patients without squamous differentiation. Antunes et al. (1), also found squamous differentiation as independent predictor of survival in patients with bladder cancer after radical surgery. This study provides nicely performed evidence on the usefulness of reporting the presence of squamous differentiation in urothelial carcinoma. Other studies have emphasized squamous differentiation as predictor of a poor response to radiation therapy, and possibly also to systemic chemotherapy, although the controversy still exists on this issues. To avoid some problems related to the criteria in assessing squamous differentiation, the use of immunohistochemical technique in addition to appropriated conventional analyses is advised (2). Cytokeratin 14, caveolin, uroplakins and L1 antigen have been reported as immunohistochemical markers of squamous differentiation since they are expressed in urothelial carcinoma and not in squamous differentiation (2). Finally, the main limitation of the study by Antunes et al. (1) is the small number of cases entering the analysis; therefore studies on the issue including larger series might be necessary to confirm the data by Antunes et al.

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Re: The Use of Enoxaparin to Prevent Venous Thromboembolism in Patients Undergoing Radical Retropubic Prostatectomy: Feasibility and Utility

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Int Braz J Urol, 33: 347-354, 2007

To the Editor:

It is very interesting to me that the use of an anticoagulant such as heparin is "standard" prophylaxis after an open radical prostatectomy (RP) in much of Western Europe but not in the US. I do not know if it is used in conjunction with a laparoscopic RP but it would seem that there would be little difference.

There is no argument that venous thromboembolism (VTE) is the most important nonsurgical complication following major urologic surgery and this would include RP. The rate of VTE has been steadily declining over the past two decades thanks to improved techniques during surgery and thus less blood loss, i.e. less risk of hypotension, a lower operative time, earlier mobilization, and the use of VTE prophylaxis. Despite these advances, the incidence of symptomatic VTE ranges between 1 and 5%. Pulmonary embolus, although quite uncommon, is the most often cited cause of post RP death (< 1 in 500).

Indeed patients undergoing a RP have known risk factors for a VTE, such as older age, pelvic surgery, node dissection, cancer. Thus the consensus for some method to reduce the risk of a VTE. There are very few recent prospective trials, which compare different methods for VTE prophylaxis in urologic surgery. The three commonly used approaches to VTE prophylaxis are graduated compression stockings (GCS), intermittent pneumatic compression devices (IPCD), and pharmacologic therapy, i.e. one of the heparin products.

An outstanding review of VTE prophylaxis was published in 2004 (1). The recommendation for urologic surgery and specifically major open procedures such as RP was routine prophylaxis with low dose unfractionated heparin two or three times daily. Acceptable alternatives include IPCD and /or GCS or low molecular weight heparin. Thus, we have a choice. No perfect answer.

What do I do? For the past 15 years our anesthesia team and I have used a protocol which consists of a long acting spinal supplemented by general anesthesia(2). Patients are positioned in the supine flexed position with the kidney rest raised. IPCD are placed when the patient enters the operating room and are maintained during surgery and until the next morning when the patient is out of bed and ambulating. Ninety percent of patients are discharged the day after surgery without additional VTE prophylaxis.

We reported our incidence of VTE in 1,364 consecutive RP in 2005 (3). There were three VTE events (0.21%) in lower (n = 2) or upper (n = 1) extremities. No patient had a clinical pulmonary embolus. The only postoperative death was from a myocardial infarction. Since that publication, there have been no additional clinical VTE.

The use of a spinal anesthetic may be an important component to our low incidence of VTE. Prospective trials have convincingly demonstrated that patients receiving a spinal or epidural anesthetic with or without a concurrent general component have a significantly reduced chance of a VTE (4). The precise mechanism is not clear but less stasis in the lower extremities or lower blood loss may be factors. The long acting spinal actually encourages early

ambulation since the patients have less postoperative pain.

The article by Nakamura et al. asks what to do when patients do not comply with the IPCD. My suggestion would be to emphasize to the nurses and the patient the importance of the devise and in addition use a spinal anesthetic. Our patients remove the devices the morning after surgery and begin ambulation.

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Re: Inflammatory Atrophy on Prostate Needle Biopsies: Is There Topographic Relationship to Cancer?

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Int Braz J Urol 2007;33:355-63

To the Editor:

The editorial comments of our paper by Dr.H.Samaratunga, Dr. Rodolfo Montironi, and Dr. Liang Cheng were very informative on a lesion that is one of the most frequent mimics of prostatic adenocarcinoma. It occurs most frequently in the posterior lobe or peripheral zone (1-3) and gained importance with the increasing use of needle biopsies for the detection of prostatic carcinoma (4). Moore (1), in 1936, was one of the first authors to describe prostatic atrophy in a systematic autopsy study. He found that there was a strong correlation with age and, according to his study, prostatic atrophy is initi-

ated during the 5th decade and continues as a progressive process into the 8th decade. It is a frequent lesion: 85% in autopsies and 83.7% in needle biopsies (5,6).

Why this lesion mimics adenocarcinoma? Histologically prostatic atrophy may be partial or complete. The latter is subtyped in simple, hyperplastic (or post-atrophic hyperplasia), and sclerotic (5). It seems that the subtypes represent a morphologic continuum of a single lesion (4). Partial atrophy and hyperplastic (or postatrophic hyperplasia) most frequently mimic adenocarcinoma. Hyperplastic atrophy shows small acini closely packed together and lined by atrophic epithelium. Fibrosis is present or not in the stroma. When present, the proliferation is irregular and can result in distortion of the acini simulating stromal infiltration (Figure-1). Partial atrophy was described by Oppenheimer et al. (7). The name is due to the fact that there is partial preservation of the cytoplasm simulating neoplastic micro-acini (Figure-2). An additional pitfall for the surgical pathologist is the fact that in partial atrophy the basal cells may be scattered and in some acini may be completely absent (Figure-3).

There are some findings associated to the etiopathogenesis of the lesion. Atrophy is clearly associated to advanced age (1,5). Radiotherapy and hormonal deprivation are associated with diffuse atrophy. Inactive or active inflammation is a frequent cause for the lesion (8) and based on a study on autopsies there is evidence that chronic local ischemia may also be a cause of atrophy (5). However, many examples of atrophy are still considered idiopathic in nature. Both inflammation and ischemia are associated with focal forms of atrophy.

The relation of prostatic atrophy to neoplasia is exciting and controversial. This topic was thoroughly commented in our study and discussed in the editorial comments by Dr.H.Samaratunga, Dr. Rodolfo Montironi, and Dr. Liang Cheng (6).

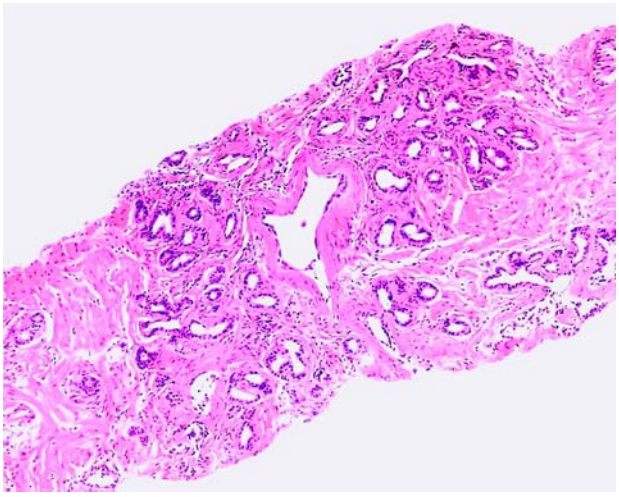

***Figure 1** – Hyperplastic atrophy (or postatrophic hyperplasia).*

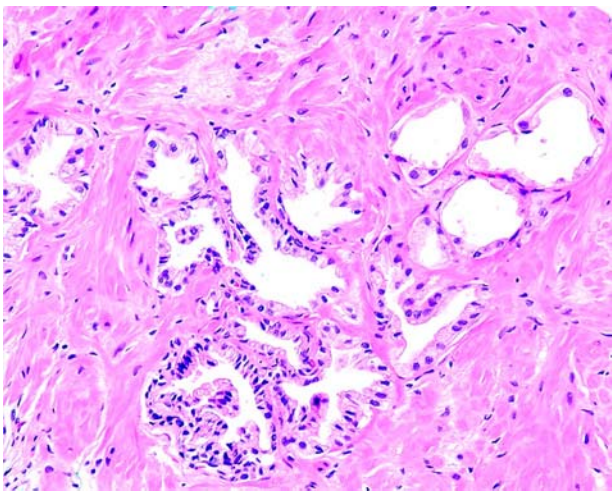

***Figure 2** – Partial atrophy.*

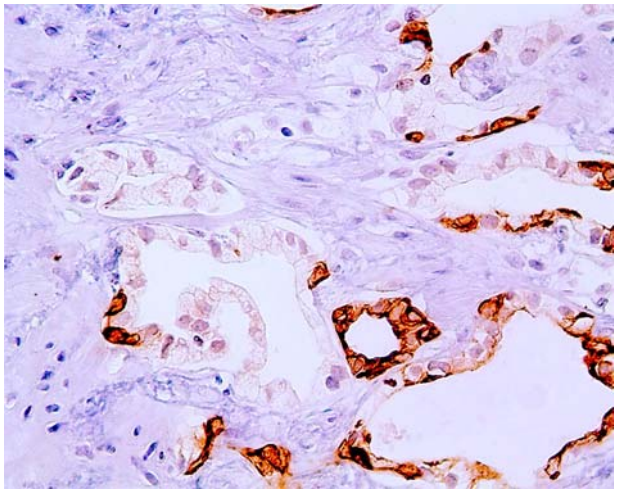

***Figure 3** – Partial atrophy (immunohistochemistry: 34âE12).*

In diagnostic practice it is not rare to find patients with serum prostate- specific antigen (PSA) elevation and several biopsies showing no atypical, preneoplastic or neoplastic lesions, except prostatic atrophy. Regardless of the cause, we hypothesized that damaged epithelial cells in atrophic acini could be a source of the elevation of PSA. Our study was based on 131 needle prostatic biopsies corresponding to 107 patients. The only diagnosis in all biopsies was focal prostatic atrophy without the presence of cancer, high-grade prostatic intraepithelial neoplasia, or areas suspicious for cancer. A positive and significant association was found between the extent of atrophy and the total or free serum PSA elevation (9). All patients showing 35mm or higher linear extent of atrophy in the biopsy cores, had serum PSA above 4ng/mL. The findings suggest that damaged epithelial cells in atrophic acini, regardless of cause, could be a source of serum PSA elevation.

Prostate-specific antigen is a single chain glycoprotein with proteolytic enzyme activity mainly directed against the major gel-forming protein of the ejaculate (semenogelin). PSA induces liquefaction of semen with release of progressively motile spermatozoa (10). There are several efficient physiologic barriers to prevent the escape of any significant amounts of PSA from the prostatic ductal system: basement membrane of the acini, basal cells lining the acini, prostatic stroma, basement membrane of capillary endothelial cells, and endothelial cells. These barriers normally prevent PSA from entering the general circulation at concentrations of more than 3ng/mL (10).

Focal prostatic atrophy represents a form of adaptive response to injury most commonly to inflammation and/or local ischemia. It is intriguing that atrophic acini may produce an excess of serum PSA. Inflammation and/or ischemia are injurious stimuli resulting in diminished oxidative phosphorilation, membrane damage, influx of intracellular calcium, and accumulation of oxygen-derived free radicals (oxidative stress) (11). We speculate that these injurious stimuli may interfere in the physiologic barrier that prevent the escape of any significant amounts of PSA to the general circulation.

Atrophy is a frequent, exciting, intriguing lesion and a relevant subject for further research. Pathologists should include the presence and extent of the lesion in the pathology report.

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Re: Lower Urinary Tract Dysfunction in Children. What Do Pre-School Teachers Know About It?

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Int Braz J Urol, 33: 383-388, 2007

To the Editor:

The authors devised a questionnaire that they administered to 50 pre-school teachers "to evaluate the basic knowledge of lower urinary tract dysfunction". Teachers of young children can have a significant impact in detecting children who may need urologic care. In addition, they may be, in part, responsible for reinforcing the voiding habits of these children, for better or for worse. Pre-school teachers in this study appeared to have mixed notions about what should be considered as normal and abnormal voiding behavior. It should not be surprising that there was little difference in responses based on the education or experience of the teachers, as this is generally not part of the formal training or continuing education of teachers.

The age range of children taught by these teachers may also serve to explain the discrepancies among the teacher's perceptions of what is normal. Frequency in a 4-year-old child whose voiding habits are still immature probably warrants less attention than a 7-year-old with frequency. Such nuances in the development of urinary control only serve to reinforce the need to educate teachers of young children about proper voiding habits, as the authors have advocated.

Behavioral therapy can reduce both urinary tract infections and urinary incontinence in a significant number of children. Because children spend a good proportion of their waking hours at school, teachers can have a significant impact on this health issue by reinforcing proper voiding habits and alerting parents and healthcare professionals to those children at risk for clinically significant underlying urologic disease. Further studies demonstrating the effectiveness of educational programs for teachers are needed.

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UROLOGICAL SURVEY

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STONE DISEASE

The Learning Curve in the Training of Percutaneous Nephrolithotomy

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Objectives: To investigate the learning curve in the training of percutaneous nephrolithotomy (PCNL).
Methods: A total of 104 PCNL cases were included in this evaluation to define the learning curve of a surgeon with no previous experience at performing solo PCNL. Two parameters of expertise were reviewed, namely the operation and fluoroscopic screening times. The operation time was calculated as the beginning of access with the needle until the nephrostomy tube was placed and secured. PCNL procedures were analyzed in seven sets of 15 cases regarding the operation and fluoroscopy times, stone size, stone clearance rate, blood transfusion rate, and estimated blood loss.
Results: The mean operation time was 2.4 h for the first 15 patients. It decreased to a mean of 1.5 h for cases 46 through 60. No further decrease in the operation time was observed after case 60. The fluoroscopic screening time was a peak of 17.5 min in the first 15 cases, whereas it dropped to a mean of 8.9 min for cases 46 through 60. The decline in the mean fluoroscopy screening time continued in cases 61 to 104, but the decline was not significant. There was no significant difference in stone size, stone clearance rate, blood transfusion rate, and estimated blood loss among each set of cases.
Conclusions: This study suggests that the surgical competence in PCNL can be reached after 60 cases. PCNL and fluoroscopy times drop to a steady-state level after performing 60 procedures.

Editorial Comment

It is important first to note that this study reflects the learning curve for only one surgeon, and one would anticipate a range of learning curves dependent on prior experience with other procedures that require the Seldinger technique and fluoroscopic guidance and certainly innate skills might play a role. If safety is the primary outcome, then the transfusion rate suggests that after 15 cases, competency is achieved. If efficiency is the primary outcome, then the fluoroscopic time and operative time suggests that after 60 cases, competency is achieved. However, if stone-free results are the bar to judge competency, it appears that more experience is needed. The authors report only a 75% stone-free rate, though a liberal definition of 3 mm residual fragments or less was utilized. In addition, one should note that though 17% of patients had staghorn calculi and more had upper calyceal stones, only 4% of patients had an upper calyceal puncture. Defining the learning curve for an intercostal puncture may require another study!

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Antegrade Pyelography versus Unenhanced Multidetector CT in the Assessment of Urinary-Tract Stones after Percutaneous Nephrostomy Insertion: A Prospective Blinded Study

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Background and Purpose: In patients with a percutaneous nephrostomy tube (PCN) inserted for symptomatic stone disease, antegrade pyelography is an accepted modality to assess the collecting system and residual stone status prior to PCN removal. Recently, unenhanced multidetector CT (UMDCT) has shown its superiority for the assessment of urinary-tract stones. Comparison of UMDCT with antegrade pyelography has never been done; hence, our aim was to compare the two methods for the assessment of urinary stones in patients with a PCN.

Patients and Methods: Between July 2004 and July 2005, we prospectively imaged 49 consecutive patients with known urinary-tract stone disease who had PCN (27 men and 22 women; average age 57 +/- 20 years; range 4-88 years). All patients underwent UMDCT and antegrade pyelography within 24 hours. Both examinations were prospectively and blindly evaluated by two attending radiologists for the presence, location, and size of urinary-tract stones.

Results: According to the findings of both imaging modalities, 18 patients were stone free, and 31 patients had urinary stones. In 20 of the latter 31 patients (64.5%), the urinary stones were diagnosed only by UMDCT. Antegrade pyelography missed renal as well as ureteral stones, with a significant mean size (5.1 x 6.2 mm, and 6 x 5.3 mm, respectively). Antegrade pyelography missed radiolucent (8/20) as well as radiopaque (12/20) stones. In 11 of the 31 patients (35.5%), urinary stones were diagnosed by both UMDCT and antegrade pyelography. The average size of these renal stones was 6 x 11 mm, and the mean ureteral stone size was 11 x 13 mm. In 64% (7/11), the stones were radiolucent and in 36% (4/11) radiopaque. There was no patient in whom urinary stones were diagnosed by antegrade pyelography but missed by UMDCT.

Conclusions: Unenhanced multidetector CT is more accurate than antegrade pyelography via a PCN for the assessment of urinary-tract stones, with the advantage of reducing the risks of contrast injection side effects.

Editorial Comment

Resolution of stones on antegrade nephrostogram may be dependent on the patient's body mass index and the density of the stone composition. It would be helpful to re-evaluate the relative accuracy of antegrade nephrostogram stratified by these two parameters – one might hypothesize that the Hounsfield units on the CT prior to placement of the percutaneous nephrostomy tube might predict whether reimaging with antegrade nephrostogram would be useful. Similarly, stone location may be an important variable – stones in the ureter or in the pelvis close to the retention coil may be more difficult to discern on CT compared to calyceal stones.

It is important to note that the antegrade nephrostogram performed in this study utilized fluoroscopy. Antegrade nephrostograms that incorporate tomograms prior to instillation of contrast might have a higher sensitivity for stone detection. Though the authors state that sensitivity of a stone-protocol CT scan is 100% with a nephrostomy tube in place, they did not repeat the CT scan after nephrostomy tube removal in those patients thought to be stone-free. It is possible that some stones were "masked" by the presence of the nephrostomy tube.

It is important to note that antegrade nephrostogram will at times be an important post-operative study, specifically if one is evaluating for urinary extravasation, adequate positioning of the nephrostomy tube, residual ureteral obstruction unrelated to calculus, or adequacy of access for a second-look procedure.

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ENDOUROLOGY & LAPAROSCOPY

Complications of Laparoscopic Surgery for Urological Cancer: A Single Institution Analysis

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J Urol. 2007; 178:786-91

Purpose: We determined the incidence of and risk factors for perioperative complications associated with laparoscopic oncological surgery for urological malignancy.
Materials and Methods: All records of patients undergoing laparoscopic surgery for urological malignancy at a tertiary care institution from April 1997 through January 2006 were reviewed. Relevant demographic and perioperative data during and within 6 weeks of surgery were evaluated retrospectively. Various factors were analyzed to estimate risk of a perioperative complication such as the Charlson Comorbidity Index, American Society of Anesthesiologists score, European Scoring System for laparoscopic urological operations and surgeon experience. Logistic regression was used to identify independent risk factors for perioperative complications.
Results: A total of 1,867 laparoscopic oncological surgeries were performed, including radical or partial nephrectomy, nephroureterectomy, radical prostatectomy and radical cystectomy. Perioperative complications occurred in 12.4% of patients, including 3.5% intraoperatively and 8.9% postoperatively. Intraoperative (2.3%) and postoperative hemorrhage (2.7%) accounted for 40% of all perioperative complications. All cause perioperative mortality occurred in 8 patients (0.4%). On multivariate analysis radical cystectomy (adjusted OR 4.9, $p < 0.001$), partial nephrectomy (adjusted OR 2.4, $p < 0.001$), length of surgery greater than 4 hours (adjusted OR 2.5, $p < 0.001$) and preoperative serum creatinine greater than 1.5 mg/dL (adjusted OR 2.1, $p = 0.04$) were independent risk factors for perioperative complications. Comparing the periods of 1997 to 2000 vs. 2001 to 2005, despite a significant increase in technical complexity of procedures (European Scoring System 9.8 vs. 60.6, $p < 0.001$), the incidence of complications tended to decrease (17.3% vs. 12.5%, $p = 0.3$).
Conclusions: In appropriately selected patients laparoscopic urological oncological surgery is safe. These data on perioperative complications could possibly serve as a reference benchmark for practicing urologists.

Editorial Comment

Since the first laparoscopic surgery in urology was performed in 1990, questions about the efficiency and safety of this minimally invasive technique have been challenged, particularly in the urological oncologic field. The strength of this manuscript is the large experience with complex oncological procedures performed laparoscopically in a single institution. The complication rates are comparable to open technique even when the complexity of the cases increased. The authors should be congratulated for the improvement of minimally invasive surgery in Urological oncology benefiting patients with good clinical outcome.

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Imperative Indications for Conservative Management of Upper Tract Transitional Cell Carcinoma

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Purpose: We report our experience with patients with imperative indications for endoscopic treatment for upper tract transitional cell carcinoma.
Materials and Methods: Between 1983 and 2004 we identified 37 patients with a solitary kidney, bilateral disease or preoperative creatinine greater than 2.0 mg/dL who underwent endoscopic treatment for localized upper tract transitional cell carcinoma. A retrospective chart review was performed.
Results: Of the 37 patients 32 had a solitary kidney, 3 had bilateral disease and 2 had preoperative creatinine greater than 2.0 mg/dL. Median age at diagnosis was 75 years (range 56 to 88). Bladder cytology was positive or atypical in 15 of 31 patients (48%). Tumors were grade 1 to 3 in 2, 13 and 7 patients, respectively, and diagnosed visually in 15. At a median followup of 2.7 years for survivors 23 patients (62%) had a total of 56 upper tract transitional cell carcinoma recurrences. Grade and stage progression occurred in 3 and 3 patients, respectively. Ten of the 23 patients who experienced upper tract recurrence died of transitional cell carcinoma. Overall kidney preservation was achieved in 24 of the 32 patients (75%) with a solitary kidney. At last followup 24 patients had died, including 11 (29.7%) of transitional cell carcinoma, at a median of 2.9 years. Cancer specific survival at 5 years for this cohort was 49.3%.
Conclusions: Our results indicate that upper tract tumor recurrence occurs in a majority of patients with imperative indications for endoscopic treatment, underscoring the need for frequent surveillance. While most kidneys can be preserved, cancer specific death is common.

Editorial Comment

Transitional Cell Carcinoma (TCC) of the Upper Tract is one of the most challenges diseases, especially when involves solitary kidneys. The development of digital imaging may have improved the diagnosis of the TCC in the upper tract, as well as, the treatment of small burden disease with laser technology. The treatment of adjuvant intra-collecting system therapy with BCG or other agents was not expanded in this article due to the small number of patients. It will be helpful to establish a multi-center trial to define the role of conservative endoscopic therapy with adjuvant intra-collecting system chemotherapy agents for upper tract TCC.

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IMAGING

Comparison of Effective Radiation Doses in Patients Undergoing Unenhanced MDCT and Excretory Urography for Acute Flank Pain

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Objective: The purpose of this study was to measure and compare the effective radiation dose in patients undergoing unenhanced MDCT and excretory urography for acute flank pain, and to explore technical and practical factors affecting the effective dose.
Subjects and Methods: One hundred nineteen patients with acute flank pain were included. All patients were examined using both MDCT and excretory urography. CT involved one acquisition from the upper kidney margin to the symphysis pubis. The only protocol variation was in the tube current (mAs), which was made according to patient body mass. The excretory urography protocol consisted of three images, with more when supplementary images were needed. Effective radiation doses were computer-simulated using dosimetry programs for CT and conventional radiography, based on Norwegian Radiological Protection Board dose data sets. Mean and SDs of measured patient doses were calculated and compared. Further analyses of dose variations in body mass categories (body mass index) were conducted, as were analyses concerning the number of images taken.
Results: The mean effective doses were 7.7 mSv with MDCT and 3.63 mSv with excretory urography. The effective dose varied both in and between techniques but could be predicted. Radiation risk decreased significantly with increased patient weight. Conclusion: The average effective dose with MDCT was more than double that with excretory urography. However, the appropriate dose could be strongly predicted by the patient's body mass index and by procedure. An optimum low-dose protocol should be considered before initiating unenhanced MDCT for ureteral colic in order to minimize the radiation-induced cancer risk and to secure adequate image quality.

Editorial Comment

In many institutions, nonenhanced computed tomography has largely supplanted intravenous urography as the primary modality for evaluation of patients suspected of having urolithiasis. As we know, nonenhanced multidetector CT (MDCT) examination, on average, doubled the effective radiation dose to the patient when compared with intravenous urography (if a total of 5 films are obtained). This is particularly important to the young female patients due the direct radiation exposure to the gonads. Some young female patients might present with chronic episodes of urolithiasis, and therefore will be submitted to multiple radiologic examinations during their lifetime The aim of this study was to use commercially available software to evaluate effective radiation doses between different radiologic examination procedures and to explore the relationship between technical and practical factors that could affect the effective radiation dose, both during and between the chosen imaging procedures.

The authors presents an interesting observation; they found that a significantly wide dose range of effective doses with both MDCT and excretory urography, mainly influenced by body size (BMI). Patients of normal weight were exposed to a significantly higher radiation risk with MDCT than with excretory urography when compared with the other weight categories. The mAs with both excretory urography and CT varied considerably according to BMI. With excretory urography, an exponential variation in BMI might be expected from the automatic exposure control system (photo timing). However, with MDCT, the mAs varied as a consequence of subjective considerations. This was possibly caused by operator attempts to avoid an increased noise level for patients with high BMI. Recently, several studies has been show that low-dose MDCT protocols, which delivers radiation dose comparable to those of excretory urography are appropriate for the diagnosis of ureteral stones, and that it provides excellent intraobserver and interobserver agreement and does not obscure alternative diagnosis. Nowadays it is imperative to adapt technical parameters of MDCT on the basis of clinical indication. It is not acceptable to use protocols based on subjective considerations and thus delivering increased radiation risk for patients of normal weight. Based on the authors' conclusion we should keep in mind that BMI should also be taken into consideration because it is too a risk predictor. As a rule, unenhanced optimized low-

dose CT should be used routinely in clinical practice and we must pursue in the development of optimized low-dose MDCT protocols.

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The Utility of Magnetic Resonance Imaging and Spectroscopy for Predicting Insignificant Prostate Cancer: an Initial Analysis

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Objective: To design new models that combine clinical variables and biopsy data with magnetic resonance imaging (MRI) and MR spectroscopic imaging (MRSI) data, and assess their value in predicting the probability of insignificant prostate cancer.
Patients and Methods: In all, 220 patients (cT stage T1c or T2a, prostate-specific antigen level < 20 ng/mL, biopsy Gleason score 6) had MRI/MRSI before surgery and met the inclusion criteria for the study. The probability of insignificant cancer was recorded retrospectively and separately for MRI and combined MRI/MRSI on a 0-3 scale (0, definitely insignificant; - 3, definitely significant). Insignificant cancer was defined from surgical pathology as organ-confined cancer of </= 0.5 cm (3) with no poorly differentiated elements. The accuracy of predicting insignificant prostate cancer was assessed using areas under receiver operating characteristic curves (AUCs), for previously reported clinical models and for newly generated MR models combining clinical variables, and biopsy data with MRI data (MRI model) and MRI/MRSI data (MRI/MRSI model).
Results: At pathology, 41% of patients had insignificant cancer; both MRI (AUC 0.803) and MRI/MRSI (AUC 0.854) models incorporating clinical, biopsy and MR data performed significantly better than the basic (AUC 0.574) and more comprehensive medium (AUC 0.726) clinical models. The P values for the differences between the models were: base vs. medium model, < 0.001; base vs. MRI model, < 0.001; base vs. MRI/MRSI model, < 0.001; medium vs. MRI model, < 0.018; medium vs. MRI/MRSI model, < 0.001.
Conclusions: The new MRI and MRI/MRSI models performed better than the clinical models for predicting the probability of insignificant prostate cancer. After appropriate validation, the new MRI and MRI/MRSI models might help in counseling patients who are considering choosing deferred therapy.

Editorial Comment

Insignificant prostate cancer defined as pathologically organ-confined cancer with a total volume of ≤ 0.5 cm 3 and no poorly differentiated component (Gleason grade 4 or 5) on histology is not infrequent but patients with this cancer are very difficult to identify clinically. The authors presented their pioneering work emphasizing that after appropriate validation this new magnetic resonance imaging (MRI) and MRI / magnetic resonance spectroscopic imaging (MRSI) models, might improve the overall accuracy of clinical models in predicting the likelihood of insignificant prostate cancer .Information obtained with conventional MRI and with magnetic resonance spectroscopic imaging were combined with clinical variables and biopsy results in order to build this new clinical nomogram. Both MRI models and the MRI/MRSI model were more accurate than the

clinical models for discriminating insignificant prostate cancer from significant prostate cancer. Since MRSI is more specific than conventional MRI for identification of prostate cancer, one could expect that the MRI/MRSI model was the most discriminating (area under the curve 0.854) and performed significantly better than MRI model alone and other clinical models. As pointed out by the authors the major limitation of the model is that they are vulnerable to upgrading of the biopsy Gleason grade after radical prostatectomy; 26% of the patients of this series had their Gleason scores upgraded. This was particularly important in 7% of the patients of this series. The authors emphasizes that their goal was not produce MRI models ready for clinical use, but rather to test the feasibility of creating such models. In our institution, we already started a prospective clinical study in order to validate this MRI/MRSI model.

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UROGENITAL TRAUMA

Blunt Renal Trauma: Comparison of Contrast-Enhanced CT and Angiographic Findings and the Usefulness of Transcatheter Arterial Embolization

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Background: The purpose of this study was to evaluate the role of contrast-enhanced CT and the usefulness of superselective embolization therapy in the management of arterial damage in patients with severe blunt renal trauma.
Patients and Methods: Nine cases of severe renal trauma were evaluated. In all cases, we compared contrast-enhanced CT findings with angiographic findings, and performed transcatheter arterial embolization (TAE) in six of them with microcoils and gelatin sponge particles. Morphological changes in the kidney and site of infarction after TAE were evaluated on follow-up CT Chronological changes in blood biochemistry findings after injury, degree of anemia and renal function were investigated. Adverse effects or complications such as duration of hematuria, fever, abdominal pain, renovascular hypertension and abscess formation were also evaluated.
Results: The CT finding of extravasation was a reliable sign of active bleeding and useful for determining the indication of TAE. In all cases, bleeding was effectively controlled with superselective embolization. There was minimal procedure-related loss of renal tissue. None of the patients developed abscess, hypertension or other complications.
Conclusions: In blunt renal injury, contrast-enhanced CT was useful for diagnosing arterial hemorrhage. Arterial bleeding may produce massive hematoma and TAE was a useful treatment for such cases. By using selective TAE for a bleeding artery, it was possible to minimize renal parenchymal damage, with complications of TAE rarely seen.

Editorial Comment

The use of transcatheeter arterial embolization is a useful tool when managing renal traumatic injuries. There are typically two situations where embolization is needed, in the acute setting bleed and in a delayed bleed (usually 10-14 days after initial injury). In the acute setting, on the arterial phase images of the CT there is a characteristic "blush" (as in splenic trauma), which suggests a significant arterial injury. While we speak of the retroperitoneum as a confined space that can hold up to 4 to 8 units of blood, the tamponade effect is typically applicable to significant venous bleeding and not arterial injuries. Most major trauma centers are lucky to have a skilled vascular and intervential radiologist who can perform a super selective branch of the renal artery embolization. In the delayed setting, bleeding usually occurs 7 to 14 days after the initial injury. It is at this time that the hematoma starts to lyse and thus releases the tamponade effect. It is also the time it usually takes for a pseudoaneurysm to occur. While AAST Grade V real injuries are life threatening arterial injuries that warrant exploration, all lesser degrees of renal injuries usually do not cause hemodynamic instability and can thus be managed expectantly. With lesser degree renal injuries, the cause for hypotension is typically from associated intra-abdominal injuries and not the kidney injury itself. The reasons for such hemodynamic stability is that fracture lines in the shattered kidney are typically radial in fashion and parallel to the interlobar arteries, and not through them. This is why the kidney can often seem to be broken into multiple pieces yet the parenchyma still be bright, with intravenous contrast on the nephrographic phase images. As to the infarcted parenchyma after embolization, when the segment of parenchyma is large (usually more than 25%) the patient will often have "post-infraction" spiking fevers and a white count for 2 to 3 days, which resolve spontaneously. I have had the same experience as the authors as to complications after embolization. I have not seen a single case of abscess or sustained hypertension. While episodes of transient hypertension are not uncommon, prolonged hypertension is exceedingly rare (less then 1% overall).

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Single Kidney and Sports Participation: Perception versus Reality

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Objectives: Physician opinions and practice patterns regarding the participation of children and adolescents with single, normal kidneys in contact/collision sports are widely varied. We hypothesize that limitation of participation from play based only on the presence of a single kidney is not supported by available data. We sought to determine recommendations of pediatric nephrologists regarding the participation of patients with single, normal kidneys in contact/collision sports and review the literature to determine the rate of sports-related kidney injury compared with other organs.
Methods: Members of the American Society of Pediatric Nephrology were surveyed regarding their recommendations for participation of patients with single, normal kidneys in contact/collision sports. Medical and sports literature databases were searched to determine sports-related kidney, brain, spinal cord, and cardiac injury rates and the sports associated with kidney injury.
Results: Sixty-two percent of respondents would not allow contact/collision sports participation. Eighty-six percent of respondents barred participation in American football, whereas only 5% barred cycling. Most cited

traumatic loss of function as the reason for discouraging participation. The literature search found an incidence of catastrophic sports-related kidney injury of 0.4 per 1 million children per year from all sports. Cycling was the most common cause of sports-related kidney injury causing > 3 times the kidney injuries as football. American football alone accounted for 0.9 to 5.3 fatal brain injuries and 4.9 to 7.3 irreversible spinal cord injuries per 1 million players per year. Commotio cordis causes 2.1 to 9.2 deaths per year.
Conclusions: Most pediatric nephrologists prohibit contact/collision sports participation by athletes with a single kidney, particularly football. The available evidence suggests that cycling is far more likely to cause kidney injury. In addition, kidney injury from sports is much less common than catastrophic brain, spinal cord, or cardiac injury. Restricting participation of patients with a single, normal kidney from contact/collision sports is unwarranted.

Editorial Comment

Recommendations for patients who have a solitary kidney and participation in organized sports and so-called alternative extreme sports is controversial. Admittedly, children are more likely than adults to sustain renal injury from blunt abdominal trauma due to kidney relative size and lack of peri-renal fat and lack of bone and rib ossification. In general, patients with two normal kidneys and injury to one kidney in an accident or sports related event, I typically tell these patients to limit their activity to non strenuous activities and no lifting greater then 20 pounds for 1 to 3 months (1 month for non contact sports and 3 months for contact sports, such as football). The recommendation of the American Academy of Pediatrics Committee on Sports Medicine and Fitness is that children with a solitary kidney should not play team contact sports. However, what is the true incidence of high-grade renal injuries broken down by type of sport?

Johnson et al. (1) noted that high-grade injuries and renal loss in children occurred as a result of motor vehicle accidents, pedestrian versus motor vehicle and falls. No kidneys were lost to contact sports. Sledding, skiing and rollerblading resulted in kidney loss. Brown et al. (2) noted that all high-grade renal injuries resulted from bicycle accidents and none from team sports. It appears, therefore, that activities like bicycling, motorcross, skiing and the like, entail much higher speed and momentum then contact sports. Thus the mechanism of injury is much more severe with such activities then with contact sports, and helps to explain why high-grade injuries are rare with team sports (such as soccer and football). In conclusion, we feel that recommendations about participation in team sports and a solitary kidney appear to be overly protective and need to be re-evaluated with a metanalysis. However, non-team sports such as sledding, skiing, biking, atving and motorcross are risky activities for the solitary kidney child.

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PATHOLOGY

Updated Nomogram to Predict Pathologic Stage of Prostate Cancer Given Prostate-Specific Antigen Level, Clinical Stage, and Biopsy Gleason Score (Partin Tables) Based on Cases from 2000 to 2005

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Objectives: To update the 2001 "Partin tables" with a contemporary patient cohort and revised variable categorization, correcting for the effects of stage migration.
Methods: We analyzed 5730 men treated with prostatectomy (without neoadjuvant therapy) between 2000 and 2005 at the Johns Hopkins Hospital. Average age was 57 years. Multivariable logistic regression was used to estimate the probability of organ-confined disease, extraprostatic extension, seminal vesicle involvement, or lymph node involvement. Predictor variables included preoperative prostate-specific antigen (PSA) level (0 to 2.5, 2.6 to 4.0, 4.1 to 6.0, 6.1 to 10.0, and greater than 10.0 ng/mL), clinical stage (T1c, T2a, and T2b/T2c), and biopsy Gleason score (5 to 6, 3 + 4 = 7, 4 + 3 = 7, or 8 to 10). Bootstrap resampling was used to generate 95% confidence intervals for predicted probabilities.
Results: Seventy-seven percent of patients had T1c, 76% had Gleason score 5 to 6, 80% had a PSA level between 2.5 and 10.0 ng/mL, and 73% had organ-confined disease. Nomograms were developed for the predicted probability of pathologically organ-confined disease, extraprostatic extension, seminal vesicle invasion, or lymph node involvement. The risk of non-organ-confined disease increased with increases in any individual prognostic factor. The dramatic decrease in clinical stage T2c compared with the patient series used in the previous models resulted in T2b and T2c being combined as a single predictor in the nomogram.
Conclusions: These updated "Partin tables" were generated to reflect trends in presentation and pathologic stage for men diagnosed with clinically localized prostate cancer at our institution. Clinicians and patients can use these nomograms to help make important decisions regarding management of prostate cancer.

Editorial Comment

It is worth noting in this updated nomogram that Gleason score 7 has been stratified to 3+4=7 and 4+3=7. Tumors with a Gleason score of 7 have a significantly worse prognosis than those with a Gleason score of 6. Given the adverse prognosis associated with Gleason pattern 4, one would expect that whether a tumor is Gleason score 3+4 or 4+3 would influence prognosis (1). This issue has been controversial in the literature, however, most of the studies have shown that Gleason score 4+3 has a worse prognosis than Gleason score 3+4 (2,3). Recently we evaluated the biochemical (PSA) progression following radical prostatectomy in 300 patients according to Gleason score 3+4 and 4+3 in the surgical specimens. Of the total of 300 patients, 140/300 (46.6%) patients were Gleason score 3+4=7 and 37/300 (12.3%) patients Gleason score 4+3=7. The 4-year biochemical (PSA) progression-free survival rate with Gleason score 3+4 and Gleason score 4+3 was 60% and 30%, respectively (log-rank, p=0.046).

Another topic in the updated nomogram relates to clinical stage. According to the authors the dramatic decrease in clinical stage T2c compared with the present series used in the previous models resulted in T2b and T2c being combined as a single predictor in the nomogram. According to the 2002 TNM classification of malignant tumors, T2b involves more than half of one lobe, but not both lobes. Some studies did not found this stage in surgical specimens. Eichelberger & Cheng (4) question the existence of a true pathologic stage pT2b tumor. They studied 369 prostate cancer patients treated by radical prostatectomy. Prostate cancers were multifocal in

312 cases (85%). The majority of the specimens were pathologic stage pT2 (276, or 75%). Using the 2002 TNM staging criteria, 54 (15%) of the tumors were stage pT2a, 222 (60%) were pT2c, 75 (20%) were pT3a, and 18 (5%) were pT3b. No pathologic stage pT2b tumors were identified. The findings of Quintal et al. (5) using a point-count method for evaluating tumor extension, are in accordance with Eichelberger and Cheng (3). No tumor pathologic stage pT2b was found and the frequency of the stages in Quintal's series is very similar to theirs: stage pT2a, 28 (12.50%); pT2c, 138 (61.61%); pT3a, 30 (13.39%); and, pT3b 28 (12.50%).

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Basal Cell Carcinoma of the Prostate: A Clinicopathologic Study of 29 Cases

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Am J Surg Pathol. 2007;31:697-705

We studied 29 cases of basal cell carcinoma of the prostate including what others call adenoid cystic carcinoma of the prostate. Patients' age ranged from 42 to 89 (mean 69) years. The most common methods of diagnosis was transurethral resection (TURP) (n=29) and needle biopsy (n=9). In 28/29 cases, slides were reviewed and 24 (86%) cases showed more than 1 pattern: adenoid cysticlike (AC-P) pattern and small solid nests with peripheral palisading were the most predominant patterns, each seen in 18 cases (64%). Other patterns included: basal cell hyperplasialike in 9 cases (32%); small tubules occasionally lined by a hyaline rim in 9 cases (32%), with 4 of these cases also demonstrating intermingling cords of cells; and large solid nests in 8 cases (28.5%), 5 of which had central necrosis. Fourteen cases of small nests and tubules were centrally lined by eosinophilic cells. Desmoplasia was noted in 20 (71%) cases. Infiltration around benign glands was seen in 10 (36%) cases, with predominantly small nests and AC-P. Invasion of thick muscle bundles of the bladder neck was seen in 10 of 21 TURP cases. Perineural invasion was noted in 3 cases with AC-P and 1 case of small basaloid nests. Perineural and vascular invasion was seen in 2 basal cell carcinomas with large basaloid nests.

Mitoses ranged from 0 to 60/10 hpf (mean=4). bcl2 was diffusely positive in 22/24 (92%) cases. Ki67 ranged from 2% to 80% (mean=23%). Ki67 > or =20% was seen in 13 (56.5%) cases, including all patterns except small solid nests. Basal cell markers (HMWCK, p63) either: (1) highlighted multiple layers of cells in 15/25 (60%) cases with sparing of the inner most luminal layer; (2) labeled just the outermost layers in 6/25 (24%) cases; or (3) reacted with only a few scattered cells in 4/25 (16%) cases (3 with large solid nests with central necrosis, 1 with tubules and cords). Seven patients had RP with: 5/7 showing extraprostatic extension with 1/5 also showing seminal vesicle involvement and 2/5 also with a positive margin; 1/7 having organ confined disease; and 1/7 showing no residual disease. An additional 11 cases showed extraprostatic extension on TURP with bladder neck invasion (n=10) or periprostatic adipose tissue invasion (n=1). Of 29 (65.5%) cases, 19 had follow-up > 1 year with a mean of 4.3 years (1 to 19 y). Of 19 (77%) cases, 14 had no evidence of disease after 1 to 19 (mean 5.8) years. Of 19 patients, 4 locally recurred with 2 after TURP, 1 after enucleation, and 1 after RP. Metastases developed in 4/29 patients: 1 in lung, 1 in lung and liver, 1 in lung, bone and liver, 1 in penile urethra. Basal cell carcinomas are rare tumors with a broad morphologic spectrum. These tumors predominantly show an indolent course with local infiltrative behavior. A small subset behaves aggressively with local recurrences and distant metastases. The most common morphology among those with an aggressive behavior is large solid nests more often with central necrosis, high Ki67%, and less staining with basal cell markers.

Editorial Comment

Basal and stem cells comprise the proliferative compartment of the prostatic acinus. There is a spectrum of basal cell lesions including typical hyperplasia, atypical hyperplasia, adenoma, and carcinoma (or adenoid cystic carcinoma). The latter is a rare tumor initially considered with an indolent biologic potential (1). In 2003, Iczkowski et al. (2) published the largest series at that time calling attention to the potential aggressiveness of this tumor requiring ablative therapy. From a total of 19 patients, 54 (21%) developed metastases.

Ali and Epstein's is the largest series so far of basal cell carcinoma (or adenoid cystic carcinoma) of the prostate. Of a total of 29, 19 patients had follow-up >1 year: 14 patients had no evidence of disease after 1 to 19 (mean 5.8 years); 4 locally recurred and 4 developed metastases.

The authors conclude that these tumors predominantly show an indolent course with local infiltrative behavior. A small subset behaves aggressively with local and distant metastases. The most common morphology among those with aggressive behavior is large solid nests more often central necrosis, high Ki67%, and less staining with basal cell markers.

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INVESTIGATIVE UROLOGY

The Complex Structure of the Smooth Muscle Layer of Spermatic Veins and Its Potential Role in the Development of Varicocele Testis

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Eur Urol. 2007; 51: 1402-9; discussion 1410

Objectives: Varicocele, a dilatation of the pampiniform venous plexus, is considered to cause male infertility. The exact mechanism of varicocele development is not clarified yet. This study focused on the structure of varicocele veins, compared with normal spermatic veins, and its potential role in varicocele development.
Methods: Morphologic and immunohistochemical studies using antibodies against vWF and neurofilament-200 (NF-200) were performed on spermatic vein fragments of 20 varicocele patients and 40 normal spermatic cords. Casting preparation of veins was performed on five normal spermatic cords.
Results: Casting preparation frequently revealed circular constrictions of normal spermatic vein lumina. Histologic evaluation showed a strong longitudinal smooth muscle layer in the adventitia of large veins in addition to the circularly organised tunica media. Serial sections showed smooth muscle fibres branching from the outer longitudinal into the inner circular layer. Immunostaining for vWF revealed high vascularisation of this outer layer. Interestingly, the number of nerve fibres marked by NF-200 immunostaining was considerably higher in large veins compared to the testicular artery. The longitudinal smooth muscle layer was significantly degraded in the presence of varicocele grades I and II, and did not even exist in varicocele grade III. Correspondingly, the number of vasa vasorum and nerve fibres was reduced in varicocele veins.
Conclusions: Our data show a complex smooth muscle organisation of spermatic veins, which serves the basis for a contractile mechanism, providing an effective blood transport through pampiniform plexus. This mechanism is obviously damaged in the varicocele. Molecular processes behind this impairment remain to be clarified.

Editorial Comment

The authors of this interesting and original study aimed to assess whether there are anatomic and structural differences between normal spermatic veins and varicocele veins, and whether these differences might serve as a basis for an explanation of the development of varicocele.

They demonstrated by the first time that the anatomic structure of the large spermatic veins of the pampiniform plexus is composed of a strong longitudinal smooth muscle layer in the tunica adventitia with oblique muscle fibers that reach the inner circular smooth muscle layer of the tunica media. The authors proposed that this assemblage of muscle layers could lead to a mechanism of peristaltic venous transportation. This contractile function apparently is disturbed in varicocele by morphological changes of the venous wall that may lead to impairment of blood venous return, promoting the development of varicocele.

The take home message of this paper is that the morphologic changes of the venous wall of spermatic cord veins, including a degeneration of the outer smooth muscle layer, lead to an impairment of the contractile function and blood return of the veins, promoting the development of varicocele testis.

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An Electron Microscopic Examination of the Intravesical Ureter in Children with Primary Vesico-Ureteric Reflux

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BJU Int. 2007; 99: 1127-31

Objective: To determine the structure of the intravesical distal ureteric wall of patients with primary vesico-ureteric reflux (VUR), and to compare the findings with previous reports.
Materials and Methods: Specimens of the distal intravesical ureteric segments were taken surgically from children undergoing ureteric reimplantation surgery for primary VUR. There were 24 distal intravesical ureteric specimens from 15 children (nine female and six male). Ultra-thin sections were cut from the specimens and examined with a transmission electron microscope.
Results: The appearance of the muscular layers of the specimens of different grades differed markedly. There were intercellular oedematous areas in the muscular layer in specimens from patients with grade 2 and 3 VUR. In specimens from grade 4 VUR there were also intracytoplasmic vacuoles in the smooth muscle cells. The most marked and striking changes were in the specimens from children with grade 5 VUR, in which there were large intercellular oedematous areas and prominent large intracytoplasmic vacuoles.
Conclusion: Refluxing ureters differ from normal ureters in having disorganized smooth muscle fibres and altered smooth muscle cell structure, leading to incompetence of the valve mechanism. Although we cannot confirm that these pathological changes in the smooth muscle layer of the intravesical ureteric wall are caused by VUR we conclude that, with increasing degrees of reflux, the degree of smooth muscle damage increases, and that the rate of spontaneous resolution decreases.

Editorial Comment

The authors taken specimens of intravesical distal ureteric segments surgically removed from children undergoing ureteric reimplantation due to primary vesicoureteral reflux (VUR) of different degrees. They studied by histological methods and for the first time by transmission electron microscopy (TEM), the structure and structural changes of the specimens. The results were compared with controls and with the grades of VUR.

The authors found no marked differences in the morphology of the tunica adventitia, and no pathology was detected. The structure and distribution of collagen fibers, fibrocytes and fibroblasts in the adventitia were similar in all specimens. The transitional epithelial cells were closely arranged in the tunica mucosa and the submucosa contained collagen fibers, fibrocytes and fibroblasts in variable proportions. Further, the morphology of the lamina propria and the tunica mucosa were similar in all specimens, and no ultrastructural change or pathology was detected.

On the other hand, the findings demonstrated that the appearance of the muscular layers of the specimens differed markedly with VUR grade. The distribution of intracytoplasmic vacuoles in smooth muscle cells and intercellular edema are clearly shown by semi-quantitative methods. Intercellular edema was sparse in specimens of grade 2–3 VUR, moderate in specimens of grade 4 and common in specimens of grade 5. Intracytoplasmic vacuoles were absent in specimens of grade 2–3 VUR, sparse in grade 4 and common in grade 5.

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RECONSTRUCTIVE UROLOGY

Artificial Urinary Sphincters Placed After Posterior Urethral Distraction Injuries in Children are at Risk for Erosion

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J Urol. 2007, 178: 1813-1815

Purpose: Management for posterior urethral disruption and concurrent bladder neck incompetence is controversial. Some groups recommend treatment with a Mitrofanoff catheterizable stoma, while others advocate urethral reconstruction with delayed placement of an artificial urinary sphincter. We report our experience with the latter strategy.
Materials and Methods: We reviewed the records of all patients with the above injury who were treated with end-to-end urethroplasty followed by delayed bladder neck artificial urinary sphincter placement from 1986 to 2006.
Results: Five patients had videourodynamic evidence of bladder neck incompetence coexisting with traumatic posterior urethral disruption. The etiology of bladder neck incompetence in all 5 patients was a known longitudinal tear through the bladder neck that occurred at the time of trauma. Each patient underwent end-to-end urethroplasty. Six to 12 months later the patients had persistent incontinence. Bladder function and urethral patency were documented by urodynamic, radiographic and endoscopic studies. A bladder neck artificial urinary sphincter was subsequently placed. Each operation was technically demanding due to fibrosis in the pelvis and around the bladder neck. All patients were initially continent but erosion of the artificial urinary sphincter into the bladder neck in 4, and the bladder neck and rectum in 1 occurred at a mean of 3 years (range 6 months to 8 years).
Conclusions: Placement of a bladder neck artificial urinary sphincter for managing urinary incontinence due to concurrent posterior urethral disruption and bladder neck incompetence is difficult and it risks delayed erosion. In this patient population we would strongly consider urinary diversion with a Mitrofanoff catheterizable stoma.

Editorial Comment

Stress urinary incontinence as a result of urethral injury occurs in approximately 10% of pelvic trauma cases. Urinary stress incontinence usually only occurs in those boys with posterior urethral disruption and an additional rabdosphincter injury. The primarily reconstructive approach with the placement of a suprapubic catheter secures healing but does not give any guarantee for functionality. Two possibilities occur after the removal of the transurethral catheter: incontinence or stricture. The incidence of urinary stress incontinence is lower compared to stricture development. The two major questions that occur are, when and which surgical approach to offer the pediatric patient, who suffers from stress urinary incontinence. Ashley & Husmann reported in their group of five patients to place an artificial sphincter 6-12 months after the reconstructive approach, which might be still too early regarding the extensive surgical approach and the not ideal position for the cuff of an AMS 800. In addition, the treated males were on average 11-year-old, who are still growing. This is most probably due to a consequence of one or all of the three mentioned arguments' failure.

Because of surgery for the after effects of the injury, the approach is sometimes invasive resulting in scars and poor vascularization. Secondly, especially the cuff around the bladder neck / prostate might cause not only obstruction but – due to the poor tissue quality with reduced vascularization – result in erosion in those patients in the follow-up because they are still growing. This might be an explanation of the average explantation time of 3 years (6 months to 6 years) after the implantation.

If an artificial urinary sphincter is at all considered in children and adults, it should be placed through the penoscrotal approach to the bulbar urethra (1). It is easier to access and the tissue is in most cases untouched,

which supports the healing and makes the whole approach less invasive. In the follow-up, an age-adapted cuff size exchange is easier to be performed. Some might argue that the smallest cuff might still be too big for the bulbar urethra, but local tissue or acellular matrices can be placed in-between the urethra and the cuff. This tissue or matrix protects the urethra and the cuff, avoiding erosions. The authors are correct that the approach to perform the Mitrofanoff catheterizable stoma in these patients is a very elegant way, too and an artificial urinary sphincter with an age-adapted cuff size is the second best choice beside the Mitrofanoff catheterizable stoma.

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Autologous Myoblasts and Fibroblasts versus Collagen for Treatment of Stress Urinary Incontinence in Women: A Randomised Controlled Trial

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Lancet. 2007 Jun 30;369(9580):2179-86

Background: Preclinical studies have suggested that transurethral injections of autologous myoblasts can aid in regeneration of the rhabdosphincter, and fibroblasts in reconstruction of the urethral submucosa. We aimed to compare the effectiveness and tolerability of ultrasonography-guided injections of autologous cells with those of endoscopic injections of collagen for stress incontinence.
Methods: Between 2002 and 2004, we recruited 63 eligible women with urinary stress incontinence. 42 of these women were randomly assigned to receive transurethral ultrasonography-guided injections of autologous myoblasts and fibroblasts, and 21 to receive conventional endoscopic injections of collagen. The first primary outcome measure was an incontinence score (range 0-6) based on a 24-hour voiding diary, a 24-hour pad test, and a patient questionnaire. The other primary outcome measures were contractility of the rhabdosphincter and thickness of both the urethra and rhabdosphincter. Analysis was by intention to treat. This trial is registered with Controlled-Trials.com, number CCT-NAPN-16630.
Findings: At 12-months' follow-up, 38 of the 42 women injected with autologous cells were completely continent, compared with two of the 21 patients given conventional treatment with collagen. The median incontinence score decreased from a baseline of 6.0 (IQR 6.0-6.0; where 6 represents complete incontinence), to 0 (0-0) for patients treated with autologous cells, and 6.0 (3.5-6.0) for patients treated with collagen ($p<0.0001$). Ultrasonographic measurements showed that the mean thickness of the rhabdosphincter increased from a baseline of 2.13 mm (SD 0.39) for all patients to 3.38 mm (0.26) for patients treated with autologous cells and 2.32 mm (0.44) for patients treated with collagen ($p<0.0001$). Contractility of the rhabdosphincter increased from a baseline of 0.58 mm (SD 0.32) to 1.56 mm (0.28) for patients treated with autologous cells and 0.67 mm (0.51) for

controls ($p<0.0001$). The change in the thickness of the urethra after treatment was not significantly different between treatment groups. No adverse effects were recorded in any of the 63 patients.
Interpretation: Long-term postoperative results and data from multicentre trials with larger numbers of patients are needed to assess whether injection of autologous cells into the rhabdosphincter and the urethra could become a standard treatment for urinary incontinence.

Editorial Comment

In recent years, the knowledge and awareness for female stress urinary incontinence has grown with the result that a wide range of different treatment options has become available. Treatment options improved with the increased knowledge of pelvic floor dysfunction and surgical options became less invasive by the year.

Obtaining autologous myoblasts of skeletal muscle-biopsies, cultivating them and transplanting them after differentiation into the external urethral sphincter herald a new era of incontinence therapy. In the current study of Strasser et al., 42 patients were treated by a transurethral, ultrasound-guided injection of myoblasts and fibroblasts. The control group of 21 patients received collagen in the conventional method.

After a mean follow-up of 12 months, urinary continence and improvement of the urethral rhabdosphincter was evaluated with questionnaires, voiding diaries, pad tests, transurethral ultrasonograpy and electromyography. Out of those treated with autologous myoblasts and fibroblasts, over 90% were completely dry, whereas in the control group, a success rate of only 9% was recorded.

Currently, experience with this new incontinence treatment comes from a single center, which has started to collaborate with others in order to verify the presented striking results. In addition to some doubts about the allocation concealment and ascertainment bias, it might be important which way the “material” is injected. The ultrasound-guided application might be more precise and effective than the classic visual-judged injections. The number of deposits needed to ensure good filling as well as coaptation of the urethral wall and thus compression of the urethral lumen, which must still be proven.

The presented results, the development of the clinical pathways of this procedure and new sources of stem cells to be transplanted might be one of the most important achievements in reconstructive urology of the last decade. By presenting a minimal invasive technique with a precise application into the location for a physiological function, a treatment option to regenerate sphincter function and to prevent urinary incontinence at an early stage becomes feasible.

Additional stem cell sources (1), which can be harvested easier and may be even true omnipotent stem cells in order to better reconstruct a rhabdosphincter are currently tested experimentally and might offer the possibility to treat high grade stress urinary incontinence.

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UROLOGICAL ONCOLOGY

Perioperative Complications of Radical Cystectomy in a Contemporary Series

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Eur Urol. 2007; 51: 397-401

Objectives: Radical cystectomy is the preferred standard treatment for patients with muscle-invasive bladder cancer. With improvements in intra- and perioperative care lower complication rates have been reported. We retrospectively evaluated our series of patients who underwent radical cystectomy for advanced bladder cancer for perioperative complications as well as operative time, postoperative hospital stay and transfusion rates.
Patients and Methods: Between April 1993 and August 2005, 516 radical cystectomies were performed for muscle infiltrating transitional cell carcinoma and other types of neoplastic diseases of the bladder at our institution. The average age was 66.3 yr (31-89).
Results: The perioperative mortality rate was 0.8%. A total of 141 patients (27.3%) developed at least one perioperative complication. The most frequent medical complications were subileus in 20 (3.9%) patients, deep venous thrombosis in 24 (4.7%), and enterocolitis in 10 (1.9%). Surgical complications included pelvic lymphoceles in 42 (8.1%) patients, wound dehiscence in 46 (8.9%), pelvic hematoma in 4 (0.8%), peritonitis in 4 (0.8%) and small bowel obstruction in 4 (0.8%). The total early reoperation rate was 6.2%. Operative time, postoperative hospital stay and average number of blood units transfused decreased over the period 1993-2005.
Conclusions: Radical cystectomy today is a procedure with an acceptable rate of perioperative morbidity and mortality. Improvements in surgical technique and anaesthesia as well as increased quality of perioperative care in recent years have resulted in reduced morbidity and shorter hospital stay.

Editorial Comment

This article focuses on the complications of a large cystectomy series of a so-called high-volume center with around 40 cystectomies annually. The complication rate in this series, which is very identical to other large volume series, is roughly around 30%, mortality at 1%. Interestingly, median operative time for ileal conduits was 5.7 hours and for neobladders 6.5 hours.

Patients should be counseled about these realistic data before surgery.

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Natural History of Biochemical Recurrence after Radical Prostatectomy: Risk Assessment for Secondary Therapy

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Eur Urol. 2007; 51: 1175-84

Purpose: A persistently elevated or rising serum level of prostate-specific antigen (PSA) after radical prostatectomy is indicative of recurrent prostate cancer. The natural history of PSA-defined biochemical recurrence (BCR) is

highly variable. While a rising PSA level universally antedates metastatic progression and prostate cancer-specific mortality (PCSM), it is not a surrogate for these endpoints. Thus, the management of patients with BCR is controversial.
Methods: A literature review was conducted to determine the incidence and natural history of BCR, prognostic factors for clinical progression (CP), and the available evidence supporting local or systemic salvage therapy for these patients.
Results: BCR is best defined as two successive PSA levels > or =0.4 ng/ml, as this correlates most accurately with CP. PSA doubling time (PSA-DT) and prostatectomy Gleason score are the variables that best predict the development of distant metastasis and PCSM. Prognostic models based on these and other variables are useful for assessing the need for salvage therapy and the anticipated outcome following local salvage therapy. A treatment algorithm for managing patients with post-prostatectomy BCR was devised.
Conclusions: Management of patients with BCR after prostatectomy continues to be a complex and challenging issue. Improved methods for risk stratification allow for identification of patients who require treatment. Furthermore, these methods aid in determination of the pattern of disease recurrence, thereby guiding treatment modality. Randomized trials are essential to determine the value of local or systemic salvage therapy strategies in this patient population.

Editorial Comment
The percentage of biochemical recurrence after radical prostatectomy (RP) in several large series varies between 15% and 33% with a median time to failure between 2 and 3.5 years. This article gives a straightforward summary of several published trials on this patient group. Several definitions of failure are discussed and an overview on the results of different series is given. Interestingly, only two of seven trials showed a benefit of early hormone therapy in recurrent prostate cancer. Based on these data, a meaningful treatment algorithm is provided.

Article focuses on the complications of a large cystectomy series of a so-called high-volume center with around 40 cystectomies annually. The complication rate in this series, which is very identical to other large volume series, is roughly around 30%, mortality at 1%. Interestingly, median operative time for ileal conduits was 5.7 hours and for neobladders 6.5 hours .

Patients should be counseled about these realistic data before surgery.

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NEUROUROLOGY & FEMALE UROLOGY

Correlation of Bladder Base Elevation with Pelvic Floor Hypertonicity in Women with Lower Urinary Tract Symptoms

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Neurourol Urodyn. 2007;26:502-6

Aims: To determine whether the bladder base elevation as revealed by cystogram under fluoroscopy is associated with pelvic floor hypertonicity or bladder outlet obstruction (BOO) in women.
Methods: Sixty-two women who were referred to our videourodynamic laboratory for assessment of lower urinary tract symptoms (LUTS) were included in this retrospective analysis. Thirty-one of these women with bladder base elevation-revealed by cystogram under fluoroscopy during videourodynamic study-served as the experimental group, and another group of 31 women without bladder base elevation served as control. None of the patients had neuropathy, previous pelvic surgery or chronic urinary retention. The clinical symptoms, urodynamic diagnosis, and parameters were compared between the two groups.
Results: The mean voiding pressure (Pdet. Qmax) and postvoid residual (PVR) were significantly greater, and maximum flow rate (Qmax) and voided volume were significantly lower in the bladder base elevation group. When a Pdet. Qmax of >or=35 cm H2O combined with a Qmax of <or=15 ml/sec in pressure flow study was used to diagnose BOO, significantly more patients in the bladder base elevation group had BOO than controls (51.6% vs. 9.7%, P=0.0003). Pelvic floor muscle electromyogram (EMG) was dyscoordinated during the voiding phase in 18 (58.1%) and 9 (29%) of the patients with and without bladder base elevation, respectively (P=0.0212).
Conclusion: Women with LUTS and bladder base elevation revealed in the filling phase of videourodynamic study had significantly higher voiding pressure and incidence of dyscoordinated pelvic floor EMG activities during voiding, suggesting a higher incidence of BOO and pelvic floor hypertonicity. Copyright (c) 2007 Wiley-Liss, Inc.

Editorial Comment

The authors in this study highlight another potential advantage of radiographic imaging of the bladder during the evaluation of urinary incontinence. They noted that female patients with lower urinary tract symptoms and fluoroscopic bladder base elevation would exhibit higher voiding pressures and abnormal pelvic floor EMG activity. Though this study population did not have any additional radiographic imaging of the pelvis to preclude a mass effect causing the elevation of the bladder base, it was noted that the bladder base did descend during the voiding phase in all patients except for those who had evidence of bladder outlet obstruction. It would be of interest to see if patients who have iatrogenic induced bladder base elevation on radiographic imaging from surgical repair of the anterior compartment will have the same degree of voiding dysfunction as noted by these patients. The value of fluoroscopy in the evaluation of female lower urinary tract symptoms has already been highlighted in the literature (1).

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Pelvis Architecture and Urinary Incontinence in Women.

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Eur Urol. 2007; 52:239-44.

Objectives: To examine anatomic features in the pelvic bones and muscles in women with urinary incontinence (UI).
Material and Methods: Between October 2005 and January 2006, 212 consecutive women underwent pelvic computerized tomography in our center. Preceding the examination, all women completed a clinical and demographic questionnaire including detailed questions about UI. Several anatomic parameters using multiplanar reformation and three-dimensional techniques (volume rendering) were examined. We specifically evaluated different bony parameters, pelvic floor muscle angles, densities, and cross-sectional areas. Ninety-three women (46.5%) had UI; the remaining women served as the control group. A logistic regression model was used to evaluate risk factors for UI.
Results: The mean age was 55.5 yr (range: 19-90). Women who suffered from UI were older (60.97 vs. 50.77 yr, $p<0.0001$), had higher body mass index (27.65 vs. 25.49, $p<0.01$), had more previous hysterectomies (21.5% vs. 6.5%, $p<0.005$), underwent more pelvic irradiation (9.7% vs. 1.8%, $p<0.05$), and had more diabetes mellitus (31.2% vs. 13.1%, $p<0.005$). Patient's age and previous hysterectomy were found to be the major clinical risk factors for UI (OR: 1.029, $p=0.002$; OR: 2.94, $p=0.024$, respectively). Logistic regression analysis on all clinical and morphologic variables yielded the following risk factors: pelvic-inlet diameter (OR: 1.216, $p<0.0001$), pelvic-inlet anterior-posterior diameter (OR: 1.109, $p=0.003$), pelvic-outlet diameter (OR: 1.077, $p=0.011$) and transverse perineal muscle cross-section diameter (OR: 0.773, $p<0.0001$).
Conclusions: Pelvic inlet and outlet dimensions are major risk factors for developing UI in women. These findings may lead to a better comprehension of the pathophysiology of UI in women.

Editorial Comment

The authors present a very interesting review noting that pelvic inlet and outlet diameters were significantly larger in the incontinent women of their study group than those who were continent. That these increased diameters were congenital or from maturational changes remained unanswered. Perhaps the etiology is unimportant; and in addition, continence rates also depend on the pelvic muscle mass present as noted in this paper. This presentation raises the thought that perhaps the hormonally induced relaxation of the pelvic ligaments and the subsequent increased pelvic diameter associated with childbirth may be the significant contributor to the transient urinary incontinence of pregnancy.

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PEDIATRIC UROLOGY

Recurrent Urinary Tract Infections in Children: Risk Factors and Association with Prophylactic Antimicrobials.

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JAMA. 2007;298:179-86

Context: The evidence regarding risk factors for recurrent urinary tract infection (UTI) and the risks and benefits of antimicrobial prophylaxis in children is scant.
Objectives: To identify risk factors for recurrent UTI in a pediatric primary care cohort, to determine the association between antimicrobial prophylaxis and recurrent UTI, and to identify the risk factors for resistance among recurrent UTIs.
Design, Patients and Setting: From a network of 27 primary care pediatric practices in urban, suburban, and semirural areas spanning 3 states, a cohort of children aged 6 years or younger who were diagnosed with first UTI between July 1, 2001, and May 31, 2006, was assembled. Time-to-event analysis was used to determine risk factors for recurrent UTI and the association between antimicrobial prophylaxis and recurrent UTI, and a nested case-control study was performed among children with recurrent UTI to identify risk factors for resistant infections.
Main Outcome Measures: Time to recurrent UTI and antimicrobial resistance of recurrent UTI pathogens.
RESULTS: Among 74 974 children in the network, 611 (0.007 per person-year) had a first UTI and 83 (0.12 per person-year after first UTI) had a recurrent UTI. In multivariable Cox time-to-event models, factors associated with increased risk of recurrent UTI included white race (0.17 per person-year; hazard ratio [HR], 1.97; 95% confidence interval [CI], 1.22-3.16), age 3 to 4 years (0.22 per person-year; HR, 2.75; 95% CI, 1.37-5.51), age 4 to 5 years (0.19 per person-year; HR, 2.47; 95% CI, 1.19-5.12), and grade 4 to 5 vesicoureteral reflux (0.60 per person-year; HR, 4.38; 95% CI, 1.26-15.29). Sex and grade 1 to 3 vesicoureteral reflux were not associated with risk of recurrence. Antimicrobial prophylaxis was not associated with decreased risk of recurrent UTI (HR, 1.01; 95% CI, 0.50-2.02), even after adjusting for propensity to receive prophylaxis, but was a risk factor for antibimicrobial resistance among children with recurrent UTI (HR, 7.50; 95% CI, 1.60-35.17).
Conclusion: Among the children in this study, antimicrobial prophylaxis was not associated with decreased risk of recurrent UTI, but was associated with increased risk of resistant infections.

Editorial Comment

This is a very large network of 27 primary care pediatric practices using a common electronic health record attempting to identify: the risk factors for recurrent UTI's in pediatrics, the association between prophylactic antimicrobials and recurrent UTI's and the risk factors for resistance of recurrent UTI's in patients six years or younger

This is a retrospective study and the authors tried to review data on their patients that were outside their health care network and laboratory and x-ray data were reviewed manually. There was a 5% random sampling of the actual charts to validate the study. Patients had to have at least two clinic visits in the health network. Positive cultures were defined at 50,000 colony forming units and these were all catheterized specimens and they excluded voided or bagged urine specimens. Patients were excluded that had significant other comorbidities. It is important to note that a resistant culture was defined as a pathogen, resistant to "any" antimicrobial. They reviewed VCUG's that were performed on their patients and did a highly credible job of analyzing the statistics.

They had a total of 74,974 patients six years or under who had at least two clinic visits. Six-hundred sixty-six of them had a confirmed UTI and 611 were in the study group. There was a 13.6% recurrence rate resulting in 12% recurrence per year. 61% of the recurrences were due to a pathogen with antimicrobial resistance. 88.9% with a first UTI were female and 65.5% of all patients did not undergo a VCUG even though under two years of age the American Academy of Pediatrics recommends the VCUG to be performed. 58% of the children under two years-of-age in the study had a VCUG performed. Antimicrobial prophylaxis considered as a time-varying covariate had no significant effect on the risk of recurrent urinary tract infection in a multivariate analysis. Conversely exposure to prophylactic antimicrobials significantly increased the likelihood of resistant infections.

Their data showed the cumulative incidence from 0-6 years of having a first UTI was 4.2% and the rate of recurrence per year was 12%. Their conclusions were that Caucasians from three to five years of age with Grade IV-V vesicoureteral reflux were associated with increased risk of recurrent urinary tract infection. Sex of the patient and Grade I-III vesicoureteral reflux were not associated with increased risk of recurrence. An antimicrobial prophylaxis was not associated with lower risk of recurrent UTI but prophylaxis was associated with increased risk of resistant infections.

Electronic medical record data from insurance networks have significant study difficulties especially with missed results from outside the network and with a large group of physicians treating a large group of patients, the patterns of care may vary significantly. Noted in this study was the absence of VCUG in nearly ? of patients in spite of the recommendations of the American Academy of Pediatrics to do so. Also all patients had catheterized specimens and yet most physicians would accept a clean-catch negative specimen or a clean-catch single organ positive specimen. Antibiotic exposure is difficult to judge especially since patients may have had antibiotics for different etiologies prior to joining the network and having their first UTI.

One of my biggest concerns about the data is the definition of antibiotic resistance as the pathogen having resistance to any of the antibiotics tested for sensitivity. It almost seems unusual in my practice to have urine cultures that are pan-sensitive, even in first time UTI patients on an outpatient basis. A second large concern was no attempt to ask questions about bladder or bowel function and it is well-known that constipation and voiding dysfunction have a large impact on vesicoureteral reflux and urinary tract infection occurrences and this is a significant oversight in their study. This study still has produced provocative data and should be read and studied because of its wide circulation.

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Is Antibiotic Prophylaxis Necessary in Infants with Obstructive Hydronephrosis?

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Purpose: We investigated the relationship between the level of obstruction of the upper urinary tract and the risk and onset of urinary tract infection in infants with severe obstructive hydronephrosis to determine the need for antibiotic prophylaxis.

Materials and Methods: A total of 105 patients were prenatally diagnosed with severe hydronephrosis (Society for Fetal Urology grade III or IV) due to upper urinary tract obstruction between 1994 and 2004. Of these patients 75 had ureteropelvic junction obstruction and 30 had lower ureteral obstruction. We retrospectively evaluated the clinical course and incidence of urinary tract infection during the first 12 months postnatally without antibiotic prophylaxis.
Results: The incidence of overall urinary tract infection during followup was 36.2% (38 of 105 patients), and it demonstrated a higher trend with lower ureteral obstruction than with ureteropelvic junction obstruction (50% vs 30.7%, p=0.063). Most cases of urinary tract infection (92.8%) occurred before age 6 months, with a mean age at onset of 2.6 months. Of 105 patients 77 (73.3%) underwent corrective surgery at a mean age of 3.8 months. The incidence of urinary tract infection before surgical correction was 33.8% at a mean age of 2.1 months. The incidence of urinary tract infection in surgical cases was significantly higher with lower ureteral obstruction than with ureteropelvic junction obstruction (54.2% vs 24.5%, p=0.011).
Conclusions: Urinary tract infection in infants with severe obstructive hydronephrosis has a high incidence, occurs before age 6 months and is more common with lower ureteral obstruction than with ureteropelvic junction obstruction. These findings indicate that infants with severe hydronephrosis due to obstruction of the upper urinary tract should receive antibiotic prophylaxis.

Editorial Comment

105 congenital hydronephroses due to upper urinary tract blockages were evaluated during a ten year period. 99 were unilateral and six were bilateral. Forty-seven had SFU Grade III hydronephrosis and 58 had Grade IV. None of the 82 males were circumcised. All patients were followed without prophylactic antibiotics. Seventy-five had ureteropelvic junction obstruction and 30 patients had lower urinary tract obstruction, 18 of which had ureterovesical junction obstruction. There were 10 ureteroceles and 2 ectopic ureters. Surgery was performed if a UTI occurred, or when there was an increased anterior and posterior pelvis diameter or an increased drainage time with worsening obstructive curve or decreasing relative renal function less than 40.

The overall incidence of UTI during follow up was 36.2% (38/105 patients), 50% of the lower urinary tract obstructions and 30.7% of the upper urinary tract obstructions had a UTI. 92.8% of these infections occur before six months of age with a mean age of onset of 2.6 months. Of the 105 patients, 77 underwent corrective surgery at a mean age of 3.8 months. Their data suggested that there is a higher risk of infection for obstructions near the bladder and they recommended prophylactic antibiotics for infants with SFU Grade III and IV obstruction during observation periods.

This is a higher rate of infection than is sometimes reported and a much higher surgery rate at earlier ages than is usually recommended. For ureteropelvic junction obstructions, half of the patients will resolve spontaneously by waiting 18 months or more. It is surprising that their patients either had infections or other indications for surgery by a mean age of 3.8 months. This probably indicates that this is a highly selective group of patients but still suggests that prophylactic antibiotics may be required.

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