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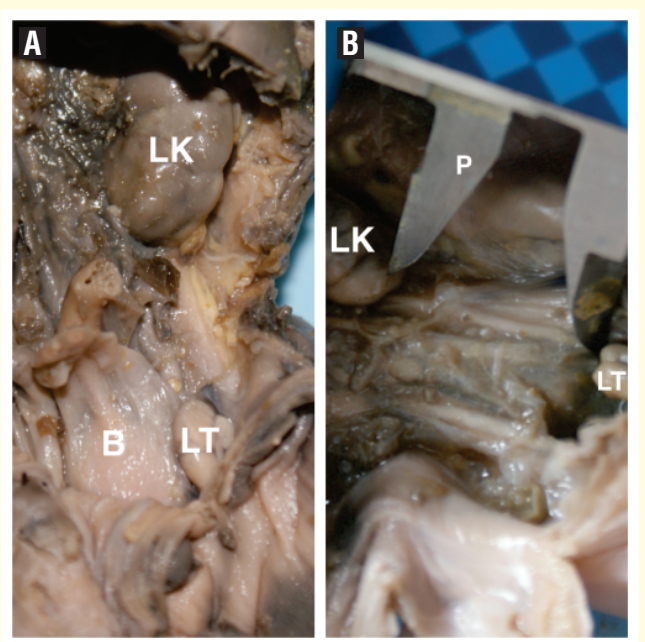

Figure 2 - Measurement of the distance between the lower pole of the kidney and the upper extremity of the testis. A) Male fetus with 22 weeks post-conception. The abdominal wall and the intra-peritoneal organs were removed, revealing the left kidney (LK) and the left testis (LT). B=bladder. B) The same fetus, where the distance between the lower pole of the left kidney (LK) and the upper extremity of the left testis (LT) was measured with a digital pachymeter (P). (Page 561)

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EDITOR'S COMMENT

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Bucal Mucosa Graft in Long Anterior Urethral Stenosis – Dorsal or Ventral?

The May-June 2016 issue of the International Braz J Urol presents original contributions with a lot of interesting papers in different fields: Urinary Incontinence, Urethral Stricture, Bladder Cancer, Pelvic-Ureteric Junction Stenosis, BPH, Prostate Cancer, Renal stones, Uroginecology, Pediatric Urology and basic research. The papers come from many different countries such as Brazil, USA, Turkey, Italy, Austria, Australia, Israel, Netherlands, India, Mexico, China, Saudi Arabia, United Kingdon, Korea and France, and as usual the editor´s comment highlights some papers. We decided to comment 2 papers about a very usual topic in urologic practice: The Urethral Stricture.

Doctor Prabha and collegues from India performed on page 564 an interesting study about the single stage dorsolateral onlay buccal mucosal urethroplasty for long anterior urethral strictures. The authors studied 20 patients with urethral strictures: Lichen sclerosis in 12 cases (60%), Instrumentation in 5 cases (25%), and unknown in 3 cases (15%). Strictures were approached through a perineal skin incision and penis was invaginated into it to access the entire urethra. All the grafts were placed dorsolaterally, preserving the bulbospongiosus muscle, central tendon of perineum and one-sided attachement of corpus spongiosum. The mean stricture length was 8.5cm (range 4 to 12cm) and the overall success rate was 85%. There were 3 failures (meatal stenosis in 1, proximal stricture in 1 and whole length recurrent stricture in 1). Other complications included wound infection, urethrocutaneous fistula, brownish discharge per urethra and scrotal edema. The authors concluded that dorsolateral buccal mucosal urethroplasty for long anterior urethral strictures using a single perineal incision is simple, safe and easily reproducible by urologists with a good outcome.

The success of urethroplasty using bucal mucosa graft (BMG) is significantly better compared to others grafts (1). The BMG placement can be ventral, dorsal and lateral, but the first 2 are most commonly done (2). Dorsal placement of the graft has the advantage of using the corporal bodies to provide a secure well-vascularized graft bed that helps to prevent the protrusion of the graft with resulting pseudodiverticulum formation (3). Ventral location provides the advantages of ease of exposure and good vascular supply by avoiding circumferential rotation of the urethra (4). Early success rates of dorsal and ventral onlay with BMG were 96 and 85%, respectively. However, long-term follow-up revealed essentially no difference in success rates (5-8). Most recently, in a interestig meta-analysis review of the literature on dorsal or ventral graft urethroplasty the success rates of ventral onlay urethroplasty (750 cases) and dorsal onlay (513 cases) were 82.5 and 86.9% ($p = 0.034$) (9).

We can conlude that the two techniques (Ventral and Dorsal BMG) had similar sucess results in long anterior urethral strictures and the surgeon experience and preference with the technique is the most important factor for the sucess of the surgery.

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EDITORIAL
IN THIS ISSUE

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From robot to molecule, the behavior

In general Urology, forty per cent of ambulatory consultations are intended to prostate care, as well as consultation in geriatrics and clinical medicine. It is observed statistically that one in every six men over 50 years will present prostate cancer (PCa) throughout live (1). It is the second most prevalent cancer in men, following skin cancer, with an estimate of 61,200 new cases in 2016, according to INCA (National Cancer Institute of Brazil).

Recent scientific knowledge and incorporation of new technologies lead to higher interaction with molecular epidemiology and cancer genetics. They explain why some patients will present slower progression of the disease, allowing for active surveillance, and also the use of newer and lesser aggressive treatments with higher survival with good quality of life. Epigenetic and genetic alterations provide a mosaic of tumor clones that determine respectively heterogeneous histologically phenotypic tumors, with corresponding indolent clinical symptoms or a more aggressive progression (2).

Currently, renal tumors are efficiently treated due to precision and richer details provided by modern image technologies. We are able to detect in daily practice the aggressiveness of the lesion according to dimension, morphology, tissue density, perfusion and anatomic relations, allowing the choice of the most adequate treatment. Actually, current image exams reflect more accurately the tumor microenvironment. In the same way, evaluation of prostate gland by multiparametric magnetic resonance provides data related to morphology, perfusion, diffusion and spectroscopy, that matches more adequately tumor histology and neoplastic alterations of PCa. After 2010, based on the BIS-RADS model system, Breast Imaging and Reporting Archiving Data System, many studies have been proposed to study the prostate gland. PI-RADS, Prostate Imaging and Reporting Archiving Data System, was proposed to determine image patterns obtained by MRI of PCa, in order to distinguish between "insignificant lesions" and clinical significant lesions, and to determine where to perform biopsy (prostate targets). In 2012 European Urology magazine proposed a guideline using PI-RADS system with five grades of suspicion of prostate cancer. In the first two grades, it is unlikely the presence of clinical significant disease and biopsy is not recommended; grade three is undetermined and the last two grades present respectively increased rate of predictive value/positivity of prostate cancer, determining the need of prostate biopsy (3). This method of prostate evaluation presents an intrinsic correlation of histopathological findings according to Gleason system and morphological and functional images classified according to PI-RADS system, related to the molecular content of tumor cells. This classification allows for therapeutic variations, from active surveillance to minimally invasive focal ablations or radical surgeries and expanded lymphadenectomy. The better understanding of cellular

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signal alterations of prostate cancer resulted in the development of new treatments, such as the new generation of anti-androgens.

In a similar way, Gleason system has been modified over the years since its first publication. It is a morphological and analogical system fundamental to diagnostic, prognostic and treatment of prostate cancer. In November 2014 a new recommendation of International Society of Urological Pathology (ISUP), proposed the grouping of scores in five categories (4), based on the recognition that previous score valued some benign lesions (Table-1).

Table 1 - New recommendation of International Society of Urological Pathology (ISUP) (4).

Grade I	Score 3 + 3
Grade II	Score 3 + 4
Grade III	Score 4 + 3
Grade IV	Score 8 (3 + 5, 5 + 3 and 4 + 4)
Grade V	Score 9 and 10 (4 + 5, 5 + 4 and 5 + 5)

This valuable system of morphological classification of prostate tissue since the beginning showed the heterogeneity of tumor histological findings present in the same gland with obvious different biological behavior and distinct evolution according to focus, making treatment approach complex. These variations of PCa histology are being scientifically endorsed, correlating each grade of Gleason scale with a respective profile of genic expressions, related to a specific assortment of carcinogenic cell signals, that will act as tumor progression markers. Welsh et al work described 20 genes with different expressions correlated to three grades of Gleason score. Insulin-binding proteins (IGFRP 2 and 5) were expressed in higher grade tumors (5).

Current urological practice is guided by a clinical rationale based on molecular biology of PCa, and urologists, pathologists and oncologists apply laboratory research data and clinical daily practice evidences in clinical treatments.

In the current treatment of our patients, it is mandatory to understand proliferation and cellular differentiation according to epigenetics, cellular cycle regulations and possible alterations of signalization among androgens, co-activators and androgen receptors.

Many years have passed in order to aware global male population about the importance of early diagnosis of prostate cancer, with unquestionable positive results. But current prostate cancer screening methods are controversial and maybe the explanation of these troublesome epidemiological polemics is based on the PCa heterogeneity including molecular aspects and familiar history; the understanding of those aspects may help us redirect PCa screening.

For many years, it has been shown that first degree relatives with PCa and relatives with breast cancer with less than 36 years old increase four-fold the chance of

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PCa. Five to 10% of all cancer are hereditary transmitted by mutations that occurred in germ cells, being defined as constitutional tumors. Hereditary cancer usually presents more clinical and aggressive evolution. It is mandatory to have in mind that individuals are born frequently with loss of one of two tumor genic suppressor activity alleles. Consequently, timing of phenotypically expression of tumor is shortened when the remaining "health' allele loses its function. This is the concept that explain predisposing syndromes of cancer, and typical examples of hereditary cancer are breast and colon tumors. Although it is not described a specific characterization of hereditary prostate cancer, others syndromes of hereditary tumors that include PCa are known (6). Also, PCa presents a great number of studied polymorphisms that explains the genesis of PCa (common genetic alteration of general population that may predispose to tumor (6, 7)) (Table-2).

Table 2 - Genes more involved in PCa (6, 7).

Gene	Gene	Gene
DAB2IP	HERC2	LEPR
IL4	RNASEL	CRY
ARCF	HOXB13	OGGI
HPC1	HPC2	MSR1
PON1	MIC1	BRCA1 / BRCA2

It is recommended during anamnesis to construct a heredogram in men over 40 years old with at least three generations by which it is possible to choose individual preventive measures mainly for hereditary syndrome of breast and ovary cancer (HBOC) whose sites are closely related to PCa. Hereditary tumors usually present some of the following characteristics (8):

1. Increase number of cases in a particular population
2. Multiple cases in the same family, involving many generations
3. Bilateral tumors, or more than one primary tumor in the same individual, synchronous or metachronous
4. Rare histological type of tumors
5. Cases in younger age than in general population

Currently, we observe the duel between professional performance and surgical technique of robotic laparoscopic radical prostatectomy compiling results and complications, and each urologist is invited to analyze his personal limits and personal skills. Also, the urologists are presented with several forms of treatment, from resection of advanced tumors to simple

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clinical observation and the use of new drugs that interact with molecular signs, such as abiraterone and enzalutamide and he must adequately understand molecularly the phenomena and their clinical consequences.

In conclusion, it is important to recognize and understand that molecules determine distinct biological behaviors and when we are able to identify and assimilate different molecular profiles we will be capable to practice a precision medicine, with adequate treatment of our patients, from simple surveillance to robotic surgery.

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DIFFERENCE OF OPINION

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Active surveillance in intermediate risk prostate cancer: is it safe?

Opinion: Yes

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Keywords: Prostatic Neoplasms; Prostate cancer, familial [Supplementary Concept]; Watchful Waiting; Disease; Therapeutics

Most men with prostate cancer will not die from it. Although the most frequent cancer in men in the western world it ranks only 3rd place for cause of death (1). In men over 60 years of age prostate cancer is found at autopsy in over 60% (2). Overdiagnosis by PSA screening is estimated to be 57% when screened until 75 years of age (3). Considering treatment toxicity, careful selection of men for treatment is essential. A shift towards more conservative management is apparent in larger registries (4, 5).

In large cohorts of men with biopsy Gleason 6 cancer adverse pathology at prostatectomy is observed in over one-third of men (6, 7) suggesting undersampling of Gleason 7 cancer that is often present in men with Gleason 6 prostate cancer on biopsy. Even in men with very low risk at biopsy (T1c, PSAD<0.15, GS<7, <3 positive cores containing less than 50% cancer), one in 10 will have significant disease at prostatectomy (8).

Reese et al. (9) found the presence of Gleason 7 at biopsy a strong predictor of adverse pathology at prostatectomy. Based on a large prostatectomy series Ploussard et al. (10) concluded that although 46% of men with biopsy Gleason 7 prostate cancer had poor prognostic characteristics at prostatectomy such as upgrading or upstaging at final pathology a subgroup of men with PSA<10ng/ml, PSAD <0.15 cT1c and less than 3 positive cores this risk was only 19% suggesting that in selected men with intermediate risk cancer with otherwise favorable characteristics conservative management can be considered.

Gleason score 7 on biopsy, therefore, does not exert a poorer outcome perse and smaller lesions with this Gleason score may have similar outcome when compared to Gleason 6 prostate cancer on biopsy. The amount of high grade (5) cancer in both biopsy and prostatectomy was found predictive of outcome, rather than Gleason score (11).

These observations show that Gleason 7 on biopsy not necessarily indicates poorer prognosis than Gleason 6 in men with limited Gleason grade 4 disease. Large randomized studies were unable to show a survival benefit of local treatment versus observation in men with Gleason 6 prostate cancer in whom active surveillance is frequently (12).

Moreover, in the Pivot trial no difference in survival between active surveillance and prostatectomy was observed for men with intermediate risk prostate cancer. Considering the prognostic overlap between Gleason 6 and 7 prostate cancer on biopsy, men with Gleason 7 prostate cancer could be considered for active surveillance.

The feasibility of active surveillance for intermediate prostate cancer is confirmed by data from Sweden that showed that for men with delayed prostatectomy (median 19m after diagnosis) outcome was similar to early treatment in men with low and intermediate risk prostate cancer (13). Cancer specific survival was 0.7% of men in the primary radical prostatectomy group and 0.9% in men with deferred radical prostatectomy at 8 years follow-up. In a similar report from this registry Stattin et al. report on 93 men with Gleason 7 cancer and active surveillance and 881 with early local therapy consisting of prostatectomy (n=601) or radiotherapy (n=280) (14). Compared to low risk patients, mortality of prostate cancer was twice as high in the intermediate risk group (5.2% versus 2.4%) in active surveillance patients. But the relative risk reduction in the prostatectomy group was less in intermediate risk cancers compared to that of the low risk population (adjusted relative risk in low risk 0.29, intermediate risk 0.53). This observational data suggests that intermediate risk patients were not more likely to be cured by local treatment than low risk patients when compared to active surveillance although the absolute risk of disease specific death in intermediate risk patients is higher.

Several studies on active surveillance did include men with Gleason 7 or intermediate prostate cancer (15). Cooperberg et al. (15) studied outcome in 90 men with intermediate risk prostate cancer and active surveillance. Biopsy Gleason 7 was present in 29 men. Although no difference in survival for low and intermediate risk cancers was found, this study did not report on Gleason 7 intermediate risk cancers separately.

Van den Bergh et al. (16) reported on 50 men with Gleason 7 (6 had Gleason 4+3) prostate cancer managed with active surveillance. Median follow-up was 3.4y. All men with Gleason 4+3 received active treatment compared to 34% of men with Gleason 3+4 suggesting that active treatment rate of Gleason 3+4 is similar to larger low risk active surveillance populations (17).

Longer follow-up is available from the study by Klotz et al. (18, 19). In the initial report, in 72 of 416 men Gleason 3+4 was found at initial biopsy. At a median follow-up of 6.8 years Gleason 3+4 at initial biopsy was a predictor of active treatment, whereas PSA>10ng/ml was not (18). In a recent update from the same institute, Klotz et al. (19) report 993 men on active surveillance with a median follow-up of 6.4 years, shorter than the initial report, but 260 patients within the population had follow-up longer than 10 years. Men over 70 years or a life expectancy less than 10 years and Gleason 3+4 on biopsy and PSA<15ng/ml were allowed to enter. Overall 1.5% died of prostate cancer and 2.8% developed metastases. In the entire population 13% was initially diagnosed with Gleason 7 cancer on biopsy whereas in the men that developed metastases this was 44%. Men with Gleason 7 were 72% more likely to receive active treatment during follow-up, but in the multivariate analysis only Gleason score at one-year rebiopsy and baseline PSA were predictive of active treatment. An important note is the acknowledged limitation of the study that regrading according to current ISUP standards of early cases was not performed, nor were MRI targeted biopsies available at the initial years of inclusion. Both factors suggest that an underestimation of actual Gleason 7 cancer has occurred in men with longer follow-up. Still disease specific survival at 15 years was only 6%, lower than the reported 7% in a large prostatectomy series from the PSA era (20). Patients were 9.2 times more likely to die of other reasons than prostate cancer. It should be noted that patients with an initial Gleason 3+4 were by inclusion criteria more likely to die of non-prostate cancer reasons than low risk men in the study. Additionally, outcome after active local treatment in men with Gleason 6 and Gleason 7 disease treated during follow-up was not different.

Current diagnosis of prostate cancer is often accompanied by MRI imaging (21). Multiparameter MRI (mpMRI) is recommended before starting on active surveillance by the EAU 2016 guidelines for prostate cancer. A recent systematic review (22) revealed that a positive MRI was twice more likely to indicate upgrading on repeat biopsy or prostatectomy. In one-third of men an unrecognised significant lesion may be identified on MRI (23), reclassification is found in 14-20% of men where this lesion is biopsied (23, 24). In men

eligible for active surveillance the mpMRI-based PIRADS score improved staging and prediction of upgrading at prostatectomy with a sensitivity of 99% for upgrading and an odds ratio 2.72 in the multivariate prediction. mpMRI with targeted biopsies was shown to increase the detection rate of Gleason 7 cancers while reducing detection of low grade cancers versus repeat random biopsy (25, 26). Due to its low specificity recent smaller series suggest that mpMRI may not replace systematic biopsies in the workup of active surveillance patients (27-29) but may be useful in the follow-up of these men where mpMRI improved the prediction of Gleason progression (30). ADC below median of the population predicted at least a 2-fold higher risk of Gleason progression during follow-up in a population of 86 men with a median follow-up of 9.4 year (31). Whether mpMRI may replace systematic follow-up biopsies is still unclear since in a multivariate analysis mpMRI did not add diagnostic value of high grade cancer to PSA density and biopsy tumor length (32). In the ASIST (Active Surveillance Magnetic Resonance Imaging Study) trial the value of MRI guided confirmatory biopsy in men on surveillance is being studied by the Ontario Institute for Cancer Research and Canadian Urology Research Consortium and data are to be awaited. The use of targeted biopsies will results in the detection of smaller Gleason 3+4 prostate cancers what will make active surveillance in these men more likely.

With respect to including men with Gleason 7 on biopsy and intermediate risk cancer in active surveillance management the following statements should be considered:

A) As for GS 6 prostate cancer, no level-1 evidence supports the use of AS for management of GS7/intermediate risk cancers, although randomized studies did not find an advantage of treatment of these cancers.

B) In larger series progression to active treatment was found to be twice as high for GS 3+4 compared to biopsy GS 6 cancers.

C) Disease upstaging and –grading after active treatment during active surveillance is not more frequent in GS7 compared to GS6 cancers.

D) In initial series with longer follow-up tumors may have been undergraded more frequently due to changing Gleason grading criteria (ISUP) and improved detection by MRI. This may have resulted in including a considerable number of men for active surveillance with actual Gleason 7 disease in older series.

E) MRI imaging may reveal small Gleason 7 lesions, but with a high certainty of correct risk classification, these may still be amenable to active surveillance.

F) Selection for active surveillance should ideally comprise multi-factorial risk estimation, taking into account all tumor and imaging characteristics. With other criteria particularly favorable, Gleason 3+4 or PSA 10-20 may be accepted for active surveillance.

Recommendations from the Canadian Urological Association contain a statement on AS in Gleason 7 disease: “For select patients with low-volume GS 3+4=7 localized prostate cancer, AS can be considered. Survival in men with intermediate risk prostate cancer on active surveillance is high” (33). Although these recommendations are not echoed in the EAU guidelines, the NCCN guidelines now also contain the following phrase: “Patients with favorable intermediate-risk prostate cancer (predominant Gleason grade 3 [i.e., Gleason score 3+4=7], and percentage of positive biopsy cores<50 percent, and no more than one NCCN intermediate risk factor) may be considered for active surveillance” (NCCN website jan. 2016)

Clearly, AS is an option for men with small Gleason 3+4 (but not 4+3). Close follow-up, preferably including mpMRI, is to be considered and men should be informed on the fact that longer term (>10 year) follow-up data are limited.

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DIFFERENCE OF OPINION

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Active surveillance in intermediate risk prostate cancer: is it safe?

Opinion: No

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INTRODUCTION

Active surveillance (AS) is a management strategy for early-stage prostate cancer (PCa) designed to balance early detection of aggressive disease and overtreatment of indolent disease (1). It is advocated as the treatment of choice for favourable-risk disease in several national guidelines (National Comprehensive Cancer Network, National Institute for Health and Clinical Excellence) (2). Despite it's significant role in low risk PCa, AS is not established as a standard of care for intermediate risk disease. A contemporary registry-based population study in Australia ascertained the treatment trends and patterns of care of 980 men with PCa on AS. It reported that 251 men (8.9%, Median 70.4) with intermediate risk were placed in AS, of whom 53.8% had Gleason score (GS) 3+4 PCa and 10.4% with 4+3 disease (3). The most recent update of the CaPSURE database, a longitudinal, observational study of approximately 15.000 men with all stages of biopsy-proven prostate cancer, also reflected this trend in AS, but questions remain about the safety of this practice and its role in intermediate risk disease.

Literature and Evidence

Active surveillance consists of close observation via a regimen of periodic PSA measurements, digital rectal examinations and serial prostate biopsies, with the goal of offering curative therapy in the event of disease progression or reclassification (4). Despite long-term data having confirmed the safety and efficacy of AS for low-risk cancers with 10 and 15-year actuarial cause-specific survival rates of 98.1 and 94.3%, respectively (5), the evidence does not extend to completely support its use in intermediate-risk disease. A retrospective analysis of 2.323 patients with localized GS 3+4 prostate cancer who underwent a radical prostatectomy between 2005 and 2013 from 6 academic centres

found that 46% of patients with biopsy GS 3+4 cancer have unfavourable disease at final pathology (6). When applying the University of Toronto, Royal Marsden Hospital and Prostate Cancer Research International Active Surveillance (PRIAS) criteria (7) to the above cohort, 78, 59 and 20% of men were eligible for AS, respectively, and the risks of unfavourable disease were decreased to only 42.4, 41.0 and 30.5%, respectively (8). The Cancer Council Ontario (CCO) currently recommends active treatment (surgery or radiotherapy) for patients with intermediate-risk localized prostate cancer (9).

A number of studies also support the role of surgery in men in this intermediate risk group. The PIVOT study found men with intermediate-risk tumours who underwent radical prostatectomy (PSA 10.1 to 20.0ng/ml, GS 7, or a stage T2b tumour) had a 31% relative reduction in all-cause mortality, as compared with those assigned to observation (HR 0.69; 95% CI, 0.49 to 0.98; ARR 12.6%) (10). PCa mortality in this group was not significant despite a similar trend. This was compared with the Scandinavian Prostate Cancer Group 4 (SPCG-4) trial of radical prostatectomy versus watchful waiting in men with prostate cancer, which showed the benefit of surgery in relation to death from PCa was largest in those with intermediate-risk prostate cancer (relative risk, 0.38) (11). There was a significant absolute reduction in men with intermediate risk disease in overall mortality, rate of death from PCa, and in the risk of metastases (11%).

Klotz et al. performed a large cohort Canadian study with 993 patients and up to 16 years of follow-up, with 25% of the patients fulfilling the D'Amico criteria for intermediate risk (5). There were 15 deaths (2.8%) due to PCa in total, all of whom had confirmed metastases before death. 12 (44%) of the 28 patients with metastases had a Gleason score of 3+4 at diagnosis; with a median time to metastasis was 7.3 years (95% CI, 5.81 to 8.76 years). Only 2 of the 28 patients who developed metastasis were not upgraded to GS 7 before developing metastatic disease, neither of whom had surgical grading. Klotz et al. therefore suggested that in a screened population, only selected men older than age 70 years with intermediate-risk PCa are candidates for surveillance (the 15-year PCa mortality is low). This was consistent with Cooperberg et al. who followed 640 men on AS at University of California, San Francisco (UCSF). Among 74 men on AS electing to undergo RP, 16 had intermediate risk disease, with 50% of these patients having pT3 disease (P=09). AS was therefore recommended only for low volume GS 3+4 patients, particularly those with comorbid conditions and appropriate counselling prior to AS. The American Society of Clinical Oncology (ASCO) has recently reinforced the CCO guidelines and also recommended AS for only select patients with low-volume, intermediate-risk patients, with factors such as younger age, prostate cancer volume, patient preference, and ethnicity taken into account when making a management decisions (12).

DISCUSSION

Although the lifetime risk of receiving a diagnosis of prostate cancer is about 17%, the risk of dying from the disease is approximately 3%, suggesting that conservative management may be appropriate for select men (13). Thus, the way forward for AS must be lighted by improved tools for risk stratification at diagnosis and for early identification of progressive disease (14). A recent systematic review of novel tools for improving patient selection and monitoring low-risk prostate cancer by AS found that magnetic resonance imaging (MRI) has a high specificity for low-risk prostate cancer and new serum markers are associated with unfavourable disease (15). The potential of multi-parametric MRI lies in its high negative predictive value (80-90%) for the intermediate endpoint of disease upgrading, which may make it useful as an AS endpoint predictor (16). It is also beneficial in identifying anterior and higher volume tumours, as well as aiding in disease reclassification. A significant proportion of low risk patients do harbour more aggressive disease, and MRI can provide better risk stratification in both low and intermediate risk patients. This observation is demonstrated by several series of patients meeting AS criteria who underwent radical prostatectomy, revealing Gleason score upgrading in 23%-56% (17). Klotz et al. observed that 16% of patients had histological progression (2). Such observations encourage the need for future research of both MRI and molecu-

lar biomarkers such as PCA3 or PSA isoforms in these patients.

When managed with non-curative intent, intermediate-risk PCa is associated with 10-year and 15-year prostate-cancer-specific mortality rates of 13 and 19.6% (18). Thus, men with this disease are at risk of developing incurable disease in the future as they may miss the window of curability when opting for AS (8). Thomsen et al. estimated average 5-year and 10-year probabilities of discontinuing AS at 33% (14%–41%) and 55% (40%–59%) respectively, with a majority undergoing delayed curative treatment (RP or RT) (19). Thus, AS can only be warranted in select intermediate risk PCa patients, with consideration for individual tumour metrics, patient age and overall health, as well as patient preferences and the potential side effects of curative treatments. For those young patients (<65) with longer quality-adjusted life expectancy in this group, surgery should still be considered the definitive approach.

CONCLUSIONS

At least 50%-60% of individuals diagnosed with PCa ultimately die of other causes, and as a result, AS has become a chosen management option for low risk PCa patients (20). The latest literature however, demonstrates surgery as the mainstay of treatment in intermediate risk patients, with the role of AS limited to select men in this group. The use of MRI and prostate serum and genetic markers are still being evaluated, and until that time, it is recommended that definitive intervention remain the optimal choice of management in this group of patients.

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REVIEW ARTICLE

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Metabolic syndrome and prostatic disease: potentially role of polyphenols in preventive strategies. A review

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ABSTRACT

Benign prostatic hyperplasia and prostate cancer are two common urological diseases of the elderly. Scientific community has always looked for a link that could explain the correlation between the two diseases and the role of chronic inflammation in the pathogenesis of BPH and PCa. As shown by the reports of the two diseases relationship with oxidative stress and metabolic syndrome, the use of compounds with antioxidant action could therefore affect both the symptoms and their onset. Polyphenols appear to act not only against oxidative stress but also at different levels. The aim of this review is to evaluate the role of the most important polyphenols on these two urological diseases. As antioxidants these compounds seems to have a direct action on the cell cycle and hormone function, important for both prostate cancer and BPH. Despite a large number of articles about the relationship of the polyphenols with prostate cancer, very little evidence exists for BPH. Additional clinical trials or meta-analysis are necessary on this topic.

ARTICLE INFO

Keywords:
Oxidative Stress; Prostatic Hyperplasia; Prostatic Neoplasms; Polyphenols

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most frequent causes of Lower Urinary Tract Symptoms (LUTS) in men and about 50% of men between 50 and 60 years suffer from this disease (1). Even today, the exact molecular mechanisms underlying the development and progression of LUTS/BPH have not been fully understood. Certainly, recent studies have shown that chronic inflammation represents a crucial component in the pathogenesis of BPH, probably determining hyperplasia of prostate cells. Inflammatory cells in fact, produce growth factors such as vascular endothelial growth factors (VEGF) or tumor growth factor-β (TGF-β), which can support the fibromuscular growth in BPH (2-4). The etiology of BPH is still far from being fully understood but multiple partially overlapping and complementary theories have been proposed (5). Very recently, epidemiologic and clinical studies have provided emerging evidences of a possible role of metabolic syndrome (MetS) and its components in benign prostatic hyperplasia (BPH) and related lower urinary tract symptoms (LUTS) (6, 7). MetS can broadly be considered a systemic inflammatory state and a chronic inflammation driven tissue remodeling, including BPH pathogenesis (8). A

recent review summarized a direct and significant relationship between some components of MetS (obesity, high dyslipidemia, insulin resistance, and hypertension) and the BPH-LUTS complex. Furthermore, recent evidences suggested that severity of BPH-LUTS is strictly associated with increase in the number of components of MetS (9). The influence of dietary fat on BPH has been linked to specific fatty acids (FAs). In vivo studies have indicated that low-fat diets high in omega-3 polyunsaturated FAs reduce the development of prostatic disease. The omega-3 polyunsaturated FA serum composition was significantly decreased in patients with BPH (10). MetS is often characterized by oxidative stress that is involved in the pathogenesis of a variety of human diseases including atherosclerosis, diabetes, hypertension, aging, and cancer. The level of oxidative stress increases during aging and it could be related to prostatic diseases (11, 12). There are some evidences that prostatic inflammation could be a key component in BPH and BPH progression.

The level of oxidative stress increases during aging and could be either because of an increased production of reactive oxygen species or a reduced ability to scavenge them. High glucose concentrations increase oxidative stress, in part by down regulating catalase and mitochondrial superoxide expression, leading to a higher risk of insulin resistance (13). Recent studies suggest that oxidative stress and hyperinsulinemia, secondary to insulin resistance, are risk factors for cell proliferation and cell remodeling present in BPH. Insulin resistance can also lead to dyslipidemia characterized by high triglyceride and low high-density lipoprotein cholesterol (HDL-C) levels. Abdominal obesity is commonly associated with the development of vascular diseases, insulin resistance, and associated complications. Excessive visceral and subcutaneous fat increase oxidative stress and simultaneously decrease the expression and activity of key cytoprotective enzymes, including the heme oxygenase (HO) system (14). We have evaluated the activity of Heme oxygenases system in patients affected by BPH and found that low HDL-C and high triglyceride levels significantly affected HO-1 and HO-2 prostatic levels, with consequent increase of oxidative stress and remodeling of prostate tissue (7). Obesity-mediated adipocyte dysfunction may impact the function of other organs, including the prostate.

A major clinical study on BPH (Reduce study) recently demonstrated the link between histological prostatic inflammation and prostate enlargement or symptoms scores (15). Numerous major key players in chronic inflammation have been studied in BPH: varieties of growth factors and cytokines have been shown to be involved both in the inflammatory process and in the epithelial/stromal prostatic cells interactions (16). These mediators are released in the prostatic gland by inflammatory cells that can be found on most of the surgery-derived BPH specimens (17). The inflammatory cells may trigger a sophisticated and well-orchestrated inflammatory cascade, resulting in excessive oxidative stress, activation of the transcription factor nuclear factor-kappa B (NF-κB), production of several cytokines and overexpression of inducible-cyclooxygenase (COX-2), inducible-nitric-oxide-synthase (iNOS) and 5-lipoxygenase (5-LOX), leading, in turn, to the release of prostaglandins, nitrates, and leukotrienes. Furthermore, inflammatory cells produce growth factors, such as vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β), which may support fibromuscular growth in BPH (18).

Also for prostate cancer is described in literature the possibility that the pathogenesis of the disorder is linked to chronic inflammation: as disclosed by De Nunzio et al. the presence of oxidative stress associated to chronic inflammation in the cellular environment causes an increase of pro-inflammatory cytokines and growth factors, which determine an increase of the speed of cell replication, and therefore the possibility of incurring mutations (19). Furthermore according to the authors, the presence of PIA (proliferative inflammatory atrophy) precursor HGPIN and prostate cancer charged to the prostatic parenchyma, involves the presence of abnormal values of GSTP1 (gene coding for glutathione S-transferase), GSTA1 (gene coding for glutathione S-transferase A1) and COX-2 (enzyme determining the conversion of arachidonic acid (AA) in the prostaglandin endoperoxide H2 precursor of PGD2, PGE2, PGF2α, PGI2 and thromboxane A2).

Therefore, if a correlation between prostate diseases and oxidative stress or chronic inflammation could hypothesized, the use of components with exhibit antioxidant action could determine not only an improvement of prostatic symptoms but also counteract pathogenesis.

The aim of this review is to understand the role of polyphenols in prostatic diseases and their preventive role in preventive strategies.

MATERIALS AND METHODS

This analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis guidelines (20). An electronic search of the Medline and Embase was undertaken until September 2014. The search was limited to English-Language articles. The search terms included prostate, benign prostatic hyperplasia, benign prostatic enlargement, metabolic syndrome, prostate volume, insulin resistance, obesity, hypertension, triglycerides, cholesterol, lower urinary tract symptoms, polyphenols, oxidative stress, anti-oxidant, prevention. Citation lists of retrieved articles were screened manually to ensure sensitivity of the search strategy. References of the included papers were hand searched to identify other potential relevant studies.

Studies were reviewed by two independent reviewers (G.I.R. and G.R.); differences in opinion were discussed in consultation with the last author (G.M.). Figure-1 shows the flowchart of included studies. Table-1 lists the characteristics of included studies.

POLYPHENOLS AND PROSTATE CANCER

From a careful analysis of the literature there are several studies that evaluated the use of polyphenols in the treatment of prostate cancer

Figure 1 - Flow Diagram of included studies.

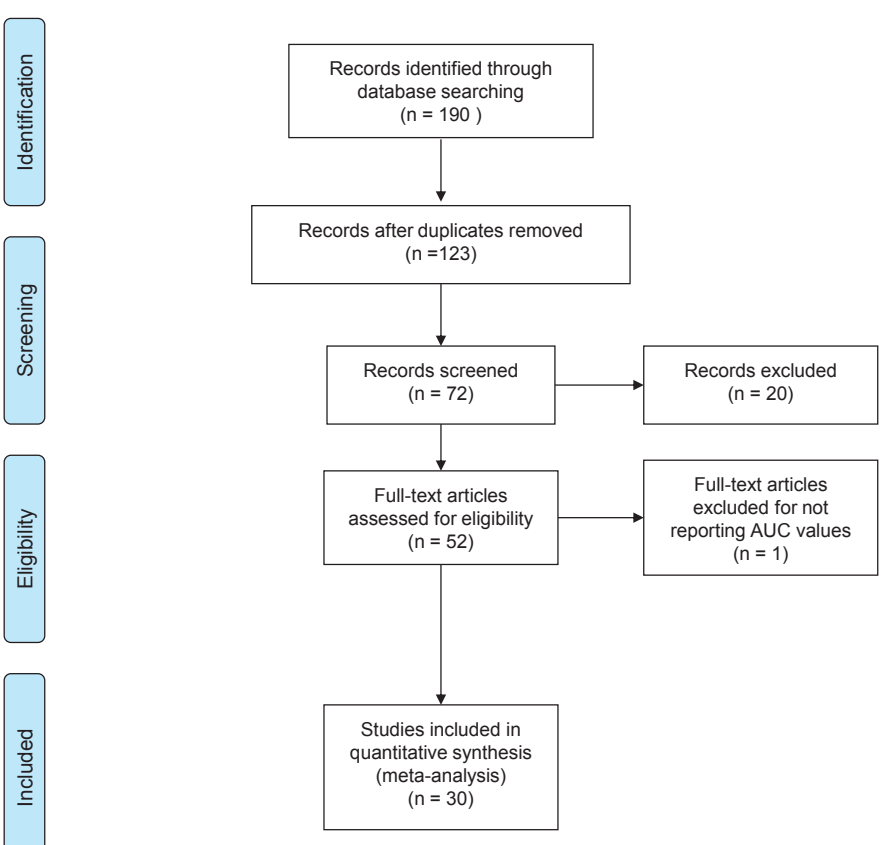

Table 1 - Characteristics of selected study.

Polyphenols and prostate cancer				
Compound	Type of study	Cell culture system or animal studies	Concentration used	Mechanisms of action
Epigallocatechin-3-gallate (23, 24, 28,30,31,32,34,36)	In humans (23, 24, 29,30,36) In vivo (32,34) In vitro (28,33)	LNCaP (28,33) PC-3, and CWR22Rnu1 (28) LAPC-4 (33) TRAMP (32,34)	EGCG (10-40 micromol/L) (28) 0.06% EGCG in tap water (32) Solution of 0.1% green tea polyphenols EGCG (62%) (34) Green tea extract capsules ,250 mg twice daily (36)	Action on transcription factor Nf-kB inducing oxidative stress and downregolation of p53 (23, 24, 28, 29, 30) -antagonize the activity of IGF-1 and induce an receptorial antagonism for IGF-1 receptor (32,34) -inactivator of COX-2 (24, 31)
Curcumin	In vitro (40,42,43)	LNCaP (40,42) PC-3 (42,43)	2-4 mg/L (about 5-10μM) (40) 15 μM (43)	Increased the ratio of Bax to Bcl-2 proteins, decreased the activation of NFκB, PI3K/Akt and Stat3 pathways and cell migration (40) Down-regulation of transactivation and expression of AR, AP-1, NF-kB, and CREB-binding protein (CBP) (42) Inhibition of the IκB-kinase ,reduction in expression of CXCL1 and -2 ,downregulation of several important metastasis-promoting factors like COX2, SPARC and EFEMP (43)
Resveratrol	In vitro (45,46)	LNCaP (45,46,47) PC3 (45,46) and DU145 (45,46,47)	2–40 μM (46); 1 μmol/L (47)	Production of NO (45) Formation of free radicals (46) p53 activation and apoptosis (47)
Polyphenols and BPH				
Compound	Type of study	N° patients	Concentration used	Outcome
Isoflavones (53) Isoflavones and lignans (55)	In humans (53,55)	176 patients with BPH (53) 25 patients (55)	40 mg of isoflavones (53)	Superiority of isoflavones over placebo over 12 months[53] Isoflavones, but not lignans, have some influence the benign prostatic growth (55)

both in terms of primary prevention and secondary prevention of cancer. Polyphenols occur naturally in different foods, and today there are more than 8000 divided into different subclasses, of which the most represented are flavonoids stilbenes phenolic acids, and lignans (21). The importance of the polyphenols as anti-cancer substances shall be represented by fact that they possess properties that act at different levels (molecular and cellular), as described in several papers (21-24).

Among these compounds, as previously described, one of the most investigated is undoubtedly the green tea, the second most widely consumed beverage in the World after water (25). The tea plant (Camellia sinensis) has been cultivated in Asia for thousands of years and used for centuries in China, Japan, and Thailand as a traditional medicine with a variety of applications (26). Many beverages are rich of-epigallocatechin (EGC),-epicatechin-3-gallate (ECG) and-epicatechin (EC), gallic acid, chlorogenic acid, caffeic acid, like flavonols kaempferol, myricetin and quercetin and the most represented-epigallocatechin-3-gallate (EGCG), and several studies have investigated their role in the treatment of prostate cancer (24). To the best of our knowledge, particularly in prostate cancer cells, EGCG activates growth arrest and apoptosis primarily via p53-dependent pathway that involves the function of both p21 and Bax such that downregulation of either molecule confers a growth advantage to the cells. In androgen--sensitive LNCaP and androgen-insensitive PC-3 human prostate carcinoma cells, EGCG inhibited COX-2, (inducible enzymatic isoform, rapidly induced by growth factors, tumor promoters, oncogenes, and carcinogens) without affecting COX-1 expression at both the mRNA and protein levels (25, 27). Among the mechanism that make the polyphenols in green tea of primary importance in the treatment of prostate cancer is the action of the epigallocatechin-3-gallate as a transcription factor Nf-kB that underlies both inflammatory cellular processes that induce oxidative stress both anti-apoptotic events (downregulation p53) resulting in a cascade of events that leads to carcinogenesis: the activity of this factor is extremely elevated in tumor cells in patients with prostate cancer and this has been highlighted (23, 24, 28-30) as the epigallocatechin-3-gallate decreases the intracellular concentration of the protein by blocking the activity of the via connected to it.

The relationship between prostate cancer and the intake of green tea and then directly the action of polyphenols (in particular 'epigallocatechin-3-gallate or EGCG) is expressed at different levels in prostate cancer etiology by modulating different pathways linked to inflammation chronic (action on NF-kB and COX-2) and also the metabolic syndrome itself (IGFR). Overexpression of NF-kB leads to the activation of several signaling pathways and among these also the activation of COX-2 which increases levels of pro-inflammatory cytokines. This determines as final result the pro oxidative imbalance and the formation of a eligible pabulum for carcinogenesis: to this regard it has been observed that the ECGC is also an inactivating of COX-2 without interfering with the activity of COX-1 (24, 31) supported by studies on transgenic mice (32). The anti-inflammatory action of 'EGCG is also evident by its action on COX-2.

As reported by De Nunzio et al. (6) insulin resistance associated to metabolic syndrome, widely spread throughout the World, is manifested by an increased production of somatomedin C or IGF-1 receptor. Since the insulin like growth factor 1 has a potent mitogenic and anti-apoptotic action is evident how it is an important parameter for the development of cancer cells, and this process appears to be comparable to prostate cancer onset mechanism (33). It has been shown, in studies involving TRAMP mice (34) that EGCG is able to directly antagonize the activity of IGF-1 and induce a receptor antagonism for IGF-1 receptor (32).

Furthermore, other qualities have been recognized in the green tea and its phenolic component regarding prostate cancer: it was noted that the action of ECGC has not target only the proinflammatory pathways but also can play a role as antiandrogen. A review by Lecumberri et al. showed that ECGC has not only a direct role reducing testosterone levels, but also indirectly by inducing a receptor downregulation on prostate tissue in animal models (35). However, we must emphasize that studies in prostate cancer castration resistant patients showed no clinically valid results for the use of green tea (36).

Curcumin (diferuloylmethane) is a major chemical component of turmeric (Curcuma longa Linn.) and is used as a spice to give a specific flavor and yellow color to food in the Indian subcontinent (37). It has been used for centuries throughout Asia not only as a food additive but also as cosmetic and as a traditional herbal medicine to treat a variety of inflammatory conditions and chronic diseases. Over the past decade, several studies have substantiated the potential prophylactic or therapeutic value of curcumin and have unequivocally supported reports of its anti-carcinogenic properties, such as its ability to influence a diverse range of molecular targets within cells. To date, no studies have reported any toxicity associated with the use of curcumin in either animals or humans (38).

Likewise to 'ECGC, many others polyphenols like curcumin exhibited anticancer/chemopreventive activity that is expressed at different levels. Wang et al. shown that the growth of human prostate cancer cell cultures is inhibited both by single administration curcumin (22%) or EGCG and (11%) or arctigenin (29%). However, they found that polyphenolic combination EGCG+curcumin, curcumin+arctigenin and curcumin+EGCG+arctigenin reduce tumor growth of cell lines respectively by 34%, 49% and 62% compared to control. The mechanism underlying these modifications, according to investigators, would be related primarily to an arrest of cell division of cancer cells in G1/G0 phase (directly related to the action of curcumin), to an increase of apoptotic factors Bcl-2/Bax (39) and to an inhibition via phosphorylation of nF-Kb (40). Other studies based on nanotechnology that administered curcumin to prostate cancer cell lines have shown that this method is more efficient than free curcumin to reduce the growth of cell colonies by arresting fosforilation of STAT 3 and dell'AKT, promoting the action of anti-apoptotic protein (Mcl-1, Bcl-xL) and inducing a PARP lysis. Additionally curcumin has antioxidant and anti-inflammatory mechanisms (41) and, likewise ECGC, has an activity which is expressed at the level of receptors androgens inducing downregulation of their own receptors (39, 42). The anti-tumor action of curcumin seems to be explained, according to Killian et al. (43,) also by the reduction process of metastatization of the cancer: in murin model it has been shown that in cell lines treated with curcumin there is a reduction of the genetic factors that promote the formation of lung metastases (SPARC (osteonectin), COX2 (PTGS2, prostaglandin--endoperoxidesynthase 2), ALDH3A1 (aldehyde dehydrogenase-3 family member A1) and EFEMP (EGF-containing fibulin-like extracellular matrix) through a reduction of the overexpression of the proteins CXCL1 and-2).

Resveratrol (trans-3, 4, 5-trihydroxystilbene, C14H12O3) is a plant-derived polyphenolic phytoalexin produced by the enzyme stilbene synthase in response to infection by the pathogen Botrytis cinerea and to a variety of stress conditions, such as vicissitudes in climate, exposure to ozone, sunlight and heavy metals. It exists in two isoforms: trans-resveratrol and cis-resveratrol where the trans-isomer is the more stable form. Resveratrol is present in red grapes, peanuts, some common drinks, and dietary supplements (44). Kampa et al. tested the anticancer ability of a mixture of polyphenols (catechin, epicatechin, quercetin, and resveratrol) extracted from wine on three prostate cancer cell lines: LNCaP and PC3 (hormone--sensitive), and DU145 (not hormone-sensitive) (45). They found that on LNCaP all three flavonoids were active (catechin, epicatechin, quercetin) and resveratrol was ineffective. On PC3 the action of the three flavonoids was more prominent and resveratrol acted only in high concentrations compared with DU145 which was more sensitive to resveratrol and not to the three flavonoids. As already noted for the other polyphenols, the mechanisms that explain the action of resveratrol are to be found in the different levels on which it performs the action of the various components of the wine: mechanisms of hormonal receptor antagonism concerning LNCaP and PC3 and molecular mechanism concerning DU145. Authors suggest that an important role of these molecules in question is represented by the balance of the antioxidant and NO production. Similar results were found in other in vitro studies on the same cell lines (LNCaP and, PC3 and concerning DU145) and has been shown that resveratrol, in addition to the mechanisms described above, would have

inhibitory effect on the formation of free radicals in human macrophages, reducing oxidative stress within premalignant cells (46) and on the MAP kinase pathway (47).

POLYPHENOLS AND BPH/LUTS

Despite numerous evidences that correlate benign prostatic hyperplasia, metabolic syndrome and oxidative stress (7, 8, 48-51), the correlation between polyphenols (high antioxidant dietary components) and BPH are still very limited. Little evidence can be found by searching each polyphenolic compound in relation to benign prostatic hyperplasia.

There are very few evidences in literature regarding green tea and its polyphenols (especially the ECGC): in a review Ranjan et al. (52) stated that the anti-proliferative activity of green tea antioxidant activity combined with the 'action on 5a-reductase inhibitors may have a protective role both on the onset of BPH and on disease progression.

Certainly various studied correlated isoflavones and BPH: in a double-blinded, randomized controlled trial Wong et al. (53) examined 176 patients with BPH divided into two groups, one of which that was administered with isoflavones 40mg daily (n=88) and a placebo Group (n=88). Patient's then underwent a control visit every three months during a 12 months period and were evaluated in terms of IPSS, Qmax, and 36-Item Short Form Health Survey (SF-36). At the end of 12 months, IPSS (SF-36) was not statistically significant between the two groups. The increase in Qmax (from 6 to 12 months) and incomplete emptying subscore in IPSS from baseline to the 12th month was slightly significant. The effect of this kind of polyphenols on BPH may be explained by its action on the prostatic parenchyma both on the epithelial tissue cell (throughout a 5α-reductase action and a uridine 5-diphospho--glucuronsyltransferase activation) and on the stromal cell (throughout aromatase inhibition, and estrogen receptor antagonism) (54). The authors emphasized that actually there are no indication for the use of isoflavons as therapy for BPH (54). Parenchymal level of isoflavons in BPH patients are lower than control, while blood level of isoflavons didn't show any statistically difference (55).

CONCLUSIONS

In conclusion, this review aimed to research which could be the use of polyphenols on BPH and prostate cancer. As revealed from the papers examined, the action of polyphenols is directed to different levels in the prostate cell: the primary action of these molecules is opposing to oxidative stress, but other evidences confirm that these compounds influence the growth of the prostate androgenic mediated cells and the cell cycle phases. Although a large amount of studies in vitro and in murin model have been conducted until now, few clinical trials, using precise concentrations of these compounds, have been performed. If we consider the relationship between polyphenols and BPH, we observe that there are very few studies carried out on this topic. Therefore, since the use of the polyphenols seem to have good perspectives, randomized clinical trials and meta--analyzes are needed in patients with prostate cancer and especially in patients with BPH.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Radical cystectomy with pelvic lymphadenectomy: pathologic, operative and morbidity outcomes in a Brazilian cohort

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ABSTRACT

Introduction and Objective: Radical cystectomy (RC) with pelvic lymph node dissection is the standard treatment for muscle invasive bladder cancer and the oncologic outcomes following it are directly related to disease pathology and surgical technique. Therefore, we sought to analyze these features in a cohort from a Brazilian tertiary oncologic center and try to identify those who could negatively impact on the disease control.

Patients and Methods: We identified 128 patients submitted to radical cystectomy, for bladder cancer treatment, from January 2009 to July 2012 in one oncology tertiary referral public center (Mario Penna Institute, Belo Horizonte, Brazil). We retrospectively analyzed the findings obtained from their pathologic report and assessed the complications within 30 days of surgery.

Results: We showed similar pathologic and surgical findings compared to other large series from the literature, however our patients presented with a slightly higher rate of pT4 disease. Positive surgical margins were found in 2/128 patients (1.5%). The medium number of lymph nodes dissected were 15. Major complications (Clavien 3 to 5) within 30 days of cystectomy occurred in 33/128 (25.7%) patients.

Conclusions: In the management of invasive bladder cancer, efforts should focus on proper disease diagnosis and staging, and, thereafter, correct treatment based on pathologic findings. Furthermore, extended LND should be performed in all patients with RC indication. A critical analysis of our complications in a future study will help us to identify and modify some of the factors associated with surgical morbidity.

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INTRODUCTION

Radical cystectomy (RC) with pelvic lymph node dissection is the standard treatment for muscle invasive bladder cancer and a curative procedure for patients with organ confined and some with extravesical and node positive disease (1, 2). This surgical approach also provides proper disease staging based on specimen pathology and, thereafter, adjuvant treatment strategies when indicated.

Oncologic outcomes after RC are highly associated with pathologic features of the disease and surgical technique factors. Among them, extravesical disease and lymph node involvement are related to decreased overall and recurrence-free survival

(2-4). Furthermore, these oncologic outcomes are also determined by the operative technique, what plays an important role in the disease control (5, 6).

The pelvic lymphadenectomy (LND) is not standardized among surgeons and institutions and its extension has been shown to be a determinant factor for improving progression-free and overall survival in patients with invasive bladder cancer submitted to RC (7). Another important point in the management of this disease is the reconstruction of the urinary tract and different urinary diversions have been described, however none of them showed superiority compared to others in terms of complications and quality of life in prospective randomized trials.

Together with the fact that muscle-invasive bladder cancer predominantly affects an elderly population, RC with pelvic LND is a major operative procedure and, therefore, is associated with an important rate of complications (8-10). The surgical morbidity impacts on hospital costs and patients survival.

Although extensively studied in different populations worldwide (1-5), bladder cancer information from Brazilian patients is lacking. Therefore, we sought to analyze the data from a cohort submitted to RC with LND for bladder cancer treatment in a Brazilian tertiary referral center and, using surgical, pathologic and morbidity parameters, compare it to the largest series from the medical literature.

MATERIALS AND METHODS

Patients

We identified 128 patients submitted to radical cystectomy from January 2009 to July 2012 in one oncology tertiary referral public center (Mario Penna Institute, Belo Horizonte, Brazil). In all of the cases the reason for cystectomy was bladder cancer, either invasive or non-invasive disease.

Surgical intervention

All the patients included in the study were submitted to open radical cystectomy by 8 experienced urologic surgeons with over 5-years prior experience in urology oncologic surgeries.

Patients underwent a standard surgical procedure, including a meticulous pelvic lymphadenectomy (LND) with en bloc RC and urinary diversion. Men were submitted to prostate removal and women to hysterectomy, resection of anterior vaginal wall and bilateral salpingo-oophorectomy if those organs were present. The extent of the LND was based on surgeon's judgment. After RC with pelvic LND, urinary diversion was performed based on preoperative and intraoperative assessments and previous patient discussion. There were not specific criteria for choosing the type of diversion, this choice was made by the surgeon and patients after discussing the risks and benefits of each type of diversion on each individual situation.

All the pathologic specimens were analyzed from the same pathologist with more than 10 years of pathology oncology experience.

Demographic and pathologic data

Pathologic and demographic characteristics of the patient's population were collected retrospectively from electronic medical records.

Cystectomy and lymph node specimens were evaluated according to the standard pathology protocol. Pathologic data included tumor stage and grade. AJCC TNM classification (11) was used for pathologic staging and the WHO classification (12) from 2004 for histological typing and grading.

Post-operative complications

Complications within 30 days of surgical resection were graded using the modified Clavien classification system (13). Grade 1 and 2 complications were defined as minor, and grade 3 to 5 complications were defined as major. Regular correspondence with patients and their physician ensured that treatment received outside of our institution was accounted for in the database.

RESULTS

The majority of the patients submitted to cystectomy in our institution were men with a median age of 67 years, ranging from 36 to 86 years and more than 90% of them presented with invasive disease in the specimen pathology; 47% with pT3-pT4 disease and 16% with pT4 tumors. Positive

Table 1 – Demographic, neoadjuvant chemotherapy and post operatory pathologic data, reported as absolute numbers for gender and age in years, frequency and relative number (%) for the other variables.

Male	102 (80%)
Age (range)	67 (36-86)
Neoadjuvant chemotherapy	2 (1.5%)
Pathologic T stage	
T0	4 (3%)
T1	8 (6%)
T2	55 (43%)
T3	40 (31%)
T4	21 (16%)
Pathologic N stage	
N0	99 (78%)
N1	4 (3%)
N2	24 (18%)
N3	1 (1%)
Positive margins	2 (1.5%)

surgical margins were only present in 2/128 (1.5%) patients. In one of them the bladder adenocarcinoma invaded the rectal wall and in the other the high grade transitional cell carcinoma infiltrated the ileus and abdominal wall (Table-1).

Based on pre operatory histology, RC was performed because of muscular invasive disease (pT2) in most part of the cases and in 34/128 (26%) of the patients the reason for RC with LND was multiple T1 recurrence or impossibility to approach the lesion with transurethral resection. Transitional cell carcinoma was the pre cystectomy histology subtype in 117/128 (92%), squamous cell carcinoma in 7/128 (5%) and adenocarcinoma in 3/128 (3%) patients (Table-2).

Table 2 – Pre operatory biopsy.

pT stage	128 (100%)
pT1	34 (26%)
pT2	84 (65%)
Squamous cell carcinoma	7 (5%)
Adenocarcinoma	3 (2%)

Data reported as frequency and relative number (%)

Ileal conduit was the choice of diversion in 97/128 (75%) of the cases and orthotopic neobladder and ureterocutaneostomy was the diversion performed in 15/128 (12%) patients each (Table-3). Transitional cell carcinoma was the histologic diagnosis in the cystectomy specimen in 117/128 patients (92%) (Table-4).

Regarding N stage, we found a 22% rate of node invasion and 86% of the patients had 10 or more nodes removed, with a median number of 15 (Table-5).

Median length of stay (LOS) was 10 days and 21/128 (16%) patients had to be re-hospitalized within 30 days of surgery (Table-6). The

Table 3 – Urinary diversion.

Urinary Diversion	128 (100%)
Ileal conduit	97 (75%)
Orthotopic neobladder	15 (12%)
Ureterocutaneostomy	15 (12%)
Ureterosigmoidostomy	1 (1%)

Data reported as frequency and relative number (%)

Table 4 – Post operative histologic subtype.

Patients submitted to RC	128 (100%)
Transitional cell carcinoma	117 (92%)
Adenocarcinoma	4 (3%)
Squamous cell carcinoma	7 (5%)

Data reported as frequency and relative number (%)

Table 5 – Node status and number of nodes removed.

Node Status	128 (100%)
Negative	97 (76%)
Positive	31 (24%)
Nodes removed	
Median	15
10 or more nodes removed	110 (86%)

Data reported as frequency and relative number (%)

Table 6 – Distribution and detailed description of length of stay, operative time, perioperative deaths, re-hospitalization and 30-day complications. Data reported as frequency and relative number (%) when applied.

Median operative time	240 min
Median length of stay	10 days
Perioperative death	0
Re-hospitalization	21 (16%)
Patients with major complications (Grade ≥3), n (%)	33 (25.7%)
Highest grade of complications, n (%)	
Grade 1	59 (46.1%)
Grade 2	36 (28.1%)
Grade 3	8 (6.2%)
Grade 4	14 (11%)
Grade 5	11 (8.5%)
Major complications (Grade ≥3, n) (%)	33 (25.7%)

most common cause was urinary infection, responsible for 13/128 (81%) events. Other reasons were dehydration, upper gastrointestinal bleeding, evisceration, deep venous thrombosis, pain requiring venous analgesics, acute renal failure, pelvic abscess.

Major complications (Clavien-dindo 3 to 5) within 30 days of cystectomy occurred in 33/128 (25.7%) patients (Table-6). Eight patients had complications classified as Clavien-dindo grade 3. In detail, the cause of re-intervention was evisceration in 4/8 (50%), pelvic abscess in 2/8 (25%), lymphocele 1/8 (12.5%) and ileal conduit ischemia in 1/8 (12.5%) patient. Among the 14/128 (11%) patients with Clavien-Dindo grade 4 complications, urinary, abdominal and pulmonary sepsis was the causes for intensive care unit (ICU) admission in 12/14 (86%) patients. The other 2/14 (14%) patients were admitted in the ICU due to myocardial infarction and hemodynamic instability with undefined cause. Re operation was needed in 8/14 (57%) of these patients and the reasons were perforated gastric ulcer 1/8 (12.5%), pyonephrosis 1/8 (12.5%), abdominal abscess 1/8 (12.5%), evisceration in 2/8 (25%) and anastomosis ileal fistula in 3/8 (37.5%) patients.

Grade 5 Clavien-Dindo complications occurred in 11/128 (8.5%) patients. The cause of death in these patients were abdominal abscess in 1/11 (9%), ureteroileal fistula in 1/11 (9%), mesenteric ischemia in 1/11 (9%), intestinal hernia 1/11 (9%), pulmonary sepsis in 1/11 (9%), urinary sepsis in 2/11 (18%), severe inflammatory response syndrome in 2/11 (18%) and cardiac events in 2/11 (18%) patients.

DISCUSSION

Due to durable local control, long term, recurrence-free and bladder cancer specific survival there is a consensus that RC with lymph node dissection is the gold standard treatment for invasive bladder cancer. In a large series with 1054 patients, Stein et al. showed recurrence--free and overall survival at 5 years of 68% and 66%, respectively, for all patients (1), regardless of cancer stage. Other smaller series reported similar rates (2-4) and all of them showed that RC outcomes are overwhelmingly associated with the pathology, and tumor stage and lymph node status are the most important predictors for outcome (14-16). The differences in survival and recurrence rates were observed when bladder confined was compared to extravesical tumors, and intravesical muscle invasive masses showed equivalent outcomes to noninvasive ones for patients submitted to RC (1-4).

Our results show a similar rate of positive resected lymph nodes compared to cohorts from Europe (2), United States (1, 4, 17) and from a multicentric study with patients from Canadian and American centers (3). Furthermore, the rate of patients with pT3-pT4 disease reported in our current series is similar to the ones observed in the cited studies. However, if we only consider the patients classified as pT4 and compare to the contemporary cohort from Bochner et al. (17), we observe a higher percentage of patients in this pT stage in our cohort. Nevertheless, when we analyze histologic subtype, we show similar rates of transitional cell carcinoma and other bladder cancer subtypes.

Together with pathological features, surgical variables play an important role in bladder cancer outcomes and it has been shown in the SWOG-Intergroup study. In this cohort, Herr et al. (5) found substantial differences in cystectomy operative technique and patients achieved better oncological and survival outcomes when operated by urologic oncologists. Furthermore, they showed that surgical margins and number of nodes dissected were independent predictors of local recurrence and survival (5). Indeed, positive surgical margins increase the metastatic progression risk and adversely affect cancer-specific survival (18). We observed positive margins in less than 2% of our cases, finding that is in accordance with the ones from other series (5, 19) and in part reflects the surgical expertise of the surgeons from our institution.

Although the number of pelvic nodes varies widely between individuals (20) it is associated to the extent of the lymph node dissection among experienced surgeons (21). Knowing that, the SWOG researchers analyzed the number of lymph nodes dissected and its importance for disease control, showing better outcomes for patients with more than 10 nodes removed. Also, other series measured the extension and quality of the lymphadenectomy (LND) by defining a quantity of nodes that should be dissected, and this minimum number ranged from 10 to 16 (15, 22-24). In our cohort, we report a 86% rate of 10 or more and a median of 15 nodes removed, acceptable numbers when we take into account the cutoff number from the SWOG group (5).

The boundaries of extensive LND for bladder cancer include the ones from the limited LND and the cephalad dissection extended to the crossing of the ureters with common iliac arteries and tissue along the lateral and medial portion of internal vessels (25). This LDN approach was important for increasing the survival in node positive and negative patient groups. In the Stein et al. series, despite cancer node involvement, 31% and 23% of the patients were alive 5 and 10 years after RC with extensive LND, respectively. For patients with node negative disease, it also showed a positive effect on survival, suggesting a role in removing occult microscopic metastasis (15, 26, 27). Furthermore, in a retrospective study comparing limited to extended LND, the second approach was responsible for increased overall and recurrence-free survival (7). Therefore, since higher lymph node yield impacts positively in overall and disease-specific survival (6, 28), efforts must be made to its widespread adoption in our and other centers worldwide.

Another important step in the surgical management of invasive bladder cancer is the reconstruction of the urinary tract either with orthotopic or heterotopic, continent or incontinent urinary diversions. The surgical morbidity following them is significant (29) and has not been associated with the type of diversion (30). Orthotopic neobladder provides the patient with the potential for normal voiding function and continence together with superior cosmetic appearance compared to heterotopic conduits. Nevertheless, randomized prospective trials using appropriate quality of life instruments to compare the different types of diversions are lacking. In our institution, the ileal conduit was used in the vast majority of the cases and its choice was driven by patient option and surgeon experience.

Prior series reported early complications, defined as the ones affecting patients within 30 days of surgery, and their rate ranged from 20-57% (10). In a study from our colleagues from São Paulo, Brazil, Meller et al. (8) showed a rate of immediate and late complications of 19% and the group from the University of Michigan (9), in a study with 2.538 patients, reported at least 1 complication in 774 (30.5%) patients. A common characteristic of these cited studies and others from the literature is the lack of a formal complication reporting system. Without this, it is difficult to compare data from different studies and the morbidity of the procedure may be underestimated. Therefore, we report our complications with a well defined and accepted reporting method, the Clavien-Dindo classification (13).

Compared to a large series with 1142 patients from Shabsig et al. (10), we found a higher rate of major complications, defined as Clavien-Dindo grade ≥3 within 30 days. In a multivariable analysis from this same series (10), it has been shown that advanced age, prior abdominal/pelvic surgery, blood loss and ASA score >2 were significant predictors for complications. In our cohort,

different types of complications were observed and identifying the factors that are associated with them should be the aim of a future study. This will help us improve our institution quality of care and will also be important for proper patient counseling.

This is a retrospective descriptive analysis of the surgical and pathologic outcomes from a contemporary Brazilian cohort submitted to RC and pelvic LND. The short follow-up did not allow us to make a meaningful oncologic and survival analysis of our data, and we believe this is the greatest limitation of our study.

CONCLUSIONS

Survival and oncologic outcomes following RC are associated with pathologic stage and surgical variables. Therefore, efforts should focus on proper disease diagnosis and staging, and, thereafter, correct treatment based on pathologic findings. Furthermore, extended LND should be performed in all patients with RC indication. A critical analysis of our complications and their correlation with patient's characteristics, pre, per and post-operative management plans will help us to identify and modify some of factors associated with surgical morbidity. This should be the aim of a future study in our institution.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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4–Ports endoscopic extraperitoneal radical prostatectomy: preliminary and learning curve results

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ABSTRACT

Introduction: There is a lack of studies in our national scenario regarding the results obtained by laparoscopic radical prostatectomy technique (LRP). Except for a few series, there are no consistent data on oncological, functional, and perioperative results on LRP held in Brazil. As for the LRP technique performed by extraperitoneal access (ELRP), when performed by a single surgeon, the results are even scarcer.

Objective: To analyze the early perioperative and oncologic results obtained with the ELRP, throughout the technical evolution of a single surgeon.

Patients and methods: A non-randomized retrospective study was held in a Brazilian hospital of reference. In the 5-year period, 115 patients underwent the ELRP procedure. Patients were divided into two groups, the first 57 cases (Group 1) and the following 58 cases, (Group 2). A comparative analysis between the groups of efficacy results and ELRP safety was carried out.

Results: The average age of patients was 62.8 year-old and the PSA of 6.9ng/dl. The total surgery time was 135.8 minutes on average, and the urethral-bladder anastomosis was 21.9 min (23.3 min versus 20.7 min). The positive surgical margins (PSM) rate was 17.1%, showing no difference between groups (16.4% versus 17.9%; p=0.835). There was statistical difference between the groups in relation to the anastomosis time, estimated blood loss and the withdrawal time of the urinary catheter.

Conclusion: The ELRP technique proved to be a safe and effective procedure in the treatment of prostate cancer, with low morbidity.

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Keywords:
Endoscopy; Prostatectomy; Learning; Minimally Invasive Surgical Procedures

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INTRODUCTION

The first series of laparoscopic radical prostatectomy (LRP) was described by Schuessler et al (1) in 1997. Nine surgeries were performed by the transperitoneal technique (TLRP). In the year 1997, Raboy et al (2) described the extraperitoneal laparoscopic radical prostatectomy (ELRP).

The first ones to carry out the ELRP procedure in Brazil were Andreoni et al (3) in 2001. They had an exceptional higher incidence of hypercapnia with conversion, maybe due to longer operative time. No functional and oncological results were provided. The first successful nationwide series of ELRP procedures was described by Tobias-Machado et al (4) in 2004.

In the 2010 cohort study, Guillonneau et al (5) observed that the percentage of positive surgical margins (PSM) gets stabilized after the performance of 250 cases, occurring in 22% of patients. They concluded that, previous experience in retropubic radical prostatectomy (RRP) did

not influence the result of the PSM, and that this rate decreases more slowly during the learning curve (LC) in LRP compared with the open technique. Thus, it suggests that the results depend directly and exclusively of the laparoscopic technique training.

In a series of 760 cases, Mirandolino et al (6) found that the percentage of PSM in LRP was similar to the studies using the open technique. The PSM average was from 11% to 26%. In five years time, there was a biochemical recurrence rate of 11%.

In a study comparing the LC from different surgeons, Siqueira et al (7) observed that the rate of complications from both ELRP and TLRP techniques were similar. On the other hand, the overall rate of PSM was lower when using the TLRP technique.

In a nationwide series, with 270 cases performed by different surgeons, Starling et al (8) observed that there was a drop from 15% to 10% in the PSM rate after a LC of 70 cases.

There is a lack of national studies with respect to the results obtained from the LRP technique. Except for the series of the cases described above, there are no consistent data on oncological, functional and perioperative results on LRP held in Brazil. Concerning the ELRP technique when performed by a single surgeon, the results are even scarcer.

The present study analyses the early perioperative and oncologic results obtained with ELRP performed by a single surgeon.

MATERIALS AND METHODS

It was a backward-looking, non-randomized study held in a Brazilian hospital of reference. It only represents the first 115 cases (with patients operated from 2008 through 2013), who underwent the laparoscopic extraperitoneal technique, using only a four-port. It does represent the learning curve of a single surgeon in ELRP technique. All patients had PSA<8, clinical stage T1 and T2. The initial 40 cases performed by TLRP technique were excluded. The patients involved in the study were divided into two groups, the first 57 cases were called Group 1 and the 58 following cases were called Group 2.

The configurations of the ports were the same for all the cases. The camera port was done by an infraumbilical incision of about 4cm, followed by the digital dissection of the pre-peritoneal space and closed with Prolene thread (Figures 1 and 2). After Trendelenburg position (Figure-3),

Figure 1 – Digital dissection of the pre-peritoneal area.

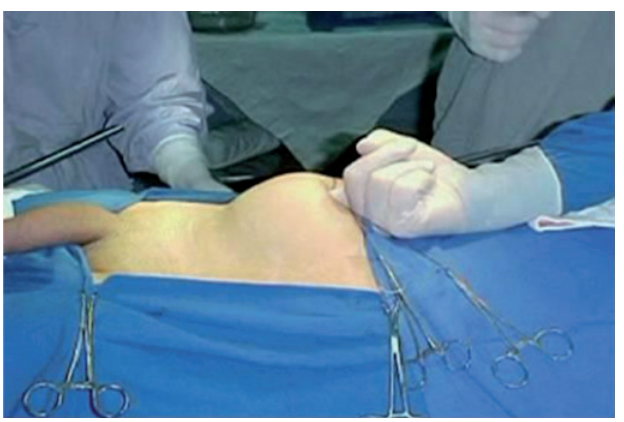
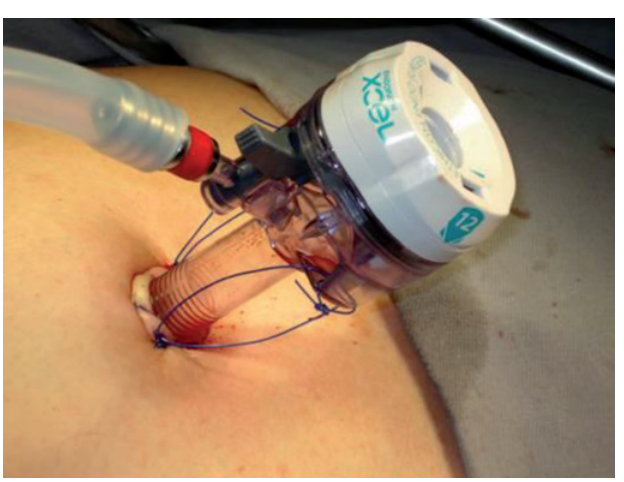


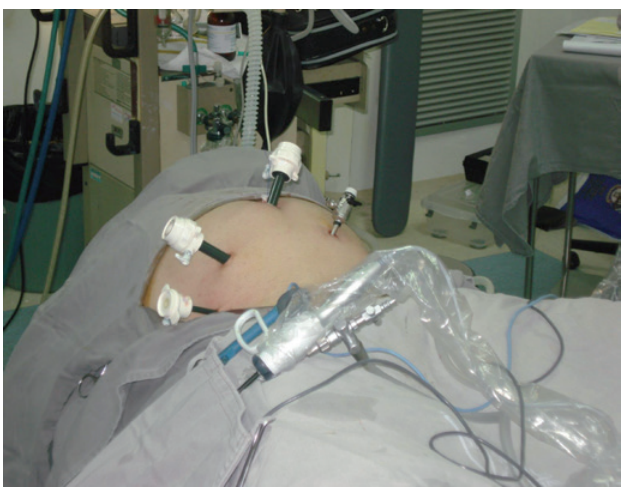
Figure 2 – Port closure with an umbilical point "X" on each side of the optical trocar.



the surgeon's work port was inserted into the edge of the rectus abdominis muscle at the midway between the iliac crest and the umbilicus, the left port had 5mm and the right one, 10-12mm. The 5mm port of the first assistant surgeon was inserted on the left side near the iliac crest. When the first assistant surgeon was left-handed this portal stood on the right side (Figure-4).

Figure 3 - Patient and surgical team positioning.

Figure 4 - Arrangement of ports when the first assistant surgeon is left-handed.



In the surgical technique used, the extraperitoneal area is digitally created followed by the opening of the endopelvic fascia bilaterally. The complex of the dorsal penile vein is tied with polyglactin sutures 0, and the bladder neck is opened with an ultrasonic scalpel. After the dissection of the seminal vesicles and the vas deferens, the neurovascular bundles are separated from the prostate with the use of ultrasonic energy or by placing polymer clips (Hem-O-Lok®), followed by the section with laparoscopic scissors, always using the preservation of nerves interfascial technique. After the removal of the prostate, the urethra is anastomosed to the bladder neck with a polyglactin 3.0 suture, making use of the Van Velthoven (9) technique.

A comparative analysis between groups of early perioperative and oncological outcomes was performed. In order to compare the groups regarding the qualitative variables, the chi-square test of Pearson or the Fisher exact test were used. In the cases where the normal distribution assumption was not rejected, the t-Student test was applied. As for the normality rejection situations, the nonparametric Mann-Whitney test was used.

RESULTS

Table-1 shows the results of the characterization of the entire sample as well as for each Group. The groups were homogeneous, with no difference between them. The average age of patients was 62.8 years old, with the average preoperative PSA of 6.9ng/ml, and average prostate weight of 39.3g taken by the trans-rectal ultrasound. The majority of cases (80.9%) were diagnosed solely due to the increase of PSA in routine tests (clinical stage T1c) and in most cases with a Gleason 6 (50.4%) and Gleason 7 (40%), respectively. Table-2 shows the results of oncological data according to D'Amico classification (10).

Table-3 shows the results of the intraoperative variables of the evaluated technique. The total surgical time was on average 135.8 min. with the UV anastomosis time average of 21.9 min. In one case, there was conversion to transperitoneal technique. There was no statistical difference between the groups when comparing the number of conversions to open surgery, as well as when compared surgical complications.

From the results (Table-3), we can see that there was a significant reduction in the time of anastomosis and bleeding estimated between groups in favor of Group 2. On the other hand, there was no statistical difference regarding the need for blood transfusion. We can see that there was a significant reduction in the hospital stay and the urinary catheter removal time between the two groups, also in favor of Group 2.

Among the complications, there was no statistical difference between the groups (p=0.92). Table-4 shows all the complications that hap-

Table 1 – Characterization of the entire sample.

	Total (n=115)	Group 1 (n = 57)	Group 2 (n = 58)	p
Age (years): average (±SD)	62.8 (±7.3)	62.8 (±8.0)	62.7 (±6.5)	0.941_t
ICM (kg/m²): average (±SD)	27.2 (±3.4)	21.1 (±3.3)	27.3 (±3.6)	0.827_t
PSA (ng/ml): average (±SD)	6.9 (±4.4)	7.1 (±4.5)	6.6 (±4.4)	0.510_t
weight (g): average (±SD)	39.3 (±13.0)	40.8 (±14.9)	37.8 (±10.9)	0.070_t
Nodule: n (%)	22 (19.1%)	12 (21.1%)	10 (17.2%)	0.603
Clinic Stage: n (%)				0.775_F
T1b	1 (0.9%)	1 (1.8%)	-	
T1c	93 (80.9%)	45 (78.9%)	48 (82.8%)	
T2a	13 (11.3%)	6 (10.5%)	7 (12.1%)	
T2b	8 (7.0%)	5 (8.8%)	3 (5.3%)	
Gleason Score: n (%)				0.173_F
4 (2+2)	1 (0.9%)	1 (1.8%)	-	
5 (2+3)	1 (0.9%)	1 (1.8%)	-	
5 (3+2)	3 (2.6%)	1 (1.8%)	2 (3.4%)	
6 (3+3)	58 (50.4%)	23 (40.4%)	35 (60.3%)	
7 (3+4)	34 (29.6%)	18 (31.6%)	16 (27.6%)	
7 (4+3)	12 (10.4%)	9 (15.8%)	3 (5.2%)	
8 (3+5)	1 (0.9%)	1 (1.8%)	-	
8 (4+4)	5 (4.3%)	3 (5.3%)	2 (3.4%)	

SD = standard deviation; **t** = T-Student test; **F** = Fisher's exact test; **ICM** = index of corporal mass

Table 2 – D'Amico risk stratification groups for prostate cancer.

Risk Escore	Total (n=115)	Group 1 (n = 57)	Group 2 (n = 58)	p
Low Risk	48 (41.7%)	19 (33.3%)	29 (50.9%)	0.171
Intermediate Risk	56 (48.7%)	31 (54.4%)	25 (43.1%)	
High Risk	11 (9.6%)	7 (12.3%)	4 (6.9%)	

pened in this study according to Clavien-Dindo classification system (11).

Table-5 analyzes the variables related to the postoperative pathologic evaluation. No statistical difference was observed between the groups. In relation to the Gleason scores, the most prevalent was (3+4) in 45.9% of the cases. The perineural invasion could be observed in 24.5% of cases, and the invasion of the prostate capsule in 13.5%. The positive surgical margin variable (PSM) was 17.1%, with no difference between groups (16.4% versus 17.9%; p=0.835).

In terms of disease staging, 86.5% of cases were classified as pT2, and 13.5% were classified as pT3. There was no difference between groups when analyzing the variable pathologic stage (p=0.17).

Table 3 – Intraoperative and post-operative variables.

	Total (n=115)	Group 1 (n = 57)	Group 2 (n = 58)	p
Anastomosis Time (min): Average (±SD)	21.9 (±6.2)	23.3 (±6.9)	20.7 (±5.2)	0.027_t (*)
Blood Transfusion: n (%)	4 (±3.5%)	2 (±3.5%)	2 (±3.4%)	$> 0.999_F$
Surgical Time (min): Average (±SD)	135.8(±34.3)	139.5 (±32.8)	132.3 (±35.7)	0.269_t
Estimated Bleeding Rates (ml): Average (±SD)	178.4(±80.9)	200.7 (±89.5)	156.4 (±65.0)	0.003_M (*)
Conversion Number: n (%)	5 (4.3%)	3 (5.3%)	2 (3.4%)	0.679_F
Time in the Hospital (days) Average (±SD)	2.2 (±0.5)	2.3 (±0.7)	2.0 (±0.2)	0.022_t (*)
Urinary Catheter Time (days): Average (±SD)	9.7 (±2.6)	10.6 (±2.9)	8.8 (±1.8)	$<0.001_M$ (*)

T = T-Student test; **F** = Fisher's exact test; **M** = Mann-Whitney test

Table 4 – Complications according to Clavien-Dindo classification system.

Complication	Total (n=115)	Group 1 (n = 57)	Group 2 (n = 58)	p
No complications	83 (72.2%)	40 (70.2%)	43 (74.1%)	
Urinary infection (grade II)	14 (12.2%)	6 (10.5%)	8 (13.8%)	
Seroma (grade IIIa)	1 (0.9%)	1 (1.8%)	0 (0%)	
Urinary extravasation (grade I)	2 (1.7%)	2 (3.5%)	0 (0%)	
Anastomosis rupture (grade IIIa)	1 (0.9%)	0 (0%)	1 (1.7%)	
Hematuria (grade I)	1 (0.9%)	0 (0%)	1 (1.7%)	
Urinary retencion	1 (0.9%)	1 (1.8%)	0 (0%)	0.924_F
Bleeding from the drain (grade I)	1 (0.9%)	1 (1.8%)	0 (0%)	
Urethral stricture (grade IIIa)	2 (1.7%)	1 (1.8%)	1 (1.7%)	
Bladder neck stenosis (grade IIIa)	2 (1.7%)	1 (1.8%)	1 (1.7%)	
Blood transfusion (grade II)	4 (3.5%)	2 (3.5%)	2 (3.4%)	
Rectal injury (grade IIIb)	2 (1.7%)	1 (1.8%)	1 (1.7%)	
Epigastric artery injury (grade IIIb)	1 (0.9%)	1 (1.8%)	0 (0%)	

Table 5 – Postoperative pathologic evaluation.

Variables	Total (n = 111)*	Group 1 (n = 55)	Group 2 (n = 56)	P
Gleason Escore: n (%)				0.497_F
5 (2+3)	1 (0.9%)	1 (1.8%)	-	
5 (3+2)	2 (1.8%)	-	2 (3.6%)	
6 (3+3)	34 (30.6%)	18 (32.7%)	16 (28.6%)	
7 (3+4)	51 (45.9%)	22 (40.0%)	29 (51.8%)	
7 (4+3)	15 (13.5%)	9 (16.4%)	6 (10.7%)	
8 (4+4)	4 (3.6%)	2 (3.6%)	2 (3.6%)	
9 (4+5)	4 (3.6%)	3 (5.5%)	1 (1.8%)	
Perineural Invasion: n (%)	27 (24.5%)	14 (26.4%)	13 (22.8%)	0.660
Prostate Capsule Invasion: n (%)	15 (13.5%)	5 (9.1%)	10 (17.9%)	0.177
Positive Surgical Margin: n (%)	19 (17.1%)	8 (16.4%)	11 (17.9%)	0.835
Pathological Stage: n (%)				0.177

F = Fisher's exact test

*= 02 cases with benign prostatic hyperplasia result were excluded and 02 cases in which the operative specimen were lost.

Table 6 - Postoperative Gleason.

			Postoperative Gleason							
			2+3	**3+2**	**3+3**	**3+4**	**4+3**	**4+4**	**4+5**	**Total**
Preoperative Gleason	2+2	N	0	0	1	0	0	0	0	1
		%	0.0%	0.0%	100%	0.0%	0.0%	0.0%	0.0%	100%
	2+3	N	1	0	0	0	0	0	0	1
		%	100%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	100%
	3+2	N	0	0	0	2	0	0	1	3
		%	0.0%	0.0%	0.0%	66.7%	0.0%	0.0%	33.3%	100%
	3+3	N	0	1	26	22	8	0	0	57
		%	0.0%	1.8%	45.0%	38.6%	14%	0.0%	0.0%	100%
	3+4	N	0	1	4	21	2	1	2	31
		%	0.0%	3.2%	12.9%	67.7%	6.5%	3.2%	6.5%	100%
	3+5	N	0	0	0	0	0	1	0	1
		%	0.0%	0.0%	0.0%	0.0%	0.0%	100%	0.0%	100%
	4+3	N	0	0	2	4	4	1	1	12
		%	0.0%	0.0%	16.7%	33.3%	33.3%	8.3%	8.3%	100%
	4+4	N	0	0	1	2	1	1	0	5
		%	0.0%	0.0%	20.0%	40.0%	20.0%	20.0%	0.0%	100%
Total		N	1	2	34	51	15	4	4	111
		%	**0.9%**	**1.8%**	**30.6%**	**45.9%**	**13.5%**	**3.6%**	**3.6%**	**100%**

p-value = 0.001

Table-6 shows that there was significant change in the Gleason score in the pre and postoperative period. There was an increase of 38.6% of the Gleason 6 (3+3) to the Gleason 7 (3+4), and of 14% for Gleason 7 (4+3), showing a understaging on the preoperative Gleason score, when analyzing the surgical specimens.

Table-7 shows the incidence of PSM regarding the pathological stage. We observed that 8.3% of the cases with pT2 stage, and 73.4% of the cases with pT3 stage showed PSM (p<0.001).

There was no difference in the incidence of PSM for Groups 1 and 2, when the PSM rate was analyzed by separate groups (Table-8). Furthermore, in Group 2 there was a statistical trend of positive margin with pT3 stage (Table-9).

DISCUSSION

In all three technical procedures (open, laparoscopic or robotic), there is a specific goal which is the healing treatment of localized prostate cancer (12). Some authors argue that in the TLRP the initial dissection of the seminal vesicles and vas deferens facilitates the dissection step and the preservation of the neurovascular bundle. On top of that it is easier as it promotes more physical space and light, and it also allows greater visibility of the anatomical structures leading to less tension in the anastomosis (13).

On the other hand, the ELRP brings a similar procedure to the conventional retropubic one, while maintaining the integrity of the peritoneum, allowing for less possibility of intra-abdominal complications (2). Therefore, this access is defined as the safest one as it does not violate the peritoneal cavity (14-16).

The robotic assisted laparoscopic radical prostatectomy extraperitoneal access (RALRP-EX) is just used in a few institutions, as it holds a long and difficult LC. This technique provides very limited space for the robotic movements, and difficult to make lymphadenectomy. It is recommended to be just started by surgeons with extensive expe-

Table 7 – Incidence of PSM regarding the pathological stage.

Surgical Margins	Pathological Stage			P
(Group 1)	**pT2**	**pT3**	**Total**	
Negative	88 (91.7%)	04 (26.7%)	92 (82.9%)	0.001_F
Positive	08 (8.3%)	11 (73.4%)	19 (17.1%)	
Total	96 (100%)	15 (100%)	111 (100%)	

F = Fisher's exact test

Table 8 - Incidence of PSM for groups 1 and 2.

Surgical Margins	Pathological Stage			P
(Group 1)	**pT2**	**pT3**	**Total**	
Negative	44 (95.7%)	02 (4.3%)	46 (100%)	0.027_F
Positive	06 (66.7%)	03 (33.3%)	09 (100%)	
Total	**50 (90.9%)**	**05 (9.1%)**	**55 (100%)**	
(Group 2)	pT2	pT3	Total	
Negative	44 (95.7%)	02 (4.3%)	46 (100%)	$<0.001_F$
Positive	02 (20.0%)	08 (80.0%)	10 (100%)	
Total	**46 (82.1%)**	**10 (17.9%)**	**56 (100%)**	

F = Fisher's exact test

Table 9 - Comparison of groups in relation to the final stage (only for patients with positive margins).

		Final stage		Total
		pT2 n = 8	pT3 n = 11	N = 19
Group	1	6 (66.7%)	3 (33.3%)	9 (100%)
	2	2 (20.0%)	8 (80.0%)	10 (100%)

p-value = 0.070 (Fisher's exact test)
Through the result above, a statistical trend can be observed, ($p<0.10$) difference between the groups (80% vs. 33%).

rience in transperitoneal robotic assisted laparoscopic radical prostatectomy (RALRP-TP) (14).

According to Mitre et al, high costs, lack of accessibility to training and reduced budgets are the biggest problems for the spread of robot technology in low-volume centers, especially in developing countries (17).

The best parameter to evaluate the oncologic efficacy is disease-free survival, but with the impossibility to assess this parameter due to short segments, the recurrent biochemical rate is the most appropriate way, and is directly associated with the PSM rate (18).

According to Guillonneau et al (5), the percentage of PSM only stabilized after 250 cases performed in LRP, with an incidence of 22%. It was suggested that these results are due to the training in laparoscopy (19).

As oppose to the above study, our series with only 115 cases had the overall rate of PSM of 17.1%, with no significant difference between groups. Thus, the continuous learning in the extraperitoneal technique did not influence the oncological results obtained from surgical specimens. We also observed that most cases of PSM occurred in the pathological stage pT3 (73.4%). If we just analyze the cases of pT2 stage, we can see a very low PSM rate (8.3%), below the average of published data.

Similarly to our results, Mirandolino et al (6) reported that the PSM average obtained in cases under LRP was from 11%-26%.

In general, it is observed that during the LC, the perioperative results are lower than the ones observed with large laparoscopic or RRP series. Such results begin to improve after the learning period, which happens around 10-80 cases (20, 21). However, the sufficient number of surgeries to bridge this period may be higher when the oncological and functional results are also evaluated. In the present study, the initial 40 cases performed by transperitoneal access, were excluded to obtain two comparable and homogeneous groups, in which all the surgeries were performed by the same surgical technique, via the extraperitoneal access and by the same surgeon.

According to Leroy et al (22) the fellowship training in robotics, considerably improves the LC in the RALRP and that in the first 30 surgeries performed by the group in which there was training, the PSM rate was significantly lower, 15% versus 34%. At the same time, Kown et al (23) demonstrated that the LC in robotics is extremely short, with only 25 procedures. On the other hand, Peters et al (24) reported that the PSM rate improved significantly after performing 800 robotic surgeries. However, their LC only finished with the average of 1600 procedures, showing a PSM rate lower than 10%.

Novarra et al (25) reported the oncological aspects related to RALRP technique in meta-analysis. In that article, the general average of PSM in RALRP was of 15%, and when stratified for the pT2 stage it was 9%. Despite the quality of the meta-analysis described above, Picozzi et al (26) found selectivity and the heading of some cases for treatment with robotic technology.

Alongside with the critics of Picozzi et al (26), an article entitled "PRLRA–fake innovation or the real deal?", recently written by Albertsen (27), questions the indiscriminate use of robotics technology in detriment to the benefit on patients.

Emanuel (28) strongly criticizes the robotic technique, and refers to RALRP as a "pseudo-innovation" and also, as "a technology that dramatically increases costs without providing increase in the health of patients."

In our series, when we analyze the surgical performance data from both groups, we can verify that the average time to perform anastomosis, the time for the urinary catheter removal and estimated blood loss were much lower in Group 2 than in Group 1. These data suggest that there was a technical improvement during the course of time, reflecting the learning process of the extraperitoneal technique. Even so, we found that the estimated bleeding rates for both groups were at the lower limit of the rates found in the literature, ranging from 201.5 to 1323mL in the ELRP and 69-534ml in the RALRP (29).

In our series there was no conversion to open surgery due to bleeding. All conversions occurred due to technical difficulties, mainly because of obesity and retropubic adhesions, the latter being probably caused by the inflammatory process associated with the prostate biopsy. The creation of the physical space in the extraperitoneal access can be obtained to some technical difficulties in some cases. In this series specifically, there was one case in one patient during the creation of the retroperitoneal space, a tiny perforation in the peritoneal envelope. Therefore, the conversion to TLRP was necessary.

There were no cases of hypercarbia because the operative time was not too long (average of 135.8 min.), probably due to the previous experience in TLRP procedures. Therefore, the learning curve is more difficult than in the TRLP technique, but gradually overcome with the previous experience in laparoscopy.

I believe that ELRP could be taught at residency or special programs for the urological community in Brazil.

Due to the retrospective nature of this study, it was not possible to properly assess functional aspects such as sexual potency and urinary incontinence.

In our study, there were rectal lesions in two cases, which were promptly corrected intraoperatively.

Although the anastomosis was done with continuous suture, in two cases there were prolonged urinary extravasation through the drain. These complications were treated only with prolonged bladder catheterization (average length of 14 days). In only one case, after the removal of the urinary catheter, the patient had urinary retention due to the localized edema in anastomosis.

Late complications presented in our study may be inherent to any surgical technique, by either the open or laparoscopic technique.

CONCLUSION

It was observed during learning curve a significant reduction in the average time to perform the urethral-bladder anastomosis, the estimated blood loss and the removal time of the urinary catheter, seen in Group 2, that suggest that there was an improvement of the surgical technique with time. These data only reflect the surgeon's learning process while using the ELRP.

There was no difference in early oncological results during the technical evolution, when analyzing the ELRP technique.

ABBREVIATIONS

LRP = laparoscopic radical prostatectomy technique
ELRP = laparoscopic radical prostatectomy technique performed by extraperitoneal access
TLRP = laparoscopic radical prostatectomy technique performed by the transperitoneal access
RALRP-EX = robotic assisted laparoscopic radical prostatectomy extraperitoneal
RALRP-TP = robotic assisted laparoscopic radical prostatectomy transperitoneal
LC = learning curve
RRP = retropubic radical prostatectomy
PSA = prostate-specific antigen
PSM = positive surgical margins
ICM = index of corporal mass
SD = standard deviation
t - T = Student test
M = Mann-Whitney test
F = Fisher's exact test

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Evaluation of PCA3 and multiparametric MRI's: collective benefits before deciding initial prostate biopsy for patients with PSA level between 3–10ng/mL

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ABSTRACT

Objective: To analyze the contribution of multiparametric MRI and PCA3 assay, predecision of initial biopsy in PSA level between 3-10 ng/mL patients with normal digital rectal examination(DRE).

Materials and Methods: PSA level 3-10 ng/mL ,patients, with normal DRE results and no previous prostate biopsy history, were included in this study. Each patient underwent multiparametric MRI one week before biopsy. Urine sample taking for PCA3 examination preceded the biopsy. Systematic and targeted biopsies were conducted.

Patients with high PSA levels were seperated into two groups as: high PCA3 scored and low PCA3 scored. Then each group was divided into two sub-groups as: MRI lesion positive and negative. Tumor incidence, positive predictive values(PPV) and negative predictive values(NPV) were calculated.

Results: 53 patients were included between February 2013 and March 2014.Mean age 61.22 ± 1.06. Mean PSA value 5.13 ± 0.19 ng / mL. Mean PCA3 score 98.01 ± 23.13 and mean prostate size was 48.96 ± 2.67 grams.

Fourty nine patients had both PCA3 score and multiparametric MRI. The PCA3's PPV value was 58.33%. If multiparametric MRI lesions are added to high PCA3 scores , the PPV appears to elevate to 91.66%.

NPV of PCA3 was 96%. NPV was 95% when there was no lesion in the multiparametric MRI with low PCA3 scores. Sensitivity was 91.66% , specificity was 95% respectively.

Conclusion: Adding multimetric MRI can also support biopsy decision for patients with high PCA3 value. When PCA3 value is low, patients can be survailled without any need to take a MRI.

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INTRODUCTION

Prostate cancer (CaP) is the most commonly diagnosed cancer in men (1). CaP diagnosis relies on prostate specific antigen (PSA), digital rectal examination (DRE) and transrectal ultrasonography (TRUS). However, prostate is the only solid organ on which biopsy is made without seeing the lesion. Thirty per cent of tumors can be missed with TRUS-guided biopsies (2). As some tumors are missed, some clinically insignificant tumors are also extra detected. To avoid these occurrences and to

increase the success rate, MRI is performed prior to the second biopsies and MRI guided biopsies are done according to lesions. Today, MRI evaluation is done before initial biopsies to increase this success (3). Although several MRI methods are used, the most sensitive and specific MRI method is multiparametric MRI which is a combination of several MRI methods (4). PCA3 is a non-coding mRNA which is isolated from initial urine after prostate massage (5). In studies after the identification for the first time in 1999, it has been shown that PCA3 is superior to PSA for the presence of prostate cancer (6). Subsequently, it has been used used prior to the initial biopsy (7).

In our study, we investigated the collective benefits of PCA3 and multiparametric MRI for grey area patients whose DRE are normal and serum PSA values are between 3-10ng/mL before initial biopsy decision.

MATERIALS AND METHODS

The study was planned as a prospective and single-centered. Consent of the local ethics committee for this study was taken with B.30.2.IST.0.30.90.00/16077 numbered decree of Dean of the Cerrahpasa Faculty of Medicine Clinical Research Ethics Committee in 8 June 2012. Serum PSA level 3-10ng/mL patients with normal digital rectal examination scheduled for initial prostate biopsy were included in the study between February 2013 and March 2014. Each patient underwent multiparametric MRI a week before biopsy. After 3-minute prostate massage 20-30mL initial urine sample for PCA3 examination were taken pre-biopsy.

Although biopsy was performed schematically, additional cores were taken from lesions shown in the multiparametric MRI.

MRI STUDY

Each patient underwent multiparametric MRI evaluation one week before biopsy. Siemens Avanto 1.5 Tesla MRI equipment was used. T2 sequence MRI, diffusion MRI, dynamic contrast--enhanced MRI and MRI spectroscopy were evaluated in multiparametric MRI. Intensity loss regions in T2 sequence MRI, diffusion loss zones in diffusion MRI, contrast involvement and after the early wash-out common areas in dynamic contrast--enhanced MRI, (choline+creatine)/citrate>3SD (this ratio is above 0.86) regions in spectroscopic MRI were considered to be significant. Biopsies were directed to these regions, described and accepted as significant by at least two MRI methods and multiparametric MRI.

PCA3 STUDY

Initial 20-30cc urine sample after 3 minutes prostatic massage was taken from each patient before the biopsy. Massage from lateral to medial and from baseline through the apex was conducted. After urine was centrifuged within 15 minutes, supernatant section was discarded and RNA preservative was added for later work. The mix was stored at-80^{o}C. PCA3 study was done with real time multiplex PCR posteriorly (PCA3 mRNA copy number/PSA mRNA copy number) X 1000 formula was used for PCA3 score calculation (5).

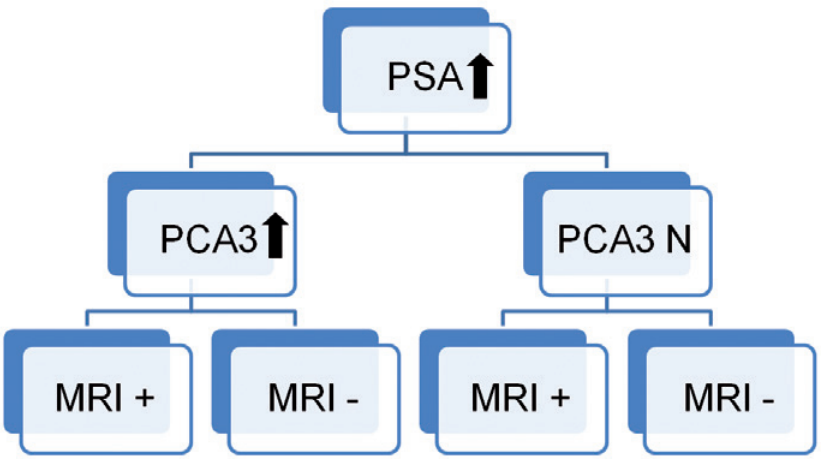
Patients with high PSA levels were divided into two groups: with high PCA3 score and low PCA3 score. Then each group was divided into two groups: with MRI lesion positive and negative. Tumor incidence and positive predictive values for patients with high PSA, high PCA3 score and positive multiparametric MRI were calculated. Tumor incidence and negative predictive values in patients with high PSA level and low PCA3 scores and negative multiparametric MRI lesions were calculated as well (Figure-1).

RESULTS

Fifty three patients were included in our survey conducted between February 2013 and March 2014. One patient's only urine was sent for PCA3 study without MRI screening. Two patient's urine wasn't examined for PCA3, because the urine wasn't taken to the laboratory within 15 minutes and urine PCA3 RNA preservative could not be added. For one patient's urine sample didn't work in PCR, and it was disregarded for PCA3 study.

The mean age of patients was 61.22±1.06. The mean PSA value was 5.13±0.19ng/mL. The

Figure 1 - Study Diagram.



mean PCA3 score was 98.01±23.13 and the mean prostate size was 48.96±2.67grams. Digital rectal examination did not reveal any abnormalities in any patient (Table-1).

Mean biopsy cores were 12.73±0.13. Prostate cancer was detected in 19 of 53 (35.8%) patients. Tumor detected mean cores was 3.21±0.45. ASAP was found in two patients, Gleason 3+3 PCa in thirteen patients and Gleason 3+4 PCa in four patients. None of the patients had Gleason 4+3 or above tumor grade. Two patients' second biopsy conducted after two months was reported as benign, whose first biopsies were ASAP. As the second biopsies were benign, these two patient's results were accepted as benign for further evaluation.

Fifty patient's urine samples were suitable for PCA3 evaluation. Prostate cancer was detected in 15 of them. PCA3 scores were over 35 in 25 patients. In 14 (56%) of these 25 patients tumor was detected. PCA3 score was low in 25 patients. In 1 (4%) of these 25 patients, tumor was detected. Tumor of this patient was present in 1 core and Gleason score was 3+3.

Table 1 - General Features.

	Age	ProstateVolume	PSA	PCA3
Mean	61.22	48.96	5.13	98.01
St Deviation	1.06	2.67	0.19	23.13
Median	62	45	5	37.28
St Deviation	7.73	19.47	1.45	163.6
Minimum	43	17	3	0
Maximum	79	93	8.9	1000

In patients with high PCA3 score tumor detection rate was high and statistically significant (p=0.0001) (Table-2).

In our survey PCA3's sensitivity was 93.33%, specificity 68.57% for the threshold of PCA3 of 35. PCA3' s positive predictive value was 56%, and negative predictive value was 96%. PCA3 score was not related to prostate volume and patient's age (Table-3).

PCA3 score was not significantly different between Gleason score 3+3 and 3+4 tumors (Table-4).

Multiparametric MRI lesions were detected in 18 patients (when seen at least in two MRI they were accepted as multiparametric MRI lesion). Twelve tumors were screened in 18 lesions (66.6%). Twenty nine lesion negative patients among 34 had no tumor (85.2%).

Significantly more tumors were found in the MRI lesion positive patients than MRI lesion negative patients (p=0.0001) (Table-5). Sensitivity of multiparametric MRI was 70.58% and specificity was 82.80%. Positive predictive values were calculated as 66.60% and negative predictive values were 85.2%.

Patients with both PCA3 score and multiparametric MRI available totaled 49. There were 24 patients with high PCA3 scores. Fourteen of these

Table 2 - Tumor Detection According to PCA3 Score.

		Tumor Negative	Tumor Positive		P
PCA3	<35	24	1	25	0.0001
	>35	11	14	25	

Table 3 - Relationship Between PCA3 and Age and Prostate Volume.

		R	P
PCA3	Age	0.002	0.988
	Prostate volume	-0.018	0.904

Table 4 - Relationship Between PCA3 and Gleason Score.

	Biopsy Gleason	Count	Mean	Standard Deviation	p
PCA3	6	12	1.91	0.28	0.635
	7	3	2	0	

Table 5 - Comparison of Multiparametric MRI and Biopsy.

		Multiparametric MRI Lesion Tumor-	Multiparametric MRI Lesion Tumor+	Total	p
Multiparametric MRI Lesion	**Lesion-**	29	5	34	0.0001
	Lesion+	6	12	18	
Total		**35**	**17**	**52**	

patients had tumors. Accordingly, the PCA3's positive predictive value detected was 58.33%. Twelve patients had both high PCA3 score and multiparametric MRI lesion and tumor was detected in 11 of these. Our study revealed that if multiparametric MRI lesions are added to high PCA3 scores, the positive predictive value appears to increase to 91.66%.

There were 25 patients with normal PCA3 scores and only one patient had tumor whereas 24 patients didn't. Accordingly, the negative predictive value of PCA3 was calculated as 96%. In 20 of these 25 patients, any MRI lesion was observed. Of these patients, tumor was detected in only one patient. Negative predictive value was calculated as 95% when no lesion existed in the multiparametric MRI with low PCA3 scores. Sensitivity was 91.66% and specificity was 95% respectively (Figure-2).

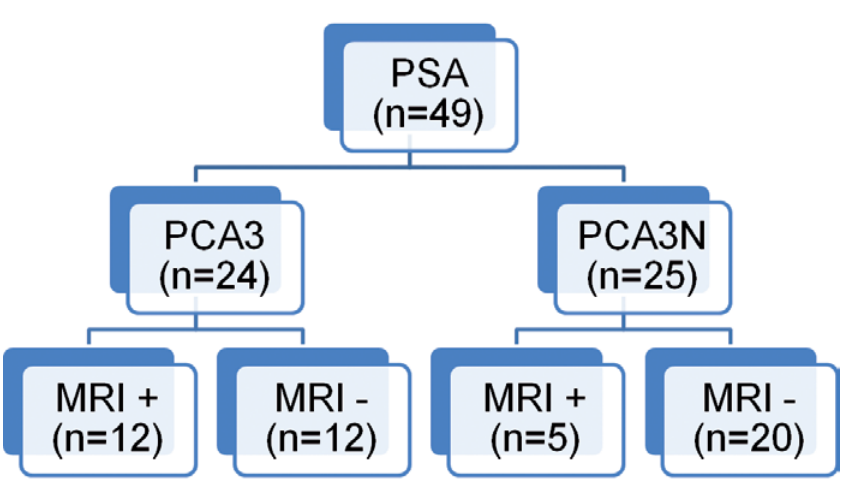
DISCUSSION

The systematic TRUS-guided prostate biopsy still continue to be the standard method when cancer is suspected (8). However, prostate biopsy is a procedure where can occur serious complications such as urinary infections that can go to sepsis (9), rectal bleeding (10), catheterization requirement for retention (10). Also pre-biopsy anxiety affects the patients psychologically (11). On the other hand, decreasing PSA threshold when deciding on biopsy can increase the rates of clinically insignificant tumors (12). Therefore, biopsy decision should be taken more carefully and new diagnostic methods should be developed for the detection of tumors that are required to be treated.

Nowadays PCA3 is usually used to decide on second biopsy in patients with continuous PSA elevation whose first biopsies were reported as benign (13). Considering the pre-biopsy anxiety and post-biopsy complications PCA3 is also used in making decision for the first biopsies (7). It was observed that PCA3 is significantly higher in patients with tumors at the Chevli's 3073 first biopsy planned patients study. This study also showed that higher PCA3 scores were detected in patients with higher Gleason scores (7).

In our survey PCA3's sensitivity was 93.33% and specificity was 68.57% for the threshold of PCA3 35. PCA3' s positive predictive value was 56%, and negative predictive value was 96%. In the literature, it's stated that sensitivity was 47-69%, and specificity ranged from 72 to 79% (14, 15). In our study sensitivity was higher than literature, although specifity was slightly lower, but similar. Positive predictive value of our study was similar to 55% that Leyten and colleagues reported (16). PCA3 in this study performed better than in other studies.

Figure 2 - Diagram of the patients with high PSA level, have PCA3 value and multiparametric MRI.



Also PCA3 wasn't related with age and prostate volume (p=0.988, p=0.904). This can represent that PCA3 is superior to PSA. In our study, detected tumor's Gleason scores were 6 and 7. No difference was detected between the Gleason scores for PCA3 (p=0.823, p=0.635). There was also no difference between the high grade tumors and low grade tumors for PCA3 in Leyten and his colleague's study (16). Unlike our study, Busetto and colleagues showed that patients with high--grade tumor had the higher PCA3 scores (13). In our study, a meaningful result could not be obtained because of the low-risk group of patients evaluated and patients with Gleason score 6 and 7 were in close proximity to clinical data.

MRI can be used in several areas of prostate cancer diagnosis and treatment. MRI can be used in patients with ongoing high PSA whose previous biopsy resulted benign, before the second biopsy, to increase the success, to preoperative evaluation of the tumor relationship neurovascular bundles, radiotherapy planning, in focal treatment planning, and for patients undergoing active surveillance (17).

In addition to these areas, today MRI is used before the initial biopsy decision to increase the biopsy success. Although various MRI methods are used, the most sensitive and specific method is multiparametric MRI which is a combination of several multiparametric MRI methods (4). In our study, significantly more tumor was determined in patients with multiparametric MRI lesion compared to patients without multiparametric MRI lesion (p=0.0001). Multiparametric MRI's sensitivity was 70.58%, specificity was 82.80%, positive predictive value was 66.60%, and negative predictive value was 85.2%. Multiparametric MRI was found to be most useful for detecting tumor in terms of the presence of multiparametric MRI lesions. Although our findings in MRI were very little low compared to literature, they were similar to it. In the literature, multiparametric MRI's sensitivity was 75%, and specificity was 94% for 0.2cc to larger lesions (18).

There is no study which determines combined benefits of PCA3 score and multiparametric MRI in this patient group in the literature. Fourty nine patients had both PCA3 score and multiparametric MRI available. There were 24 patients with high PCA3 score and fourteen of these patients (58.3%) had tumors. Twelve patients had both high PCA3 score and multiparametric MRI lesion. Tumor was detected in 11 of 12 patients. Our study showed that if multiparametric MRI lesions are added to high PCA3 scores, the positive predictive value appears to increase to 91.66%. There were 25 patients with a normal PCA3 score. Of these 25 patients, only one patient had tumor. Accordingly, the negative predictive value of PCA3 was calculated as 96%. Fradet and colleagues stated that PCA3 positive predictive value was 75% and negative predictive value 84% (19). In Tinzl and colleague's study positive predictive value was 67% and negative predictive value was 87% (20). Hessels et al. found the negative predictive value of 90% in their evaluation by PCR (21). In our study, the negative predictive value was higher than in literature. Because MRI lesions were low in patients with low PCA3 score, systemic biopsies were taken in this patient group. Some tumors could have been missed in this patient group. In conclusion, the importance of pre-biopsy MRI evaluation for targeted biopsy is emerging.

No lesion was observed in MRI of 20 of 25 patients with normal PCA3 score. Among these patients, tumor was detected only in one patient. Negative predictive value was calculated 95% (no lesion in multiparametric MRI with low PCA3 scores). Sensitivity was 91.66% and specificity 95%.

Our study revealed that using only PSA score for tumor detection, accuracy rate is 35.9%, but this rate raised to 58.33% by adding PCA3. PCA3 score, along with multiparametric MRI findings, elevated this rate to 91.66%. Likewise, in this study we observed that NPV was calculated as 96% using the PCA3 score (<35). There wasn't any increase in the NPV when we added absence of lesions in the multiparametric MRI. Thus, our data suggest that when patient's PCA3 is low (<35), we can affirm there is no tumor with 96% of accuracy without MRI study.

CONCLUSIONS

In patients with PSA level between 3-10ng/mL and normal DRE, PCA3 score and multipara-

metric MRI seems to provide additional contributions to first biopsy decision for the detection of prostate cancer. When these methods and approaches are combined used, PPV is significantly increased for predicting tumor presence.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Safety and feasibility of radiofrequency ablation for treatment of Bosniak IV renal cysts

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ABSTRACT

Purpose: To describe our initial experience with radiofrequency ablation (RFA) of Bosniak IV renal cysts.
Materials and Methods: From 2010 to 2014, 154 renal tumor cases were treated with percutaneous thermal ablation, of which 10 cases (6.4%) from nine patients were complex renal cysts and were treated with radiofrequency ablation.
Results: All complex cysts were classified as Bosniak IV (four women and five men; mean age: 63.6 yrs, range: 33–83 years). One patient had a single kidney. Lesion size ranged from 1.5 to 4.1cm (mean: 2.5cm) and biopsy was performed on four cysts immediately before the procedure, all of which were malignant (two clear cell and two papillary carcinoma). Mean volume reduction of complex cysts was 25% (range: 10–40%). No patients required retreatment with RFA and no immediate or late complications were observed. The follow-up of Bosniak IV cysts had a median of 27 months (interquartile range [IQR], 23 to 38) and no recurrence or significant loss of renal function were observed.
Conclusions: Mid-term follow-up of the cases in our database suggests that image--guided percutaneous RFA can treat Bosniak IV cysts with very low complication rates and satisfactorily maintain renal function.

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INTRODUCTION

Renal cell carcinoma (RCC) is the third most common malignancy of the genitourinary tract and accounts for approximately 3% of all cancers in adults. The incidence and mortality rates of RCC have increased over the past years (1) and approximately 15% of RCC cases are cystic (2). The incidental diagnosis of renal cysts has become more common as the use of advanced cross--sectional imaging techniques increases, and because some of these cysts are highly suspicious for malignancy, they must be excised based on the Bosniak classification.

The Bosniak classification of renal cysts classifies cysts as either benign or potentially malignant (complex) and is widely used to assist clinical decisions (3). Nephron-sparing approaches

such as partial nephrectomy, tumor enucleation, and percutaneous ablation (e.g., cryoablation, radiofrequency, and microwave ablation) are viable options to treat these tumors while preserving renal function and lowering the risk of cardiovascular events and overall mortality (4).

A retrospective study that compared perioperative, renal functional, and oncologic outcomes of renal cryoablation and partial nephrectomy reported that postoperative glomerular filtration rate (GFR) was 6% lower than preoperative GFR in the percutaneous cryoablation group and 13% lower in the partial nephrectomy group. Additionally, this difference persisted in the multivariate analysis, but cryoablation was associated with an increased recurrence risk (5).

Percutaneous thermal ablation is an efficient and safe procedure for the treatment of small solid renal tumors (6-8), but there are two major drawbacks when treating renal cystic tumors: the possible risk of spreading tumor cells to adjacent tissues and the uncertainty of whether the procedure is effective over the entire lesion. For instance, radiofrequency ablation (RFA), in which alternating electrical current is converted into resistive heat until temperatures rise to cytotoxic levels (50–60°C), has been well documented for the treatment of benign liver and thyroid cystic lesions (9-11).

However, few studies have investigated the use of RFA for the treatment of suspected malignant renal cysts with only short- or medium-term follow-up after RFA (12, 13).

This study describes our experience with RFA of Bosniak IV cysts with an emphasis on its feasibility, safety, and local control.

MATERIALS AND METHODS

After institutional review board approval, we assessed our radiological database and all Bosniak IV cyst cases treated with percutaneous radiofrequency ablation (RFA) were retrospectively analyzed.

Percutaneous RFA procedures were performed in an interventional suite with CT (computer tomography) fluoroscopy capabilities under general endotracheal anesthesia using a Cool-Tip 200-W RF generator (Covidien, Mansfield, Massachusetts, USA) with single (ACT1530/ACT2030) or cluster (ACC1525) 17-gauge needle RF electrode kits.

In four cases, biopsies were conducted immediately before RFA under CT guidance, which was essential for the radiologist to position the needle inside the solid component or the septa of the lesion. An on-site pathologist confirmed that the biopsy had been adequately performed and that a sufficient amount of cells had been collected.

Prior to needle insertion, the point of entry, safe trajectory, and end position of the needle were planned with the aid of CT and the percutaneous electrode was placed inside the tumor with needle progression guided by real-time CT fluoroscopy. RFA energy was applied for 12min. Overlapping sessions were required to encompass the entire volume of the lesion with a safety margin and a CT scan was performed immediately after RFA to assess potential immediate complications.

Patients were evaluated with magnetic resonance imaging (MRI) or CT three, six, and 12 months after the procedure, and annually thereafter, to identify residual tumor and tumor recurrence. Treatment success was based on post-ablation axial imaging: increased attenuation in non-enhanced CT, reduced ablation zone size, and no enhancement on enhanced CT (<10HU) or MRI (<15% signal increase) were indicative of a successful ablation. Recurrence was defined as postablation enhancement in the ablation zone or enhancement growth on subsequent follow-up imaging.

The Clavien-Dindo classification (14) was used to report and grade the possible immediate or late complications. The immediate complications were evaluated in the CT images performed immediately after the procedure in all patients, and the late complications were analyzed by CT scan or MRI performed in the first 6 months after the ablation.

RESULTS

From 2010 to 2014, percutaneous thermal ablation was performed in 154 renal tumor cases. Of these, 10 renal cysts (6.4%) from nine patients were Bosniak IV (four women and five men; mean age: 63.6 yrs, range: 33–83 years)

and were treated with radiofrequency ablation (RFA), and one was from a single kidney patient; other comorbidities are summarized in Table-1.

Lesion size ranged from 1.5 to 4.1cm (mean: 2.5cm) and biopsies were performed on four cysts, all of which were malignant (two clear cell and two papillary carcinomas). The others were treated based on the risk of malignancy of Bosniak IV lesions.

The location of the lesions are summarized in Table-2. Six of them were localized in places with risk of complications due to their proximity (distance <3cm) with other organs such as liver, lung or bowel, and the hydrodissection was needed and then performed. After the procedure, no complications were found.

The follow-up of Bosniak IV renal cysts had a median of 27 months (interquartile range [IQR], 23 to 38).

Table 1 - Patient's age and comorbidities submitted to radiofrequency ablation.

Patient	Age	Gender	Comorbidities	Histology
1	60	Female	none	unknown
2	83	Male	colon cancer	unknown
3	33	Female	none	unknown
4	66	Female	Stroke	Papillary carcinoma
	68	Female	Stroke	unknown
5	64	Female	none	Clear cell carcinoma
6	48	Male	Chronic liver disease	unknown
7	72	Male	Colon cancer	unknown
8	75	Male	none	Papillary carcinoma
9	64	Male	**Single kidney**	Clear cell carcinoma

Table 2 - Characteristics of the Bosniak IV cysts, with location and risk of adjacent organs injury.

Lesion/Size (cm)	Location*	Organ with risk of injury (distance <3cm)	Complications
A (3.0cm)	Exofitic (P/S)	Adrenal and pancreas	0
B (1.8cm)	Central (A/M)	Coletor system	0
C (1.5cm)	Peripheral not exofitic (A/S)	Liver	0
D (2.0cm)	Exofitic (AL/I)	Colon	0
E (4.1cm)	Exofitic (L/M)	Liver	0
F (3.0cm)	Exofitic (L/M)	Colon	0
G (2.8cm)	Exofitic (L/MI)	-	0
H (1.9cm)	Exofitic (P/S)	-	0
I (3.3cm)	Exofitic (P/S)	-	0
J (1.8cm)	Exofitic (P/I)	-	0

***P** = posterior; **A** = anterior; **L** = lateral; **S** = superior; **M** = middle; **I** = inferior.

A reduction in tumor size was observed in all Bosniak IV cyst cases immediately after the first RFA session (Figure-1). Mean volume reduction was 25% (range: 10–40%).

The procedure was successful in all cases, with CT revealing no lesion enhancement in the ablation zone immediately after the RFA, indicating that there was no residual tumor. No patients required a second RFA and no immediate or late complications were observed in this cohort.

The creatinine serum levels of each patient before and after the procedure were retrospectively assessed and the estimative of the glomerular filtration rate (GFR) was done using the Modification of Diet in Renal Disease (MDRD) formula. There was an mean variation of 10mL/min (range: 1.3–20.7) of the GFR, and no patients displayed a decrease in renal function.

Patients were evaluated with cross-sectional exams (contrast-enhanced CT or MRI) after the procedure, and no recurrence was found (Figure-2).

DISCUSSION

This study describes our experience with percutaneous RFA of Bosniak IV renal cysts with an emphasis on its feasibility, safety, and local control. We showed that the procedure was effective for the treatment of Bosniak IV renal cysts.

Figure 1 – (a-d) Tomographic images of radiofrequency ablation of Bosniak IV cystic lesion. CT without intravenous contrast (a) and post contrast (b) shows the hypoattenuation lesion in the left kidney and the exophytic cortical cyst in the upper third of the left kidney, containing thick internal septa that enhances after contrast. Non-enhanced CT (c) shows the positioning of the cluster needle in the axial plane. Enhanced-CT (d) immediately after the ablation shows the volumetric reduction of the lesion and the margins obtained after contrast injection, confirming proper treatment during the procedure.

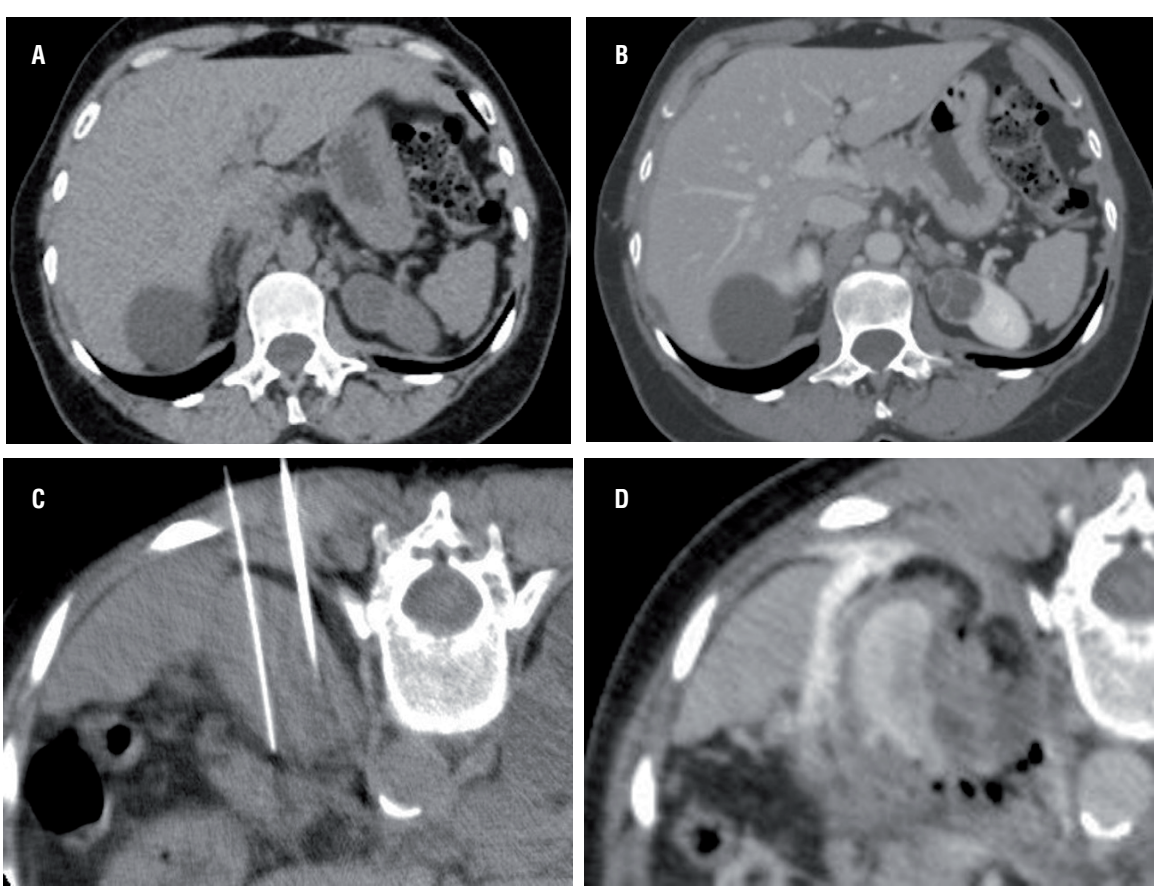
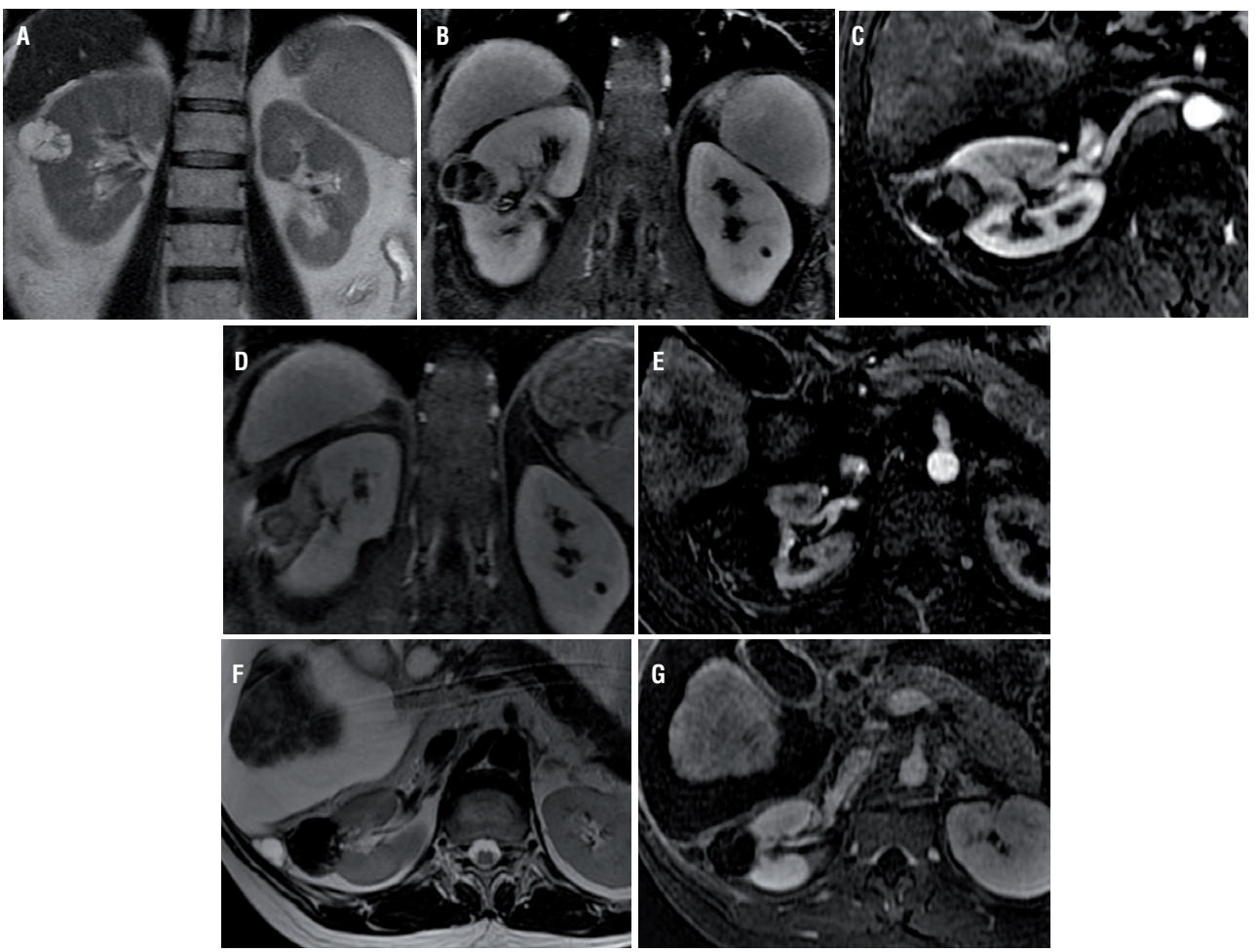


Figure 2 – (a-g) 48-years old man with a Bosniak IV lesion. Coronal T2-weighted (a), Coronal T1-weighted gradient echo axial MRI sequences with fat suppression (b) and coronal subtraction image (postcontrast arterial phase data - precontrast data) (c) show a cystic renal mass with thickened enhancing septa and a small solid component. Coronal T1-weighted gradient echo axial MRI sequences with fat suppression (d) performed immediately after the procedure show complete ablation of cystic lesion and no measurable enhancement within ablation zone. Axial subtraction image (postcontrast arterial phase data - precontrast data) (e) three months after the procedure show no enhancement and no recurrent of the neoplasm. Axial T2-weighted (f) and axial subtraction image (postcontrast arterial phase data - precontrast data) (g) 3 years after the procedure show ablation changes in the right kidney, without residual enhancement to suggest recurrent neoplasm.



The success rate of RFA was 100%, which was confirmed by a lack of enhancement on CT and MRI scans of the treated areas within the median follow-up time of 27 months (interquartile range [IQR], 23 to 38). Our findings are in line with previous case reports and preliminary studies (12, 13, 15).

Even though Bosniak III and IV complex renal cysts are uncommon renal tumors, they are an important subgroup due to their risk of malignancy, which ranges from 16–100% and 90–100%, respectively (16). The current standard of care for both Bosniak III and IV lesions is surgical treatment. Because of their indolent growth and overall early detection, they have a better prognosis than solid tumors, and thus a more conservative approach to their treatment has been advocated. Even though ablative therapies for the treatment

of small solid renal tumors are accepted options, cystic renal lesion ablation has been restricted to a few case series (12, 13).

The ablative treatment of Bosniak IV cysts is a minimally-invasive procedure that has not been yet associated with major complications to the best of our knowledge, and it leads to preservation of the renal parenchyma.

Among 10 Bosniak IV cysts of our study, four were histologically proven to be renal cell carcinomas (two clear cell subtypes and two papillary subtypes). Some theoretical questions about the treatment of Bosniak IV renal cysts still remain unanswered, especially the concern about neoplastic implants and cyst rupture caused by biopsies and therapeutic punctures. Anecdotal cases of implants related to biopsy of solid lesions have been reported, but there are no studies to date of cystic lesion implants after percutaneous biopsies or RFA treatments. We biopsied four lesions that proved to be malignant and found no neoplastic implants at follow-up. Felker et al. (15) also reported no neoplastic implants related to biopsy or treatment of 23 cystic neoplastic lesions during a 24-month follow-up period.

There were no procedure-related complications, showing that percutaneous RFA is a safe method, especially in selected cases. In our sample, almost all cases were classified as clinical stage T1a tumors, and most were predominantly exophytic, with a safe distance to the collector system and in polar location. Although there is no adequate information on the selection criteria for RFA mentioned above, previous studies have not reported clinically relevant complications either (12, 13, 15).

All biopsies and RFA procedures in our study were done under CT fluoroscopy. We believe that CT provides good visual control of the procedure. Additionally, needle trajectory was planned and controlled with Multiplan views. The radiologist was able to identify and prevent possible complications by planning the best access and performing hydrodisplacement of bowel or other structures when those were adjacent to the renal lesion. This supports the use of CT guidance over other imaging modalities such as ultrasound.

Needle positioning was CT-guided, which enabled three-dimensional visualization of the lesion. Thus, the interventional radiologist was able to plan the needle trajectory, detect possible injuries in adjacent structures, and prevent complications such as lesions in intestinal or vascular loops. Because no acute or late complications were observed in our sample, the success rate of RFA can be partly attributed to CT-planning.

To our knowledge, only three retrospective series evaluated percutaneous RFA for the treatment of renal cysts, and only one included just biopsy-proven malignant cystic disease (Table-3) (12, 13, 15).

The procedure was successful in all cases, with no lesion enhancement in the ablation zone on CT immediately after percutaneous RFA and on follow-up CT or MR exams, indicating that there was no residual tumor after the median of 27-months follow-up.

In our study, we found a shrink of tumor size in all Bosniak IV cyst cases with the mean volume reduction of approximately 25% in all lesions immediately after the RFA procedure.

Table 3 - RFA of cystic renal lesions to date.

Study	Patients	Tumors	Biopsy	Size (cm)	Follow-up (months)	Efficacy	Major Complications
Park et al. 2008 (13)	9	14	0	2.5	8	100%	0
Allen et al. 2013 (12)	38	40	90% (60% cancer)	2.3	32	100%	1 (pulmonary edema)
Felker et al. 2013 (15)	16	23	100%	3.1	24	91%	0
Current, 2014	9	10	40% (100% cancer)	2.5	29	100%	0

Because there was no recurrence during the follow-up period, the mean volume reduction could be used as an intraoperative measure of treatment success. Nevertheless, a larger sample and more studies are needed to support this finding.

Although the "heat sink effect" caused by undesired RF energy dispersion is less frequent in small cystic lesions and more evident in large, highly vascularized tissues, it represents one of the most important limitations of the RFA technique. In our sample, we treated small lesions (diameter: 1.5–4.1cm; mean: 2.5cm) and our results were not affected by this limitation. Interestingly, microwave ablation (MWA) may minimize thermal dispersion and reduce the "heat sink effect", resulting in a positive outcome in larger cystic lesions, but only a single study to date has investigated the efficacy of MWA in only seven cystic renal lesions, which was not enough to adequately assess the efficacy of MWA (16).

The relatively small sample size, intermediate follow-up time and selection biases due to the retrospective series are limitations of our study. However, even though more comprehensive studies are needed to support the effectiveness of RFA for the treatment of Bosniak IV renal lesions, its efficacy and safety in our study were similar to those reported in the few studies available.

Another limitation of our study was the percentage of lesions submitted to biopsy prior to the RFA (40%). However, the technical difficulties of performing percutaneous biopsies of predominantly cystic lesions should be considered, because some lesions have a small solid component where the needle should be positioned for collecting material for pathological analysis. Moreover, even if no malignant cells are found in the biopsy, Bosniak IV renal cysts still can be excised based on the presumed risk of malignancy based on the Bosniak classification (17), and based on the fact that there are still few studies that demonstrate the negative predictive value of the biopsy of Bosniak IV renal cysts (18). Additionally, if the lesion is not excised after biopsy, follow-up is compromised because of parenchymal distortion and changes in cyst density and signal on CT and MRI, respectively. The other Bosniak IV cysts were not biopsied and therapeutic indication was supported by presumed malignancy based on the Bosniak classification.

In conclusion, despite the limitations of our study, the results suggest that image-guided percutaneous RFA can properly treat Bosniak IV renal cysts with very low complication rates and satisfactorily maintain renal function.

CONFLICT OF INTEREST

None declared.

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Prostate MRI: a national survey of Urologist's attitudes and perceptions

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ABSTRACT

Introduction: The use of multi-parametric (MP) MRI to diagnose prostate cancer has been the subject of intense research, with many studies showing positive results. The purpose of our study is to better understand the accessibility, role, and perceived accuracy of MP-MRI in practice by surveying practicing urologists.

Materials and Methods: Surveys were sent to 7,400 practicing American Urological Association member physicians with a current email address. The survey asked demographic information and addressed access, accuracy, cost, and role of prostate MRI in clinical practice.

Results: Our survey elicited 276 responses. Respondents felt that limited access and prohibitive cost of MP-MRI limits its use, 72% and 59% respectively. Academic urologists ordered more MP-MRI studies per year than those in private practice (43.3% vs. 21.1%; p<0.001). Urologists who performed more than 30 prostatectomies a year were more likely to feel that an MP-MRI would change their surgical approach (37.5% vs. 19.6%, p-value=0.002). Only 25% of respondents agreed or strongly agreed that MP-MRI should be used in active surveillance. For patients with negative biopsies and elevated PSA, 39% reported MP-MRI to be very useful.

Conclusions: Our study found that MP-MRI use is most prominent among practitioners who are oncology fellowship-trained, practice at academic centers, and perform more than 30 prostatectomies per year. Limited access and prohibitive cost of MP-MRI may limit its utility in practice. Additionally, study participants perceive a lack of accuracy of MP-MRI, which is contrary to the recent literature.

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INTRODUCTION

Prostate cancer is the second leading cause of cancer-related death in men, claiming almost 30.000 lives in 2013 (1). It is a heterogeneous disease with differences in biological aggressiveness, and the natural history of prostate cancer is highly variable from patient to patient. It has been shown that over half of those diagnosed with prostate cancer will die of other causes (2). In light of the United Service Preventative Task Force recommendation against the use of prostate specific antigen (PSA) for cancer screening, as well as several studies demonstrating no survival advantage with aggressive treatment, there has been a growing interest in the use of active surveillance in prostate cancer management (3). As the treatment algorithm for prostate cancer continues to

evolve, there has been increased emphasis on the use of multi-parametric magnetic resonance imaging (MP-MRI) to aid in the diagnosis and management of prostate cancer, especially within the active surveillance population.

MRI provides high-resolution anatomic detail via T2 weighted images and allows for functional assessment of the prostate. Dynamic contrast enhanced imaging measures the vascularity of tumors, and the vascular nature of prostate cancer shows both increased uptake and washout of gadolinium contrast when given intravenously (4). Diffusion weighted imagining measures the diffusion of water through tissue, causing prostate cancer to exhibits reduced diffusion compared to normal prostate tissue due to its densely packed cells.

Despite demonstration of the benefit within the literature, MP-MRI has been slow to gain widespread acceptance (5). The practice patterns, experience, and attitudes of American urologists regarding the use of MRI in the management of prostate cancer have not been previously examined. The goal of our study is to characterize the opinions amongst current American urologists concerning the role of MP-MRI in prostate cancer management.

MATERIALS AND METHODS

This study was reviewed and approved by the Institution Review Board at Washington University. A web-based survey consisting of twenty questions was developed and sent electronically to 7,400 current American Urological Association (AUA) members. All survey participants were practicing urologic physicians in the United States had current email addresses as of September 01, 2013. An initial email with a brief explanation of the study and an invitation to complete the survey was sent on September 12, 2013, and a reminder email for those who had yet to complete the survey was sent on September 25, 2013. Respondents were not required to answer all questions for submission of their survey. Each email was embedded with a personalized link to ensure that each respondent could only submit a single survey, and all responses were confidential.

Each survey was de-identified and responses were collected using our institutional RedCap electronic data-capturing tool (6). Survey questions addressing practitioner demographics included: how many years since finishing residency, post-residency training, proximity to nearest tertiary care center, structure of medical practice, practice setting, and number of prostatectomies performed yearly. Questions addressing practitioner opinion of MP-MRI included: evidence in literature supporting MP-MRI, reliability of the results of MP-MRI, and accuracy of MP-MRI measured by correlation between MP-MRI results and positive biopsies/final pathology after prostatectomy.

Categorical responses to survey questions were assessed using Chi-square test of independence analysis and Fisher's exact test. Continuous variables were compared with the Student's t-test, and statistical analyses were two-sided using a significance of 0.05.

RESULTS

Our survey elicited 276 (3.8%) responses from practicing AUA member physicians. Unfortunately, not all participants answered every survey question. The demographics that were obtained from the survey question can be found in Table-1. Overall, a majority of survey participants reported ordering 1-10 MP-MRIs a year to evaluate prostate cancer. Forty-two percent of respondents agreed that there was adequate evidence within the literature supporting the use of MP-MRI in localized prostate cancer (114/272), 31% disagreed (84/272), and 27% could not decide (74/272). A summary of survey responses can be found in Table-2.

Access

When respondents were stratified by their type of practice, there was a statistically significant increase in the reported number of MP-MRIs ordered by physicians who practice in an academic setting compared those who do not (>11 MP-MRIs/year, 43% versus 21% p=0.0001). Eighty-nine percent of respondents endorsed having local access (less than 1hr) to facilities with MP-MRI capabilities (245/276). However, when all respondents were asked if they felt that access to qualified imaging centers and radiologists limited their use of MP-MRI, 72% of respondents agreed or

Table 1 - Survey Demographics.

How many years since you finished residency?	**Total = 276**
0-5 years	54 (19.5%)
6-10 years	39 (14.1%)
11-20 years	77 (27.8%)
21-30 years	77 (27.8%)
Over 31 years	29 (10.5%)
What training, if any, did you complete after residency?	**Total = 274**
None	159 (58%)
Minimal Invasive/Endourology Fellowship	21 (7.7%)
Oncology Fellowship	66 (24.1%)
Reconstructive Fellowship	9 (3.3%)
Other	19 (6.9%)
Approximately how close is the nearest tertiary care center to your practice?	**Total = 276**
I primarily practice at a tertiary care center	134 (48.6%)
Less than 1 hour	95 (34.4%)
Less than 2 hours	32 (11.6%)
Less than 3 hours	5 (1.8%)
More than 3 hours	10 (3.6%)
What type of practice do you work in primarily?	**Total = 276**
Private Group or Solo	164 (59.2%)
Academic	91 (32.9%)
Government (VA, Military service, National Health Service)	7 (2.5%)
Other	15 (5.4%)
What type of setting do you practice in?	**Total = 276**
Urban	151 (54.7%)
Suburban	103 (37.2%)
Rural	22 (8%)
On average, how many prostatectomies do you preform yearly for Prostate cancer?	**Total = 275**
Under 10	105 (38.2%)
30-Oct	85 (30.9%)
30-100	71 (25.8%)
Over 100	14 (5.1%)

strongly agreed (192/268). When asked if the cost of MP-MRI was prohibitive for its use, 59% of all respondents agreed or strongly agreed (156/263).

Role of MRI

Overall, 34% of respondents reported using MP-MRI targeted biopsies, either ultrasound fusion or cognitive techniques (91/270). When these responses were stratified by fellowship training, we found that respondents with oncology fellowship training performed significantly more MP--MRI targeted biopsies compared to those who did not (44.6% versus 30.1%, p=0.032). In our survey, 38% of all respondents found MP-MRI to be

Table 2 - Survey Responses.

There is adequate evidence supporting the use of MP-MRI to manage localized prostate cancer.	Total = 272
Agree	114 (42%)
Disagree	84 (31%)
Can not decide	74 (27%)
Access to MP-MRI limits my ability to use it in my practice.	Total = 268
Agree/Strongly agree	192 (72%)
Disagree/Strongly disagree	76 (28%)
The high cost of MP-MRI is prohibitive for its use.	Total = 263
Agree/Strongly agree	156 (59%)
Disagree/Strongly disagree	107 (41%)
MR-MPI guided biopsies are utilized in my practice.	Total = 270
Agree	91 (34%)
Disagree	179 (66%)
MP-MRI is helpful in patients with elevated PSA/abnormal prostate exam prior to biopsy.	Total = 270
Agree/Strongly agree	102 (38%)
Disagree/Strongly disagree	168 (62%)
MP-MRI is helpful in patients with negative biopsy and abnormal PSA/prostate exam.	Total = 225
Agree/Strongly agree	88 (39%)
Disagree/Strongly disagree	137 (61%)
MP-MRI is useful prior to definitive treatment with prostatectomy or radiation.	Total = 225
Agree/Strongly agree	32 (14%)
Disagree/Strongly disagree	193 (86%)
MP-MRI changes my treatment approach of intermediate/high risk prostate cancer.	Total = 253
Sometimes/often	66 (26%)
Rarely/never	187 (74%)
MP-MRI should be used in all patients for active surveillance.	Total = 276
Agree/Strongly agree	69 (25%)
Disagree/Strongly disagree	207 (75%)
How often do MP-MRI guided biopsies turn out to be positive?	Total = 233
Often/Very often	65 (28%)
Sometimes	77 (33%)
Rarely/Never	91 (39%)
How closely do MP-MRI results correlate with final pathology after prostatectomy?	Total = 233
Strong correlation	26 (11%)
Moderate correlation	145 (62%)
Weak correlation	46 (20%)
No correlation	16 (7%)

helpful in a patient with an elevated PSA or abnormal prostate exam prior to biopsy (102/270). When these responses where stratified by fellowship training, we found 48.2% of respondents with oncology training found MP-MRI somewhat or very helpful in this situation compared to 33.5% of respondents without oncology training. This difference was found to be trending towards significance with a p value of 0.057.

In patients with a negative biopsy and an elevated PSA/abnormal prostate exam, 39% of all respondents reported MP-MRI to be very helpful (88/225). Fourteen percent of respondents reported MP-MRI to be very useful when utilized prior to definitive treatment with either prostatectomy or radiation (32/225). In patients with intermediate or high risk prostate cancer who appear to be candidates for a nerve sparing prostatectomy, 26% of respondents report that getting an MP-MRI will sometimes or often change their surgical approach to a non-nerve sparing prostatectomy (66/253). When stratified based on average number of prostatectomies performed per year (<30 versus >30); we found that surgeons who perform more than 30 prostatectomies per year are more likely to change their surgical approach based on MP-MRI than those who perform less than 30/year (37% versus 20%, p=0.002).

Regarding the use of MP-MRI in active surveillance, 25% of all respondents agreed that it should be used in all patients (69/276). When asked if MP-MRI should be used to evaluate patients for active surveillance, 30.7% of respondents who were 10 years or less out of residency reported MP-MRI to be very helpful compared to 24.8% of respondents 11 years or more out of residency (30/98 versus 45/183).

Accuracy

When asked approximately what proportion of patients with positive MP-MRI findings who subsequently undergo MP-MRI targeted prostate biopsies are found to have biopsies positive for prostate cancer, 28% reported positive biopsies "often" or "very often" (65/233), 33% reported positive biopsies "sometimes" (77/233), and 39% reported positive biopsies "rarely" or "never" (91/233). Similarly, when asked about how closely respondents find MP-MRI results to correlate with final pathology after prostatectomy, 11% reported strong correlation (26/233), 62% reported moderate correlation (145/233), 20% reported weak correlation (46/233), and 7% reported no correlation (16/233).

DISCUSSION

The use of multi-parametric (MP-MRI) to diagnose prostate cancer has been the subject of intense research, with many studies showing positive results. To our knowledge, no other studies have attempted to better understand the accessibility, role, and perceived accuracy of MP-MRI in practice by surveying practicing urologists. We found practicing in an academic center to be strongly associated with increased use of MP-MRI (p=0.0001), which is likely due to a combination of increased access, familiarly with recent literature, and interdisciplinary efforts within academic institutions.

Access

There is very little within the literature evaluating practitioner access to MP-MRI, particularly outside academic centers. While 89% of our respondents reported to be within one hour of a facility with MP-MRI capabilities, 72% still felt that their use of MP-MRI was limited by lack of access. While the exact reasons for this discrepancy could not be gleaned from the survey data, causes may relate to perceived lack of quality in the MP-MRI provided, difficulty with patient scheduling, or lack of strong multi-disciplinary relationship with radiologists.

Another possible reason that MP-MRI has been slow to gain wide spread popularity is that many (59% within our study) feel that the cost of these studies is prohibitive, and that issues surrounding insurance reimbursement negate the perceived value of the study. As the presence of MP-MRI becomes stronger in national and international management guidelines, insurance approval and payment for these studies may become more streamlined (7-9). Likewise, as the guidelines for active surveillance continue to evolve, MP--MRI may be incorporated into these algorithms,

which will support this study as a reimbursable indication.

Role

The use of MP-MRI in the management of prostate cancer has gained a lot of attention in recent literature; however, the appropriate use in clinical practice has not yet been established. Despite the growing body of evidence supporting the use of MP-MRI guided biopsies in lieu of saturation biopsies, many of our respondents did not echo this sediment. We found that only 42% of respondents felt that the current literature provided evidence for some role for MP-MRI in localized prostate cancer patients, while 31% disagreed and 27% could not decide. These results further prove the level of controversy surrounding MP-MRI.

MP-MRI can be used to provide guidance for tissue sampling either directly, via a cognitive approach, or through fusion software. MP--MRI guided biopsies have been shown to upgrade Gleason grade and detect otherwise undiagnosed anterior gland tumors in a significant number of patients (10-13). Despite this, only 34% of respondents reported using MP-MRI guided biopsies in their clinical practice. However, level of training was found to be associated with an increased use of MP-MRI guided biopsies. Completion of an oncology fellowship resulted in statistically significant increases in usage (p=0.032), and completion of any urologic fellowship also trended towards a significant increase (p=0.057). While this may be in part due to the fact that many of these urologists practice at academic centers, these results suggest that further training and education on MP-MRI guided biopsies may be useful to guide practice.

In intermediate or high-risk prostate cancer patients who appear to be candidates for a nerve sparing prostatectomy, MP-MRI can be helpful for surgical planning (14-15). Of our respondents, 38% found MP-MRI to be helpful when used in this capacity. We also found those urologists who reported doing more than 30 prostatectomies a year used MP-MRI for surgical or treatment planning at a higher frequency compared to their colleagues (p=0.002). It is possible that urologists with more operative experience may have increased expertise and familiarity with MP-MRI. It is also possible that they handle more complex cases, requiring the use of additional imaging modalities.

It has also been proposed to incorporate MP-MRI into active surveillance protocols (16-17). While the majority of current evidence suggests a benefit to its incorporation, there have been some studies that failed to demonstrate an improvement in the stratification of patients (18-19). In our study, only 25% of all respondents agreed or strongly agreed that MP-MRI should be used in all patients on active surveillance. In patients with a previous negative biopsy and a rising PSA or abnormal DRE there are several studies that have found MP-MRI to be helpful and this has been incorporated in to many current guidelines (7-9, 20-21). Despite this, only 39% of respondents in our study agreed that MP-MRI was helpful or very helpful for these patients. Reasons for this disconnect may be related to the dissemination of this information to practicing urologists or perceived poor performance of MRI in practice.

Accuracy

While several studies have shown the high accuracy of MP-MRI, respondents seemed to largely express skepticism (13, 22-23). There were a large proportion of respondents who felt that MP-MRI was relatively inaccurate, with moderate--poor correlation with pathology and little positive impact on patient care. While the reason for these opinions was not elucidated in our study, this negative impression of MP-MRI may reflect differences in local radiologist and pathologist ability to interpret and correlate MP-MRI findings. It is well accepted that achieving accurate radiology-pathology correlation with MP-MRI findings is challenging, and it has been suggested that standardization of protocols is the best way to overcome these challenges (24-25). The European Society for Urogenital Radiology has developed guidelines to standardize reporting and acquisition of prostate MRIs, named the Prostate Imaging Reporting and Diagnostic System (PI-RADS) (8). Unfortunately, this system has not been universally adopted in the United States. Further standardization may help to ensure that the use of MP-MRI in the

community mirrors the same accuracy and provides the same patient benefits as those reported in the literature. As urologists are able to master this learning curve, one would expect accuracy to improve.

There are several limitations to our study. The response rate of only 3.8% is clearly less than ideal, and it would have been preferable if all respondents had answered every survey question. Never the less, with 276 respondents exhibiting a wide range of demographics, we feel that the responses provide an adequate sample size. The survey was designed to provide data that could be easily analyzed, yet multiple choice answers carry the risk of being leading. It might be anticipated that the survey would have promoted a bias toward MP-MRI, yet the results indicate otherwise. Further directions for research include a survey administered to a large number of practitioners across different vendor platforms and in various institutional settings. Also, it would be helpful to obtain insight into why practitioners chose their various answers, would could be accomplished with a more in-depth amended to include the option for free response.

CONCLUSION

Prostate MRI has been shown within the literature to be a highly useful diagnostic tool. However, our study indicates a relatively low level of support for the use of MP-MRI in clinical practice. This indicates the need for improved education, access, and standardization of treatment recommendations to address the challenges of implementing this new technology into practice. Further research is needed to confirm the favorable results of MP-MRI across different vendor platforms, in various institutional settings, and using available radiologic-pathologic correlation.

ABBREVIATIONS

PSA = Prostate Specific Antigen
MP-MRI = multi-parametric magnetic resonance imaging
AUA = American Urological Association

CONFLICT OF INTEREST

None declared.

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Effect of ejaculation on Serum Prostate-Specific Antigen concentration

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ABSTRACT

Abstract: Purpose:To evaluate the effect of ejaculation on serum prostate-specific antigen (PSA) concentrations in patients with lower urinary tract symptom (LUTS).
Materials and Methods: Our study includes 98 men (62 study and 36 control). After three days of sexual abstinence, blood samples were drawn for the measurement of baseline PSA levels. Then the patients were told to ejaculate. One, 5, 24 and 72 hours after ejaculation, serum total (tPSA), free (fPSA) and complexed PSA (cPSA) levels were measured. Serum PSA sampling was performed at the same intervals in the control group without ejaculation.
Results: The mean age in study and control groups patients were 59.03±0.99 years, 61.14±1.30 years, respectively. In the study group, changes in tPSA and fPSA levels after ejaculation were found statistically significant while changes in cPSA levels and f/tPSA ratios were not significant (p=0.016, p=0.0003, p=0.176, and p=0.173, respectively). Baseline values showed significant differences with 1st and 5th hours. No significant changes in tPSA, fPSA, cPSA levels and f/tPSA values were found in control group (p=0.223, p=0.224, p=0.444, and p=0.718, respectively). The changes in the number of patients exceeding the cutoff values after ejaculation were not statistically significant for tPSA, cPSA, and f/tPSA ratio.
Conclusions: In this study, ejaculation increased tPSA and fPSA concentrations but it didn't have a significant effect on serum cPSA levels and f/tPSA ratios. However, recent ejaculation may affect the biopsy indication at least near cut off PSA values. Further studies are needed to explain the mechanisms of alterations in the concentration of PSA.

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INTRODUCTION

Prostate-specific antigen (PSA) is a serine protease produced by epithelial cells of the prostate and it is involved in the liquefaction of seminal fluid. PSA has been widely used as a tumor marker in the screening and follow-up of prostate cancer (1). In serum, PSA exists in different molecular forms, being predominantly complexed with a1-antichymotrypsin (ACT) and a2-macroglobulin (A2M). The form of PSA which forms complexes with A2M remains undetectable because of the nature of the macroglobulin molecule. The major form which is bound to ACT is known as complexed PSA (cPSA) and the smaller unbound portion as free PSA (fPSA) cPSA and fPSA represent the main fraction of total PSA (tPSA) (2) cPSA is the dominant form in prostate cancer, whereas fPSA represents a bigger fraction in patients with benign prostatic hyperplasia.

The tPSA assay has low specificity for prostate cancer detection. Several approaches, such as those employing PSA density, PSA velocity, age-specific reference ranges, fPSA: tPSA ratio and cPSA, have been introduced to improve the diagnostic efficiency of serum PSA measurements. Similar results are obtained with cPSA compared to the fPSA: tPSA ratio, but the former process measures a single analyse instead of two, which is an economic advantage.

Since serum PSA measurement plays such a crucial role in the workup and management of prostate cancer, any urologic intervention that can cause PSA elevation has to be identified. It has been well documented that various diagnostic and therapeutic procedures causing elevations of serum PSA levels have been documented (3, 4). Also several studies have looked at the effect of ejaculation on the serum tPSA, and fPSA levels (5-16). However, no data have been available on the effect of ejaculation on the serum cPSA levels.

To examine this issue further, we conducted a prospective clinical study in order to evaluate the effects of ejaculation on serum PSA concentrations and possible contribution on clinical decision in patients with lower urinary tract symptom (LUTS).

MATERIALS AND METHODS

Between June 2012 and May 2014, 140 male patients over 45 years of age who presented to our outpatient clinic for the first time with LUTS were screened. The International Prostate Symptom Score (IPSS), digital rectal examination, prostate volume and post void residual urine (PVR) volume measurement using suprapubic ultrasonography, uroflowmetry, urinalysis and culture were performed in all patients. Patients with a history of prostatic surgery, prostatic needle biopsy, prostate cancer, and those taking alpha-reductase inhibitors were excluded from the study. Patients with urethral catheters, urethral stricture, acute urinary tract infection, or urinary retention were also not included. A total of 42 (30%) patients (entry criteria not met by 25 patients, patient decision in 12 patients, and physician decision in 5 patients) were excluded from the study.

Remaining 98 sexually active heterosexual men (mean age 60.58±0.85 years) were included in this study. Sixty two of them masturbated and constituted the study group and 36 men who didn't accept masturbation were taken as the control group. This study was approved by the Hospital Ethics Committee (Approval no. 15.05.2012-06). Written informed consent was obtained from all participants before enrolment.

All participating patients were instructed to abstain from ejaculation for 3 days preceding blood sampling. Blood samples were drawn by venipuncture from all men at 9-10a.m. for measurement of the baseline PSA values. Then sixty two men in the study group masturbated. The presence of semen in a specimen container confirmed the ejaculatory event. Controls experienced no ejaculation during the study period. Repeated blood samples were taken from all men at 1^{st}, 5^{th}, 24^{th}, and 72^{th} hours after ejaculation. There was no further ejaculation during this period.

All serum samples were separated within 2 hours for analysis of the PSA forms and stored at -20°C according to the manufacturer's recommendations. All measurements were held in one run to exclude any between-run variations. Levels of tPSA and fPSA were measured on Immulite 2000 (Siemens, USA) and cPSA on ADVIA--Centaur (Bayer Diagnostics, Germany) analysers by chemiluminescense technology. Analytical coefficient of variation (CV) for tPSA, fPSA, and cPSA assays were 2.59%, 3.26%, and 3.0% respectively. Cut-off values for tPSA, cPSA and the fPSA: tPSA ratios were defined as ≤2.5ng/mL, ≤2.3ng/mL, and ≥0.25, respectively (17-19). Change in PSA values before and after ejaculation was given as 'percentage of change' (Δ%) (Difference between timely measurement with basal level/basal level x 100).

Data are presented as mean±standard error of mean (SEM). Statistical calculations were performed using the paired and unpaired t-tests, ANOVA, Tukey post-test analysis, McNemar's tests, and Pearson correlation analysis using Prizm 5.0 (GraphPad Software, USA). $p<0.05$ was considered significant.

RESULTS

The mean age of study and control group were 59.03±0.99 years and 61.14±1.30 years, respectively (p=0.203). The mean±SEM values for patient age, IPSS, prostate volume, maximal urine flow rate (Qmax), PVR, and baseline PSA forms are presented in Table-1. No statistically significant differences were found for any of the parameters between two groups (Table-1).

The mean values of all PSA forms at baseline (zero), 1st, 5th, 24th and 72th hours' time points of study and control groups are presented in Figure-1. In study group, comparing to baseline levels, tPSA, fPSA, and cPSA concentrations seemed to increase progressively beginning from the first hour, changes exceeding the analytical CV's of the tests, and turn to baseline levels after 24th hour. This increase of tPSA and fPSA levels were also statistically significant (p=0.016, p=0.0003, respectively), but of cPSA was not (p=0.176). In post-test analysis, tPSA and fPSA, on both 1st and 5thhours values showed statistically significant differences from baseline values (Figure-1).

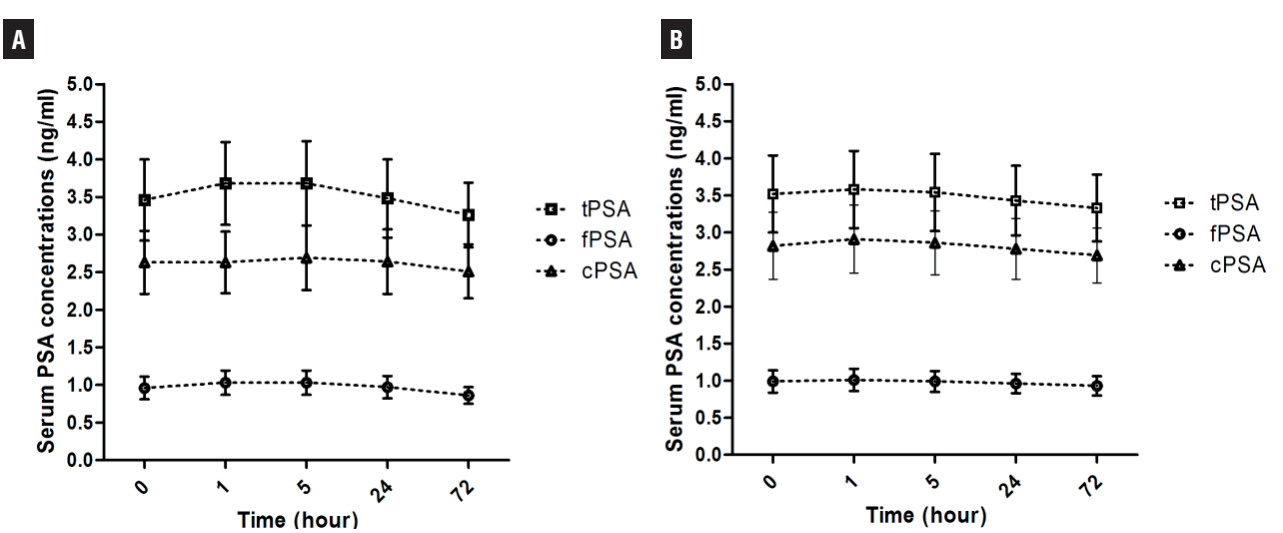
In control group, comparing to baseline levels tPSA, fPSA, and cPSA seemed to increase during

Table 1 - Baseline characteristics of the patients.

Variable	Study group (n= 62)	Control group (n=36)	p*
Age (years)	59.03±0.99	61.14±1.30	0.203
IPSS	12.46±0.97	14.11±1.06	0.267
PV (mL)	54.40±3.76	60.06±5.65	0.388
Qmax (mL/s)	14.80±0.58	13.23±0.89	0.122
PVR (mL)	33.79±5.68	40.56±6.82	0.453
tPSA (ng/mL)	3.46±0.54	3.52±0.52	0.937
fPSA (ng/mL)	0.96±0.15	0.99±0.15	0.908
fPSA/tPSA ratio	0.29±0.01	0.28±0.00	0.538
cPSA (ng/mL)	2.63±0.42	2.82±0.45	0.775

(Mean ± SEM) *Unpaired t test. (**IPSS =** International Prostate Symptom Score; **PV =** prostate volume; **Qmax** = peak flow rate; **PVR** = postvoid residual urine volume; **tPSA** = total prostate-specific antigen; **fPSA** = free PSA; **cPSA** = complexed PSA).

Figure 1 - The mean values of PSA forms at baseline (zero), 1st, 5th, 24th and 72th hours' time points of study (A) and control (B) groups. (Mean±SEM) (tPSA=total prostate-specific antigen; fPSA=free PSA; cPSA=complexed PSA).



the first hours and all PSA forms turned to basal levels after the 5th hour. But the magnitude of these changes was within the analytical CV's of tests. Hence none of them were statistically significant (p=0.223, p=0.224, and p=0.444, respectively).

When study and control groups were compared, a statistically significant difference was detected between Δ% 1st hour and Δ% 5th hour values of total and free PSA (p<0.05). However, there weren't any significant differences between Δ% 24th hour and Δ% 72th hour values (p>0.05). Δ% cPSA values didn't differ significantly from each other at any time points (p>0.05) (Table-2).

The number of patients exceeding the cut-off points of tPSA, f/tPSA ratio, and cPSA before and after ejaculation is shown in Table-3. In the study and control groups, the changes in the number of patients exceeding the cut-off values after ejaculation were not statistically significant for tPSA, cPSA, and f/tPSA ratio (Table-3).

In our study, prostate volumes of study group showed significant correlation with Δ% values of 5thhour for both tPSA (p=0.003, r=0.381) and fPSA (p=0.005, r=0.364). Also a significant correlation was detected between baseline PSA levels and % values of 5th hour for both tPSA (p=0.0002, r=0.452) and fPSA (p=0, 0003, r=0.443). We did not detect any correlation between the patient age and Δ% values of total and free PSA.

DISCUSSION

Although PSA is thought to be the best marker for detecting early prostate cancer, its low specificity comprises problem. In order to increase diagnostic efficiency, it's important to know and avoid the conditions causing PSA elevations other than prostate cancer.

Ejaculation has been claimed to be one of the factors which might increase PSA values, and its effect was evaluated in some studies (5-16), but recent studies are lacking. Also, majority of these studies examined the effect of ejaculation on serum tPSA. To our knowledge, there is only one published human study about fPSA, and no study about cPSA levels. In this study about fPSA, Herschman et al. found increases in fPSA after ejaculation (12). Our study confirms their finding.

These studies investigating the effect of ejaculation on total and fPSA levels, with different conclusions, are summarized in Table-4. Researchers reported conflicting data showing increased (10-12, 16), unchanged (5, 7-9, 13-15), or decreased (6) levels of tPSA after ejaculation. However, in studies which reported PSA decreased or unchanged, sample collection time intervals after ejaculation is too long for detection of early PSA elevations we observed during first hours. Thus these studies seem to miss the detection of

Table 2 - The mean %Δ PSA values for study and control groups.

	%Δ1st hour	%Δ5th hour	%Δ24th hour	%Δ 72th hour
Study group tPSA	10.52±1.64	7.86±1.77	1.53±1.66	1.49±1.76
Control group tPSA	1.69±1.08	-0.19±1.21	2.00±5.82	-3.00±2.66
p*	0.0002	0.0018	0.9238	0.1469
Study group fPSA	9.91±3.00	8.82±2.01	1.12±1.63	-4.06±1.71
Control group fPSA	1.25±1.05	-0.14±1.16	1.44±5.74	-3.22±2.64
p*	0.0338	0.0018	0.9483	0.7798
Study group cPSA	4.26±2.08	4.68±1.77	1.72±2.22	2.84±2.50
Control group cPSA	2.57±2.24	1.54±2.47	0.47±2.59	-0.91±3.17
p*	0.6000	0.2948	0.7239	0.3601

(Mean ± SEM). (tPSA = total prostate-specific antigen; fPSA = free PSA; cPSA = complexed PSA). *Unpaired t test.

Table 3 - Number of patients exceeding cut off points for tPSA, f/tPSA ratio, and cPSA before and after ejaculation.

	tPSA>2.5 ng/mL		fPSA/tPSA<0.25		cPSA>2.3 ng/mL	
	Study Group (n=62) n (%)	Control Group (n=36) n (%)	Study Group (n=62) n (%)	Control Group (n=36) n (%)	Study Group (n=62) n (%)	Control Group (n=36) n (%)
Before	26 (41.9)	23 (63.9)	15 (24.2)	14 (38.9)	22 (35.5)	17 (42.7)
1. hour	26 (41.9)	23 (63.9)	13 (20.9)	13 (36.1)	22 (35.5)	18 (50.0)
5. hour	27 (43.5)	23 (63.9)	11 (17.7)	14 (38.9)	22 (35.5)	16 (44.4)
24. hour	27 (43.5)	22 (61.1)	10 (16.1)	15 (41.7)	23 (37.1)	17 (42.7)
72. hour	26 (41.9)	23 (63.9)	11 (17.7)	15 (41.7)	23 (37.1)	17 (42.7)
*p	0.480 †/‡/§;1.000 ¶	0.480 †/¶; 0.617 ‡/§	0.617 †/‡; 1.000 §/¶	0.480 †/‡/§/¶	0.480 †/‡/§/¶	0.480 †/‡/§/¶

*McNemar's test; †basal vs. 1hour; ‡basal vs. 5hour; §basal vs. 24hours; ¶ basal vs. 72hours (tPSA=total prostate-specific antigen; fPSA=free PSA; cPSA=complexed PSA)

Table 4 - Summary of previous reports of the effect of ejaculation on the forms of PSA.

Reference	n	PSA	Time of Blood Sampling	Findings
Glenski et al. (5)	30 (study)	Total	Before and 17.5-28.8 hour after ejaculation.	Ejaculation has an insignificant effect on serum PSA values.
Simak et al. (6)	18 (study) 3 (control)	Total	Before and 1, 7 days after ejaculation.	PSA decreased after ejaculation
McAleer et al. (7)	35 (study) 81 (control)	Total	Before and mean 14.6 hour after ejaculation.	Ejaculation has an insignificant effect on serum PSA values.
Kirkali et al. (8)	18 (study)	Total	Before and 5 consecutive days after ejaculation.	Ejaculation has an insignificant effect on serum PSA values.
Netto et al. (9)	40 (study) 10 (control)	Total	Before and 1, 7. days after ejaculation.	Ejaculation has an insignificant effect on serum PSA values.
Tchetgen et al. (10)	64 (study)	Total	Before and 1, 6, 24, 48 hours after ejaculation.	PSA significantly increased after ejaculation up to 48 hours.
Zisman et al. (11)	18 (study) 16 (control)	Total	Before and 1 hour after ejaculation.	PSA significantly increased after ejaculation.
Herschman et al. (12)	20 (study)	Total and free	Before and 1, 6, 24 hours after ejaculation.	Both tPSA and fPSA significantly increased after ejaculation up to24 hours.
Heindreich et al. (13)	100 (study)	Total	Before and 1, 24 hours after ejaculation.	Ejaculation has an insignificant effect on serum PSA values.
Yavasçaoglu et al. (14)	25 (study) 20 (control)	Total	Before and 1, 5 days after ejaculation.	Ejaculation has an insignificant effect on serum PSA values.
Stenner et al. (15)	89 (study)	Total	Before and mean10.18 hour after ejaculation.	Ejaculation has an insignificant effect on serum PSA values.
Rajaei et al. (16)	60 (study)	Total	Before and 1, 24 hours after ejaculation.	PSA significantly increased within 1 hour after ejaculation.

PSA increase. Some of the reported differences may have been due to population biases owing to the small groups of patients studied (6, 8, 11, 12). Five of the studies included control group (6, 7, 9, 11, 14). Only six of them were done with men over 45 years of age that is proposed for prostate cancer screening (7, 9, 10, 12, 15, 16). Also, the evaluation of ejaculation, sample timing, and PSA measurement methods vary importantly among studies. This variability causes difficulties in interpretation. Our study includes control group, tPSA, fPSA and cPSA as parameters, and regular sampling times for both groups after ejaculation as different from previous studies. Additionally, our study is the first to report the effects of ejaculation on serum cPSA levels in human beings (Table-4).

In the study group, the serum levels of all forms of PSA increased at 1st hour after ejaculation and returned to baseline at 24th hours. Ejaculation induced a more pronounced increase in tPSA (10.5%) than in fPSA (9.9%) and in cPSA (4.3%). These increases were statistically significant for tPSA and fPSA. A statistically significant increase in the control group was not detected in any form of PSA. In this case we can say that serum PSA levels increase after ejaculation. Indeed, some studies have confirmed this result (10-12, 16).

In our study, we found a statistically significant increase of tPSA and fPSA after ejaculation in the study group; but not in the control group. In contrast to other PSA forms, less and insignificant cPSA elevations were observed after ejaculation. Changes in the number of patients exceeding the cut-off values after ejaculation were also not statistically significant for tPSA, cPSA, and f/tPSA ratio. This situation, although not statistically significant, should be expected to be of clinical significance in individual patients close to the threshold levels.

We consider that increase in tPSA levels after ejaculation may be due to the increase in fPSA levels. The site of cPSA formation is controversial; it may be in the prostate gland, or in the circulation (20). In vitro studies sustain that complex formation of fPSA with ACT lasts longer than that with α2 macroglobulin (21). Insignificant variation of cPSA levels after ejaculation may be explained with kinetics of serum PSA isoforms.

The effect of ejaculation on serum PSA forms might be different in various prostatic diseases as BPH, prostate carcinoma, and chronic prostatitis. We did not investigate this this issue in this study. This may be the limitation of our study.

The prostate volume and baseline PSA concentration were found as factors affecting serum PSA levels after ejaculation. Elevation of PSA levels after ejaculation is greater in patients with a larger prostate volume and higher baseline PSA values. However, the change in serum PSA after ejaculation was independent of the patient's age. Tchetgen et al. found that declining to basal levels after ejaculation take longer in older patients and in patients with higher baseline PSA levels (10). Benign prostatic hyperplasia causing ductal obstruction, acinar dilatation, and secretion retention besides membrane weakness and thus disturbed barrier permeability can cause PSA leakage during ejaculation (10). Additionally, pelvic muscle and periprostatic contractions can cause PSA passage into circulation (15). Studies showing PSA increases in elderly or patients with BPH supports the mechanism of hyperplastic tissue compression and barrier disturbance.

CONCLUSIONS

In this study, ejaculation increased tPSA and fPSA concentrations but it didn't have a significant effect on serum cPSA levels. However, increase of cPSA and decrease f/tPSA ratio after ejaculation may cause some patients to exceed corresponding cut-off levels, although not statistically significant. Therefore, sexual abstinence should be advised for 24 hours before any PSA measurement to avoid nonspecific interpretations of serum PSA levels. Further research is needed to explain the mechanism of alterations in the concentrations of PSA.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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A prospective multicenter European study on flexible ureterorenoscopy for the management of renal stone

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ABSTRACT

Purpose: The aim of this study was to describe the outcomes and the complications of retrograde intrarenal surgery (RIRS) for renal stones in a multi-institutional working group.

Materials and Methods: From 2012 to 2014, we conducted a prospective study including all RIRS performed for kidney stones in 4 European centers. Demographic information, disease characteristics, and perioperative and postoperative data were gathered. Patients and stone data, procedure characteristics, results and safety outcomes were analyzed and compared by descriptive statistics. Complications were reported using the standardized Clavien system.

Results: Three hundred and fifty-six patients underwent 377 RIRS with holmium laser lithotripsy for renal stones. The RIRS was completed in all patients with a mean operative time of 63.5 min. The stone-free status was confirmed endoscopically and through fluoroscopic imaging after the first procedure in 73.6%. The second procedure was performed in twenty patients (5.6%) achieving an overall stone free rate of 78.9%. The overall complication rate was 15.1%. Intra-operative and post-operative complications were seen in 24 (6.7%) and 30 (8.4%) cases, respectively.

Conclusions: RIRS is a minimally invasive procedure with good results in terms of stone-free and complications rate.

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INTRODUCTION

The management of kidney stones has evolved radically over the years. Previously, extracorporeal shockwave lithotripsy (SWL) and percutaneous nephrolithotomy (PCNL) were the preferred treatment modalities for renal calculi. The impressive technologic improvement in endoscopic flexible equipment with the recent advent of digital technology made ureteroscopic approach to kidney calculi evolve from a mere diagnostic tool to a real operative procedure capable to treat the vast majority of renal stone.

Several studies have demonstrated the advantages and high success rates of PCNL in the management of larger renal stones. However, experiences with RIRS have revealed comparable stone free rate (SFR) with less risk of renal damage and bleeding (1). Recently, it has been demonstrated that retrograde intrarenal surgery (RIRS) can be a good management option for mid-sized stones between 2 to 4cm (2, 3) and in special circumstances

such as pregnancy, anatomic malformations or coagulopathy and solitary kidney (4, 5) although it still not is the standard of care.

In 2013, the European Association of Urology's (EAU) Guidelines on Urolithiasis for the first time listed RIRS as a viable treatment option for all kidney stones, including stones larger than 2cm in diameter, in experienced hands in high-volume centers (6). It is noteworthy, that for stones smaller than 2cm, SWL is no longer considered mandatory as first approach so that indications to RIRS have massively been broadened.

However, RIRS is associated with some disadvantages being the possible need for staged procedures one of the major. Secondly, risk of ureteral injuries and the costs of acquisition and maintenance of the complex endourological armamentarium are other concerns that might have been limited the capillary diffusion of this endoscopic procedure (7). Herein we describe a multi-center prospectively study of RIRS for renal stones whose aim is to highlight the clinical outcomes with particular attention to the complications rate.

MATERIALS AND METHODS

Clinical Data

A prospective study of all patients who underwent RIRS for kidney stone disease in four European referral centers was performed from 2012 to 2014. Data were recorded prospectively on each patient. Patient data obtained included: age, sex, body mass index (BMI), history and physical examination findings, specific comorbidities, American Society of Anesthesiologists (ASA) class risk. The stone parameters evaluated were: the number of stones, stone location, previous treatments for stone, stone diameters and stone composition. Double-J stent preoperatively, congenital renal anomalies (pelvi-ureteric junction obstruction, horseshoe kidney), anticoagulant therapy were evaluated.

Stone location was classified as renal pelvis/ureteropyelic junction, superior/middle/inferior major calyces and multiple caliceal location. The preoperative assessment included non-contrast computed tomography (CT) or KUB (kidney-ureter-bladder) plain radiograph and renal ultrasound (US).

An antibiotic therapy, either as prophylaxis with cephalosporin or fluoroquinolone or adapted 5 days antibiotic therapy in patients with an intraoperative positive urine culture was administered. Informed consent was obtained from all patients, and the possible need for a staged procedure in order to obtain satisfactory stone clearance was mentioned. Exclusion criteria were as follows: pregnancy and cachexia.

Operative and Postoperative Data

The operative time was defined as the time that passed from insertion into the urethra of the cystoscope/semirigid ureteroscope for introducing the guidewire to the completion of ureteral stent placement. All the RIRS were performed using different types of flexible ureteroscopes: Flex-X2 or Flex-XC (Karl Storz Endoscope, Germany), the URF-P5 or URF-V (Olympus Europe, Germany). Lithotripsy was achieved by means of 200/273µm Holmium laser fibers. A guidewire was placed in the upper urinary tract through a rigid cystoscope or semirigid ureteroscope under fluoroscopic guidance. According to surgeon preference, visual assessment of the ureter and ureteropelvic junction was performed with the semirigid ureteroscope. Alongside a second safety guidewire an Ureteral Access Sheath (UAS) (Flexor 9.5/11.5Fr or 12/14Fr, Cook Medical Bloomington, IL, USA, Navigator 11/13Fr, Boston Scientific, Natik, MA, USA or Retrace 10/12Fr, Coloplast/Porges Humlebæk, Denmark) up to the proximal ureter was placed. If the UAS placement was impossible, a sheathless procedure was attempted. If this last attempt failed, a pigtail, double J ureteral catheter (DJ) was left in situ for passive dilatation and the procedure was delayed.

A tipless nitinol basket was used to extract the fragments and to re-position lower pole calculi to a more accessible calyx prior to intracorporeal lithotripsy. The procedure was concluded after stone-free status was confirmed by both ureteroscopic inspection and fluoroscopy (leaving only ungraspable gravel or fragments <2mm) or in case of bleeding or at the decision of the surgeon. By the end of the procedure, the ureter was ureteroscopically and fluoroscopically assessed

for possible lesions. The ureteral injuries were classified in major and minor (8). The classification of ureteral wall injuries proposed by Traxer et al. (9) was not used as it was not available at the time of the beginning of the series. A DJ was applied at the end of procedure according to surgeon preference or after complicated procedures.

Follow up

The "stone-free" status was defined as no evidence of stones or stones less than 2mm on one-month postoperative CT and/or KUB and/or US, prescribed following the surgeon preferences. Patients with residual fragments, requiring a further RIRS, were routinely scheduled for the second treatment 30-45 days following the previous procedure and were evaluated at 4 weeks from the last procedure. All patients were followed up to 6 months, with serial plain radiograph or renal ultrasound. Postoperative complications were assessed according to the modified Clavien classification (10).

RESULTS

Clinical Data and Patient Characteristics

Three hundred and fifty-six patients underwent 377 RIRS with holmium lasertripsy for renal stones. The cohort included 226 (63.5%) male and the mean age was 53.5 years (SD: 14.3). One third of patients (34.3%) had a history of urolithiasis, and the 32% already received a previous treatment. In 64% of patients we found a single stone (mean diameters: 12.4x9.5mm) and in 165 cases (46%) the stone was located in the pelvis/ureteropyelic junction. Demographic data and clinical characteristics of the cohort are listed in Tables 1 and 2.

Operative and Postoperative Data

RIRS was safely completed in all patients with a mean operative time of 63.5 min (range 13–250 min). The mean number of procedures per patient was 1.05. The UAS was placed in 283 patients (79.5%), among these the 65% received a large UAS (11/13FR or 12/14F or larger) and the remaining 35% a smaller one (9.5/11.5F or 10/12F).

In 262 cases (73.6%) a complete stone-free status was confirmed endoscopically and through fluoroscopic imaging. Postoperatively a DJ was positioned in 332 patients (93.2%). Twenty patients (5.6%) with a greater diameter than the overall average (mean diameters: 13x9.9mm) received a second retreatment and 1 of these (0.2%) required a third treatment. The second procedure achieved complete stone clearance for 281

Table 1 - Demographic data and clinical characteristics.

	N or mean	% or ±SD
Gender		
Male	226	63.5%
Female	130	36.5%
Age, years	53,5	±14.3
BMI, kg/m²	26.5	±4.2
ASA score	1.6	±0.8
Diabetes	41	11.5%
CKD	10	2.8%
Hyperuricemia	13	3.7%
Other metabolic disease	26	7.3%
Renal malformation	30	8.4%
Previous stone treatments	114	32.0%
Hydronephrosis	152	42.7%

Values are mean and SD or absolute number and percentage. BMI = Body Mass Index; **CKD** = chronic Kidney disease; **ASA** = American Society of Anesthesiologists class risk.

Table 2 - Operative and postoperative data.

	N or mean	% or ±SD
Operative time (min)		
UAS	63.5	±32.4
Number of stone	283	79.5%
- Single	228	64.1%
- Multiple	128	35.9%
LOS	2	±2
Stone size		
- length (mm)	12.5	±5.3
- width (mm)	9.4	±4.5
Stone location		
- upper calyx	9	2.5%
- mild calyx	29	8.1%
- lower calyx	58	16.2%
- pelvis	92	25.8%
- UPJ	73	20.5%
- pelvis + calyx	79	22.1%
- multiple calyces	34	9.5%
Stone composition		
- Ca oxalate	164	46%
- Uric acid	16	4.5%
- Mixed (Ca oxalate+Uric acid)	28	7.8%
- Brushite	43	12%
- Struvite	7	2%
- Cystine	18	5%
- Other	7	2%
- Unknown	92	25.8%
Pre-operative stent or nephrostomy	77	21.6%
Stone X-ray characteristics		
- radiopaque	274	76.9%
- radiolucent	90	23.1%
Post-operative stenting	332	93%
Re-intervention	20	5.5%
SFR		
- First procedure	262	73.6%
- Second procedure	281	78.9%

Values are mean and SD or absolute number and percentage. **N** = number; **LOS** = length of stay; **UPJ** = ureteropyelic junction; **SFR** = stone free rate; **Ca** = calcium.

patients, for an overall SFR of 78.9%. Complete operative and postoperative data are provided in Table-2. If we analyze the subgroup of lower pole stone and sheatless procedures, the SFR is 68.9% and 77.4%, respectively.

Complications

The overall complication rate was 15.1%. Intra-operative and post-operative complications were experienced in 24 (6.7%) and 30 (8.4%) cases, respectively. A detailed description of the complications and the action taken are showed in Table-3. No major ureteral injuries occurred. Minor ureteral wall injuries were noted in 11 patients (3%) and managed successfully with a stent placement (for 3 to 6 weeks) (mucosal abrasion not reported). Two patients (0.5%) were re-admitted following discharge from hospital with non obstructive pyelonephritis: they were treated with intravenous antibiotics and bladder catheter. Two patients (0.5%), left unstented after the procedure, required DJ insertion after readmission for an obstructive pyelonephritis. No complications higher than Clavien grade IIIa were observed. No patients complained late complications to follow-up visit after 6 months.

DISCUSSION

This prospective multi-institutional study on RIRS for renal calculi has shown this approach to have excellent stone clearance rates with an acceptable complication profile. Major technical and surgical developments in endoscopic technologies and technique for the treatment of urolithiasis have led to changes in treatment approach, and subsequently to international guidelines (6). In this large study, we have demonstrated that the SFR achieved after the first treatment of RIRS to be as high as 73.6%. This finding is comparable to similar studies that demonstrated SFR of 65-79% (11-15).

We also noted that only 20 patients (5.6%), with a mean diameter greater than the overall average, required a second look RIRS to ensure the stone-free status. We do not regard this as a treatment failure of the first procedure, but rather as a necessary part of a planned staged procedure

Table 3 - Overall Complications according to Clavien classification.

	Intraoperative		Postoperative	
Complication	Patients, N (%)	Action	Patients, n (%)	Action
Clavien Grade I				
Hematuria	7 (1.9)	Fluid irrigation	2 (0.5)	DJ placement
Lumbalgia	-	-	1 (0.2)	Analgesics
Fever	-	-	23 (6.4)	Antipyretics
Clavien Grade II				
Perforation of pelvis/ calyx	5 (1.4)	DJ placement	-	-
Ureteral injury	11 (3)	DJ placement	-	-
Non obstructive pyelonephritis	-	-	2 (0.5)	Antibiotics
Clavien Grade IIIa				
Obstructive pyelonephritis	-	-	2 (0.5)	DJ placement Antibiotics
Total	**24 (6.7)**	**30 (8.4)**		

N = number; **DJ** = double J stent; **Clavien grade I** = Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions. **Clavien grade II** = Requiring pharmacological treatment with drugs other than such allowed for grade I complications. **Clavien III**= complicaiton requiring surgical, endoscopic or radiological intervention.

to ensure stone clearance, in particular for large renal stones (eg. stones>2cm). This strategy allowed us to achieve an overall SFR equal of 79%.

Over the last 10 years, RIRS has become an increasingly important option for the treatment of the majority of kidney stones even in the most complicated clinical scenarios such as pregnancy, obesity, coagulopathy, large renal stones, caliceal diverticula, and kidney malformations (4). RIRS is well accepted by patients, the convalescence is minimal, it generally does not require a prolonged hospital admission (2 days) or prolonged absence from work (2). In addition, using the endoscopic approach to the kidney, reduces the risk of blood loss, renal parenchyma damage and renal impairment. In contrast, in recent years we have seen a drift away from SWL and PCNL. This is in part due to SWL providing a low SFR (16) and a high re-treatment rate for large stones and for stones located in the lower pole calyx (17). Similarly, PCNL that is the gold standard for large kidney stones and is more effective than SWL for lower pole stones (18) is characterized by a risk of serious complications (19, 20). We noted that 77 patients (21.6%) had DJ stent placement prior to RIRS. DJ placement may facilitate passage of the UAS and extraction of the fragments (21), however this does not justify the routine DJ insertion before surgery except in case of a septic obstructed upper urinary tract or in case of ureter stricture that will not make possible the passage of access sheath (22). In contrast to this, a post-operative DJ stent was left in situ in 332 patients (93%). This is done to facilitate drainage, prevent post-operative ureteral obstruction. In 79% of cases the DJ stents were placed for 30 days or less. The uses of the UAS can significant facilitate RIRS and stone clearance by allowing multiple entry and reentry to the kidney, decreasing intrarenal pressure and protect the scope from damage (23, 24). However, the routine use of a UAS is matter of debate (6). In this study, an UAS was used in 80% of the cases. The size of the UAS varied according to clinical conditions. In 52% of the cases a larger UAS was employed. This probably reflects the surgeon's preference for lasertripsy. If the surgeon has a predilection for fragmentation and stone extraction, the preferred setting of laser has been low frequency/high energy using medium/large diameter sheath. This allows the extraction of slightly larger fragments. If the surgeon prefers to dust by vaporization the preferred setting of laser is high frequency/low energy using a medium/small UAS sufficient. However, the choice between vaporization and fragmentation is not only related to the surgeon preferences but also by stone size. For bigger stone could be better to start with the vaporization of the outer part of stone moving to the fragmentation of the residual part and the extraction of fragments.

The overall 30-day complication rate in this study was 15.1% being 6.7% intraoperative and 8.4% post-operative. These data are according with the data of EAU guidelines on Urolithiasis that report an overall complication rate of 9-25% (6). It's noteworthy that the complications rate of pure RIRS is lacking. In fact, the complication rate reported by EAU guidelines are based on surgical series of semirigid ureteroscopy for ureteral stone. A recent meta-analysis that included 2 randomized and 8 non-randomized studies showed an overall complication rate of RIRS of 10.4%. It was concluded by the authors, that the interpretation of complications proved to be challenging because of a lot of key information (blood transfusion, antibiotic use, definition for sepsis, need for preoperative stenting, definition of ureteral injury, timing of post-operative stenting, etc.) were not clearly stated (25). The complication rate in our study, that at first analysis could be considered slightly higher than expected, should be considered as a viable finding. In fact, in this prospective and standardized setting, we considered any deviation from normal post-operative course as a complication and described it according to Dindo-modified Clavien classification (26).

Some limitations for this study should be acknowledged. The first limitation of this multicenter study is the different imaging modalities used to assess SFR. While CT is the most sensitive modality for assessing residual fragments, logistical and cost reasons may prohibit its routine use (27, 28). Ultrasonography was used frequently as a postoperative imaging test based on its low cost, ready accessibility, and lack of radiation. Lack of uniform evaluation of residual fragment might also represent a weakness. However, even if a central residual fragment evaluation ideally increases validity by

minimizing the interobserver variability, it is useless, from a clinical viewpoint, since variability is common in clinical practice (4). A second limitation would be the non-uniform treatment approach and the different experience of the surgeons. The multi--institutional nature of our cohort may be interpreted as limitation, however we believe that, in order to evaluate the generalizability of these findings, a certain grade of heterogeneity in baseline characteristics, rather than homogeneity, is advisable and desirable.

In our opinion, it is important to remind that, as stated by Giusti et al. (4), the "key to success is avoiding the start of RIRS on your own. Furthermore, detailed and frank counselling of the patients is strongly encouraged to inform them not only about the minimal invasiveness but also about outcomes of the surgeons/centers and the potential for staged multiple procedures in the most difficult cases and the possibility, although rare, of major complications".

CONCLUSIONS

This European multicenter prospective study confirmed that RIRS performed with the newest generation of technical equipment allowed us to achieve a very high SFR without compromising on safety. Nevertheless, cost of acquisition and maintenance and reimbursement policies by national health systems represent a critical issue that should be resolved to allow RIRS become a routine procedure available in all urological departments and not just in a few tertiary centers.

CONFLICT OF INTEREST

Guido Giusti is a consultant for Boston Scientific, Cook Medical, Porges-Coloplast, Karl Storz.

All the other authors declare that they have no conflict of interest.

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ORIGINAL ARTICLE

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Efficacy of Tamsulosin, Oxybutynin, and their combination in the control of double-j stent-related lower urinary tract symptoms

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ABSTRACT

Introduction and objective: Indwelling double J ureteral stents are used routinely in the resolution of ureteral obstruction caused by different etiologies. Evaluation of urinary symptoms related to double-J stent, indicate that these affect 73-90% of patients.

We conducted a prospective, randomized study, to evaluate the efficacy of tamsulosin, oxybutinin and combination therapy in improving the urinary symptoms.

Methods: Patients who underwent ureteral stent placement after ureterolithotripsy (total 51), were randomized into three groups: Group I: Tamsulosin 0.4 mg. once per day(17 patients), Group II: Oxybutinin 5 mg. once per day (17 patients), Group III: Tamsulosin+ oxybutynin once per day (17 patients). All the groups received the drugs for three weeks and completed a Spanish validated Ureteral Stent Symptom Questionnaire (USSQ) at day 7 and 21.

Results: Repeated measures ANOVA showed mean urinary symptom index score was 22.3 vs. 15.5 in group three ($p<0.001$) at day 7 and 21 respectively. The mean work performance index was 6.6 vs 8.1 ($p=0.049$) favoring tamsulosin group, the mean sexual score was 0.5 vs 1.5 ($p=0.03$). Among additional problems the mean was 7.2 vs 6.2 ($p=0.03$). No significant difference was noted among pain and general health index. No side effects were reported.

Conclusions: Combination therapy with tamsulosin and oxybutynin improved irritative symptoms and work performance as well as sexual matters. Combination therapy should be considered for patients who complained of stent related symptoms.

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INTRODUCTION

The placement of ureteral double-J stents has become routine clinical practice for resolving ureteral obstruction caused by different etiologies (1-4). The estimated incidence of stent-related symptoms varies from 19-76% and includes frequency, urgency, dysuria, incomplete voiding, flank pain, suprapubic pain, urinary incontinence, and hematuria (5-10).

The objective evaluation of stent-related symptoms through the visual analog scale (VAS)

and the International Prostate Symptom Score (IPSS) is complex and nonspecific (11-13). Joshi et al. developed the ureteral stent symptoms questionnaire (USSQ), which is a validated and safe psychometric instrument for evaluating the impact of ureteral stents on symptoms and quality of life. This questionnaire explores 6 areas that include urinary symptoms, body pain, general health status, work performance, sexual matters, and other additional problems (14). It has been utilized in numerous clinical trials and translated into different languages, including Spanish (15).

The efficacy of pharmacologic management of these symptoms related to the double-J stent, with alpha-1 adrenergic blockers, tamsulosin and alfuzosin (16, 12, 17-19) and the antimuscarinic agents, oxybutynin and tolterodine, has been demonstrated (20). In fact, there is a meta-analysis that evaluates the efficacy of alpha-blockers and concludes that they are associated with improvement in ureteral stent symptoms and supports their use in routine clinical practice (21). Nevertheless, at present there is no study directly comparing tamsulosin and oxybutynin. Therefore, the aim of this study was to evaluate the efficacy and safety of these two drugs for the control of lower urinary tract symptoms and their impact on quality of life.

MATERIALS AND METHODS

Patient selection

From November 2012 to October 2013, patients of both sexes were included in the study; they were above 18 years of age and had unilateral double-J stent placement after ureteroscopy that was performed at the Hospital General de México.

Inclusion criteria were patients of either sex above the age of 18 years that had undergone ureteroscopy for lithiasis in the lower third of the ureteral tract, with stones under 15mm, and that required unilateral double-J stent placement.

The exclusion criteria were patients with a previous diagnosis of benign prostatic hyperplasia (IPSS≥7), a previous diagnosis of overactive bladder, a history of interstitial cystitis or chronic cystitis, a history of chronic prostatitis or chronic pelvic pain, chronic medication with alpha blockers, anticholinergic agents and analgesics, ureteral obstruction caused by malignancy, pregnant patients, patients unable to understand or sign an informed consent, patients with a history of postural hypotension (decrease in blood pressure>20mmHg of the systolic or diastolic measurements) or syncope, patients with severe or unstable heart failure, severe renal failure, severe liver failure, or patients with a history of urinary retention, gastric retention, or uncontrolled wide-angle glaucoma.

A single-blind, randomized, prospective, comparative, and experimental clinical trial was conducted that included 51 patients (26 women, 25 men).

They were assigned to one of the following three groups by means of a randomization Table:

Group 1 - Tamsulosin 0.4mg PO before food every 24h for 21 days

Group 2 - Extended release Oxybutynin 5mg PO every 24h for 21 days

Group 3 - Tamsulosin 0.4mg PO before food every 24h for 21 days+oxybutynin 5mg PO every 24h for 21 days.

The sample size was calculated with the formula for comparing independent means, based on previous studies on the efficacy of alpha blockers versus placebo (20). A power of 90% and a significance level of 0.05% were used in accordance with a finite population of 60 cases (the number of ureteroscopies per year at our hospital).

Methods

Once the diagnosis of ureteral lithiasis was established and it was confirmed that the patients met the protocol selection criteria, the characteristics of the study were explained to them. Upon accepting to participate in the study, the patients signed statements of informed consent, following the principles of the Declaration of Helsinki.

This study was approved by the institutional ethics and research committees in accordance with good clinical practices, with registration number DI/12/105/04/081.

Data were collected in a case report file that contained each patient's personal information,

demographic data, clinical history, and complete physical examination results.

Each patient underwent ureterolithotripsy and a polyurethane 24 or 22cm X 6Fr double-J stent (Cook, USA) was placed after endoscopic extraction of the stone. Adequate ureteral double-J stent placement was verified through a plain abdominal film in the immediate postoperative period.

The ureteral stent symptoms questionnaire (USSQ) was applied to all patients on postoperative days 7 and 21, registering the scores of each of the 6 topics evaluated with the assessment tool. Each section has a total score; the higher the number, the worse the general health status of the patient.

Antibiotic was administered for 7 days (Ciprofloxacin 500mg PO bid), followed by urinary antiseptic (Nitrofurantoin 100mg PO every 24h) until removal of the stent, three weeks later. Ketorolac PO 10mg was administered as needed by the patient, with a maximum of 4 tablets in 24 hours. Each patient kept a personalized register of the daily analgesic intake.

Statistical analysis

Values were expressed as means±standard deviation (SD) and the statistical analysis was carried out using the repeated measures ANOVA test for comparing the independent means of the 3 treatment groups.

Results were considered statistically significant with a value set at $p<0.05$. The IBM SPSS Statistics 20.0 for Windows (SPSS, Chicago, IL, USA) statistical package was used.

RESULTS

A total of 56 patients were enrolled in the study. Five were eliminated; four due to spontaneous stone expulsion and one for having an IPSS score above 21 points.

The remaining 51 patients (26 women and 25 men) were randomly distributed as follows:

Group 1 - Tamsulosin (17 patients)

Group 2 - Extended release oxybutynin (17 patients)

Group 3 - Combination therapy (17 patients)

Table-1 shows the demographic characteristics of the study population. There were no statistically significant differences per group with respect to age, sex, weight, height, BMI, or stone size ($p>0.05$).

Repeated measures ANOVA showed a mean urinary symptom score of 22.3 versus 15.5 in Group 3 ($p<0.001$) at days 7 and 21, respectively (Figure-1). The mean work performance score was 6.6 versus 8.1 ($p=0.049$), favoring the tamsulosin group, and the mean sexual performance score was 0.5 versus 1.5 ($p=0.03$). For the additional problems, the mean was 7.2 versus 6.2 ($p=0.03$). No significant difference was noted between pain and general health scores (Table-2). No side effects were reported and there were no differences in analgesic consumption between groups.

Table 1 - Demographic characteristics of the study patients.

Variable	Tamsulosin	Oxybutynin	Both	p*
Patients (n)	17	17	17	
Gender (M:F)	9:8	7:10	9:8	0.73
Age (years)	42.5±7.3	40.4±11.2	45.7±10.3	0.293
Weight (kg)	73.7±13.4	75±8.9	71.2±12.1	0.623
Height (cm)	166.9±5.7	161.4±5.0	161.2±5.7	0.342
BMI (Kg/m)	27.5±6.5	28.6±3.2	27.6±4.1	0.729
Stone size (mm)	8.8±3.2	11.2±4.0	10±3.02	0.135

*significance<0.05

Figure 1 - Mean urinary symptoms score.

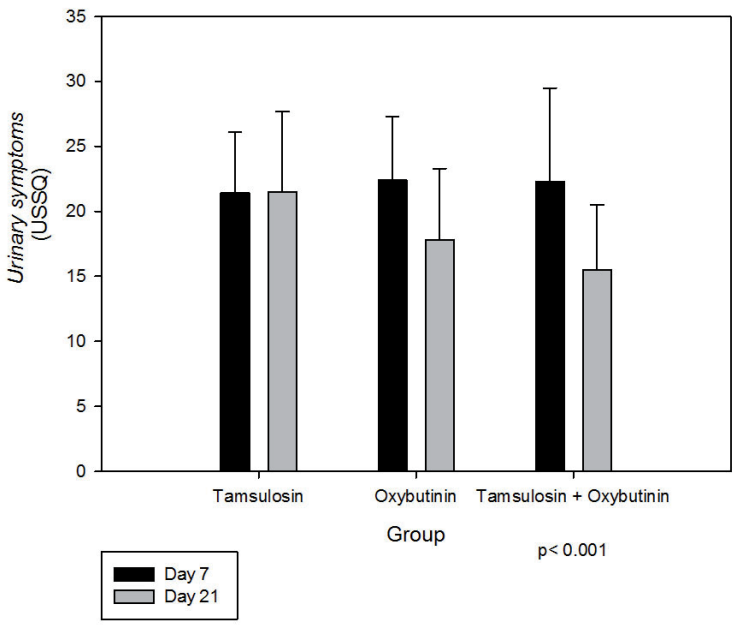

Table 2 - USSQ score comparison among the 3 groups on postoperative days 7 and 21.

Variable		Tamsulosin (Mean±SD)	Oxybutynin (Mean±SD)	Tamsulosin + Oxybutynin (Mean±SD)	p*
Urinary symptom score	Day 7	21.4±4.78	22.4±4.9	22.3±7.2	<0.001*
	Day 21	21.5±6.27	17.8±5.5	15.5±5.0	
Pain score	Day 7	13.4±2.2	11.2±2.7	13.8±5.0	0.207
	Day 21	14.2±4.3	10.9±3.1	11.2±5.8	
General health score	Day 7	11.7±1.4	11.0±1.4	11.5±1.5	0.699
	Day 21	11.6±1.2	11.7±1.3	11.2±2.5	
Work performance score	Day 7	6.6±4.0	6.3±2.5	7.0±2.3	0.049*
	Day 21	8.1±1.8	7.2±1.9	7.7±1.5	
Sexual performance score	Day 7	0.6±1.1	0.5±0.8	2.6±3.8	0.036*
	Day 21	1.2±1.2	1.5±1.2	2.6±2.5	
Additional problem score	Day 7	8.05±2.6	6.8±1.9	7.2±1.7	0.03*
	Day 21	7.4±3.0	6.4±1.1	6.2±2.8	

*Repeated measures ANOVA.

DISCUSSION

Ureteral stent placement for upper urinary tract diversion has been employed for more than four decades (22) and has become routine procedure in various urologic surgeries performed for different indications. Ureteral stents prevent urinary flow obstruction caused by edema of the mucosa; they aid in the mucosal healing process after a complicated procedure and they passively dilate the ureter, and facilitate the passage of residual stones (1).

Nevertheless, up to 76% of the patients will have symptoms associated with the presence of the stent, on occasion requiring its early removal (8). New stent designs, coatings, and biomaterials have been developed for the purpose of reducing these problems, but the ideal stent has yet to be produced (23).

Even though the exact pathophysiology of the symptoms related to the double-J stent is not known, it has been suggested that the mechanism involved could be an increase in the pressure transmitted toward the renal pelvis during micturition and bladder irritation due to the intravesical portion of the stent (24).

Both anticholinergic drugs and alpha--adrenergic blocking agents have been used to improve symptoms related to the double-J stent with good results in the majority of cases (20 21).

Our study showed that tamsulosin and oxybutynin combination therapy improved irritative urinary symptoms, as well as work performance and sexual aspects.

The combination of tamsulosin and oxybutynin was clearly superior in improving urinary symptoms. This is a very relevant clinical situation, given that symptomatology is present in 73 to 90% of patients with double-J stent. The same was true for the area of additional problems.

In our study, the group with tamsulosin, alone, had a higher work performance score, compared with the other two groups.

Even though there were statistically significant differences in relation to the sexual sphere, we felt that the USSQ was not very useful, especially during the first postoperative days, because the patients were more concerned about the result of the surgery and their general health than their sexual performance. In fact, the majority of patients stated that they had made no attempt at having sexual activity.

There are few controlled clinical trials that evaluate the pharmacologic agents used in the treatment of double-J stent-related symptoms, and to the best of our knowledge this is the first head-to-head study comparing long-acting tamsulosin and oxybutynin. It is well known that stent-related symptoms are similar to those of benign prostatic hyperplasia caused by urethral resistance and bladder instability. Damiano et al. reported that tamsulosin administration improved urinary symptoms and pain when evaluated through the visual analog scale, as well as quality of life (13).

Wang et al. stated that the selective alpha-1 blocker, tamsulosin, improved urinary symptoms, flank pain, and pain during micturition (19). Beddingfield et al. reported that patients treated with 10mg daily of alfuzosin showed improvement with respect to micturition frequency, lumbar pain, and sleep disorders (25). Deliveliotis et al. had similar study results of improved stent--related symptoms in patients treated with alfuzosin, especially in reference to pain, as well as sexual function, and general health (26).

Symptoms associated with double-J ureteral stent are similar to those of overactive bladder caused by involuntary bladder contractions, and antimuscarinic agents have been used with good results (27). Norris et al. reported that there were no statistically significant differences between patients treated with oxybutynin compared with placebo or phenazopyridine (28). Agarwal et al. demonstrated that patients that had received oxybutynin or tolterodine prior to surgery showed greater relief in regard to bladder discomfort compared with patients in the placebo group (29).

A limitation of our study resulted from the fact that even though the sample size was adequately calculated, the number of patients in each group was small and this could possibly reduce the capacity to detect other potential effects of these drugs in patients with double-J stent, when evaluated through the USSQ.

CONCLUSIONS

The administration of tamsulosin and oxybutynin markedly reduced the irritative symptoms commonly associated with a double-J stent. These drugs were also effective in the improvement of sexual performance and work performance, as well as other related problems. There was no difference with respect to pain and general health.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Transcorporal artificial urinary sphincter in radiated and non – radiated compromised urethra. Assessment with a minimum 2 year follow-up

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ABSTRACT

Purpose: to assess the efficacy of transcorporal artificial urinary sphincter (AUS) implantation on continence for male stress urinary incontinence in cases of prior surgical treatment or/and radiation failure, and as a first option in radiation patients.

Materials and Methods: From March 2007 to August 2012, 37 male patients were treated with transcorporal AUS AMS™ 800. Twelve patients had primary placement of transcorporal cuff, a surgical option due to a previous history of radiation and 25 patients had secondary procedure after failure of AUS or urinary incontinence surgery. Functional urinary outcomes were assessed by daily pad use, 24-hour Pad-test and ICIQ-SF questionnaire. Quality of life and satisfaction were assessed based on I-QoL and PGI-I questionnaires.

Results: After a median of 32 months, the continence rate (0 to 1 pad) was 69.7%. Median pad test was 17.5g (0-159), mean ICIQ-SF score was 7.3/21 (±5.4) and mean I-QoL score was 93.9/110. A total of 88% of the patients reported satisfaction with the AUS. The 5-year actuarial revision-free for AUS total device was 51%. Patients for primary implant for radiation were not more likely to experience revision than non-radiation patients. Preservation of erections was reported in half of the potent patients.

Conclusions: Transcorporal AUS cuff placement is a useful alternative procedure option for severe male UI treatment, especially in patients with a compromised urethra after prior surgery or radiation. A high continence rate was reported and implantation as first option in radiation patients should be considered.

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INTRODUCTION

Urinary incontinence (UI) is a serious adverse effect due to radical prostatectomy (1). After failure of conservative treatment, an artificial urinary sphincter (AUS) is considered the gold standard treatment for mild to severe incontinence from intrinsic sphincter deficiency (2). It provides a high continence rate and patient satisfaction, despite a reoperation rate that may reach 62.7% (3). In men the AUS cuff is implanted directly around the bulbar urethra. However, cuff placement may be difficult in a compromised urethra due to prior AUS placement, radiation or urethral surgery leading to a high risk of failure (4).

The transcorporal approach to AUS placement was created to protect the urethral wall in AUS revision for urethral atrophy and erosion (5) that protects the posterior wall of urethra during dissection, which may be critical.

AUS implantation using a transcorporal cuff was recently reported by Wiedemann et al. (6) that concluded that transcorporal AUS cuff placement is a useful alternative for challenging cases of male UI after failure of previous surgical treatment, urethral atrophy or erosion. The aim of the study was to conduct a selective evaluation in radiation and non-radiation patients to assess transcorporal AUS as a first option in radiation patients.

MATERIALS AND METHODS

Patient selection: From March 2006 to August 2012, 44 patients underwent AUS (AMS800®) implantation with a transcorporal cuff by the same surgeon in a single center. All patients were contacted by letter and telephone for evaluation, and were examined by an independent urologist. Later all patients completed a subjective satisfaction questionnaire.

Degree of continence was assessed by a 24 hour Pad-test, validated questionnaire (International Consultation on Incontinence Questionnaire--Short Form: ICIQ-SF) and number of pads per day. Total continence was defined as no urinary leakage and no pad, social continence as 0 to 1 pad with urinary leakage. In the other cases, patients were considered as incontinent. In addition, quality of life and satisfaction were assessed based on two validated questionnaires in 33 patients who completed an Incontinence Quality of Life scale (I-QoL) and Patient Global Impression of Improvement (PGI-I) respectively.

Early postoperative complication (<30 days) was recorded. Revision was defined as any additional procedure on the AUS, including explantation of the device with or without de novo implantation at the same time. In order to assess the results and complications with a sufficient period of follow-up, all patients included in the study had a minimum of 2 years of follow-up.

This study was not submitted to the local Ethics Committee for approval because it was a retrospective assessment of clinical practice.

Surgical procedure

The transcorporal cuff placement has been previously described (5, 6). Reservoir pressures were initially 61 to 70cm/H_2O in all of 37 patients. Cuff sizes were 4, 4.5; 5, 5.5, 6 and 6.5cm respectively in 1, 7, 10, 15, 2 and 2 patients. All sphincters were deactivated for 6 weeks after surgery.

Statistical analysis

Continuous data were analyzed with the nonparametric Mann-Whitney test. For categorical variables, Fisher's exact test or Chi-Square test was used. Revision-free survival of the AUS and the cuff curves were calculated using the Kaplan--Meyer method, and the significance of differences was determined using the log-rank test. Cox multivariate regression model was used to assess the relative importance of previous radiotherapy and failure of incontinence surgery on the results. Statistical significance was defined as $p<0.05$ for all analyses.

RESULTS

Patient characteristics are summarized in Table-1. Mean age at sphincter insertion was 70.1 years (±7.1).

Follow-up data were available on 37 of the 44 patients. Five patients died since AUS implantation and 2 were lost to follow-up and excluded from the analysis. Median follow-up was 32 months [24-51].

Twelve patients had primary placement of transcorporal cuff because of previous radiation. For 25 patients the transcorporal cuff implantation was done in the secondary procedure after failure of UI surgery (7 male slings, 17 AUS, 1 Pro-ACTTM balloon). The total AUS device was implanted in 31 patients and the cuff alone in 6 patients with the other components of AUS left in place. Periurethral adhesions were considered for transcorporal implantation.

Mean preoperative daily pad use was 4.5 (±2.1) and 2 patients used a penile sheath. Median preoperative pad test was 530g (400-690).

Continence results were reported at the latest follow-up, median value was 32 months (24-51). The AUS remained functioning in 33 patients whereas it was explanted in 3 patients and never activated in 1 patient due to neuropathic chronic

scrotal pain. The continence rate for social continence and total continence was respectively 69.7% and 12.1%. Six patients (18.2%) required more than 1 pad daily and were considered incontinent. Median pad test was 17.5g (0-159) and mean ICIQ-SF score was 7.3/21 (±5.4).

REVISION AND COMPLICATION

AUS overall complications occurred in 18 patients (48.7%) (Table-2). Seventeen patients (45.9%) had undergone one or more surgical revisions including 7 transcorporal cuff replacements. Median time to revision was 8 months [4-16].

Mean I-QoL score was 93.9 (±15.0) and the mean post-operative PGI-I score was 1.5 (±0.8). Kaplan-Meier curve demonstrated a 5-year actuarial revision-free AUS survival of 51.0%. The history of pelvic radiation or failure of urinary incontinence surgery showed no statistically significant differences concerning continence, pad test, PGI-I, ICIQ-SF and I-QoL score.

Table 1 - Preoperative characteristics of the study population. Some patients had more than one previous surgery.

Variable	
Mean age at AUS implantation (SD)	70.1 (±7.1)
BMI (SD)	27.2 (±3.41)
No. androgen deprivation therapy	10
No. Radical prostatectomy	34
No. Previous pelvic radiotherapy	23
No. Transurethral prostatic resection	6
No. Bladder neck contracture surgery	12
No. Urethrotomy	5
No. Urethroplasty	1
Previous surgical treatment of UI	
AUS	17
Bulbourethral sling	7
Balloon	1

BMI = body mass index

Table 2 - Complications occurred during follow-up. Reported number was 31 in 18 patients.

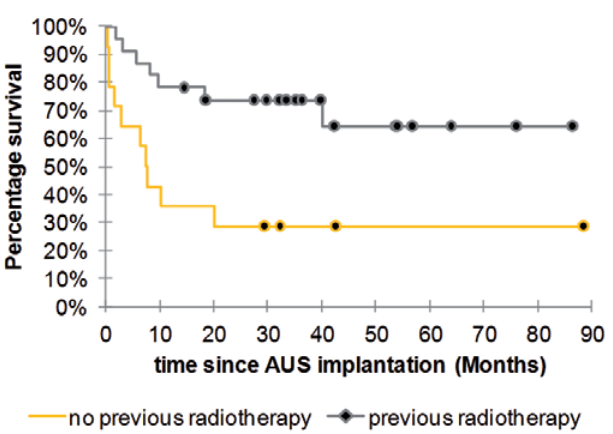
Cause of complication	No. Pts.	Delay (months)
Infection	**6**	
Cuff	1	5
Balloon	2	11/13
Pump and balloon	1	0.7
All of AUS	2	3/27/3
Erosion	3	0.7/1.5/7
Urethral atrophy	2	10/27
Mechanical failure	**11**	
Cuff	4	3/6/7/13
Balloon	5	6/8/10/20/30
Pump	1	18
Cuff and pump	1	40
Other	**9**	
Scrotal hematoma	2	0.1/1.5
Balloon migration	2	10/32
Acute urinary retention	5	0.1

Revision-free AUS survival was significantly higher in patients with previous radiation (p=0.006) (Figure-1).

In multivariate analysis, only patients with previous radiation had significantly less AUS revision than non-radiation patients (HR: 0.276; CI 95%: 0.1043-0.7295; p=0.0094).

Evaluation of outcome on potency was performed in 12 patients who presented erections before surgery, out of them 6 reported preservation of erections after the cuff implantation.

Figure 1 - Kaplan-Meier analysis comparing the revision-free AUS survival between patients with a previous history of radiotherapy (N=23) and without (N=14) a previous history of radiotherapy. (XL STAT Microsoft Excel® Addinsoft).



DISCUSSION

This study represents a large number of patients with a compromised urethra, and to our knowledge the first to specifically evaluate transcorporal AUS as a first option in radiation patients.

AUS is considered the gold-standard for the treatment of moderate to severe post prostatectomy UI (7). Despite a high satisfaction rate and few complications, revisions are still required due to erosion, infection, mechanical dysfunction or sub-urethral atrophy. A previous implantation or urethral surgery or radiation had an increased risk of AUS failure.

Different management may be proposed in a compromised urethra including male sling ProACT™ and AUS (7). In cases of AUS failure due to erosion or infection, or in cases of incontinence recurrence due to sub-cuff atrophy, a tandem cuff implantation (8) has been proposed, or a relocation of the cuff to a more proximal site on the bulbar urethra (9) whether or not associated with a down-sizing of the cuff (10) by 3.5cm.

In the literature, reimplants of bulbar urethral AUS after removal of previous AUS were not associated with a lower continence rate or complication as reported by Raj et al. (9). Conversely, Lai et al. (11) found a fourfold higher risk of erosion in a secondary reimplant patients in comparison with a virgin AUS implant. In a recent study, Bant et al. (12) reported a multicenter outcome analysis of 386 AUS placement and confirmed that urethral risk factors were prior to AUS erosion, history of urethral stent placement or radiation. Mc Geady et al. (4) assessed the compromised urethra in 86 patients and found an increased rate of failure with the tandem and 3.5 cuffs. These authors observed a 67% failure rate in the 3.5 cuff group but 36% in transcorporal group. These complications of a narrow cuff were confirmed by Bant et al. (12) and could be explained by the placement in a more distal location where the urethral wall is thin and the diameter reduced.

These findings support the transcorporal AUS placement approach in a compromised urethra patient, an option which was first proposed in 2002 (5). Transcorporal AUS in salvage of AUS or sling failure occurred in 65% of our series. The various series of this technique reported in the literature are of small sample size and only one prospective study is currently available (6). In the literature, the main indication for transcorporal AUS was urethral atrophy, salvage AUS or sling failure and previous urethral surgery (5, 13-16).

The primary objective of our study was the functional results and complications evaluation. Our data were similar to those mentioned in other reported studies (5, 6, 13-16). It is difficult to compare the continence rate due

to absence of a standardize definition of continence. Based on a more common definition of continence (0 to 1 pad), our continence rate was 81% and most patients were very satisfied. The complete continence rate was only 12% but this rate is difficult to assess from the literature. Our revision rate was higher than that reported in the literature but this was primarily due to mechanical failure (29.7%). This is possibly explained by an option to replace a standard placement cuff by a transcorporal cuff when the balloon and the pump were considered correct, instead of a total component replacement. There is a limited incision and a shorter operative time benefit from this option but there is also an increased the risk of secondary AUS revision for the components not changed. Another option could have been to routinely change all the components when the cuff is affected, particularly after few years follow-up. We also changed the balloon from 61-70 to 71-80 in 5 patients in order to pressurize when there was a secondary leakage and low urethral pressure under the cuff. A primary implantation of 71-80mL balloon could be considered depending on the low risk of erosion in the transcorporal cuff and to improve the total continence rate but this option has not yet been evaluated. Transcorporal cuff (TC) placement is not completely protected from erosion and we report an 8% rate. An 11-24% rate was reported by Brandt et al. (12) in a non-specific large number of 119 TC placements out of 386 AUS implantation. Wiedemann et al. (6) did not report erosion in a specific series of 23 TC placement but reported a 13% infection rate that may be an associated complication. Although the cavernosum is open, the hemorrhage complications were rarely reported, possibly due to non functional erectile tissue in the majority of patients.

Radiotherapy induces ischemia and urinary late-effect radiotoxicity may induce detrusor dysfunction, abnormal compliance, over activity and urethral damage such as fibrosis or atrophy (17-19). However, some patients could have had a normal urethral appearance during surgery or limited periurethral adhesions. In patients with a bulbar urethral cuff in primary implantation, results in the literature were contradictory. For Perez et al. (17) and Gohma et al. (19), there was no difference concerning continence or revision rates between patients with or without previous radiation therapy. Raj et al. (9-20) initially reported no difference. However, one year later in a study examining risk factors, the same institution found that a prior radiation therapy and a prior explant to increased the risk of subsequent erosion. In other series, patients with a history of radiotherapy presented more revision (18, 21, 22), or infection (18), but with no impact on continence. In the literature, no study, to our knowledge analyzed the impact of radiotherapy on functional results in patients with a transcorporal cuff.

In our series, a major finding was that there was no increase in the incontinence rate in patients who received radiotherapy and surprisingly significantly less revision. Moreover, when radiation patients had a transcorporal cuff as a first option (no prior incontinence surgery) the good results persisted in a multivariate analysis. A possible explanation could include the sample size and the effect of radiotherapy on cavernous tissue that can receive up to 44 Gy units (23) but induce a fibrosis which could increase the resistance of cavernous corpus. Our rate of erosion or infection was low, i.e. 13%, and no secondary urethral atrophy occurred in radiation patients within the limit of follow-up.

An evaluation of erectile function was not the primary aim of our study. However, the risk of impotence may be considered and the patient must be informed. Wiedemann et al. (6) showed a preservation of erectile function in 5/6 patients after transcorporal AUS placement. In our study, 50% of the 12 normal erection patients had persistent erection after surgery, confirming that transcorporal cuff was not inconsistent with erections, although the IIEF5-SF questionnaire was not used. An explanation for the preservation of erection could be the location of the cuff close to the tunica albuginea, thus leaving apart the erectile tissue. Patients must be informed that implantation of an erectile prosthesis inside the corpus caver-

nosum is not recommended when transcorporal cuff is performed.

The limits of our study were a retrospective analysis with a limited number of patients and single center experience, as well as the lack of a pad test and preoperative questionnaire. All of the radiation patients had external beam radiation, however we did not evaluate the relationship with the dose or brachytherapy.

The interesting results of transcorporal AUS as primary option in radiation patients must be considered, and could be more documented in a prospective study in comparison with periurethral standard cuff AUS and a longer follow-up.

CONCLUSIONS

Transcorporal AUS cuff placement is a useful alternative procedure option for the treatment of severe male UI, especially in patients with a compromised urethra after prior surgery or radiation. A high continence rate was reported and preservation of erection occurred in 50% of the patients.

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CONFLICT OF INTEREST

None declared.

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Ureterocalycostomy – final resort in the management of secondary pelvi-ureteric junction obstruction: our experience

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ABSTRACT

Ureterocalycostomy can be performed in patients in whom desired methods of treating secondary PUJ (Pelvi-Ureteric Junction) obstructions either failed or could not be used. In our study, one child and two adults in whom one redo-ureterocalycostomy and two ureterocalycostomies were performed for severely scarred PUJ. The causes for secondary PUJ obstruction were post-pyelolithotomy in one case, post-pyeloplasty and ureterocalycostomy for PUJ obstruction in the second patient and the third patient had long upper ureteric stricture post-ureteropyeloplasty due to tuberculosis. In all these cases ureterocalycostomy proved to be salvage/final resort for preserving functional renal unit.

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INTRODUCTION

Although the spectrum of indication for ureterocalycostomy has changed, it is considered an important salvage procedure to bypass extensive peripelvic scarring and provide non-obstructed and dependent drainage (1, 2).

This technique has been used for over 40 years, more frequently for the management of failed pyeloplasty (3), in case of post pyelolithotomy PUJ disruption/scarring and long stricture in upper ureter (specially due to tuberculosis).

MATERIALS AND METHODS

Three cases of ureterocalycostomy from 2009 to 2015 were reviewed. They included 3 patients (two males and one female): one child 6 years old, one adult male 35 years old and one female 23 years old. Ureterocalycostomy was done in two patients and redo ureterocalycostomy in one patient. Indications were post pyelolithotomy in one case, post pyeloplasty and post-ureterocalycostomy in one case and in one patient post uretero-pyeloplasty for upper ureteric long length

stricture due to tuberculosis. Preoperative anatomical/functional assessment was done by nephrostogram, intravenous pylography, retrograde pylography ± diethyle triamine pentaacetic acid (DTPA) renal scan.

Case 1: A 5 year-old male child had 1.5cm PUJ calculus with total intrarenal pelvis. He underwent pyelolithotomy in general surgery unit. During the procedure, he had PUJ disruption which was sutured over double J (DJ) stent. Post operative course was uneventful. DJ stent was removed after 6 weeks. Patient developed pain and fever after stent removal. He had progressive hydronephrosis on serial ultrasound (USG) scans. Retrograde Pyelography (RGP) with DJ stenting was tried but guide wire could not be passed beyond PUJ. Then the patient was submitted to ureterorenoscopy (URS) and complete blockage beyond the level of upper ureter was detected. Percutaneous nephrostomy tube (PCN) was placed as drainage procedure and nephrostogram (Figure-1) was done after 2 weeks, which confirmed complete PUJ blockage. Due to the presence of intrarenal pelvis and gross periureteric fibrosis we decided to perform ureterocalycostomy (Figure-2) as first choice which was performed after 6 months from primary procedure.

Figure 1 - Nephrostomogram showing complete blockage at PUJ.

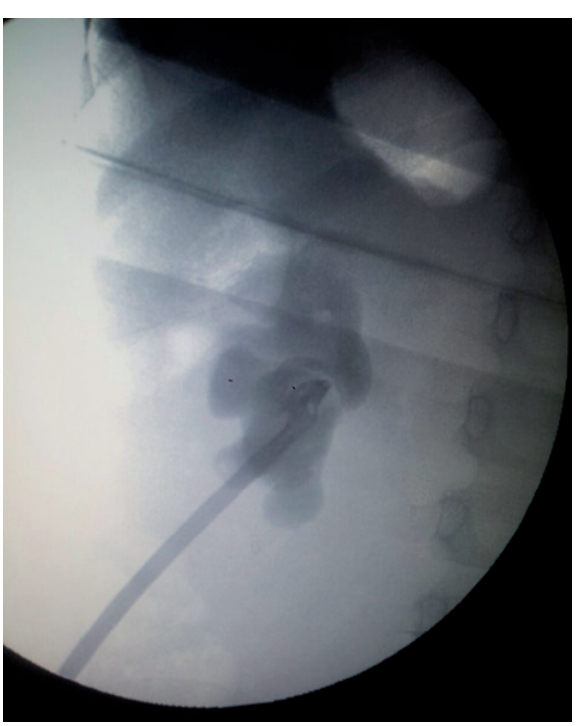
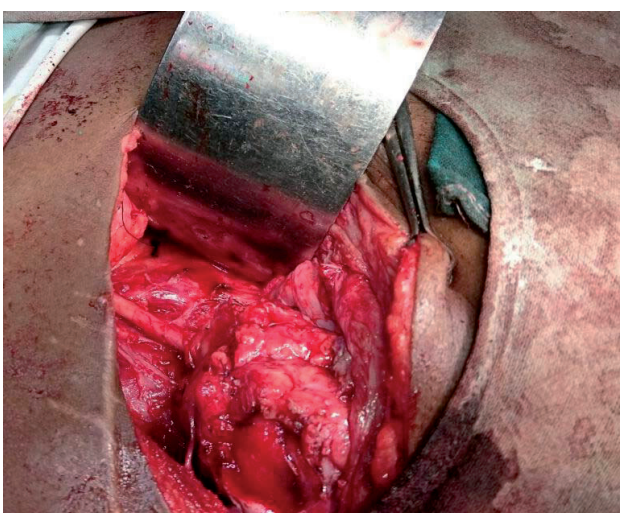
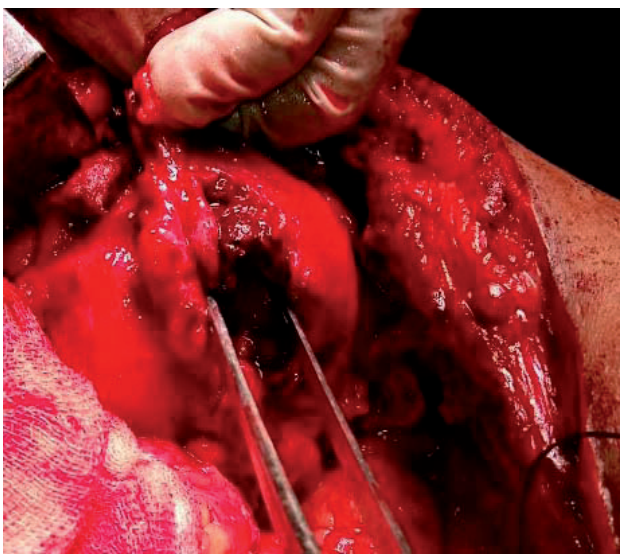


Figure 2 - Intraoperative photo–completion of procedure.



Case 2: A 35 year old male underwent left pyeloplasty for left pelviuretric junction obstruction. After DJ removal, at 6 weeks he developed pyonephrosis and perinephric abscess for which percutaneous nephrostomy and drainage of abscess was done. At that time, on evaluation by nephrostogram, DTPA renal scan and retrograde pyelography, he was found to have functioning and obstructed renal unit. On nephrostomogram he had complete obstruction distal to pelviuretric junction. He was submitted to left ureterocalycostomy with DJ and PCN elsewhere. DJ stent was removed subsequently. Patient presented to us 9 months ago with features of pyonephrosis on left side for which he underwent left PCN insertion. Subsequently he was re-evaluated by nephrostomogram, computerised tomogram, intravenous pyelography (CT-IVP), DTPA scan and found to have normal functioning obstructed left renal unit without drainage beyond ureterocalycostomy site. RGP and DJ stenting were tried but failed due to inability to pass the guide wire beyond anastomotic site, suggestive of anastomotic stricture. We performed a redo-ureterocalycostomy by guillotine technique (Figure-3) with DJ stenting. Intraoperatively we found gross

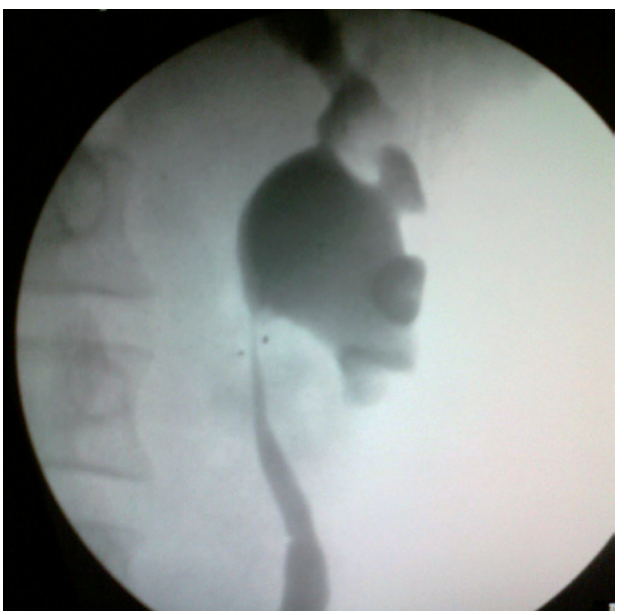
Figure 3 - Intraoperative photo-Guillotine technique.



perianastomotic site fibrosis and anastomotic site stricture. Contour of lower pole of kidney was maintained suggestive of previous anastomosis by incision/coring technique.

Case 3: a 23 year old female with left upper ureteric stricture secondary to tuberculosis (proved on urine AFB positive) with solitary functioning kidney. She underwent left DJ stenting and anti-tuberculous treatment. After completion of intensive phase, she underwent left ureteropyeloplasty over DJ with excision of strictured segment elsewhere 4years ago. After DJ removal at 6 weeks, she developed pain, fever and pyonephrosis for which PCN was placed and referred to us. Subsequently, she was evaluated by nephrostogram, CT IVP, and DTPA scan and found to have normal functioning obstructed left renal unit without drainage beyond anastomotic site. RGP (Figure-4) and re- DJ stenting tried but failed due to inability to pass the guide wire beyond anastomotic site suggesting anastomotic stricture. Three years ago, we did ureterocalycostomy by guillotine technique over DJ stent. Intraoperatively she had gross perianastomotic site fibrosis and anastomotic site stricture. After 6weeks, DJ was changed as RGP showed inadequate drainage. Subsequently she needed two more DJ stent changes, after which she had non obstructed drainage which was evident on last RGP-IVP.

Figure 4 - RGP showing left upper ureteric stricture.



RESULTS

Three patients underwent ureterocalycostomy, out of which one had redo-ureterocalycostomy. Demographic profile is shown in Table-1. Two patients underwent primary procedures in other centres and one patient in our centre by general surgery unit before referring to Urology unit. One patient was primarily treated for pelvic stone with total intrarenal pelvis, one for PUJ obstruction and one for left upper ureteric stricture secondary to tuberculosis. Pre operative profile is shown in Table-2. All three patients were asymptomatic till last follow-up (1 case after 3 times change of stent every 3 months) with objective evidence of obstruction relief (Figure-5) (Table-3).

DISCUSSION

Historically described by K. Neuwirt in 1947 (4), the surgical technique most commonly used today was delineated by Hawthorne et al. (5). Due to its particular indication, this procedure is rarely performed and operator has limited experience (6). Basically it is used for pyeloureteric union in which conventional pyeloplasty cannot be performed, whether as first treatment or repeated surgery,

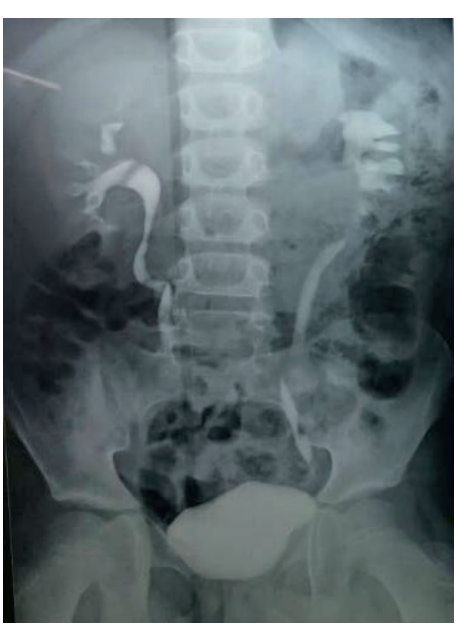
Table 1 - Demographic profile.

	Case 1	Case 2	Case 3
Age(years)	6	35	23
Gender	Male	Male	Female

Table 2 - Preoperative and Intraoperative findings.

	Case 1	Case 2	Case 3
Primary disease	Pelvic stone with intrarenal pelvis	PUJ obstruction	Left upper ureteric stricture(TB)
Primary procedure	Pyelolithotomy	Pyeloplasty and Ureterocalycostomy	stricturoplasty
Complications / event in perioperative period during primary procedure	PUJ disruption	Wound infection and long term leak, perinephric abscess	-
Primary procedure	Our centre, by Surgical unit	Other centre	Other centre
Salvage Procedure done	Ureterocalycostomy	Redo-Ureterocalycostomy	Ureterocalycostomy
Intraoperative findings	Severe peripelvic and periureteric scarring+	Severe scarring at perianastomotic site	Severe peripelvic and periureteric scarring

Figure 5 - Follow-up IVP-adequate drainage across anastomosis.



due to complications of kidney stone surgery or for the treatment of renal or ureteric complications of tuberculosis (7) The most frequent indication is scarring resulting from previous open surgery for stone removal or repair of PUJ obstruction (8). In many cases redo-pyeloplasty or endopyelotomy are the alternatives which can be used (9). In our cases, these options could not be used as in one case, pyelolithotomy was done for PUJ stone with total intra-renal pelvis having intraoperative disruption of PUJ, in the second case pyeloplasty and once ureterocalycostomy and in the last case due to post-ureteropyeloplasty for long upper ureteric stricture. Secondary PUJ stenosis following conventional pyeloplasty, open stone surgeries or endopyelotomy is complicated by peripelvic inflammation and dense fibrosis caused by urine extravasation which make them unsuitable for redo PUJ reconstruction (10).

Preoperative patient evaluation is the key to success for the procedure. It is imperative the

Table 3 – Outcome.

	Case 1	Case 2	Case 3
Hospital stay(days)	14	15	14
Follow up	1 year	6 months	3 years
Relief of obstruction	Evident on IVP	Evident on IVP	Evident on IVP after change of stent, 3 times every 3 monthly
Reduction in hydronephrosis on USG	+	+	+

location and the extent of the disease segment assessed with preoperative imaging including retrograde/antegrade pyelography/IVP and nuclear renography to assess the renal function (1). Surgical techniques used in all cases include some key points which are access through virgin area, dissection of ureter with good amount of adventitial tissue, guillotine amputation of lower pole parenchyma, wrapping of anastomosis with omental graft, stenting of anastomosis with proximal diversion and achieving additional length by renal descensus, resection of ureteric tissue until normal and vascular tissue is identified with wide lateral spatulation (10). Guillotine amputation of lower pole is better than simple wedge resection or incision technique to avoid the anastomotic stricture (11). As in our second case, in which previous surgeon used incision/wedge resection technique during redo-ureterocalycostomy, contour of lower pole of the kidney was found intact.

In genitourinary tuberculosis, long upper ureteric stricture may develop. For such cases, Couvelaire reported good result with ureterocalycostomy (12). We had one case who was treated with antitubercular treatment with double J stent and after 6 weeks, ureteropyeloplasty was done elsewhere which subsequently failed for which we have done ureterocalycostomy with renal descensus and nephropexy. Same patient needed three times change of stent every 3 months to achieve non-obstructed drainage evident on IVP.

Applying technical details meticulously leads to better results. No patient had major complication except one with proven genitourinary tuberculosis who needed three times change of stent which may be due to minimal residual disease which got settled later on.

Post operative results were assessed by USG/IVP with or without isotope renal scan in all cases and had resolving hydronephrosis with non-obstructive drainage with minimum follow--up of 6 months and maximum of 3 years. Shah TP et al. operated 25 cases of ureterocalycostomy of which 22 had clinical and radiological improvement (10). Arap et al. reported clinical and radiological improvement after laparoscopic ureterocalycostomy for complicated upper urinary tract obstruction in all 6 cases after median follow-up of 30 months (13).

CONCLUSIONS

Ureterocalycostomy is the final resort for salvaging functioning renal unit having complex secondary PUJ strictures. Likely situations include post pyelolithotomy for PUJ stone with complete intrarenal pelvis and PUJ disruption, long upper ureteric stricture (TB) and post ureterocalycostomy anastomotic stricture, if it is done by incision/wedge resection technique primarily.

CONFLICT OF INTEREST

None declared.

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The "Pelvic Harness": a skeletonized mesh implant for safe pelvic floor reconstruction

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ABSTRACT

Objectives: To evaluate the feasibility, safety and surgical results of skeletonized mesh implants to form a pelvic harness for pelvic floor reconstruction surgery.
Study design: Patients with advanced pelvic floor prolapse were enrolled to this study. Study model was a kit mesh, reduced to 75% of the original surface area by cutting out mesh material from the central mesh body. Patients were evaluated at the end of the 1st and 6th post-operative months and interviewed at the study conclusion.
Results: Ninety-five women with advanced pelvic floor prolapse had this implant. Mean follow-up duration was 9 months (6-12 months). The POP-Q point's measurements showed marked and statistically significant improvements. Bladder over-activity symptoms, fecal incontinence, pelvic pain and constipation rates were all reduced as well. No adverse effects related to the dissection or mesh implantation were marked. The first and sixth post-operative month follow-up records as well as the study conclusion interview findings were satisfactory in terms of subjective and objective cure and adverse effects occurrence.
Conclusion: This study data proposes that skeletonizing meshes might be safely and successfully implanted for potentially improved pelvic floor reconstruction.

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Reconstructive Surgical Procedures; General Surgery; Pelvic Floor Disorders

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INTRODUCTION

Pelvic organ prolapse (POP) is a common condition negatively affecting the quality of life of millions of women worldwide, with a lifetime prevalence of 11% (1). Women with advanced symptomatic POP experience daily discomfort, as well body image dissatisfaction and impaired sexual function (2). Treatment for POP requires significant health care resources (3), with an ever-growing impact in parallel with the growing elderly population (4,5).

According to recent studies, approximately one in ten women will undergo surgery for POP and/or incontinence during their lifetime (6). Many favor the trans-vaginal route over the abdominal approach; hence, the vagina is widely accepted as the natural orifice for POP reconstruction. Yet, POP repair surgeries have an unacceptably high failure rate with a 10-year reoperation rate of 17% reported by some (7) and disagreed by others (8). This may be attributed to weakness of fascial tissue, related to genetic factors, reduced collagen content or increased collagen destruction (9).

In an attempt to reduce these high failure rates, synthetic meshes were designed and implanted. They provided reinforcement and better support for vaginal surgical repair of prolapse. This led to a significant reduction in anatomical failure and reoperation rates (10, 11). However, mesh implant-related complications ranged from mild issues of transient pain and small mesh erosions to severe adverse effects such as large vaginal mesh exposures or extrusions, perforations into the bladder or bowel, and chronic pain. Mild mesh complications can be managed conservatively, but bladder or bowel injuries, fistulae, abscess formation, and debilitating pain may require repeat surgery and are not always curable (12).

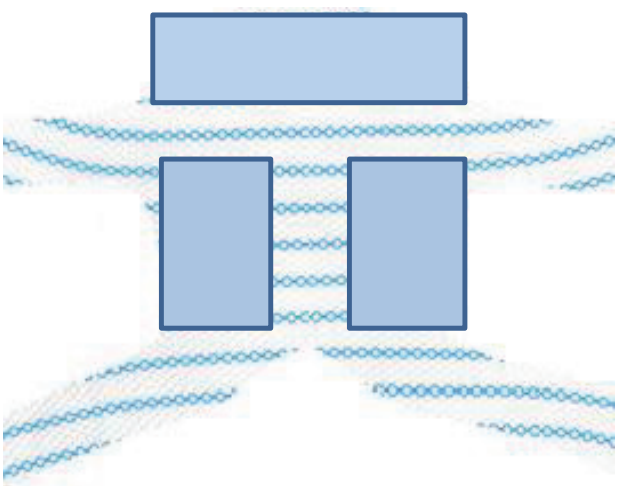
One of the recent implant modifications aimed at reducing adverse effects is the partial absorbable mesh (13-15). It is assumed that significant reduction of the implant mass may lead to reduction of the adverse effects and complications of the graft that are thought to be directly related to the mesh mass.

The current pelvic floor implant meshes are designed to cover the whole pelvic floor area, even though the native pelvic floor architecture is more ligamentary rather than a sheath-like. This leads to creation of large surface area of the mesh implants and to potentially increased rate of mesh related post-operative complications. The most significant mesh complications are erosions and post-operative pelvic pain which probably are directly related to the implant total mass and surface area. As mesh surgery is an important surgical tool for pelvic floor reconstruction, it is important to look for new ways to reduce the mesh complication rates.

In this study we suggest skeletonization of the common used pelvic floor mesh implants and making that structure more ligamentary than fascial by a significant reduction of the total implant mass, to create a pelvic harness rather than sheath-like implant (Figure-1).

The aim of this study was to evaluate the feasibility, safety and short-term surgical results of skeletonized mesh implants for pelvic floor reconstruction surgery.

Figure 1 - Anterior mesh surface area reduction.



MATERIALS AND METHODS

We conducted a prospective observational study following women, scheduled to undergo reconstructive pelvic surgery for symptomatic and advanced anterior or posterior pelvic floor compartment prolapse, using trans-vaginal mesh implants, during January 2012 to March 2013. The local IRB approved the study protocol.

All women experiencing symptomatic stage 3 vaginal wall prolapse, and being at increased risk for prolapse recurrence, who have been scheduled for POP vaginal reconstruction with a mesh implant were included in the study, after having a meticulous explanation regarding the potential benefits and adverse effects of having a small mesh implant. Risk factors for prolapse recurrence included previous POP reconstructive surgery and clinical assessment of poor pelvic floor tissue. Exclusion criteria were pelvic inflammatory disease and chronic pelvic pain.

Prior to surgery, all patients completed a comprehensive questionnaire on symptoms of prolapse, urinary, bowel, and sexual malfunction. Preoperative evaluation included a detailed pelvic site-specific vaginal examination at lithotomy position with a Sim's speculum during a maximal Valsalva maneuver and Pelvic Organ Prolapse Quantification (POP-Q) measurements and staging according to the standardized International Continence Society (ICS) scoring system (16). Each

compartment (apical, anterior and posterior) was separately evaluated for detection of defects in pelvic support.

Patients underwent trans-vaginal mesh placement using the partially absorbable mesh Gynecare Prolift+M (Ethicon, Summerville, USA), minimized by mesh body cutting down of 75% of the mesh surface, giving it a skeletonized ligamentary harness appearance. Anti-incontinence surgery was performed when indicated using sub-mid-ureteral synthetic tape, according to the surgeon's preference.

All patients were administered first generation Cephalosporin 1g intravenously, half an hour before surgery. An iodine antiseptic wash was applied to the area prior to the onset of surgery. All procedures were performed under general anesthesia. The detailed surgical technique was as published before (17). This included 50 milliliter saline hydro-dissection at the mid-line of the affected compartment vaginal wall, longitudinal incision, sub fascial lateral dissection towards the pelvic side wall up to the iliac spine and then to the mid-portion of the sacro-spinous ligament, through pass of the needle guide and the mesh arm thereafter. The other pair of arms was passed through the obturator plate for the anterior compartment or through the para-anal area for the posterior compartment reconstruction. The reduced mesh was placed and flattened, and the vaginal wall was re-sutured by two layers: first fascia and then mucosa with running absorbable sutures.

At the end of the 1st and 6th postoperative months, all patients were asked to complete the same questionnaire they had been given before surgery, and patients were re-evaluated with site-specific vaginal pelvic examination. Postoperative pain was assessed with the visual analogue scale (0-10) where 10 indicate maximal pain.

At the study conclusion, patients were interviewed by telephone for possible mesh-related complications and pelvic floor symptoms. The primary outcome measure was the mesh implant adverse effects, and the secondary outcome measure was the subjective cure rate, among the patient group.

Statistical analysis was performed with Vassar Stats Statistical Computation. The Wilcoxon signed-ranks test was used to evaluate quantitative parameters data distribution among groups.

Point bi-serial correlation coefficient was used to calculate P values for changes from baseline to postoperative parameters. Significance has been set for a value of $P<05$.

RESULTS

Of the 100 women enrolled in this study, 5 refused participation after having a thorough informed consent presentation, while 95 (95.0%) accepted participation and underwent surgery using the skeletonized non-absorbable mesh implants from January 2012 through March 2013 (Figure-2). The mean age was 64.5±9.0 year (range 43-83); all patients had advanced anterior or posterior wall prolapse, and all were admitted for corrective surgery with the skeletonized mesh implants. The mean follow-up duration was 9.5±3.8 months (6-12 months). Patient's characteristics are shown in Table-1. Only 17 women (17.9%) had previous POP surgery and 16 (16.84%) had previous hysterectomy. All patients had anterior mesh, 46 women (48.4%) had also posterior pelvic floor reconstruction (21 with mesh implants) and 33 (34.7%) had a concomitant anti-incontinence procedure.

Mesh implementation and placement was feasible in all cases. Regarding the primary outcome measure, there was not a negative effect of the skeletonization or any difference in insertion than the original mesh procedure. The perioperative complications are summarized in Table-2. No major complications were noticed, viscera were not injured, blood transfusion was not indicated, pain and infection rate and severity were modest. No adverse effects related to the dissection or mesh implantation were marked.

The postoperative POP-Q measurements showed marked statistically significant improvements: the average delta for the POP-Q Ba point was 7.51cm, for the Bp point it was 2.69cm, and for the C point the delta was 6.72cm. The secondary outcome measures, including the subjective and objective cure rates, urinary, sexual and defecation functions are shown in Table-3. Bladder over-activity symptoms, namely urgency, frequency and nocturia, were all found to be reduced

Figure 2 - Patient flow-chart

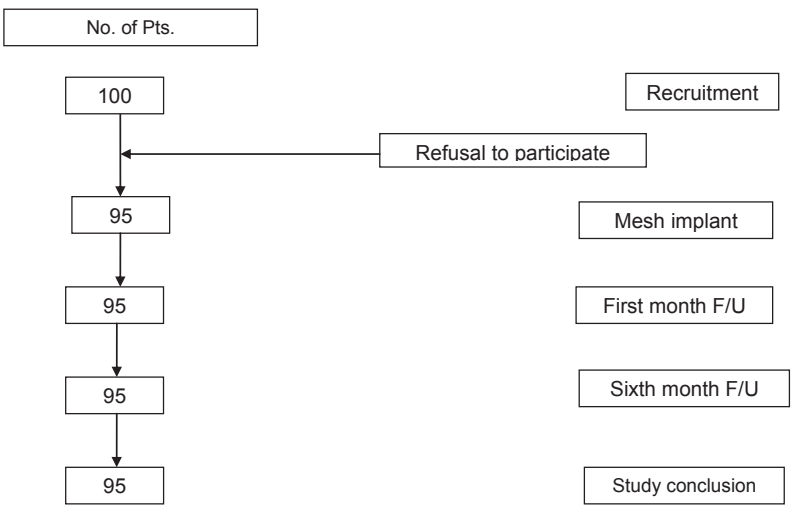


Table 1 - Patients characteristics (N = 95).

Variable	Mean±SD
Age	64.5±9.0 (Rang:43-83 Year)
Parity (no.)	2.6±1.6
BMI	24.8±2.4
Previous hysterectomy	16 (16.8%)
Previous POP surgery	17 (17. 9%)
Background chronic illness	35 (36.8%)
Follow-up duration	9.5±3.8 (6-12 Mnt)
Concomitant posterior compartment mesh*	25 (26.3%)
Concomitant posterior compartment colporrhaphy	21 (22.1%)
Concomitant anti USI operation**	33 (34.7%)

POP = Pelvic organ prolapse; **USI** = Urinary stress incontinence; **Mnt** = Month
* 12 skeletonized Prolift +M, 12-Prosima, 1-Elevate
** 22-TVTA, 9-TVTS, TVTO-2

Table 2 - Operative details.

	No. (%)	Outcome
Successful mesh placement	95 (100%)	
Urinary, bowel or ureteral injury	0 (0.0%)	
Operative bleeding > 200 ml	4 (4.2%)	No blood transfusion
Hematoma	1 (1.0%)	Self-resumed
Late post-operative pelvic pain	1 (1.0%)	Surgical mesh arm release at OR
Gluteal abscess	1 (1.0%)	Antibiotics
Granulation tissue	1 (1.0%)	Surgical removal at the outpatient clinic
Cervical elongation	1 (1.0%)	Partial cervical amputation

Table 3 - Patients outcome.

Variable	Prior to surgery	First Post-Op Mnt	Sixth Post-Op Mnt	P value
Urgency	54 (56.8)	10 (10.5)	13 (13.7)	<0.001*
Frequency	45 (47.4)	6 (6.3)	10 (10.5)	<0.001*
Nocturia	47 (49.6)	7 (7.4)	2 (2.1)	
SUI	40 (42.1)	9 (9.5)	10 (10.5)	<0.001*
Dyspareunia	1 (1.1)	1 (1.1)	2 (2.1)	NA
Anatomical objective outcome POP-Q points (Cm)				
Ba	4.7±1.1	-2.9±0.4	-2.9±0.4	<0.001*
Bp	0.3±2.5	-2.5±1.2	-2.5±1.2	<0.001*
C	0.6±3.3	-6.3±0.9	-6.3±0.9	<0.001*

* All p values were statistically significant for the difference between status prior to surgery and 1 month following surgery.
No significant differences were found between 1 and 6 months following surgery.
4 patients had asymptomatic grade 2 rectocele (Bp = 1,1,0,0) at sixth follow-up visit.

significantly. Faecal incontinence, pelvic pain and constipation rates were reduced as well. The first and sixth post-operative month's follow-up records as well as the study conclusion interview findings were satisfactory in terms of subjective and objective cure and adverse effects occurrence. There was a statistically significant improvement in bladder over-activity symptoms and stress urinary incontinence. There were only two cases (2.1%) of dyspareunia not significantly different from preoperative rate. The overall subjective and objective outcome results of this study are promising (Figure-3).

DISCUSSION

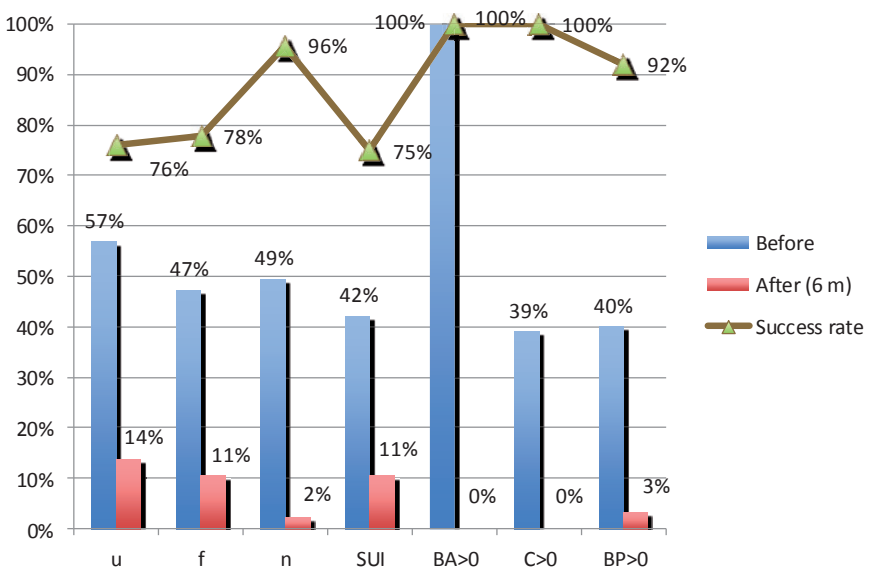
Petros previously suggested ligamentary sling rather than large mesh implants for reinforcement for pelvic floor reconstruction (18). This is the first study looking at the possibility to minimize an in-use mesh implants surface area by skeletonization to a ligamentary harness rather than a large sheath mesh support, for potential reduction of mesh related complications, mainly erosion and pain, attributed significantly to the left over mesh mass.

The main findings of this study are that minimizing this mesh to a skeletonized ligamentary harness model for primarily reinforcement of the pelvic floor ligaments is feasible, effective and safe as the original mesh implant. These findings are attributed probably to the fact that a substantial fraction of the implant, affecting the pelvic soft tissue negatively and causing pelvic pain, might be not necessary for pelvic floor reconstruction reinforcement. The native pelvic floor supportive tissue architecture is basically ligamentary rather than a flattened fascial sheath, thus the mesh reinforcing implants should have the form of a "ligamentary pelvic harness" rather than a sheath. Most of the mesh implants adverse effects are likely related to excessive implanted mesh mass, thus shifting from large and high surface area implants (17, 19) to small surface area sling framework might very well reduce unwanted adverse effects.

Pain reduction is crucial when considering mesh implantation. It is especially important in the sexually active patient who might have dyspareunia after POP reconstruction.

We found no inferiority with the outcome among women who underwent vaginal

Figure 3 - Objective and subjective success rate



u= Urinary Urgency; **f** = Urinary Frequency; **n** = Nocturia; **SUI** = Stress Urinary Incontinence; **BA** = B anterior POP-Q point; **C** = C POP-Q point; **BP** = B posterior POP-Q point

reconstructive surgery with skeletonized partially absorbable mesh implants for the pelvic floor, regarding other intra-and post-operative adverse effects or pelvic floor dysfunction symptoms. The postoperative anatomical and subjective findings were similar as well.

This technique is not more complicated, neither more hazardous to perform than the common one.

This study strength is limited by being single armed and by having rather short-term follow--up. Further larger randomized controlled long--term studies should be carried out to shed more light on this important issue of minimizing the augmented mesh surface area and adapting the concept of ligamentary rather than a fascial sheath correction of pelvic organs prolapse. Although the particular mesh used in the present study is no longer available, the principal benefits and drawbacks of the skeletonized, ligamentary mesh implant harness are valuable and meaningful.

CONCLUSIONS

Given that POP is a herniation process, one must acknowledge the importance of replacing the weakened fascia that caused the hernia defect with an implant to reinforce the reconstructive procedure, for assuring long-term cure. Yet, the surgeon must endeavor to reduce the mesh-related complications. This current study offers a new way for mesh implant adverse effects reduction, by adopting the skeletonized mesh concept.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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The outcomes of two different bulking agents (dextranomer hyaluronic acid copolymer and polyacrylate-polyalcohol copolymer) in the treatment of primary vesico-ureteral reflux

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ABSTRACT

Purpose: Subureteral injection of bulking agents in the endoscopic treatment of vesicoureteral reflux is widely accepted therapy with high success rates. Although the grade of vesicoureteric reflux and experience of surgeon is the mainstay of this success, the characteristics of augmenting substances may have an effect particularly in the long term. In this retrospective study, we aimed to evaluate the clinical outcomes of the endoscopic treatment of vesicoureteric reflux (VUR) with two different bulking agents: Dextranomer/hyaluronic acid copolymer (Dx/HA) and Polyacrylate polyalcohol copolymer (PPC).

Materials and Methods: A total 80 patients (49 girls and 31 boys) aged 1-12 years (mean age 5.3 years) underwent endoscopic subureteral injection for correction of VUR last six years. The patients were assigned to two groups: subureteral injections of Dx/HA (45 patients and 57 ureters) and PPC (35 patients and 45 ureters). VUR was grade II in 27 ureters, grade III in 35, grade IV in 22 and grade V in 18 ureters.

Results: VUR was resolved in 38 (66.6%) of 57 ureters and this equates to VUR correction in 33 (73.3%) of the 45 patients in Dx/HA group. In PPC group, overall success rate was 88.8% (of 40 in 45 ureters). Thus, Thus, this equates to VUR correction in 31 (88.5%) of the 35 patients.

Conclusions: Our short term data show that two different bulking agent injections provide a high level of reflux resolution and this study revealed that success rate of PPC was significantly higher than Dx/HA with less material.

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Vesico-Ureteral Reflux; Hyaluronic Acid; Pyran Copolymer; Therapeutics

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INTRODUCTION

The endoscopic injection technique for the treatment of VUR was first described in adults by Matouschek in 1981 and the first clinical series was reported by O'Donnell and Puri in 1984. Although the success rates mainly depend on the VUR grade, surgeon's experience, anatomic localization of ureters, the nature of the bulking material may also have an effect on the success rates (1-3). Over the past three decades different bulking agents such as collagen, polytetrafluoroethylene (Teflon®), polydimethylsiloxane (Macroplastique®), calcium hydroxyapatite (Coaptite®) have been used (4, 5). Dextranomer/hyaluronic acid copolymer (Dx/HA, Deflux®, Q-Med, Uppsala, Sweden) was introduced into clinical use by Stenberg and Lackgren in 1995. After the

approval of Dx/HA in Europe and worldwide clinical studies showing high resolution rates of VUR, it became widely accepted bulking agent in the endoscopic treatment of VUR (6). Dx/HA is composed of dextranomer microspheres and non-animal hyaluronic acid components that forms a viscous gel. Dextranomer microspheres are formed by cross-linking dextran polymers into porous beads of 80-120µm in diameter. A relatively new tissue augmenting material polyacrylate polyalcohol copolymer (PPC, Vantris®, Promedon, Cordoba, Argentina) is a non-biodegradable bulking agent that belongs to the family of acrylics: particles of polyacrylate polyalcohol copolymer. This copolymer is immersed in glycerol with a physiological solution carrier. The average diameter of PPC particles is 300µm with a higher molecular mass. After the implantation of PPC, it induces fibroblastic growth by high superficial electronegativity to be covered by a fibrous capsule. This fibrotic capsule leads to stability and endurance of injected material, affects the local and distant migration and also the success rate (7).

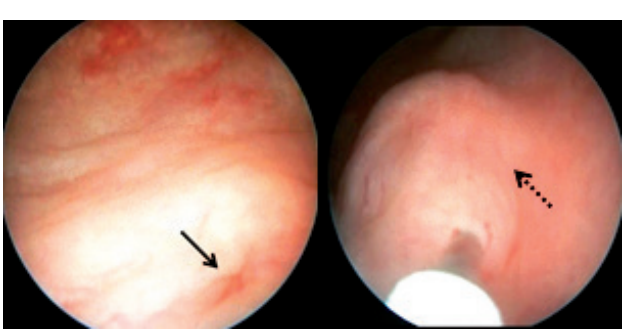
In this retrospective study, we reported the outcomes and success rates of two different bulking agents (Dx/HA and PPC) and analyzed the factors affecting the results in the endoscopic treatment of VUR in children.

PATIENTS, MATERIALS AND METHODS

We retrospectively reviewed the medical records of all cases that underwent endoscopic treatment for primary grade II-V VUR by the same surgeon between 2007 and 2014. The surgeon had previous experience with different bulking agents such as polytetrafluoroethylene, calcium hydroxyapatite and also with Dx/HA. Patients with anatomic malformations (ureteral duplication, posterior urethral valve, paraureteral diverticula) and neurogenic disorders were excluded from the study. A total of eighty patients (49 females and 31 males) were assigned into two groups: subureteral injection of Dx/HA and subureteral injection of PPC. The children with dysfunctional voiding who were diagnosed by history, uroflowmetry or multichannel urodynamics were primarily allocated to conservative treatment. The radiologic grading of VUR was based on the voiding cystourethrogram (VCUG) according to the international classification system (International Reflux Study Committee) before and after the surgery or during the conservative treatment (8). Dimercaptosuccinic acid (DMSA) renal scan was used to assess renal scarring in preoperative and postoperative follow-up. All patients received antibiotic prophylaxis until VCUG showed spontaneous resolution or definitive cure of the VUR.

The indications for intervention were breakthrough urinary tract infection (UTI) while on antibiotic prophylaxis, progression of renal scarring and persistent VUR after at least one year of non-operative management. Dx/HA was used as a bulking agent from January 2007 to December 2010, whereas PPC was preferred as injection therapy from January 2011 to December 2014. All injections were performed under general anesthesia. Briefly, the patients were placed in the lithotomy position and the skin was prepared. Bladder was filled about to 70% of the estimated bladder capacity. 9.5Fr pediatric cystoscope with a 5Fr working channel was used for the procedure. The usual technique of subureteral injection is: first the ureteral orifice is determined and the needle is introduced submucosally under the ureteral orifice at 6 o'clock position. After the injection of the bulking material the needle is left in place for 1 minute (Figure-1). Patients were maintained on their antibiotic prophylaxis until the reflux was documented to be absent on postoperative VCUG

Figure 1 - After the injection of bulking material the needle was left in place for 1 minute.



3 months after the injection. Patients who failed initial injection were offered a second injection or open surgery and a new VCUG was performed 3 months after the second injection or the surgery. Statistical analysis was performed by using SPSS statistical software, version 11.0 (SPSS Inc. Chicago, III. USA). Means, standard deviations and percentages were used for descriptive statistics. Group comparisons were performed using the independent t test for continuous data and chi-squared test for the categorical data. Values of $P<0.05$ were considered statistically significant.

RESULTS

The demographic data and the patient characteristics of both groups are presented in Table-1. There was no significant difference in baseline characteristics between the groups. Dx/HA group included forty-five patients, 29 girls (64%) and 16 boys (36%), with a mean age of 5.3 years (range 1-12 year). The mean follow-up was 32 months (18 to 60 months). In this group, VUR was unilateral in 33 (73%) and bilateral in 12 (27%) patients comprising 57 ureters. VUR was grade II in 15 (26.5%), grade III in 20 (35%), grade IV in 12 (21%) and grade V in 10 (17.5%) ureters. Eighteen patients who had voiding dysfunction were properly treated before intervention.

Thirty-five patients, 20 girls (57%) and 15 boys (43%), with a mean age of 5.4 years (range 1-11years) and 45 ureters were treated with PPC injection. The mean follow-up was 28 months (10 to 47 months). Twenty-five patients (71%) had unilateral and 10 patients (29%) had bilateral VUR. There were 12 (27 %) ureters graded as II, 15 (33%) as III, 10 (22%) as IV and 8 (18%) as V. Sixteen patients had voiding dysfunction in PPC group.

The comparative success rates between both groups and resolution of VUR in both groups according to the reflux grades are shown in Table-2 and Table-3. VUR was resolved in 30 (52.6 %) of the 57 ureters after a single Dx/HA injection. The success rate rose to 38 (66.6%) in 57 ureters after the second injection and this equates to VUR correction in 33 (73.3%) of the 45 patients. The mean injected volume of Dx/HA was 0.9ml (range 0.4-1.5ml) (Table-2). The resi-

Table 1 - Demographic data and patients characteristics of two groups.

	Dx/HA (n=45)	PPC (n=35)
Mean age (years)	5.3	5.4
Gender		
Male	16 (36%)	15 (43%)
Female	29 (64%)	20 (57%)
Number of ureter	57	45
Laterality		
Unilateral	33 (73%)	25 (71%)
Bilateral	12 (27%)	10 (29%)
VUR grade		
II	15 (26.5%)	12 (27%)
III	20 (35%)	15 (33%)
IV	12 (21%)	10 (22%)
V	10 (17.5%)	8 (18%)

P values were all non-significant for the above mentioned data.

Table 2 - Comparison of the success rates after injection treatment with two different bulking agents.

	Dx/HA (ureter=57)	PPC (ureter=45)	P value
Single injection	30 (52.6%)	37 (82%)	P<0.05
Multiple injection	38 (66.6%)	40 (88.8%)	P<0.05
Mean injected volume (mL)	0.9	0.5	P<0.05

Table 3 - Free of VUR after endoscopic treatment in both groups according to VUR grade.

Dx/HA			PPC	
VUR Grade	RRU (n=57)	Resolved (n=38)	RRU (n=45)	Resolved (n=40)
II	15	15 (100%)	12	12 (100%)
III	20	16 (80%)	15	15 (100%)
IV	12	6 (50%)	10	8 (80%)
V	10	1 (10%)	8	5 (62.5%)

dual VUR was observed in 19 ureters (grade V in 9, grade IV in 6 and grade III in 4 ureters). These refluxing ureters were corrected by open surgery.

In PPC group, the success rate with a single injection was 82% (37 of 45 ureters), while 88.8% (40 of 45 ureters) after the second injection. Thus, this equates to VUR correction in 31 (88.5%) of the 35 patients. The mean injected volume of PPC per ureter was 0.5ml (range 0.2-1.2ml). Residual VUR was observed in 5 ureters (grade V in 3, grade IV in 2 ureters) in this group. All residual VUR were treated with ureteroneocystostomy.

When the results of the injection therapy were compared statistically, a significant difference was found for success rates between the groups. The success rates of PPC injection were significantly higher than the Dx/HA group for both single injection and multiple injections ($p<0.05$). Furthermore, there was a significant difference for injected volume of bulking agent between both groups. The injected volume of Dx/HA was much more than the volume of PPC ($p<0.05$). Ureteral obstruction, as a complication, did not emerge after injection or surgical therapy in both groups. Neither adverse reactions nor any signs of toxicity were observed in either group.

After injection, none of cured patients had recurrent UTI (febrile or afebrile) during the follow-up examination. However, nine (5 afebrile, 4 febrile) patients (20%) had UTI after Dx/HA injection, and 4 patients (11.5%) had febrile UTI after PPC injection. All of them showed persistent high grade VUR in both groups.

DISCUSSION

The concept of the endoscopic correction of VUR offers a minimal invasive treatment in the management of urinary tract infection or renal parenchymal damage associated with reflux. Subureteral injection of bulking agents has recently demonstrated good success rates for endoscopic treatment of VUR and has become increasingly popular for managing VUR. This technique was first described by Matouschek in 1981 and later popularized by Puri and O'Donnell (2). Consequently, many different bulking agents have been used in the endoscopic treatment of VUR until now (4, 5, 9, 10). Since the Food and Drug Administration approved the use of Dx/HA copolymer for endoscopic treatment of VUR, it has gained popularity in many centers in the USA and Europe. It is a biocompatible substance with minimal immunogenic properties and a lack of distant migration (11). Dx/HA is the most studied bulking agent and there is enough long term data

existing for understanding its effects. Although, the overall success rates of Dx/HA injection have been reported to be tremendously variable (50-94%) by different authors (12, 13), meta-analysis demonstrated that, on average, 77% of ureters injected with Dx/HA were VUR free 3 months after injection (14, 15). Increasing experience and new injection techniques such as Hydrodistention Implantation Technique (HIT) and double HIT could have led to higher results over time, making this technique also applicable for high-grade VUR (12, 16). On the other hand, many of the studies included in meta-analysis had limited follow-up, only a single VCUG usually within the first 3-6 months postoperatively. Therefore, some recent studies with longer follow-up suggest that these results may not be durable. A recent study by Lee et al. reported a success rate of only 46% in 1 year and studies by Lackgren et al. and Oswald et al. also noted a significant failure rate with extended follow-up (17-19). Moreover, more recent data from the Swedish reflux trial, 20% of previously successfully treated children recurred after 2 years of follow-up, despite relatively high success rates (20). In our study, the overall rate was 66.6% (38/57) ureters after Dx/HA injection and this equates to VUR correction in 73.3% (33/45) of the patients. Although our results appear relatively low, they actually were consistent with other reports.

PPC, the relatively new bulking agent, is a non biodegradable synthetic material which leads to the formation a fibrotic capsule, giving stability and long term permanence. The average diameter of PPC particles is 320µm, thus, it causes a bulkiness that remains stable through time when injected into the soft tissues and reducing the risk of local and distant migration (7, 21). This material was tested with several in-vitro and in-vivo studies. These tests demonstrated that it was non-cytotoxic for cell lines in culture, didn't cause sensation in mice and no signs of inflammation or necrosis in any organ after implantation (7). On the other hand, the clinical experience with PPC is still very limited. Firstly, in 2010, Ormaecheaet al. reported a multicenter trial from South America (22). In this study, 61 patients with all grades of VUR completed a 1 year follow-up. The number of injected ureters was 88 and the mean injected volume per unit was 0.76ml. The overall success rate of this series was 83.6%. Shortly after this study, Chertin et al. published preliminary data on endoscopic treatment of vesicoureteric reflux with PPC (21). Their series contained thirty-eight children with primary or complex VUR, and the results of the study were quiet satisfactory. The overall success rate was 92.1% in this series. Recently, the results of three years of prospective follow up have been reported by the same group (23). Their success rate was 92.7% after a single injection in all grades of VUR and mean injected volume of PPC per ureter was 0, 7ml (range 0.1, 1ml). Moreover, all patients in this study have had ultrasound scan examination over a 3-year period. The results of ultrasound scan showed the proven evidence of long-term durability of PPC. Another study from Argentina showed 92.3% resolution rate according to the renal refluxing unit and 93.82% according to the number of patients with less than <1ml of material (24). According to our knowledge, there is only one study comparing these two different bulking agents in chronic renal failure adult patients indicating similar effectiveness with Dx/HA and PPC (79% versus %81) (25). In the current study, the overall success rate of PPC injection was 88.8% (40/45 ureters) and the mean injected volume per ureter was 0.5ml. Our results were in concordance with before mentioned studies.

In our study, when demographic data and success rates in both groups were compared, there was not a significant difference in age, gender, laterality and reflux grade between both groups. The overall success rates of PPC were statistically higher than in Dx/HA group. In addition, mean injected volume of Dx/HA was statistically higher than PPC.

One of the most important observations to come out of the literature concerning Dx/HA is the steep learning curve for materials. Kirsch et al. reported a dramatic improvement after the first 20-30 cases in their two surgeon experience, suggesting a 10-15 case learning curve per surgeon (26). Because all injections have been performed in our patients by the same experienced

surgeon, the learning curve for Dx/HA injections has not been considered to have negative effects on the current study. PPC is thought as a novel therapy by some authors due to its physiochemical properties, better bulking effect with lower doses and rapid learning curve (24, 27). We also believe that the differences between the results could be based on the biodegradable nature of bulking agents. As mentioned above, the molecular mass of PPC is very high in contrast to Dx/HA. Once injected, the particles of PPC are covered by a fibrotic capsule causing a bulkiness that remains stable through time.

The limitations of our study are that it is a retrospective audit and with short term follow-up. The populations were studied in different periods of time which may affect the learning curve of the surgeon. We also have a longer follow-up period for Dx/HA than PPC that may affect the recurrence rate of each material. However, each material has more than 2-year follow-up period. Another limitation is not having a volume based radiologic study to measure the bulking agent after implantation which may give information about biodegradation or long term stability of these materials.

CONCLUSIONS

Subureteral injection of bulking agents is a safe, well tolerated, effective minimally invasive outpatient procedure for treatment of children with VUR. Although, our short term data show that two different bulking agent (Dx/HA and PPC) injections provide a high level of reflux resolution, this study suggest that PPC success rates are significantly higher than Dx/HA success rates. However, multicenter studies and/or prospective randomized controlled trials with long term follow-ups are necessary to definitively compare bulking agents in their role as endoscopic therapy for VUR.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Association between ambient temperature and lower urinary tract symptoms: a community-based survey

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ABSTRACT

Purpose: The aim of this study was to evaluate the individual change of International prostate Symptom Score (IPSS) and Overactive Bladder Symptom Score (OABSS) in each patient by temperature conditions.

Materials and Methods: The severity of lower urinary tract symptoms (LUTS) was explored using the IPSS and OABSS questionnaires that were completed by 2.486 subjects (923 males and 1.563 females) aged 60 years and older. Korea Meteorological Administration data was used to determine daily average temperature and daily temperature difference on the interview dates at each site.

Results: The mean IPSS and mean age for males was 13.45±8.24 and 75.03±6.20 years, respectively. The mean OABSS and mean age for females was 4.41±3.10 and 73.74±6.03years, respectively. Daily average temperature and daily temperature difference ranged from-3.4-28.3°C and 2.2-16.9°C, respectively. Age was a significantly risk factor for IPSS, OABSS, and QoL (P<0.001, <0.001, and 0.005, respectively). After multiple regression analysis, daily average temperatures did not show a statistically significant change in IPSS and OABSS. Only daily temperature differences were associated with male LUTS.

Conclusions: While LUTS could be worsened in low temperatures generally, IPSS and OABSS were not affected by daily average temperature conditions. Daily temperature differences may be more influential than daily average temperatures.

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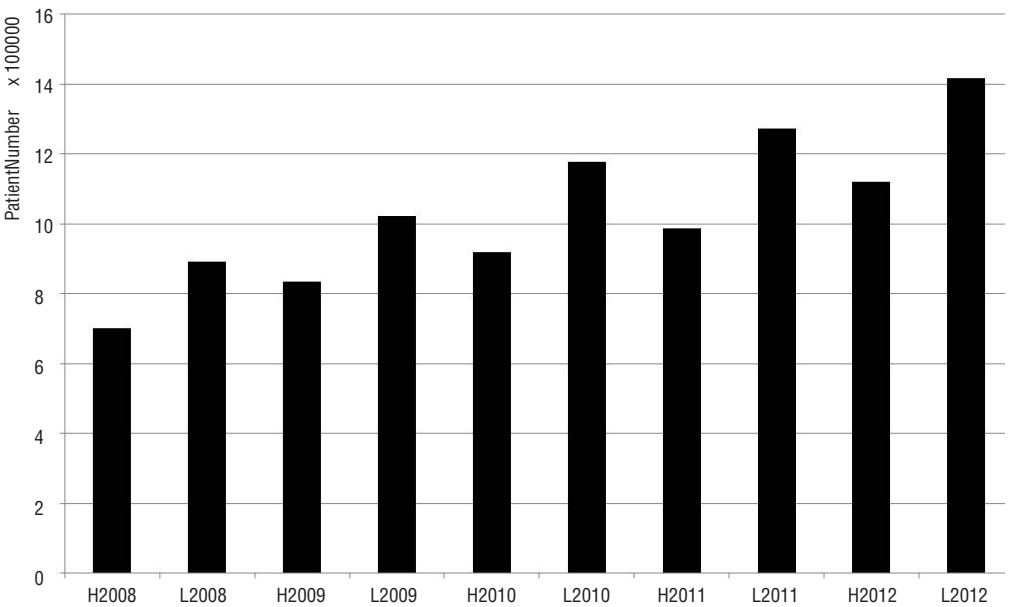
INTRODUCTION

Variance in environmental temperature has been associated with various diseases. The documented more frequent occurrence of myocardial infarction in cold temperatures is attributed to increase in plasma viscosity, serum cholesterol levels, blood pressure, sympathetic nervous activities, and platelet aggregation (1, 2). Concerning the association between benign prostate hyperplasia (BPH)/lower urinary tract symptoms (LUTS), according to the BPH/LUTS patients-based dataset of five-years (2008-2012) of National Health Insurance in Korea, seasonal variations of visiting hospital patients between summer (June to September) and winter (January to March, November, December), it was highest in 2011 (29.0%) and lowest in 2009 (22.6%) (Figure-1).

Seasonal variations of LUTS were reported in several small longitudinal studies; cold

Figure 1 - Seasonal benign prostatic hyperplasia (international classification of disease code; N40) patient number from 2008 to 2012. L, low daily average temperature (<10ºC), (Jan. to Mar., Nov., Dec.); H, high daily average temperature (>20ºC) (Jun. to Sept.). The data set of National Health Insurance in Korea.



Accessed November 28 2014.

environmental stress and ambient temperature change elicited urinary sensations and frequent urination along with increasing heart rate and blood pressure (3, 4). However, seasonal changes were not observed in the International Prostate Symptom Score (IPSS), storage symptom score, voiding symptom score, and quality of life (QoL) (5, 6). As well, changes in fluid temperature did not significantly change the threshold volume of bladder sensation or increase the incidence of idiopathic detrusor overactivity in urodynamic studies (7). There is no general consensus about the effect of environmental temperature on LUTS associated with BPH and overactive bladder (OAB). Therefore, we focused on ambient temperature as an environmental factor affecting LUTS associated with BPH or OAB, and attempted to explain the temperature difference changes in BPH or OAB severity.

To date, no large cross-sectional surveys have been performed to investigate the association between daily temperature and LUTS. The aim of this study was to investigate this association by community-based survey.

MATERIALS AND METHODS

Methodology

This was a cross-sectional study. One investigator conducted face-to-face interviews with all study participants at senior welfare centers in South Korea between August 2010 and November 2012 using the International prostate Symptom Score (IPSS) and Overactive Bladder Symptom Score (OABSS) questionnaires. The survey was conducted 36 times in 34 cities within seven major areas of South Korea: Seoul, Gyeonggi, Incheon, Daejeon, Daegu, Gwangju, and Busan (Figure-2).

Study Area

South Korea is located in the southern portion of the Korean Peninsula, which extends about 1.100km (680mi) from the Asian mainland. The mountainous peninsula is flanked by the Yellow Sea to the west and East Sea to the east. The country, including all its islands, lies between latitudes 33º and 39º N, and longitudes 124º and 130ºE. Its total area is 100.188 square

Figure 2 - Location of seven major provinces in this study. The numbers in parentheses refer to population.

kilometers (http://www.ngii.go.kr/kor/board/view.do?rbsIdx=103&idx=66). South Korea tends to have a humid continental climate and a humid subtropical climate, and is affected by the East Asian monsoon. South Korea has four distinct seasons: spring, summer, autumn, and winter. Winters can be extremely cold with the minimum temperature dropping below -20°C (-4°F) in the inland region of the country: in Seoul, the average January temperature range is -7 to 1°C (19 to 34°F), and the average August temperature range is 22 to 30°C (72 to 86°F). Summer can be uncomfortably hot and humid, with temperatures exceeding 30°C (86°F) in most parts of the country (http://countrystudies.us/south-korea/31.htm).

Study population

The study used data from a community-based interview survey conducted with 2.486 male (n=923) and female (n=1.563) subjects 60 years of age and older who provided voluntary consent to participate in the questionnaire survey. To enhance the validity of research, exclusion criteria were prior urological surgery; prior treatment for BPH, prostate cancer or OAB; evidence of a neurological condition; history of a malignancy; evidence of urinary tract infection; evidence of psychiatric illness; and evidence of alcohol or substance abuse.

Temperature data collection

In South Korea, the Korea Meteorological Administration maintains a meteorological observational network of 94 stations that measure daily average temperature, daily temperature difference, daily maximum temperature, daily minimum temperature, and daily amount of precipitation (http://www.kma.go.kr). This allowed retrieval of data concerning daily average temperature and daily temperature difference on the interview dates at the specific measurement sites.

QUESTIONNAIRES

IPSS Questionnaire: The severity of LUTS associated with BPH for males was measured by use of the IPSS questionnaire, which is based on the American Urological Association symptom index, with one additional question regarding QoL. The Korean version of the IPSS was verified in terms of its relevance and reliability, and it is now the most typical diagnostic instrument for LUTS in Korea.

The questionnaire consists of eight items, which include seven 6-point scale questions about symptoms of residual urine sensation, urinary frequency, interrupted stream, urinary urgency, weak urinary stream, urinary hesitancy, and nocturia,

and one 7-point scale question on patient satisfaction with their urinary condition. Based on the previously defined criteria (8), symptom severity was divided into three groups: mild (symptom score 0-7), moderate (8-19), and severe (20-35). QoL in LUTS patients or their level of satisfaction was represented by seven grades: "no problem" (0 point=very satisfied), "all right" (1 point), "somewhat satisfied" (2 points), "half-satisfied, half--dissatisfied" (3 points), "somewhat dissatisfied" (4 points), "distressed" (5 points), and "can't stand it" (6 points=very dissatisfied).

OABSS Questionnaire

The severity of LUTS associated with OAB for females was measured by use of the OABSS questionnaire. The OABSS was developed and validated in Japanese populations (9). The OABSS comprises only four questions regarding daytime frequency, nocturia, urgency, and urgency incontinence, and evaluates relevant symptoms from the viewpoint of the patient. Performance of the OABSS is simple and quick, and a good agreement between OABSS items and the corresponding diary variables was found in a clinical trial with anticholinergics (10). The Korean version of the OABSS was verified in terms of its relevance and reliability.

Age

Age is an important factor that has an impact on generation-specific prevalence of BPH and OAB. Therefore, this study queried each participant's date of birth.

Classification of temperature and statistical analyses

Classification of temperature was based on the daily average temperature (low, <10°C; medium, 10-20°C; high>20°C) as previously described (6) and daily temperature difference in tertiles (low, <8°C; medium 8-10°C; high>10°C). To examine the influence of topographical characteristics, the population was divided into two groups: coastal area (Incheon, Busan) and inland area (Seoul, Gyeonggi, Daejeon, Daegu, Gwangju). To examine the relationship between BPH/OAB and age in the population, an analysis of variance (11) and a post hoc analysis were performed to identify any differences in IPSS/OABSS among each age group. Multiple linear regression analysis with IPSS/OABSS as the response variable, and daily average temperature, daily temperature difference, and age as explanatory variables was done. All data are presented as mean and standard deviation (SD). Statistical analysis was performed using SPSS version 21.0 software (IBM, New York, NY, USA) and STATA version 11.2 software (StataCorp LP, Texas, USA). All statistics were two-tailed and P-values <0.05 were considered to be significant.

RESULTS

The mean IPSS and mean age for the 923 males was 13.45±8.24 and 75.03±6.20 years, respectively. The mean OABSS and mean age for the 1.563 females was 4.41±3.10 and 73.74±6.03 years, respectively (Table-1). Daily average temperature ranged from-3.4°C to 28.3°C, with the daily temperature difference ranging from 2.2°C to 16.9o C (Table-2).

One-way ANOVA analysis was conducted to determine the age-related risk of BPH, OAB, and QoL. The risk of BPH significantly increased with age (12.65±7.96 for those aged 60-69 years and 15.21±8.86 for those over 80 years; P=0.002). The risk of OAB significantly increased with age (3.93±2.82 and 4.90±3.467 for the respective age groups; P<0.001). The risk of QoL increased significantly with age (2.83±1.75 and 3.21±1.53 for the respective age groups; P=0.001) (Table-3). To evaluate the influence of topographical characteristics, there was no difference of IPSS, QoL, and OABSS between coastal and inland area (Table-4). And also there was no statistical significance for identifying which individual item of IPSS and OABSS was related to the daily average temperature except for QoL item (Table-5).

Figure-3 displays values with 95% confidence intervals after adjustment of age concerning the relationship between temperature factors and IPSS/OABSS. There was a weak negative correlation between IPSS and daily temperature difference. To examine this correlation in more detail, a multiple linear

Table 1 - Characteristics of participants and temperature.

	Male (n = 923)		Female (n = 1,563)
Age	75.03±6.20		73.74±6.03
IPSS	13.45±8.24	OABSS	4.41±3.10
QOL	2.84±1.68		
Age groups			
60 - 69	172 (18.6)		392 (25.1)
70 - 79	539 (58.4)		911 (58.3)
Over 80	212 (23.0)		260 (16.6)
IPSS severity groups			OABSS severity groups
Mild	284 (30.8)		1,117 (71.5)
Moderate	454 (49.2)		378 (24.2)
Severe	185 (20.0)		68 (4.4)
Daily average temperature groups			
Low	267 (28.9)		452 (28.9)
Medium	296 (32.1)		590 (37.7)
High	360 (39.0)		521 (33.3)
Daily temperature difference groups			
Low	349 (37.8)		475 (30.4)
Medium	226 (24.5)		519 (33.2)
High	348 (37.7)		569 (36.4)

Figures are means ± SD or numbers with percentages in parentheses.
IPSS, international prostate symptom score. OABSS, overactive bladder symptom score. QOL, quality of life.
IPSS severity groups – mild group (≤7 of IPSS), moderate group (8 - 19 of IPSS), severe group (≥20 of IPSS). OABSS severity groups – mild group (≤ 5 of OABSS), moderate group (6 - 11 of OABSS), severe group (≥ 12 of OABSS). Daily average temperature groups – low (<10.0ºC), medium (10.0 - 20.0ºC), high (>20.0ºC). Daily temperature difference groups - low (<8.0ºC), medium (8.0 - 10.0ºC), high (>10.0ºC).

regression analysis was performed to assess the change in IPSS, OABSS, and QoL during one year with respect to risk factors for BPH and OAB. In the analysis, independent variables included age, daily average temperature, and daily temperature difference, and dependent variables included IPSS, OABSS, and QoL. Age was a significantly risk factor for IPSS, OABSS, and QoL (P<0.001, <0.001, and 0.005, respectively). Regression analysis found that a one-degree Celsius increase in daily temperature difference decreased the IPSS by-0.216 points (P=0.02) and a one-degree Celsius increase in daily average temperature increased the QoL by 0.021 points (P=0.001). Daily average temperatures did not show a statistically significant change in IPSS and OABSS (Table-6). The variance inflation factor among the explanatory variables ranged from 1.005 (lowest) to 1.017 (highest) in IPSS and from 1.016 (lowest) to 1.032 (highest) in OABSS. Multicollinearity was not significantly observed.

DISCUSSION

Temperature has been linked with myocardial infarction (2), ischemic heart disease (12), brain-blood vessel obstruction (13), and respiratory infection (14). For urinary voiding symptoms, it is necessary to consider how ambient temperature changes affect IPSS in medicated patients (4). However, in Japan seasonal changes were found not to be associated with IPSS (6). Also, the report of an average

Table 2 - Daily average temperature and daily temperature difference by interview date at measurement sites.

Male (n = 923)						Female (n = 1,563)					
DAT*(ºC)	n	%	DTD†(ºC)	n	%	DAT*(ºC)	n	%	DTD†(ºC)	n	%
-3.4	27	2.9	2.2	21	2.3	-3.4	22	1.4	2.2	31	2.0
-0.7	27	2.9	4.4	17	1.8	-0.7	55	3.5	4.4	15	1.0
2.2	22	2.4	6.0	29	3.1	2.2	46	2.9	6.0	36	2.3
2.6	27	2.9	6.2	23	2.5	2.6	25	1.6	6.2	43	2.8
3.7	17	1.8	6.5	59	6.4	3.7	15	1.0	6.5	70	4.5
4.8	22	2.4	7.0	64	6.9	4.8	61	3.9	7.0	91	5.8
5.4	36	3.9	7.3	24	2.6	5.4	33	2.1	7.3	12	0.8
6.0	25	2.7	7.5	25	2.7	6.0	63	4.0	7.5	37	2.4
7.9	39	4.2	7.6	25	2.7	7.9	71	4.5	7.6	63	4.0
9.5	4	0.4	7.8	34	3.7	9.5	30	1.9	7.8	42	2.7
9.6	21	2.3	8.0	28	3.0	9.6	31	2.0	8.0	35	2.2
10.2	4	0.4	8.1	3	0.3	10.2	71	4.5	8.1	48	3.1
10.8	34	3.7	8.2	4	0.4	10.8	42	2.7	8.2	30	1.9
11.4	14	1.5	8.5	18	2.0	11.4	40	2.6	8.5	108	6.9
11.6	13	1.4	8.5	22	2.4	11.6	29	1.9	8.5	61	3.9
13.0	63	6.8	8.9	42	4.6	13.0	94	6.0	8.9	77	4.9
13.3	61	6.6	9.0	42	4.6	13.3	89	5.7	9.0	43	2.8
15.1	53	5.7	9.3	6	0.7	15.1	28	1.8	9.3	38	2.4
15.4	3	0.3	9.5	22	2.4	15.4	34	2.2	9.5	46	2.9
18.0	3	0.3	9.9	67	7.3	18.0	48	3.1	9.9	68	4.4
19.1	42	4.6	10.0	98	10.6	19.1	77	4.9	10.0	8	0.5
19.4	6	0.7	10.4	75	8.1	19.4	38	2.4	10.4	104	6.7
20.2	22	2.4	10.6	4	0.4	20.2	35	2.2	10.6	71	4.5
20.5	19	2.1	10.7	27	2.9	20.5	13	0.8	10.7	103	6.6
22.2	24	2.6	11.0	13	1.4	22.2	12	0.8	10.7	25	1.6
24.2	23	2.5	11.5	30	3.3	24.2	43	2.8	11.0	29	1.9
25.4	123	13.3	11.6	19	2.1	25.4	45	2.9	11.5	89	5.7
25.7	29	3.1	14.4	21	2.3	25.7	36	2.3	11.6	13	0.8
25.8	28	3.0	16.9	61	6.6	25.8	35	2.2	14.4	38	2.4
26.1	42	4.6				26.1	43	2.8	16.9	89	5.7
26.3	32	3.5				26.3	48	3.1			
28.3	18	2.0				27.4	103	6.6			
						28.3	108	6.9			

* Daily average temperature † Daily temperature difference.

Table 3 - Age-specific severity of IPSS, OABSS and QoL.

	IPSS				OABSS				QoL			
Age group	n (923)	Mean	SD	*P*	n (1.563)	Mean	SD	P	n (923)	Mean	SD	*P*
60- 69	172	12.65*	7.959	0.002	392	3.93	2.820	0.000	172	2.83*	1.754	0.001
70 – 79	539	13.01*	7.981		911	4.47*	3.082		538	2.70*	1.688	
Over 80	212	15.21	8.860		260	4.90*	3.459		212	3.21	1.525	

IPSS = International prostate symptom score; **OABSS** = Overactive bladder symptom score; **QoL** = Quality of life; **IPSS & QoL** are for male and OABSS is for female. P-value, one-way analysis of variances; * Same letters indicate no statistical significance based on Duncan multiple comparison.

Table 4 - Comparison of topographical groups of IPSS, OABSS and QoL.

	IPSS				OABSS				QoL			
Area	n (923)	Mean	SD	*P*	n (1,563)	Mean	SD	*P*	n (923)	Mean	SD	*P*
Coastal area	207	13.78	8.241	0.767	433	4.65	3.193	0.056	207	2.94	1.704	0.864
Inland area	716	13.35	8.238		1130	4.31	3.059		716	2.81	1.667	

IPSS = International prostate symptom score; **OABSS** = Overactive bladder symptom score; **QoL** = Quality of Life; **IPSS & QoL** are for male and OABSS is for female; **P-value** = Student t-test. Coastal area (Incheon, Busan). Inland area (Seoul, Gyeonggi, Daejeon, Daegu, Gwangju).

temperature odds ratio of chronic prostatitis--like symptoms of 0.99 (range 0.98 to 1.00) was indicative of only a weak clinical significance in Korea (5). In this present study, average temperature was not a risk factor for LUTS for adjusted age in multiple regression analysis (P=0.322). Among the variables, only QoL revealed significant association, which was only prominent among male populations. Moreover, the significant level was marginal, which could be interpreted as temporary phenomenon and needs more validation.

Concerning urinary storage symptoms, patients without neurological diseases have a heightened perception of cold in the bladder during the ice water test than patients with neurological diseases (15). Storage symptoms, frequency, urgency, and nocturia are considerably affected by seasonal changes (16). However, changes in the temperature of fluid did not significantly change the threshold volume of bladder sensation or increase the incidence of idiopathic detrusor overactivity in urodynamic studies (7). In the present study, the average temperature did not demonstrate a risk of LUTS for adjusted age in multiple regression analysis (P=0.433).

There are several reasons for the varying results. First, several previous studies reported that cold stress induces detrusor overactivity in conscious rats, a finding that occurred with a high temperature change between the treatment group and the control group (Δ24°C=room temperature 28oC-low temperature 4°C) (15, 17, 18). However, in the present study, the maximum daily temperature difference was 16.9°C, which was lower than in previous studies. Also, in general, elderly people have shorter exposure times and well-controlled body temperatures in the winter season due to their typically limited physical activity, which could lead to a smaller exposure to extreme temperature changes.

Second, the same previous studies measured outcomes during a short exposure time (20-40 min) (15, 17-19). However, in general, the human body's activity changes with the seasons and gradually adapts to the exposure temperature throughout the season. This phenomenon may account for our finding that the temperature effect on the risk of BPH/OAB may not affect urinary symptoms in the general population. For instance, in a cold stress-induced detrusor overactivity model, when skin temperature stabilized after 20 min

Table 5 - Comparison of daily average temperature groups in each item of IPSS, OABSS and QoL.

	IPSS					QOL					OABSS					
	DAT* group	n (923)	Mean	SD	*P*	DAT* group	n (923)	Mean	SD	*P*		DAT* group	n (1,563)	Mean	SD	*P*
Incomplete emptying (IPSS 1)	L	267	1.88	1.737	0.652	L	267	2.65	1.709	0.001	Frequency (OABSS 1)	L	452	0.40	0.622	0.723
	M	296	1.75	1.591		M	295	2.70	1.614			M	590	0.41	0.621	
	H	360	1.84	1.622		H	360	3.09	1.673			H	521	0.43	0.595	
Frequency (IPSS 2)	L	267	1.86	1.617	0.501						Nocturia (OABSS 2)	L	452	1.94	0.898	0.774
	M	296	1.95	1.511								M	590	1.90	0.908	
	H	360	2.01	1.603								H	521	1.90	0.938	
Intermittency (IPSS 3)	L	267	1.83	1.739	0.925						Urgency (OABSS 3)	L	452	1.09	1.480	0.101
	M	295	1.78	1.655								M	590	1.28	1.572	
	H	360	1.82	1.576								H	521	1.24	1.505	
Urgency (IPSS 4)	L	267	1.49	1.600	0.708						Urgency incontinence (OABSS 4)	L	450	0.77	1.278	0.064
	M	296	1.53	1.638								M	590	0.96	1.407	
	H	360	1.60	1.678								H	521	0.85	1.265	
Weak stream (IPSS 5)	L	267	2.36	1.736	0.927											
	M	296	2.42	1.705												
	H	360	2.38	1.721												
Straining (IPSS 6)	L	267	1.50	1.616	0.209											
	M	296	1.59	1.634												
	H	360	1.73	1.691												
Nocturia (IPSS 7)	L	267	2.40	1.259	0.657											
	M	296	2.31	1.291												
	H	360	2.39	1.308												
Total symptom score	L	267	13.24	8.347	0.702						Total symptom score	L	452	4.19	2.960	0.175
	M	296	13.29	7.865								M	590	4.55	3.293	
	H	360	13.73	8.463								H	521	4.43	2.986	

Daily average temperature groups – L (<10.0°C), M (10.0 - 20.0°C), H (>20.0°C). IPSS, international prostate symptom score. OABSS, overactive bladder symptom score. QOL, quality of life. IPSS & QOL are for male and OABSS is for female. P-value, one-way analysis of variances.

of low temperature (4±2°C) exposure and was maintained for the duration of exposure (19), demonstrated that a momentary cold stimulus can act as a trigger for the urinary responses. Also, the results of this model were associated with a sudden decrease in skin temperature (19). This present study also supports previous results that the time-dependent reductions of low temperature stimulated responses represent an adaptive response that is universal in normal healthy humans. Moreover, individual efforts to maintain warmth through the wearing of heavy clothes and heating the environment could diminish the trigger effect of low temperature on LUTS.

It has generally been thought that more LUTS patients are associated with BPH/OAB-related need for hospital examination with regard to their urinary symptoms in low temperature circumstances. However, the present results indicate that this does not mean that the urinary severity of patients in low temperature environments is higher than high temperature exposure.

The guideline by the Japanese Urological Association recommends one of the conservative treatments that males with LUTS avoid exposing the lower body to cold temperature (20). However, the American Urological Association and European Association of Urology have not provided high-quality and reliable evidence about the influence of ambient temperature on LUTS (21, 22). Only the American Urological Association guideline on the management of BPH recommended future study of

Table 6 - Multiple linear regression analysis of IPSS, OABSS and QoL.

	IPSS			OABSS			QOL		
	B*	SE	*P*	B*	SE	*P*	B*	SE	*P*
Age (years)	0.177	0.043	0.000	0.059	0.013	0.000	0.025	0.009	0.005
Daily average temperature (ºC)	0.030	0.030	0.322	0.007	0.009	0.433	0.021	0.006	0.001
Daily temperature difference (ºC)	-0.216	0.093	0.020	-0.034	0.029	0.246	-0.015	0.019	0.423

IPSS = international prostate symptom score. **OABSS** = Overactive bladder symptom score. **QOL** = quality of life; **IPSS & QOL are** for male and OABSS is for female.
* Unstandardized coefficients.

life style interventions (21). The present data address this recommendation.

There are several limitations to this study. In view of the imprecision of some geographical data, coupled with the fact that we used spatially-derived ambient temperature as a surrogate for personal temperature, the risk estimates presented here are clearly misclassified. Thus, our results may underestimate the true risk of LUTS associated with exposure to temperature in this population. However, as in most epidemiological surveys, there will be some errors in exposure classification. In this study, which was performed as a large-scale research project that covered seven major areas of South Korea, the collected data were judged to be sufficiently homogeneous. As a result, the misclassification of this study would most likely be non-differential with regard to temperature status. This would tend to bias the regression parameter toward null. Second, this study does not include the detailed biological data of each population, which means we could not determine clinical BPH or OAB. This is mainly due to the nature of this cross-sectional survey.

Topographical characteristics were taken into consideration with regard to variations in LUTS severity among areas. Since coastal and inland communities are evenly distributed in interview surveys areas 36 times in 34 cities in seven major areas of South Korea, there is no difference of IPSS, QoL, and OABSS between coastal and inland area. Thus, the topographical difference is also thought to be unrelated.

Lastly, we could not describe the longitudinal data to consider potential seasonal variation effects. The variance of daily temperature could not substitute for seasonal variation. Hence, this type of cross sectional study has to be repeated by seasonal sequence.

CONCLUSIONS

Our findings did not demonstrate an increased clinically significant risk of BPH or OAB severity in connection with daily average temperature. Only daily temperature differences were associated with male LUTS. Daily temperature differences may be more influential than daily average temperatures. A large prospective study set will be needed to validate this association in the future.

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CONFLICT OF INTEREST

None declared.

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Argus T® versus Advance® Sling for postprostatectomy urinary incontinence: A randomized clinical trial

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ABSTRACT

Objective: To compare the results of two slings, Argus T® and Advance®, for the treatment of postprostatectomy urinary incontinence (PPUI). Material and Methods: From December 2010 to December 2011, 22 patients with PPUI were randomized as follows: 11 (mean age 62.09(±5.30)) underwent treatment with Advance® and 11 (mean age 62.55(±8.54)) with Argus T®. All patients were evaluated preoperatively with urodynamic testing, quality of life questionnaire (ICIQ-SF), voiding diary and 24-hour pad test. Exclusion criteria were: neurological diseases, severe detrusor overactivity and urethral stenosis. Evaluation was performed at 6, 12 and 18 months after the surgery. After implantation of the Argus T® sling, patients who experienced urine leakage equal to or greater than the initial volume underwent adjustment of the sling tension. Results were statistically analyzed using the Fisher's test, Kolmogorov-Smirnov test, Friedman's non-parametric test or the Mann-Whitney test.

Results: Significant improvement of the 24-hour pad test was observed with the Argus T® sling (p=0.038) , With regard to the other parameters, there was no significant difference between the two groups. Removal of the Argus T® device due to perineal pain was performed in one patient (9%). Despite non uniform results, both devices were considered useful to improve quality of life (ICIQ-SF): Argus T® (p=0.018) and Advance® (p=0.017).

Conclusions: Better results were observed in the 24h pad test and in levels of satisfaction with the Argus T® device. Both slings contributed to improve quality of life (ICIQ--SF), with acceptable side effects.

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INTRODUCTION

Post-prostatectomy urinary incontinence (PPUI) is a common complication of surgical treatment in patients with prostate cancer or benign prostatic hyperplasia. It's occurrence has a negative impact on quality of life (QoL) and decrease the benefit of the treatment of primary disease (1, 2).

PPUI prevalence varies from 2.5% to 67%. This is due to the wide variation in studies, such as non-standardized definition, type of surgical technique, diagnostic assessment, patient selection and outcome measures (3).

Over the last years, suburethral slings (SUS) have been re-designed and attracted particular interest due to its promising and durable results (3), even in face of the higher good results of the Artificial Urinary Sphincter-AUS 800® (USA).

Two SUSs were available in the Brazilian market at the time of recruiting for this research:

Argus T®-(Promedon–Cordoba, Argentina) (4, 5) and Advance® (American Medical Systems-Minnetonka, United States) (6).

Both devices are transobturatory slings used to treat mild to moderate PPUI. Their technical configurations are different, as well as their mechanism of action, but both manufacturers claim that their products are effective and safe (4-6). There are no comparative studies analyzing their effectiveness and rates of complications. We present a randomized clinical trial comparing the results of these two devices at intermediate (18 months) follow-up.

OBJECTIVE

The objective of this study was to compare the results of the surgical treatment of PPUI with Argus T® and Advance® slings.

MATERIALS AND METHODS

This study was designed to be a randomized clinical trial. Randomization was made by computer-generated table of random numbers at www.random.org, and patients were assigned to one of the two treatment arms: Argus T® or Advance®.

From December 2010 to December 2011, patients with PPUI were recruited from the outpatient services at two institutions (one public and one private).

Inclusion criteria: patients with 50 to 80 years of age with PPUI for at least the past six months, regardless of the level of incontinence. Exclusion criteria: patients with urethral stricture untreated or treated for less than 6 months, severe detrusor overactivity (when involuntary bladder contractions, as identified by urodynamic evaluation, where thought to be the primary cause of incontinence), and neurological disorders associated with neurogenic bladder.

Clinical evaluation consisted of history taking, interview to collect data such as results of prior pathological examinations, classification of risk of prostate cancer progression, as proposed by D'amico (7), and adjuvant treatments.

To better determine the level and impact of incontinence, patients were also submitted to: urodynamic evaluation (conducted following the recommendations of the International Continence Society (ICS) (8);

QoL questionnaire (assessed using the Brazilian Portuguese version of the "International Consultation on Incontinence Questionnaire-Short Form"-ICIQ-SF) (9);

voiding diary completed for three days in order to determine functional capacity (median voided volume), number of episodes of urine leakage, number of urinations and volumes of fluid intake and voiding;

24 hours pad test, done as recommended by ICS: all pads used in 24 hours were stored in a bag under refrigeration and weighted; total weight in grams was recorded to estimate total urine leak.

Surgical techniques were applied as proposed by original authors and are described, in summary, below (4-6). All procedures were performed by the same surgeon: patients were submitted to regional anesthesia, in the lithotomy position and legs flexed at close to 90 degrees at the thigh level. Skin preparation was made by applying topical polvidone-iodine or chlorhexidine to the perineum, thighs, scrotum, penis and lower abdomen. Foley 16F urethral catheter was inserted. Prophylactic antibiotic therapy was started no more than two hours before surgery with 2g of intravenous cefazolin and continued for 24 hours, with 1g every eight hours. After patient dismissal, 500mg of cephalexin was prescribed to be taken orally, every six hours, for seven days (10).

For the Advance® sling, the tape was placed over the spongious body of the bulbar urethra and under the bulbospongious muscle through a perineal incision and transobturator route. A cystoscopy was performed to verify the presence of any urethral lesions and to certify that the bulbar urethral lumen had collapsed due to compression from the mesh tape. Bladder was drained with a Foley catheter for 24 hours and patient was instructed to restrain from any physical activity for the next 45 days.

The Argus T® sling was placed through a longitudinal perineal incision and a transobturatory route. The sling was positioned over the bulbospongiosus muscle. The tension applied was sufficient to interrupt a retrograde infusion of saline solution through a Foley catheter, in a column with 35-40cm

of H_2O, with occlusion of the urethral meatus. Bladder was drained with a Foley catheter for 24 hours and patients were instructed to restrain from any physical activity for 45 days. In case of readjustment, the same retrograde occlusion pressure was the goal with re-tensioning.

Patients were dismissed after removal of the Foley catheter and after first normal void; revaluation was scheduled for the 7th and 30th days after surgery. Follow-up visits at 6, 12 and 18 months were programed; they underwent the 24-hour pad test, and completed the quality of life questionnaire (ICIQ-SF) and voiding diary at each visit. We present here the results after 18 months.

Post operatively, patients in the Argus T® sling group, who experienced urine leakage equal to or higher than the baseline, underwent sling adjustment to reinforce urethral compression.

Additionally, in order to further compare both Groups, we established the following criteria to consider the patient cured:

a) Average number of incontinence episodes over 24 hours lower than two.

b) Average number of pads per day, up to one.

c) 24-hour pad test with urine leakage less or equal to 50g.

d) Assessment of quality of life (ICIQ-SF), with score reduction of 80% or more.

Finally, at the end of 18 months, the following questions were made to the patient to assess the degree of satisfaction: a) If you could return in time, would you undergo the same surgery again? b) How satisfied are you with the results obtained? c) Would you recommend to a friend, the same surgery you did? The questions were answered by the patients using a visual scale of 1 to 10, where 10 was certainly yes or satisfied and 1 certainly no or dissatisfied. To aggregate data, we used the following criteria: 1 to 3 meant no, 4 to 7, uncertain, and 8 to 10, yes.

Study protocol was approved by Institutional Review Board (Research Ethical Committee).

RESULTS

Figure-1 shows the patient recruitment and randomization flowchart.

Randomization lead to homogenous groups regarding age, comorbidities, previous radiation therapy, previous treatment of urethral stricture, risk of recurrence as per the D'Amico classification system, number of urinations, number of pads used, number of urgency episodes, number of incontinence episodes, 24-hour pad test, incontinence questionnaire–short form ICIQ-SF, time interval between primary surgery and sling placement and urodynamic parameters (Table-1).

The length of surgery, 30 to 90 minutes, was similar in both groups.

During the postoperative follow-up, two patients in the Advance® group experienced pain, which was relieved with analgesics; one had dehiscence of the surgical incision, and one had urinary retention due to sclerosis of the bladder neck after 12 months.

Complications were more frequent in the Argus T® group. Two patients died of acute myocardial infarction: one, six months after the surgery, and one, 12 months afterwards. Both deaths were not related to immediate surgical complications, although they were clinically evaluated before sling surgery and had low cardiovascular risk. Three patients experienced urinary retention

Figure 1 - Study design.

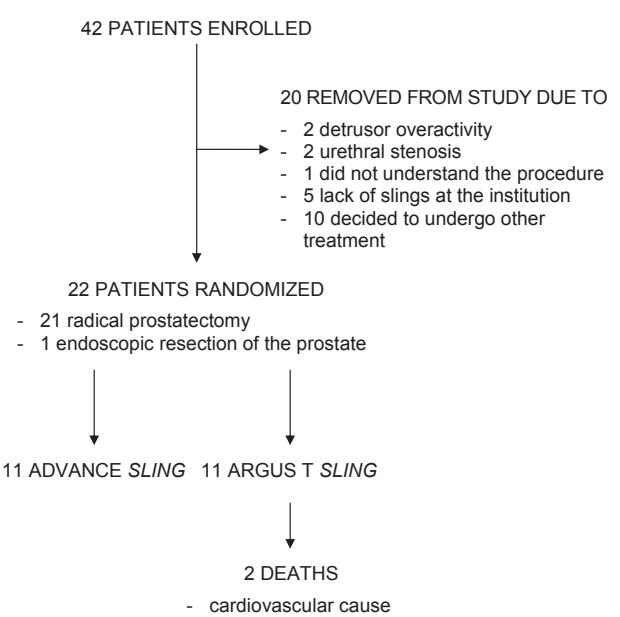

Table 1 - Distribution of patients as per preoperative characteristics and group.

	Group			p (1)
	Total	Advance®	Argus T®	
	n=22	n=11	n=11	
Comorbidities				0.361
High blood pressure	15	9	6	
Other	7	2	5	
Radiotherapy				0.586
Yes	4	3	1	
No	18	8	10	
Urethral stenosis				0.311
Yes	5	1	4	
No	17	10	7	
Risk per D'amico classification				0.750
Low	7	3	4	
Moderate	9	4	5	
High	6	4	2	
24-hour pad test - preoperative				0.658
< 100 g	1	1	0	
< 100-400 g	8	3	5	
< 400 g	13	7	6	

(1) = Descriptive level of probability of the Fisher's exact test

during 10 days and were dismissed with a Foley catheter in bladder. Four patients experienced prolonged pain: two improved with common analgesics, one is still taking medication with addition of a tryciclic antidepressant, and one had to remove the sling. Crural extrusion of the silicone column occurred in three patients. All cases were treated with antibiotics and removal of the extruded portion, with resolution of the problem without additional treatment.

Three patients underwent sling tension adjustment due to persistent leakage. Two were improved after 18 months and one remained with incontinence.

Clinical Efficacy

Table-2 presents results regarding efficacy. No improvement on functional capacity, number of urinations, number of urgency episodes and incontinence episodes were observed in either group.

Better quality of life was observed in both groups. The Argus T® group experienced a significant improvement in the 24-hour pad test, but the Advance® group did not. Neither group had a significant improvement in the number of pad changes over 24 hours. However, results with the Argus T® sling were very close to the level of significance.

The number of patients cured, based on the impact on incontinence episodes, pad changes, pad tests and quality of life scores was similar in the two groups (Table-3). The results of the quality of life questionnaire are shown in Table-4. The patients who underwent surgery with the Argus T® sling had higher satisfaction rates than patients in the Advance® group.

DISCUSSION

There is still no optimal treatment for PPIU. Treatment within the first 12 months after surgery

Table 2 - Descriptive values of the variables analyzed, according to surgery and time point of evaluation (*).

Variance	Argus T®			Advance®		
	Baseline	18 months	p	Baseline	18 months	p
Functional capacity	**118.33** (±82.92)	**147.78** (±105.57)	0.407	**134.09** (±84.11)	**162.27** (±11.31)	0.726
QoL	**17.44** (±3.40)	**7.44** (±6.98)	0.018	**19.18** (±1.89)	**11.73** (±8.36)	0.017
24 hours pad test	**674.44** (±763.78)	**97.00** (±218.60)	0.038	**620.91** (±422.64)	**561.45** (±890,09)	0.386
No. of micturitions	**6.34** (±4.92)	**5.28** (±4.14)	0.325	**5.57** (±3.94)	**7.55** (±4.93)	0.421
No. of pad changes	**4.19** (±2.52)	**1.48** (±2.79)	0.066	**3.92** (±2.59)	**3.41** (±4.22)	0.167
Urgency episodes	**1.61** (±1.98)	**1.07** (±2.25)	0.416	**1.86** (±3.02)	**0.90** (±1.96)	0.400
Incontinence episodes	**4.56** (±3.61)	**2.67** (±6.58)	0.159	**3.62** (±3.13)	**8.51** (±8.98)	0.202

(*) Descriptive level of probability of the non-parametric Wilcoxon test

should be conservative since there is possibility of spontaneous restoration of urinary continence (11).

In regard to assessment of incontinent patients, many studies report the rates of improvement in the number of pads per day, but we know that pad changing is a personal decision and it varies too much from patient to patient. Therefore, this is not an accurate parameter to determine severity of incontinence (12, 13). For this reason, we assessed our patients with three major outcome measures: number of pads, voiding diary and QoL questionnaire. We expected to have more confident results with such broad evaluation.

When choosing a surgical technique, many authors prefer to use SUS in mild and moderate incontinence, reserving AUS for the most severe cases (14, 15). In our study, we decided to include patients with all degrees of severity because we believed that SUSs could be effective even in the most severe cases. In fact, if the patient wishes, there is no reason to not try a SUS, since an AUS

Table 3 - Cure criteria assessment.

Criteria	Group		
	Advance® (n=11)	Argus T® (n=9)	
	n (%)	**n (%)**	**p***
Incontinence ≤ 2	5 (55.6%)	7 (77.8%)	0.620
Pads ≤ 1	5 (45.5%)	7 (77.8%)	0.197
Score QV ≥ 80%	3 (27.3%)	2 (22.2%)	1.000
PAD test 24 hours ≤ 50g	5 (45.5%)	7 (77.8%)	0.197

Table 4 - Patient's impressions about the results after 18 months.

Advance :10 Patients	Yes	Doubt	No
Would undergo same surgery again	6	1	3
Degree of satisfaction (VAS)	4	2	4
Would indicate surgery to another person	7	0	3
Argus: 9 patients	**Yes**	**Doubt**	**No**
Would undergo same surgery again	9	0	0
Degree of satisfaction (VAS)	9	0	0
Would indicate surgery to another person	9	0	0

VAS=Visual analog scale

still can be effective in the case of failed previous sling procedure. Nevertheless, patients should be advised not to expect the same results in severe cases, as in mild to moderate incontinence.

The basic difference between the Argus T® and the Advance® slings is that the first one is completely made of silicon and is adjustable, whereas the second one is a polypropylene mesh that is not adjustable. Moreover, the authors claim different mechanisms of action: the Argus T® sling would correct PPUI by compressing the bulbar urethra (16, 17), whereas the Advance® sling would act by repositioning the membranous urethra in the retropubic space which would increase its functional length and strengthen the sphincteric mechanism (3, 6, 15). Additionally, the authors who developed the Advance® sling suggest that it is necessary to release the central tendon of the perineum and open the bulbospongiosus muscle to place the polypropylene mesh directly over the urethra. This action permits the elevation of the bulbar urethra and, consequently, the membranous urethra what leads to improvement of any residual continence mechanism.

On the other hand, the authors who developed the Argus T® sling report that the silicone sling should be placed over the bulbar urethra, without opening the bulbospongiosus muscle. This provides better compression and lower risk of erosion. The effectiveness of the compression was determined by elevation of the closure pressure, measured by retrograde filling pressure (18, 19).

Unfortunately, observations from urodynamic examination after sling revealed that the only alteration detected in the parameters of the exam was the increase in VLPP with the Advance® (20) sling. We really don't know if any male sling led to elevation of voiding detrusor pressure.

The analysis of the efficacy parameters in our study revealed that, if we keep our focus on the quality of life criterion, both SUSs provide similar and significant improvement. However, if we direct our focus to more objective criteria, the Argus T® sling had better results than the Advance® (as observed by the pad tests results). From the patient's point of view, this difference may or may not be important. For this reason, we looked at patient's satisfaction rates in an additional questionnaire with a visual analog scale to assess their level of satisfaction with the results obtained. We then observed that most patients who underwent surgery with the Argus T® sling are clearly satisfied with the treatment, whereas only a few satisfied patients in the Advance® group. From a more technical point of view, using more strict criteria of cure, we notice that both slings are equally low effective. The sum up is that any analysis of effectiveness of the SUSs should be based on wide evaluation parameters, objective and subjective, in order to provide a better idea of the effects of the surgery. We notice that the literature does not follow this trend. Thus we think that our research adds new information by providing both patient subjective point of view and objective outcome measures.

In their early studies on Argus®, Romano et al. (5) reported: 73% of the patients were cured (no pads); 10% improved (one to two pads/day) and 17% failed and needed to use more than two

pads/day (even after sling tension adjustment). In the follow-up on these patients, Romano et al. (16) reevaluated 47 of them, three years after sling implantation, observing that 66% (31 patients) were still cured, five needed to have the sling tension adjusted, 12.8% (6 patients) improved and 21% (10 patients) failed, showing that the results were long-lasting at the 36-month follow-up. In our study, three patients underwent sling tension adjustment, which allowed the restoration of continence and increased the success rates. We observed that the average number of pads/day decreased from 4.19 before the surgery to 1.48 after surgery, at 18 months. Despite being similar to the results reported by Romano et al. (16), these findings were not statistically significant. It should be stressed that the p value almost reached the level of significance (p=0.066), suggesting a trend. Or, it could only be devoid to our small sample size. This observation deserves continuing follow-up and augmentation of sample size to correct clarification. Additionally, we observed that 77.8% of our patients used a maximum of one pad per day after 18 months, similar to what was reported by these authors.

With regard to the complications associated with SUS implantation, Rehder et al. (15) monitored 156 patients who had undergone surgery with the Advance® sling for 36 months and reported 109 complications: 50% cases of perineal pain, 9.6% temporary urinary retention, 4.4% dysuria, 5% perineal hematoma, 0.6% urinary infection, 0.6% surgical wound infection and one late complication (0.6%) from sling extrusion due to symphysite. In a study with 230 patients who underwent surgery with the Advance® sling, Bauer et al. (14) also reported 23.9% of complications, 21.3% of which were transitory urinary retention, and only two patients, one with ileal neobladder and another with urethral lesion, continued to use intermittent clean self-catheterization. Other complications totaled 2.5% (0.4% surgical wound infection, 0.4% urinary infection, 0.4% persistent perineal pain) and only 1.3% of the cases needed to undergo new surgery (0.9% extrusion and 0.4% urethral perforation). We observed that rates of complications in both groups were similarly low and not very severe.

In our study, the following complications were recorded: two patients experienced transitory perineal pain which was resolved with painkillers, one had dehiscence of the surgical incision which was satisfactorily resolved and one patient, after 12 months, experienced urinary retention due to sclerosis of the bladder, treated with endoscopic internal urethrotomy, developing severe urinary incontinence.

With regard to the complications resulting from implantation of the Argus T® SUS, in their initial results with 48 patients, Romano et al.(5) reported that 15% had transitory urinary infection, 21% had perineal pain that improved after six months, and 6% needed to have the sling removed (two due to urethral erosion and one due to infection). In the follow-up of these patients after three years, Romano et al. (16) reported that it was necessary to remove nine slings (19.1%), six of them due to erosion and three due to infection. Hubner et al. (21), in their experience with 101 patients who underwent surgery with an Argus T® sling (retropubic approach), reported that after 2.1 years of follow-up there were 16 cases (15.8%) of sling removal due to erosion or infection. Additionally, they also observed that 15 patients (15%) experienced perineal pain which was resolved three months later with the use of regular painkillers. During the intraoperative period, there were 5 cases (5%) of minor bladder perforations.

An analysis of these studies reveals that complications arising from the surgery with the Argus T® device are more frequent and severe than complications resulting from surgery with the Advance® sling, requiring removal of the device in 6% to 35% of the cases. This could be due to the action mechanism of the Argus T® sling, which probably exerts more pressure against the urethra and the surrounding tissues. Other factors, such as previous RT and urethral stricture, as well as prior treatment of PPUI, require further studies with larger samples to assess the relationship between risk factors and complications.

Our study has limitations and potential for bias. Our sample size was limited to the few slings provided to do this research. This significantly affects the power of data. We wait for funding to continue including patients to this series or star-

ting another trial with new slings, once the Advance sling will be replaced by a new generation from the manufacturer. We cannot be sure if the differences found in results of each sling are real or occurred only by chance.

In summary, after comparing our results with the literature, we concluded that slings present promising success rates, with improved patient quality of life and satisfaction. Our study compared both slings, in similar populations and with fewer restrictions on inclusion, observing worse results with the Advance® sling and more complications with Argus T®.

The new data we provide with this report is that the possibility of readjustment may be a considerable advantage for patients choosing sling for treatment of PPUI. The limitation of our study is the initial small sample size. We look forward to continue to recruit patients to enlarge our series and provide strongest evidence in the field.

CONCLUSIONS

Better results were observed in the 24h pad test and in levels of satisfaction with the Argus T® device. Both slings contributed to improve quality of life (ICIQ-SF), with acceptable side effects.

CONFLICT OF INTEREST

None declared.

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The relationship between histological prostatitis and lower urinary tract symptoms and sexual function

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ABSTRACT

This prospective analysis assessed the effect of histological prostatitis on lower urinary tract functions and sexual function. The patients were separated into two groups as histologically observed prostatitis (Group A) and no prostatitis (Group B) according to the biopsy outcomes. International prostate symptom score, international index of erectile function-5 scores, maximal and average flow rate, and residual urine volumes were compared statistically between groups. There was no significant difference (P>0.05) in baseline age (t=0.64), body mass index value (t=0.51), prostate volume (t=0.87), prostate-specific antigen levels (t=0.43), maximal (t=0.84) and average flow rate (t=0.59), and post-void residual urine volume (t=0.71). Mean international prostate symptom score in patients with prostatitis was numerically but not significantly higher than that in those without prostatitis (t=0.794, P=0.066). Mean international index of erectile function-5 score in the prostatitis group was significantly lower than that in those without prostatitis (t=1.854, P=0.013). Histological prostatitis notably affected sexual function of patients and may serve as a major risk factor for sexual dysfunction while having little effect on lower urinary tract symptoms.

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Keywords:
Lower Urinary Tract Symptoms; Prostatitis; Erectile Dysfunction

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INTRODUCTION

Histological prostatitis corresponds to prostatic inflammation confirmed by microscopic examination. The typical histologic finding of prostatitis is characterised by infiltration of the prostatic ductus and periprostatic tissue, especially with polymorphic nuclear leukocytes (1, 2).

Histological prostatitis is frequently detected in biopsy of prostate specimens during surgery or autopsy. A prostate autopsy study found inflammation in 40 of 91 adults patients (3).

Maksem et al. have reported evidence of prostatic inflammation in 45% of aspiration biopsy specimens taken because of suspicion of carcinoma (4).

Even though inflammatory cells in prostate tissue are a well-reported observation, there is no precise information about the origin of inflammation, which is thought to be multifactorial (5).

A number of factors, such as bacterial infection; chemical inflammation caused by urinary reflux, dietary factors, and hormones; and autoimmune responses, have been implicated in the development of prostatitis (6-8). Further, prostatic inflammation has an apparent correlation with symptomatic progression, risk of urinary retention, and need for surgery (9).

Recent studies have introduced data that prostatic inflammation plays an important role in the development and progression of benign prostatic hyperplasia (BPH) (10, 11).

Lower urinary tract symptoms (LUTS) caused by BPH impair quality of life and are frequently accompanied by sexual function disorders in these patients (12). Even though the mechanism underlying the relationship between BPH and erectile dysfunction (ED) is not exactly known, decrease in nitric oxide, metabolic syndrome, atherosclerosis, and the increase in Rho-kinase activity have been suggested as causes (13).

While prostatic inflammation is thought to play an active role in the progression of LUTS caused by BPH, no precise information exists on the relationship of this condition and sexual function disorders. The purpose of this study was to assess the effect of histological prostatitis on LUTS and sexual dysfunction.

PATIENTS AND METHODS

In total, 138 patients with serum PSA (ng/mL) above 4 with a normal digital rectal exam (DRE), and who were scheduled for transrectal prostate biopsy were included in the study. To evaluate lower urinary tract and sexual functions, international prostate symptom score (IPSS) and international index of erectile function-5 (IIEF-5) questionnaires were completed by patients before biopsy, respectively. Pre-biopsy uroflowmetry results (maximal flow rate [Qmax] and average flow rate [Qavg]) and post-void residual urine volume (PVR), as well as body mass index (BMI) and prostate volumes measured through transrectal ultrasonography, were recorded. Patients who received BPH or prostatitis treatment; those who were diagnosed with prostate cancer or atypia according to pathologic result; and those who had serious neurologic, cardiac, or pulmonary disorders, liver or renal failure, diabetes, or hypertension were excluded from the study. Prostatitis was diagnosed after histological observation of inflammatory cellular infiltration within the prostatic glandular tissue. Enrolled patients were divided into two groups: those with histological findings of prostatitis (Group A) (Figure-1) and those without prostatitis (Group B) (Figure-2) findings in their biopsy samples. IPSS and IIEF scores, as well as their uroflowmetry and residual urine volumes were compared statistically.

Figure 1 - H&Ex400: This is the microscopic appearance of chronic prostatitis. Numerous small dark blue lymphocytes are seen in the stroma between the glands.

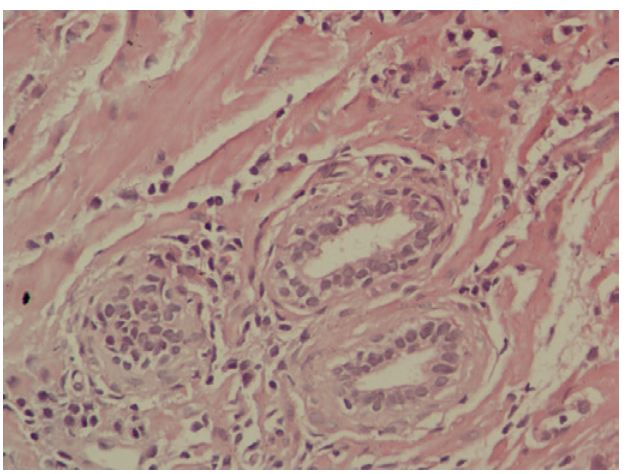
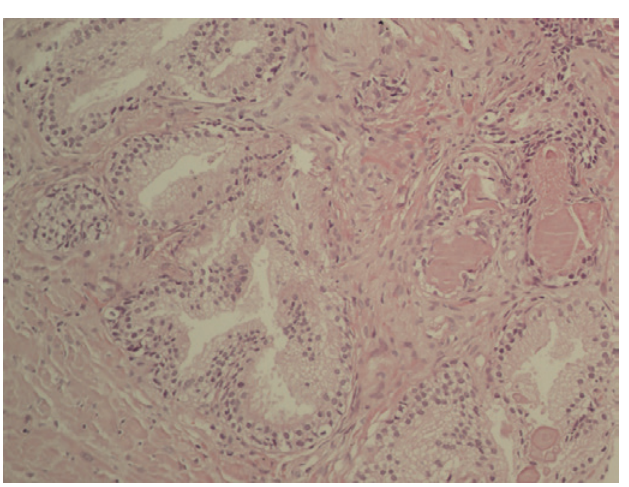


Figure 2 - H&E: The normal histologic appearance of prostate glands and surrounding fibromuscular stroma is shown here at high magnification.



Statistical analysis

SPSS software (Statistical Package for the Social Sciences; Version 15.0, SPSS Inc., Chicago, IL, USA) was used to analyse the data. The Kolmogorov–Smirnov test was used to evaluate whether

the obtained data had a normal distribution. Normally distributed variables were described using means and standard deviations. Paired t-test was used to compare groups, and a P value<0.05 indicated statistical significance.

Independent (unpaired) samples t-test was used to determine whether there was any difference between groups in age, BMI, PSA, prostate volume, uroflowmetry parameters, and mean IPSS and IIEF scores, which are continuous variables. A chi-square test was used to compare smoking status, IPSS and IIEF severity.

A multivariate regression analysis was used to calculate the adjusted means of IPSS and IIEF score. Age, BMI, smoking status, PSA value, and prostate volume were used as continuous variables and as covariates in the model.

RESULTS

Among the 138 patients in whom transrectal prostate needle biopsy was performed due to high PSA levels, 34 were excluded from the study: 28 had prostatic adenocarcinoma, and 6 had prostatic intraepithelial neoplasia (PIN). Of patients included in the study (n=104), 34.6% had histological prostatitis (Group A) and 65.4% had none (Group B).

There was no significant difference in age, BMI, prostate volume, PSA, Qmax, Qavg and PVR (Table-1). There was also no significant difference in prevalence of smoking (χ^2=2.21).

In Group A, 15.6% had mild, 43.1% had moderate, and 41.3% had severe symptoms according to the IPSS. In contrast, in Group B, 17.6% had mild, 35.3% had moderate, and 47.1% had severe symptoms. There was no significant difference between groups according to IPSS severity (Table-2). Mean IPSS scores were 19±7.4 in Group A and 17.6±8.5 in Group B. Even though mean IPSS in Group A was numerically higher than that in Group B, this result was not statistically significant (t=0.794, P=0.066) (Table-1).

ED was mild in 33.3%, moderate in 16.7%, and severe in 19.4% patients and 30.6% did not have ED in Group A according to the IIEF scores. In Group B, ED was reported as mild in 35.3% and moderate in 23.5% patients and 41.2% did not have ED. According to these results, severe ED was significantly high in group A (Table-3).

Mean IIEF scores were 16.5±6.6 in Group A and 19.6±3.9 in Group B. The mean IIEF score was significantly high in Group A (t=1.854, P=0.013) (Table-1). The multivariate regression analysis found that age, PSA, prostate volume, BMI, and smoking had no effect on IIEF scores. Age, PSA, BMI, and smoking had no effect on IPSS; however, prostate volume correlated with IPSS.

DISCUSSION

Our study found that patients diagnosed with histological prostatitis had more serious erectile dysfunction than those without prostatitis.

Table 1 - Comparison of the demographic characteristics of groups

	Group A	Group B	t value	P value
Age	63.9±5.9	64.1±6.8	0.643	0.080
BMI	26.0±2.5	26.5±3.4	0.512	0.320
Prostate volume	40.1±13.4	44.1±12.7	0.876	0.145
PSA	7.9±3.5	7.3±3.6	0.431	0.413
IPSS	19±7.4	17.6±8.5	0.794	0.066
IIEF	16.5±6.6	19.6±3.9	1.854	0.013
Qmax	11.3±5.2	10.1±4.8	0.841	0.236
Qavg	5.9±2.6	5.6±2.6	0.595	0.676
PVR	43.6±30.9	48.6±31.2	0.710	0.431

Group A = Histological prostatitis group; **Group B** = Without prostatitis group; P < 0.05; t-test for paired sample

Table 2 - Comparison of IPSS severity between the two groups (chi-square test).

IPSS severety	Group A (%)	Group B (%)	P value
Mild	15.6	17.6	0.085
Moderate	43.1	35.3	0.135
Severe	41.3	47.1	0.068

Group A = Histological prostatitis group; **Group B** = Without prostatitis group

Table 3 - Comparison of IIEF severity between the two groups (chi-square test).

IIEF severety	Group A (%)	Group B (%)	P value
No ED	30.6	41.2	0.126
Mild	33.3	35.3	0.085
Moderate	16.7	23.5	0.062
Severe	19.4	0	<0.001

Group A: Histological prostatitis group; **Group B:** Without prostatitis group

Recent studies have frequently focused on the effects of histologic inflammation of prostate tissue on progression of BPH, LUTS, and sexual function. With an extensive and extended follow--up, the Medical Treatment of Prostate Symptoms (MTOPS) study found prostatic inflammation in 544 of 1197 patients with BPH. A correlation was observed between histological prostatitis and clinical progression of BPH. Patients in all groups (placebo, finasteride, doxazosin, and combined finasteride and doxazosin) with inflammation were more likely to progress clinically in terms of symptoms, acute urinary retention (AUR), or BPH-related surgery (14).

Another study on the pathophysiology between BPH and prostatitis theorised that cytokines released from the inflammatory cells in prostate tissue and growth factors stimulated epithelial and stromal hyperproliferation (11).

In addition, cellular proliferation repaired the tissue damage caused by the free oxygen radicals arising from the released cytokines caused hypoxia (15).

The Reduction by Dutasteride of Prostate Cancer Event (REDUCE) study observed chronic inflammation on histological analysis in 78% men. Statistically significant but clinically small increases in IPSS were noted in patients with inflammation compared with those without inflammation. Similarly, statistically significant correlations were found between average chronic inflammation score and the IPSS variables (16).

In a cohort study of 282 patients, Robert et al. observed a significant correlation between the degree of prostatic inflammation, prostate volume, and urinary system symptoms. Mean IPSS was 12 in patients with lower inflammation and 21 in patients with higher inflammation (17).

In contrast, our study grouped patients by the existence of prostatitis; 34.6% patients had prostatic inflammation. Mean IPSS was 19 in patients with prostatitis and 17.6 in patients without prostatitis. The difference was not statistically significant. Similarly, Edlin et al. in their study evaluating the prevalence of prostatic inflammation in BPH and prostatic adenocarcinoma, reported histological prostatitis in 61% patients with BPH and that histological prostatitis showed a minor correlation with LUTS (18).

Sexual function disorders are frequently encountered in patients with chronic prostatitis. Liang et al. observed 2000 patients with chronic prostatitis

and found that 49% of patients had comorbid sexual dysfunction. Moreover, 26.4% of these patients had premature ejaculation, 14.9% erectile dysfunction, and 7.7% both conditions (19).

The effect of histological prostatic inflammation on ED is gaining importance recently. Abdullah et al. showed that upon reduction of post-surgical inflammation in patients with prostatitis and BPH, sexual function improved (20).

Wang et al. revealed that the presence of prostatitis in tissues of patients with BPH undergoing a transurethral prostate resection had a serious effect on the sexual function and a less effect on LUTS (21).

CONCLUSIONS

In our study, among patients in whom biopsy was performed, IIEF scores were significantly lower in those with inflammation at the tissue level than in those without prostatitis. We suggest that the mechanism underlying advances in tissue damage caused by inflammation and BPH may also affect sexual function with similar mechanisms. Additional clinically relevant study is needed.

CONFLICT OF INTEREST

None declared.

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Dipstick Spot urine pH does not accurately represent 24 hour urine PH measured by an electrode

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ABSTRACT

Objectives: To determine whether spot urine pH measured by dipstick is an accurate representation of 24 hours urine pH measured by an electrode.
Materials and Methods: We retrospectively reviewed urine pH results of patients who presented to the urology stone clinic. For each patient we recorded the most recent pH result measured by dipstick from a spot urine sample that preceded the result of a 24-hour urine pH measured by the use of a pH electrode. Patients were excluded if there was a change in medications or dietary recommendations or if the two samples were more than 4 months apart. A difference of more than 0.5 pH was considered an inaccurate result.
Results: A total 600 patients were retrospectively reviewed for the pH results. The mean difference in pH between spot urine value and the 24 hours collection values was 0.52±0.45 pH. Higher pH was associated with lower accuracy ($p<0.001$). The accuracy of spot urine samples to predict 24-hour pH values of <5.5 was 68.9%, 68.2% for 5.5 to 6.5 and 35% for >6.5. Samples taken more than 75 days apart had only 49% the accuracy of more recent samples ($p<0.002$). The overall accuracy is lower than 80% ($p<0.001$). Influence of diurnal variation was not significant ($p=0.588$).
Conclusions: Spot urine pH by dipstick is not an accurate method for evaluation of the patients with urolithiasis. Patients with alkaline urine are more prone to error with reliance on spot urine pH.

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INTRODUCTION

The urinary pH is an integral part of the metabolic workup of patients with nephrolithiasis, and can help direct management approaches to stone prevention.

The value of urine pH may vary according to the type of urine sample and the method of measurement. Urine pH may be measured by various ways. In the outpatient setting, two common approaches are dipstick testing and the use of a pH electrode. The pH electrode is regarded as the gold standard method of spot-urine assessment of pH (1) however, dipstick measurements offer the advantages of point-of-care assessments, home--monitoring, easy handling, and convenient cost.

To date, 24-hour urine collections are the "gold standard" for metabolic evaluation in urinary stone disease (2). However, it is time consuming and inconvenient, especially for working patients who constitute a big proportion of stone-formers. Such inconvenience may also impact patient motivation for completing repeat 24-hour collections that are believed to be necessary for accurate monitoring of response to dietary or medical interventions (3).

Our aim was to determine whether spot urine pH values measured by a dipstick are accurate to represent the 24 hours urine pH measured by an electrode, for evaluation and monitoring of patients with urolithiasis.

MATERIALS AND METHODS

We retrospectively identified patients who presented to the urology stone clinic and had spot urine that was taken when the patient presented for a scheduled clinic visit. The 24 hour urine was collected at home by the patient, within 4 months from the spot urine date (Litholink Corp, Chicago, Il). Patients with a documented UTI at time of urine collections or those receiving urine acidifier or alkalizer medications were excluded.

To evaluate effects of spot urine results on clinical management, the accuracy of spot urine pH for predicting 24 hours pH was defined as such that a difference of more than 0.5 pH was considered a non-matching result, as dipsticks are only precise to the nearest 0.5 pH interval. For each patient, an accuracy score of a 'yes' or a 'no' was calculated by determining if the difference between the two urine samples was within 0.5 pH. To assess influence of pH values on matching accuracy, 24 hours urine pH were also grouped into clinical relevant categories, <5.5, 5.5-6.5, and >6.5 for analysis. Time interval between spot and 24 hours pH urine samples and time of day (am versus pm) the spot samples were taken were also included in the analysis.

Results were presented as means and standard deviations (SD), medians and inter quarter ranges (IQR), proportions or percentages. Group comparisons for continuous variables were done using Wilcoxon rank sum test. For categorical variables and matching rate, chi-squared test was used. Bonferroni correction was used for multiple comparisons.

In order to evaluate factors influencing rate of matching between the two pH measures, logistic regression analysis was used to model the accuracy score as defined above. Odd ratio and its 95% CI were also estimated for a variable's influence on accuracy. All analyses and graphics were done using the statistical software package R version 3.02 (R Development Core Team, www.r--project.org). All statistics were considered significant at the level of α=0.05.

RESULTS

A total of 600 patients were retrospectively identified who had a spot urine sample within 4 months of a 4-hour urine evaluation; the median time period between spot pH evaluation and 24-hour urine collection was 31 days (IQR 15-61). 63% (377/600) spot pH samples were taken before noon with both AM and PM samples had a mean of 6.1 pH. The average (SD) spot pH was 6.1 (0.67) compared to 6.1 (0.58) for 24 hours samples. The mean difference in pH between individual spot urine values and 24 hours collections was 0.52±0.45 pH.

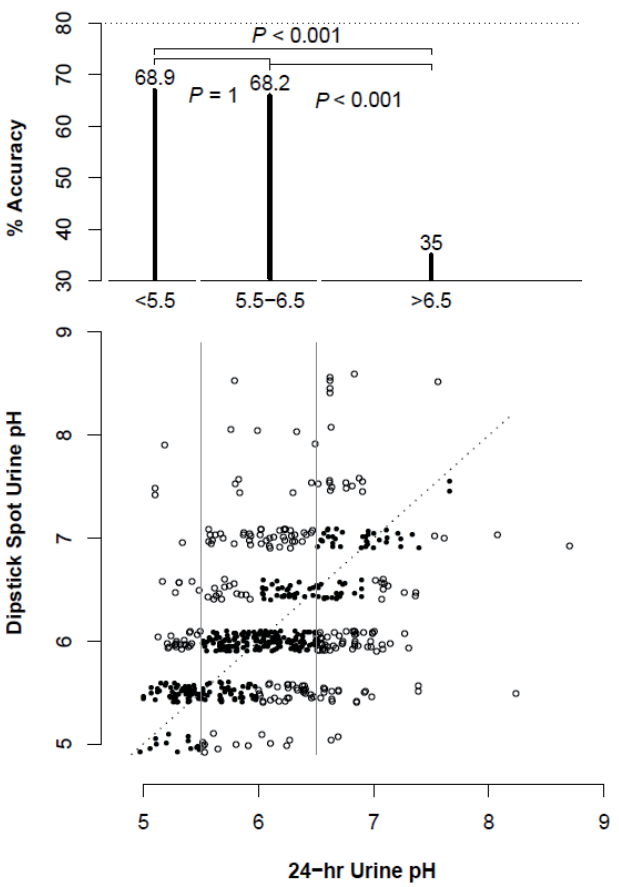
The accuracy of spot urine samples to predict 24 hours pH values of <5.5 was 68.9% (71/103). The accuracy of spot urine samples to predict 24 hours pH values of 5.5-6.5 was 68.2% (232/340), while the accuracy of spot urines to detect 24 hours pH values >6.5 was only 35% (55/157). The >6.5 pH group had accuracy significantly lower than both the <5.5 pH and the 5.5-6.5 pH groups (both p's <0.001) (Figure-1). The overall accuracy was 59.7% (358/600), which is significantly lower than an adequate accuracy of 80% (p<0.001).

Multivariable logistic regression analysis revealed that higher 24 hours urine pH was not matched by higher spot urine pH. pH >6.5 was only 19% as likely to be matched than for pH <5.5 (OR=0.19; 95% CI: 0.11-0.33; p<0.001). 24 hours urine samples and spot urine samples taken close to one day (shorter time interval) were more likely to match. Samples taken more than 75 days apart only matched 49% of the time compared to those taken in shorter intervals (OR=0.49; 95% CI: 0.32-0.77; p<0.001). Evaluating an AM or PM spot urine had no impact on the accuracy of the measurement compared to the 24-hour urine pH (OR=1.1; 95% CI: 0.78-1.57; p=0.588).

DISCUSSION

Variations in urine pH are considered one of the well-known risk factors for urolithiasis.

Figure 1 - 24 hours Urine pH.



Monitoring urine pH has become an essential tool in the prevention and treatment protocols for stone formers. Simplifying the method of pH measurement and urine collection would make the follow-up easier and likely increase patient compliance by providing the opportunity for continuous home monitoring.

The 24 hour urine pH has been proposed to be more representative of a patient's stone risk, avoiding the possibility of diurnal variation or circadian rhythm in urinary acidity occurring with spot urine pH (4). Urinary acid–base parameters follow diurnal patterns and it is thought these changes are due to periodic surges in gastric acid secretion.

Our goal was to evaluate the accuracy of using spot urine pH as an alternative to 24 hour urine pH, which is considered the gold standard for metabolic evaluation of stone disease.

The most clinically relevant pH values for stone formers are between 2 categories: <5.5 which is usually present with uric acid stone patients, to whom point alkalinization therapy might be initiated to decrease the risk of uric acid and calcium oxalate supersaturation, and >6.5 where either citrate supplementation may be decreased or concerns for calcium phosphate or struvite supersaturation may arise (5). We therefore focused on these cut-off points of pH to evaluate the accuracy in these ranges.

Our results suggest that the accuracy of a spot urine pH varies depending on the value of the pH a patient had at the time of measurement. Greater accuracy was noted for pH values <5.5 and 5.5-6.5 than those >6.5. One might conclude that spot urine values may be of benefit to help patients tailor their citrate intake to raise their urine pH above the 5.5 threshold, however greater reliance on 24-hour urine evaluations is warranted to avoid over-alkalinization once the pH has been increased above 6.5.

The timing of spot urine pH evaluation had no impact on the accuracy of the evaluation. Future investigation will focus on the accuracy of daily home pH monitoring with weekly averaging of the values.

The measurement tools for determining pH (dipstick versus electrode) as well as the urine collection method (one-time spot urine sample versus 24 hours collection) and the average days between spot urine samples versus 24 hours collection are likely to affect the outcome of the pH value.

A similar study by Tsong et al. (2013) reported that urine dipstick measurement had an approximately 1 in 4 (25%) risk of producing clinically significant difference (pH differences >0.5 pH unit) from meter values (6). The accuracy of pH electrode over the dipstick is well established by many researchers (7), but the difference between 24 hour and spot urine sample pH was, to our best knowledge, never been evaluated.

Though the timing of the spot pH did not coincide specifically with the date of 24-hour urine collection, we believe timing of evaluation mimics the common clinical practice of patient self-monitoring of pH levels at home in between 24-hour urine collections.

One limitation of our study is that the timing of the spot urine samples was linked to the patient's outpatient clinic visit; as such we were unable to evaluate the utility of a first AM void or an evening sample as a screening of therapeutic pH level.

CONCLUSIONS

We suggest that the spot urine pH by dipstick is not an accurate and dependable method for evaluation of the patients with urolithiasis. Spot pH urine evaluations are most accurate in patients with acidic urine. Its credibility should be reinforced periodically with the 24 hour electrode measured pH to avoid the high risk of errors, related to both the method of measuring and the sample used.

ABBREVIATIONS

pH = power of hydrogen

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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The effect of breastfeeding on spontan resolution of monosymptomatic enuresis

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ABSTRACT

Purpose: The aim of this study was to examine whether the duration of breastfeeding during infancy was associated with the time of spontaneous resolution of monosymptomatic enuresis (SRME).

Materials and Methods: A total of 1500 people were surveyed at four centers. One hundred and eighty-one people with a history of monosymptomatic enuresis (ME) who received no treatment and had no day time symptoms were included in the study. The relationship between the duration of breastfeeding and SRME was assessed by considering the duration of breastfeeding as both continuous and categorical (cut-off value 5 months) variable. The multivariate general linear model was used to identify independent predictors such as gender, family history, and educational status of parents.

Results: Pearson correlation analysis of the age of SRME and duration of breastfeeding found no statistically significant relationship. However, there was a significant difference in the age of SRME of those who were breastfed for 5 months or less compared to those who were breastfed for more than 5 months. According to the multivariate analysis, gender and educational status of parents were not effective on the age of SRME. Stepwise linear regression model showed that breastfeeding for five months or less and family history could affect the age of SRME. The regression formula was: age of SRME=9.599 + (3.807×five months or less of breastfeeding) + (1.258×positive family history).

Conclusions: It was found that when breastfeeding lasted for more than 5 months, there was a positive contribution to SRME.

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INTRODUCTION

Enuresis is an important and frequently seen health problem during childhood throughout the world and it is predicted that there are over 50 million children with enuresis worldwide (1). According to the definition of the International Children's Continence Society, in the absence of attendant symptoms of the lower urinary tract, such as daytime urinary frequency, urgency, hesitancy, straining, daytime incontinence etc., any wetting during sleep above the age of 5 years is defined as monosymptomatic enuresis (ME) (1-3). The overall prevalence of ME declines by about 15% each year with increasing age, occurring in 15% of children aged 5 years, and 7% aged 7 (2, 4). Although ME is less common-

ly seen after the age of 7 years, 1-2% of adults are still enuretic (3, 5, 6).

ME has been accepted as a common bio-behavioral problem in early childhood (4). The etiology seems to be multifactorial and several etiologies have been asserted for ME, including developmental delay, immature bladder function, immature sleep pattern and insufficient nocturnal antidiuretic hormone (7, 8). Most of these etiologies for ME are related to delayed development because they are normally seen in younger children and infants. The developmental theory is supported by clinical studies that report more developmental delays in children with ME compared with controls (8, 9). Other causes of ME include psychosocial and familial factors. The effects of psychosocial factors such as stress are ambiguous but have been stated to be associated with ME (7, 10, 11). Also, genetic factors have been recognized in ME and familial clustering has been observed in several studies (7-9, 12).

Although the high rate of spontaneous resolution is obvious, there are no articles investigating the effect of the factors that contribute to the time of spontaneous resolution of monosymptomatic enuresis (SRME). We examined the relationship between ME and breastfeeding because both have been reported to be strongly associated with childhood development. For example, there is a lot of clinical evidence that breastfeeding may provide neurodevelopmental advantages to children (13-16). Neurodevelopmental delays have been identified in children with ME (9, 12). In addition to this, it was determined that psychogenic factors similar to stress play a role in the etiology of ME, but breastfeeding has been shown to have positive contributions to self-esteem and some psychological diseases (17). According to numerous studies, it is clear that both breastfeeding and ME are associated with child development, so the objective of this study was to examine whether duration of breastfeeding during infancy was associated with the time of SRME.

MATERIALS AND METHODS

Patient Population

After receiving permission from the institutional ethics committee, about 1500 people were surveyed. The questionnaires were obtained by talking to individuals face to face in four referral hospitals which were located in different cities in Turkey. Only patient relatives, not the patients, were asked to answer the questionnaire in different out-patient clinics of the centers (outpatient clinics of urology, dermatology and family medicine). If the answer to the question of whether there was bed-wetting after the age of five (the 60th month after birth) was yes, the other questions were asked. To evaluate the spontaneous resolution correctly, patients who were given any treatment for bed-wetting were excluded. In those whose bed-wetting resolved spontaneously, the duration of breastfeeding, educational status of parents and family history of enuresis were questioned. The presence of ME in first degree relative was evaluated as positive family history. We excluded patients with diurnal enuresis or with any day-time symptoms such as pollakiuria, frequency, and urgency during any part of their life. Patients with illnesses which could affect micturition habits such as diabetes mellitus or neurological diseases were also excluded. Because the basis of the study is information about infancy, those over the age of 35 were excluded from the study. If the participating children were aged 16 and below, information provided by the parents of children were taken into consideration. The information given by participants who were older than 16 was confirmed by another member of the family. At the end of the questionnaire, patients and parents were all asked if they were extremely sure about the information they provided. If the answer was no, they were excluded from the study. If the double checks were inconsistent, participants were also excluded from the study. As a result, the clinical data from 181 people were evaluated.

Statistical analysis

All statistical analyses were performed using SPSS, version 20.0. All values are shown as mean ± standard deviation. The normal distribution of the sample data was checked with the Kolmogorov-Smirnov and Shapiro-Wilk tests (18). The comparison of duration of breastfeeding and age of resolution of ME was completed using the Pearson correlation analysis. The effect on SRME of gender,

family history and five months and less or longer duration of breastfeeding were evaluated with the Mann-Whitney U test. The Kruskal-Wallis tests were conducted to compare the age of SRME and the educational status of mother and father (each had 3 subgroups). The multivariate general linear model and stepwise linear regression were used to identify independent predictors such as gender, family history, educational status of parents, and five months or less duration of breastfeeding. The model fit was assessed using appropriate residual and goodness-of-fit statistics. A p value of <0.05 was accepted as significant.

RESULTS

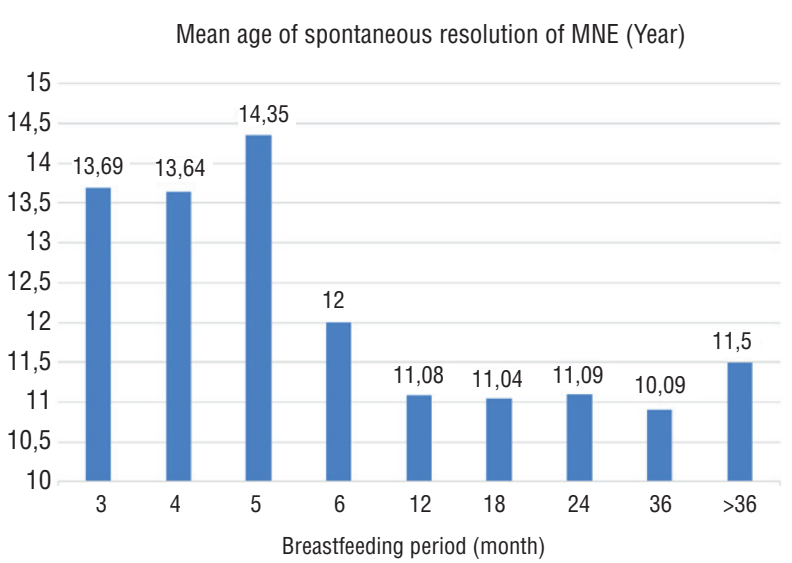
The study consisted of 103 male patients (56.9%) and 78 female patients (43.1%); 181 patients in total. The average age was 25.7±6.2 (between 7-35 years), 90% were over the age of 14. The average age of SRME was 11.0±3.5 years (range 5-30 years) and the average duration of breastfeeding was 16.5±9.8 months (range 0-60 months) (Table-1).

Pearson correlation analysis of the age of SRME and duration of breastfeeding found no statistically significant relationship (p=0.250) (Figure-1). However, there was a significant difference in the age of SRME of those who were breastfed for 5 months or less compared to those who were breastfed for more than 5 months (average age of resolution for those breastfed ≤5 months 14.35±5.0 years; for those breastfed >5 months 10.58±2.9; p<0.001). There were no statistically significant relationships between the age of SRME and gender or presence of family history (Table-2). There was no

Table 1 - The demographic characteristics of patients.

	n	Mean ± ss	Median	Minimum	Maximum
Age	181	25.7 ± 6.2	27.0	7.0	35.0
Age of spontan resolution of MNE	181	11.0 ± 3.5	11.0	5.0	30.0
Duration of breatfeeding (month)	181	16.5 ± 9.8	13.0	0.0	60.0

Figure 1 - The relationship between breastfeeding and mean age of spontaneous resolution of monosymptomatic enuresis is demonstrated.



significant correlation found between the age of SRME and educational status of parents (Table-3). A multivariate linear model was used to evaluate the independent predictors for the age of SRME. According to this analysis, the age of SRME was not affected by gender, or the educational status of mother and father (p=0.483, p=0.488, p=0.396, respectively). Stepwise linear regression showed that breastfeeding for five months or less and family history could affect the age of SRME (Table-4). The regression formula was: age of SRME=9.599 + (3.807×five months or less of breastfeeding) + (1.258×positive family history).

DISCUSSION

This is the first study to investigate the relationship between the age of SRME in children and breastfeeding. ME is regarded as a

Table 2 - Gender, breastfeeding, family history and SRMNE.

		Age of spontaneous resolution					Mann-Whitney U Test		
		n	Mean ± ss	Med	Min	Max	Mean Rank	U	p
Gender	Female	78	10.99 ± 3.80	10.0	6.0	30.0	88.00		
	Male	103	11.01 ± 3.23	11.0	5.0	18.0	93.27	3783	0.501
	All	181	11.00 ± 3.48	11.0	5.0	30.0			
Duration of breastfeeding	≤ 5 month	20	14.35 ± 5.08	13.0	8.0	30.0	129.63		
	> 5 month	161	10.58 ± 2.99	10.0	5.0	22.0	86.20	837.5	0.0001
	All	181	11.00 ± 3.48	11.0	5.0	30.0			
MNE in family history	Apsent	40	10.08 ± 3.16	10.0	5.0	17.0	77.80		
	Existent	141	11.26 ± 3.53	11.0	5.0	30.0	94.74	2292	0.07
	All	181	11.00 ± 3.48	11.0	5.0	30.0			

Table 3 - Education status of parents and SRMNE.

		Age of spontaneous resolution					Kruskal-Wallis H Test		
		n	Mean ± ss	Med	Min	Max	Mean Rank	H	p
Education status of mother	Primary school and less	122	10.97 ± 3.28	11.0	5.0	22.0	89.82	0.05	0.975
	High school	34	11.26 ± 4.43	11.0	6.0	30.0	89.69		
	University	25	10.80 ± 3.07	10.0	5.0	17.0	91.61		
	Total	181	11.00 ± 3.48	11.0	5.0	30.0			
Education status of father	Primary school and less	110	10.91 ± 3.00	11.0	5.0	21.0	91.77		
	High school	46	11.24 ± 4.61	10.0	6.0	30.0	88.23		
	University	25	10.96 ± 3.13	11.0	5.0	18.0	92.70		
	Total	181	11.00 ± 3.48	11.0	5.0	30.0		0.18	0.914

Table 4 - Results of the multivariate general linear model analysis.

	B	Beta	p	CI 95%
Constant	9.599		0.0001	8.568-10.630
Duration of breatfeeding (0: five month or less 1: longer than five month)	3.807	0.344	0.0001	2.288-5.327
Family history (0: absent – 1 present)	1.258	0.151	0.032	0.110-2.406

self-limiting condition and expected to resolve spontaneously at a rate of 15% per year (5, 19, 20). Alarm therapy and desmopressin, which are evidence-based first-line treatments, are recommended for current treatment of ME (3, 21). Some parents who have children with ME choose an observational approach instead of the treatment option. However, in spite of this high rate of spontaneous resolution, there is no study researching the factors that could affect this rate found in the literature.

There may be various factors, such as severity of symptoms, which influence the age of spontaneous resolution. Although many factors such as behavior abnormalities, immature bladder function, imamture sleep pattern, insufficient nocturnal antidiuretic hormone and hereditary factors can be coupled with ME, there is a traditional opinion that developmental immaturity of voiding control is the main reason (7, 8). The role of stress and psychological factors in the pathogenesis of ME has been shown in a variety of studies (7, 10, 11, 21). Recently many studies have identified a delay in neuromotor development in children with ME (8, 9, 12, 22). These studies assert a maturational deficit of the brainstem as the possible central dysfunction of the disorder.

It is known that breastfeeding has a positive effect on behavior problems. Breastfeeding forms a bond between mother and baby and a variety of studies have shown many positive psychological effects like increasing self-esteem and preventing depression (17, 23, 24). According to a study by Kwok et al. durations of breastfeeding of less than 3 months were linked to worse behavior and lower self-esteem (17). Additionally, a range of studies have investigated the effects of breastfeeding on cognitive development and neurodevelopment (13, 15, 16, 25). The central nervous system has the second highest concentration of lipids in the body after adipose tissue, which contains predominantly triglycerides. The lipids in the brain are present as the structural phospholipid components of cell membranes (25). Docosahexaenoic acid and arachidonic acid, which are present in breast milk, are examples of the most important and basic long chain polyunsaturated fatty acids. Babies only have a limited capability to synthesize such fats from precursors (14). It has been shown that especially the higher n-3 and n-6 long-chain polyunsaturated fatty acids in breast milk have important effects on neural and visual development (14, 16, 25). Vestergaard et al. determined that the duration of breastfeeding was a specific milestone for motor skills and early language development (16).

In the literature there were few studies investigating the relationship between breastfeeding and ME; however, none investigated the relationship between spontaneous resolution and breastfeeding. In a cross-sectional study by Gumus et al., different clinical factors in childhood bed-wetting were evaluated and, taking rates of breastfeeding in the first four months after birth as reference, there was no difference found between cases with enuresis and those without (26). Singh et al. investigated the relationship between bed-wetting and several different clinical features of 100 children. Although there was no control group in the study,

the authors found higher enuresis prevalence in children fed using a bottle compared with those who were breastfeed (27).

A study by Barone et al. compared enuretic children with a control group and showed that duration of breastfeeding longer than 3 months had a protective effect against bed-wetting (28). In a recent observational case-control study involving 200 children and adolescents from 6 to 14 years old, Oliviera et al. indicated that the duration of breastfeeding of less than 4 months is strongly associated with primary enuresis (29). In our study while there was no significant difference found between the age of spontaneous resolution and breastfeeding of children with ME, comparing the group who were breastfed for 5 months or less with those fed for longer, breastfeeding had a significant positive contribution to age of SRME ($p<0.001$). With regard to multivariate analysis, gender and educational status of mother and father were not effective on the age of SRME. Stepwise linear regression model showed that five months or less of breastfeeding and family history could affect the age of SRME. There was very weak correlation between the family history and the age of SRME. Accordingly, breastfeeding for at least 5 months can be expected to provide a contribution to the age of SRME in children. This conclusion correlates with the results of previous studies and is in accordance with our expectations due to the positive contribution on neurodevelopment and childhood psychology of breastfeeding.

None of the patients included in the study after the survey had treatment of ME in their history. However, due to the psychological effects of bed-wetting on the child and family, especially in school-going children, treatment is recommended (30). As a result, when designing prospective studies about SRME in children, it may not be ethical not to give treatment. As a result, a survey questionnaire was used for the study design. It may be considered that a case control approach would have been more appropriate. However, we investigated the factors affecting the time of SRME and it is impossible to evaluate the time of SRME in patients who were not bedwetting which is why we did not design a case control study.

The major limitation of the current study was the long time between breastfeeding, enuresis and application of the questionnaire. Nevertheless, in order to increase the reliability of data, those over the age of 35 were excluded from the study, information given only by the family in children under the age of 16 were taken into consideration, and information given by participants over the age of 16 were double-checked. Another limitation of the study was that enuresis-related diseases such as adenoid hyperplasia and obstructive sleep apnea-hypopnea syndrome were not considered in the study design.

CONCLUSIONS

One of the frequently observed disorders in childhood is ME, generally evaluated as a benign situation due to the high rate of spontaneous resolution. If it continues into the school-going period, treatment is recommended due to negative effects on the child and family, but this topic is still debated. In our study lengthening the duration of breastfeeding to more than 5 months was found to have an effect on spontaneous resolution. Before planning medication or other treatments for children with ME, the factors that can affect spontaneous resolution should be evaluated to reduce the cost of medications or other treatments and to protect children from the side effects of medication treatment. Breastfeeding, with no costs, has a positive effect on the age of SRME, similar to its effects on many aspects of childhood development. This under-researched topic requires more prospective randomized studies.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Is there a trans-abdominal testicular descent during the second gestational trimester? Study in human fetuses between 13 and 23 weeks post conception

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ABSTRACT

Objectives: To confirm if a real inner descend of testis occurs, correlating the testicular position with fetal parameters and analyzing the position of the testes relative to the internal ring.

Material and Methods: Twenty nine human fetuses between 13 and 23 weeks post conception (WPC) were studied. The fetuses were carefully dissected with the aid of a stereoscopic lens with 16/25X magnification and testicular position observed. With the aid of a digital pachymeter the distance between the lower pole of the kidney and the upper extremity of the testis (DK-T) was measured to show the position of the testis. During the dissection we also indicated the position of the testes relative to the internal ring. Means were statistically compared using simple linear regression and the paired T-test.

Results: The 58 testes had abdominal position. The DK-T in the right side measured between 0.17 and 1.82cm (mean=0.79cm) and in the left side it was between 0.12 and 1.84cm (mean=0.87cm), without statistically differences (p=0.0557). The linear regression analysis indicated that DK-T in both sides correlated significantly and positively with fetal age. All fetuses with more than 20 WPC, heavier than 350g and with CRL over 22cm had a greater distance than the average DK-T. We xobserved that the 58 testis remains adjacent to the internal ring throughout the period studied.

Conclusions: The testes remains adjacent to the internal ring throughout the period studied, indicating that there is no real trans-abdominal testicular descent during the second gestational trimester.

ARTICLE INFO

Keywords:
Cryptorchidism, Gubernaculum testis, Human fetuses, Testicular migration

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INTRODUCTION

Testicular descent is a process that depends on anatomic modifications and hormonal stimulus (1, 2). During the human fetal period, the testes migrate from the abdomen to the scrotum, traversing the abdominal wall and the inguinal canal between the 15th and the 28th week post-conception (WPC) (1-4). Some authors suggest that testicular descent has two separate stages: the first phase corresponds to the testicular descent from the abdomen to the internal inguinal ring, and the second phase corresponds to the transition of the testes through the inguinal canal until their definitive arrival in the scrotum (1-3).

Various factors have been proposed as causing testicular descent in humans, including the increase in the intra-abdominal pressure (5, 6), the development of the epididymis, spermatic vases, deferent ducts and inguinal canal (7); stimuli from

the genito-femoral nerve (8); hormonal stimulus originating in the placental gonadotrophin and the testosterone produced by the fetal testes (9); propulsion by the smooth muscle that surrounds the processus vaginalis (10) and gubernaculum development (7).

The moment when testicular descent begins is controversial. Backhouse (2) reports that this process starts at about the 24th week post-conception, while Heyns (3) and Sampaio&Favorito (4) relate cases where the descent process started as early as the 17th week.

There are only a few reports in the literature about the chronology of testicular descent in human fetuses (11). The process of descent of the testis from the abdomen to the inguinal canal during the first phase of testicular descent is not totally understood in humans. This inner testicular descent was dependent of the gonad growth, involution of mesonephros and the descending septum transversum of the anlage of the diaphragm (12).

The objective of this paper is to confirm if a real inner descend of testis occurs, analyzing the abdominal testicular descent by correlating the testicular position with fetal age, weight, crown-rump length (CRL), total length of the fetus and the position of the testes relative to the internal ring.

MATERIAL AND METHODS

This study received institutional review committee approval and was carried out in accordance with the ethical standards of the hospital's institutional committee on human experimentation.

During the period from January 2014 through March 2015, 29 male human fetuses (58 testes) ranging in age from 13 to 23 weeks post-conception (WPC) were studied. The fetuses were macroscopically well preserved, showed no signs of malformations and came to our laboratory as a donation of the obstetric section of our hospital and the demise was hypoxia. The gestational age of the fetuses was determined in WPC, according to the foot-length criterion. This criterion is currently considered the most acceptable parameter to calculate gestational age (13-15). The fetuses were also evaluated regarding total length (TL), crown-rump length (CRL) and body weight immediately before dissection. The same observer made all the measurements.

After the measurements, the fetuses were carefully dissected with the aid of a stereoscopic lens with 16/25X magnification. The abdomen, pelvis and inguinal canal were opened to identify and expose the urogenital organs.

Testicular position was classified after dissection into: a) Abdominal, when the testis was proximal to the internal ring; b) Inguinal, when the testis was found between the internal and external inguinal rings; and c) Scrotal, when the testis had passed beyond the external inguinal ring and was inside the scrotum.

With the aid of a digital pachymeter, the distance between the lower pole of the kidney and the upper pole of the testis (DK-T) was measured to show the descent of the testis during migration. The same observer made these measurements (Figure-1). During the dissection we also indicated the position of the testes relative to the internal ring.

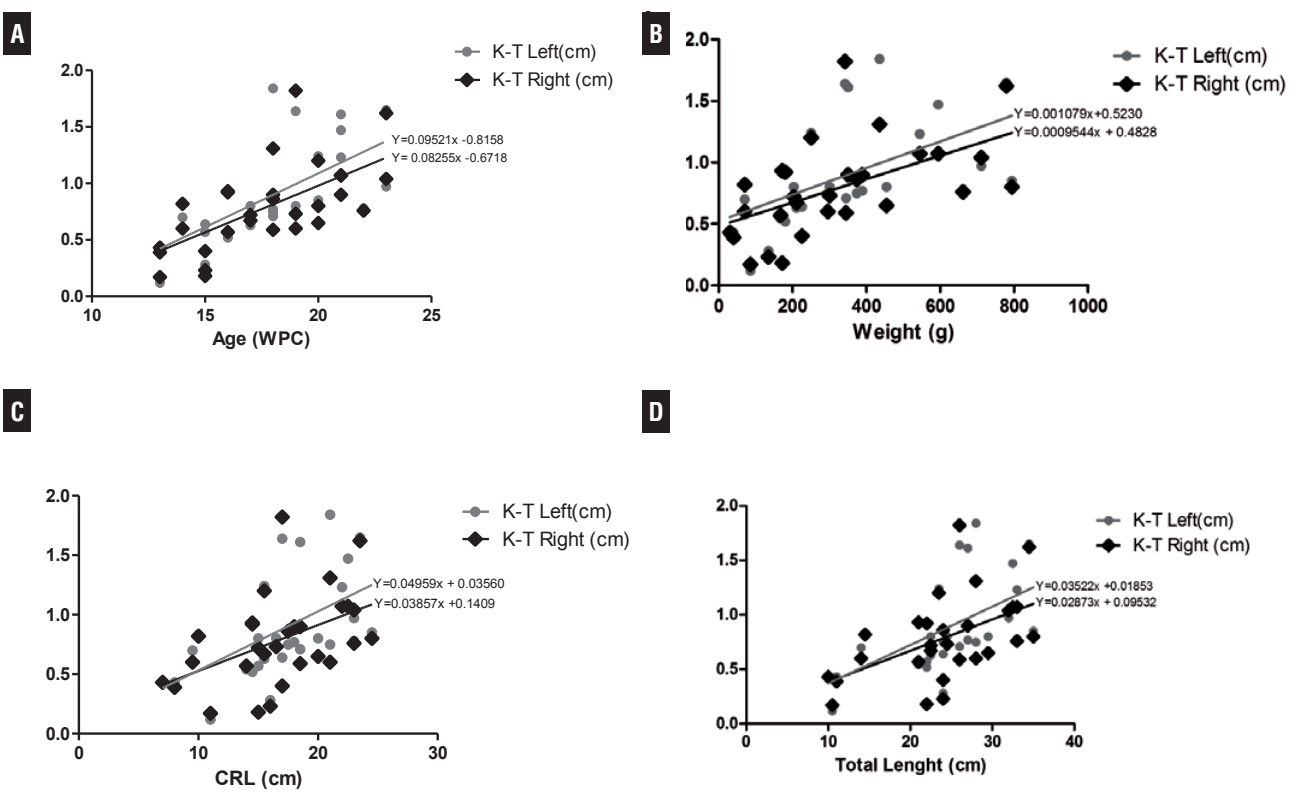
Statistical analysis

Mean values of the distance between the lower pole of the kidney and the upper extremity of the testis for each side were statistically compared using the unpaired T-test. We also performed simple linear regression to assess the association between the variables analyzed with fetal age. In addition, the correlation coefficient (r) and the p-value were obtained for each regression analysis, and $p \leq 0.05$ was considered to indicate statistical significance. The Graph pad Prism 5.0 software was used.

RESULTS

The fetuses weighed between 30 and 793.4g; had crown-rump length between 7 and 24.5cm and had total length between 10 and 34.5cm. The 58 testes all had abdominal position. The DK-T in the right side measured between 0.17 and 1.82cm (mean=0.79cm; SD=0.3868 and SE=0.07183) and in the left side between 0.12 and 1.84cm (mean=0.87; SD=0.4296 and SE=0.07978), without statistically significant difference (p=0.0557). Table-1 reports the fetal parameters and the measurements of DK-T in

Figure 1 - Correlation of the distance between the lower pole of the kidney and the upper extremity of the testis (DK-T) in the left and right side with fetal age, total fetal length, crown-rump length and weight during the fetal period studied (13 to 23 weeks post-conception-WPC). The points plotted represent the mean values obtained for each week studied. A) AGE (WPC). Linear regression indicated that DK-T is correlated significantly and positively with fetal age (right side: r2 = 0.4128, p=0.0002 and left side: r^2 = 0.4452, p<0.0001). B) Fetal weight (g). Linear regression indicated that DK-T is correlated significantly and positively with fetal weight (right side: r^2 = 0.2987, p=0.0022 and left side: r^2 = 0.3094, p=0.0017). C) Crown-rump length (cm). Linear regression indicated that DK-T is correlated significantly and positively with fetal crown-rump length (right side: r^2 = 0.2235, p=0.0096 and left side: r^2 = 0.2995, p=0.0021). D) Total length (cm). Linear regression indicated that DK-T is correlated significantly and positively with fetal weight (right side: r^2 = 0.2729, p=0.0036 and left side: r^2 = 0.3324, p=0.0011).



the right and in the left side of all fetuses studied.

Considering the average of DK-T in the right and in the left side, all fetuses with more than 20 WPC had a greater distance than the average DK-T value. All fetuses heavier than 350g and with CRL greater than 22cm had the high or very near average DK-T values.

The linear regression analysis indicated that DK-T in the right and left sides correlated significantly and positively with fetal age and weight, during the fetal period studied (13 to 23 WPC). When comparing the DK-T with TL and CRL, we observed a weak correlation in the right and in the left side. Figure-2 shows the correlations graphs, the linear regression values (r^2) and the p-values of all fetal parameters studied.

We observed that the 58 testis remained adjacent to the internal ring throughout the period studied (Figure-3).

DISCUSSION

Previous studies show that in the first phase of testicular descent, the testis descends from

Figure 2 - Measurement of the distance between the lower pole of the kidney and the upper extremity of the testis. A) Male fetus with 22 weeks post-conception. The abdominal wall and the intra-peritoneal organs were removed, revealing the left kidney (LK) and the left testis (LT). B=bladder. B) The same fetus, where the distance between the lower pole of the left kidney (LK) and the upper extremity of the left testis (LT) was measured with a digital pachymeter (P).

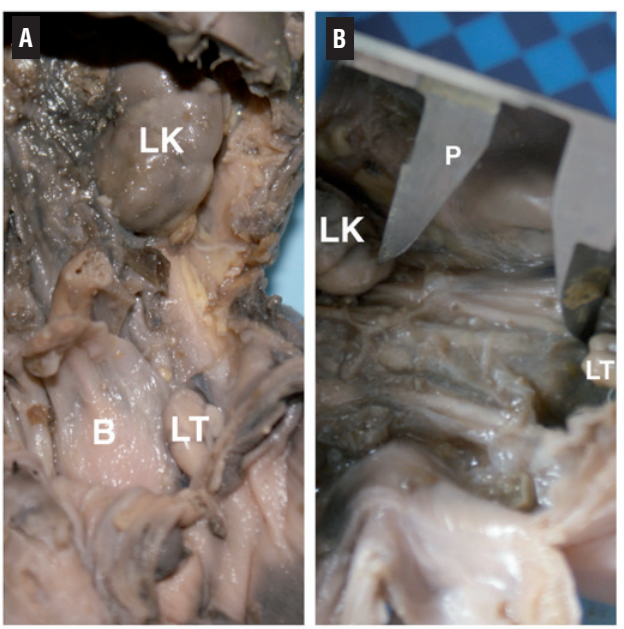
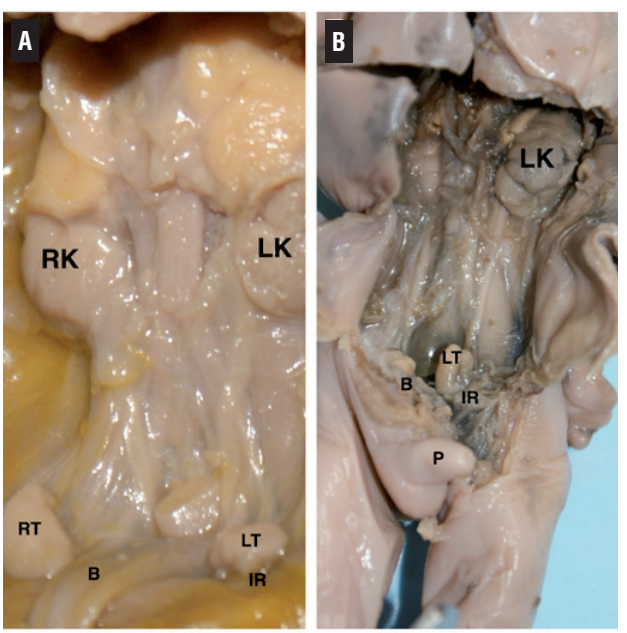


Figure 3 - Position of the testes relative to the internal ring. A) Male fetus with 13 weeks post-conception. The abdominal wall and the intra-peritoneal organs were removed, showing that the right (RT) and the left testis (LT) remains adjacent to the internal ring (IR). B) Male fetus with 23 weeks post-conception. The abdominal wall and the intra-peritoneal organs were removed, showing that the right (RT) and the left testis (LT) remains adjacent to the internal ring (IR). LK=left kidney; RK=Right Kidney; B=bladder and P=Penis.



the lower pole of the kidney to the pelvic cavity near the bladder neck (16). In this phase, the gubernaculum enlarges to hold the testis near the internal ring, regulated by insulin-like-3-hormone (INLS-3) (17, 18). INSL-3 is secreted by the Leydig cells and controls gubernaculum swelling via its receptor, a process resulting in thickening of the gubernaculum because of increases in water, glycosaminoglycan and hyaluronic acid content (17-21).

The first phase of testicular descent in human fetuses begins around the 8th WPC and lasts until the 15th WPC (22) and the second phase, or the inguino-scrotal phase, begins around the 25th WPC and lasts until the 35th WPC (23). Previous papers studying large numbers of testes show that some fetuses with 17 WPC already had the testis situated in the inguinal canal and all the fetuses older than 30 weeks already had the testes in the scrotum (4). Other authors, however, have reported that the testicular descent is only completed after the 32nd week post-conception (1-3). So the chronology of testicular descent during the second and the third trimesters of gestation are still controversial in the literature.

Previous studies in human fetuses have shown that until 21 WPC, the majority of the testes are located in the abdomen (4, 11). Sampaio&Favorito (4) studied 71 human fetuses (142 testes) and 88% of the testes in fetuses with less than 21 WPC were in the abdomen. Favorito (11) recently studied the asymmetry during testicular migration in 164 human fetuses and observed that 99% of the testes were abdominal in fetuses with less than 20 WPC. These two previous papers only report observations, without any measurements of the testicular descent in the abdomen.

In our sample, formed only of fetuses with 23 WPC or less, all the testes were abdominal, showing that the passage of the testis through

the inguinal canal rarely occurs before the 20th WPC. Heyns (3) found only 2.6% of the testes examined in his sample located in the inguinal canal, while Sampaio&Favorito (4), in a sample of 71 human fetuses, found 20.5% of the testes located there. Furthermore, 73.3% of these testes were in fetuses with ages between 21 and 25 WPC, indicating that in this period the migration through the inguinal canal intensifies.

Various parameters have been proposed to determine the gestational age of human fetuses, and crown-rump length and fetal weight are some of the most important (24, 25). Studies correlating fetal parameters with testicular migration during human fetal period are rare in literature. A previous study of fetal weight and testicular descent in human fetuses showed that almost 7% of the testes in fetuses with weight up to 500g had the testes positioned in the inguinal canal (26). In our sample, we observed that the distance between the kidney and the testis was greater in fetuses weighing more than 350g. This information indicated a progressive increase in abdominal length during gestation, and therefore do not convincingly show that the testis has progressive descent during the second trimester.

The only study that correlates the crown--rump length with testicular descent in human fetuses showed that more than 80% of the fetuses with CRL between 6.4 and 20.5cm had testes in the abdominal position and in the fetuses with CRL between 21 and 25.5cm, 45% of the testes were in the abdomen, 45% in the inguinal canal and more than 9% in the scrotum (4). In our sample, all the fetuses had the testes in abdominal position, but we observed that the fetuses with CRL longer than 22cm had high or near average DK-T values, suggesting also a progressive increase in abdominal length during gestation.

In the present study we measured the distance between the lower pole of the kidney and the testis, a very easy way to show the testicular position during the abdominal phase of testicular migration. This measurement can be easily correlated with the fetal parameters too. We observed that the DK-T correlated significantly and positively with fetal age and weight, in the right and left side.

We observed that all the 58 testes of our sample remains adjacent to the internal ring throughout the period studied (13 to 23 WPC), indicating that there is no real trans-abdominal descent of the testis during the second trimester. Previous studies indicated that the testis has progressive descent until the 15th WPC and not during the second gestational trimester, which could be confirmed by our findings (22, 23).

We should mention some limitations of this study: 1) Small sample size–access to human fetuses is limited, so observations of this sample of 29 fetuses may be important although the small number is a weakness, mainly regarding statistical results. 2) Unequal WPC distribution in the period studied–we did not have fetuses with less than 13 WPC and at some ages we had 4 fetuses and at others only 1 or 2 fetuses. Nevertheless, the sample distribution during this important period of testicular migration was adequate in our opinion.

CONCLUSION

The distance between the kidney and the testis in both sides had a strong positive correlation with fetal age and weight in human fetuses. The testes remains adjacent to the internal ring throughout the period studied (13 to 23 WPC), indicating that there is no real trans-abdominal testicular descent during the second trimester.

ABBREVIATIONS

WPC = week post-conception
TL = total length
CRL = crown-rump length
DK-T = distance between the lower pole of the kidney and the upper extremity of the testis
INLS-3 = insulin-like 3 hormone

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CONFLICT OF INTEREST

None declared.

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Single stage: dorsolateral onlay buccal mucosal urethroplasty for long anterior urethral strictures using perineal route

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ABSTRACT

Objective: To assess the outcome of single stage dorsolateral onlay buccal mucosal urethroplasty for long anterior urethral strictures (>4cm long) using a perineal incision.
Materials and Methods: From August 2010 to August 2013, 20 patients underwent BMG urethroplasty. The cause of stricture was Lichen sclerosis in 12 cases (60%), Instrumentation in 5 cases (25%), and unknown in 3 cases (15%). Strictures were approached through a perineal skin incision and penis was invaginated into it to access the entire urethra. All the grafts were placed dorsolaterally, preserving the bulbospongiosus muscle, central tendon of perineum and one-sided attachement of corpus spongiosum. Procedure was considered to be failure if the patient required instrumentation postoperatively.
Results: Mean stricture length was 8.5cm (range 4 to 12cm). Mean follow-up was 22.7 months (range 12 to 36 months). Overall success rate was 85%. There were 3 failures (meatal stenosis in 1, proximal stricture in 1 and whole length recurrent stricture in 1). Other complications included wound infection, urethrocutaneous fistula, brownish discharge per urethra and scrotal oedema.
Conclusion: Dorsolateral buccal mucosal urethroplasty for long anterior urethral strictures using a single perineal incision is simple, safe and easily reproducible by urologists with a good outcome.

ARTICLE INFO

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INTRODUCTION

Urethral stricture is a common disease encountered by urologist. Exact incidence in Indian population has not been reported. Reconstruction of long and complex anterior urethral strictures is technically demanding. Long anterior strictures with dense focal narrowing and scarred, extremely narrow urethral plates, fistula or infection are best managed with staged procedures (1, 2). Those with a salvageable urethral plate are being increasingly managed with a single stage repair using genital or non-genital tissues grafts/flaps (3, 4). Since Suprechko's first description of buccal mucosa used as a graft in 1886, it has become the tissue of choice for urethral reconstruction (5). Its popularity can be credited to extensive work by Braca and Barbagli. It is readily available and easily harvested with minimal donor site morbidity. Buccal mucosa is hairless, has a thin, elastin rich epithelium giving it excellent handling characteristics and a highly vascular lamina propria, which facilitates harvesting and imbibition. The ideal location for BMG onlay has been debated for quite some time. There is now adequate evidence that dorsal onlay has an edge over the ventral

onlay technique, especially in the penile urethra (5-7). Recently Barbagli and Kulkarni have proposed one-sided mobilization of the urethra with sparing of central tendon of perineum and dorsal anterior/lateral placement of the BMG in order to preserve the blood supply to the urethra and neuro-vascular integrity of the bulbospongiosus muscle respectively (8, 9).

We present our experience single stage urethroplasty with dorso-lateral onlay of BMG for long strictures of anterior urethra approached through a perineal incision.

MATERIALS AND METHODS

The study was conducted between August 2010 and August 2013. Approval was taken from the hospital ethical committee. Patients who presented to us with anterior urethral strictures (>4cm measured on RGU) were included in the study. Each patient was evaluated by detailed history, physical examination, uroflow with post void residual urine, RGU and VCUG, and other routine investigations necessary for surgery. A suprapubic catheter was placed pre-operatively in those presenting with acute retention of urine and/or with altered renal parameters. The cause of stricture was Lichen sclerosis in 12 cases (60%), instrumentation in 5 cases (25%), and unknown in 3 cases (15%).

Exclusion criteria were previous failed urethroplasty, urethral abscess, urethral fistulas and a scarred and unsalvageable urethral plate.

Uroflowmetry and measurement of post--void residue was done at 1 month, 3 months and 6 months after surgery and every 6 months for the first 3 years thereafter. Those who had a recurrence of voiding symptoms with an objective evidence on uroflow study underwent imaging and/or cystoscopy to identify the site of re-stricture. These cases were considered as treatment failures.

Operation was performed under general anesthesia with nasal intubation. Two teams worked simultaneously, one at the donor site and other at the recipient site. Urethroscopy was performed using a 6-7.5Fr semi rigid (Karl Storz) ureteroscope and a hydrophilic (Terumo) guide wire was passed into the bladder. A 5fr ureteric catheter was guided over it and the ureteric catheter was secured with a stich on the glans. A midline perineal skin incision is made; the bulbar urethra is exposed, preserving the midline tendon of the perineum and bulbospongiosus muscle (Figure-1). The involved bulbar urethra is dissected off the corpora cavernosa on the left side, so as to leave the right half attached and preservation of its lateral blood supply.

The penis is invaginated into the perineal incision and the involved segment of penile urethra is similarly dissected of corpora cavernosa along the left side. On the left side urethra is partially rotated and the dorso-lateral surface is incised exposing the lumen (Figure-2). The incision is extended for about 1cm beyond the stricture segment at both ends. The proximal and distal lumen is calibrated to ensure adequate patency. In case of strictures ex-

Figure 1 - Dissection up to level of bulbo spongeosis with long stricure in penile and bulbar urethra.

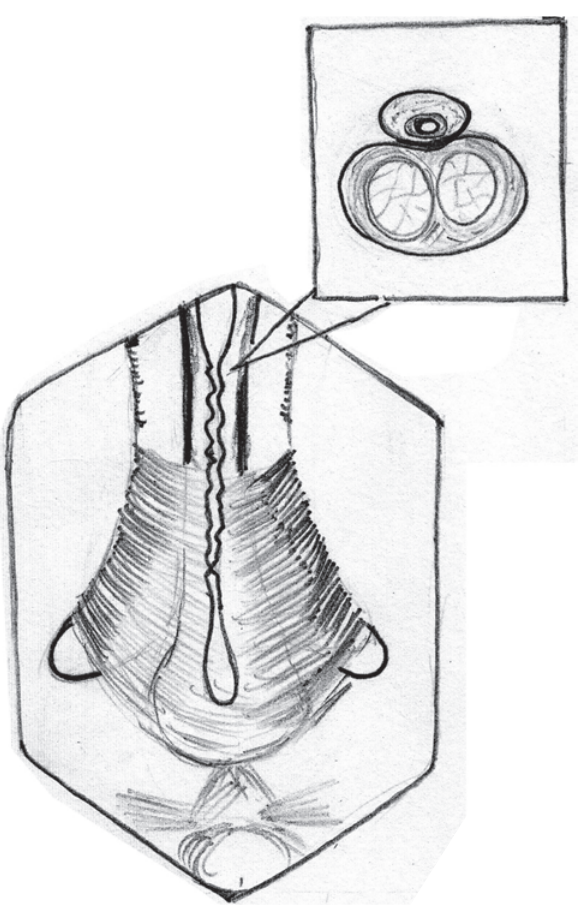


Figure 2 - Dissection of right half of copus spongiosum off the copora cavernosa dorsally and opening of the stricture segment Note: Bulbo spongiosus muscle being retracted down to facilitate exposure.

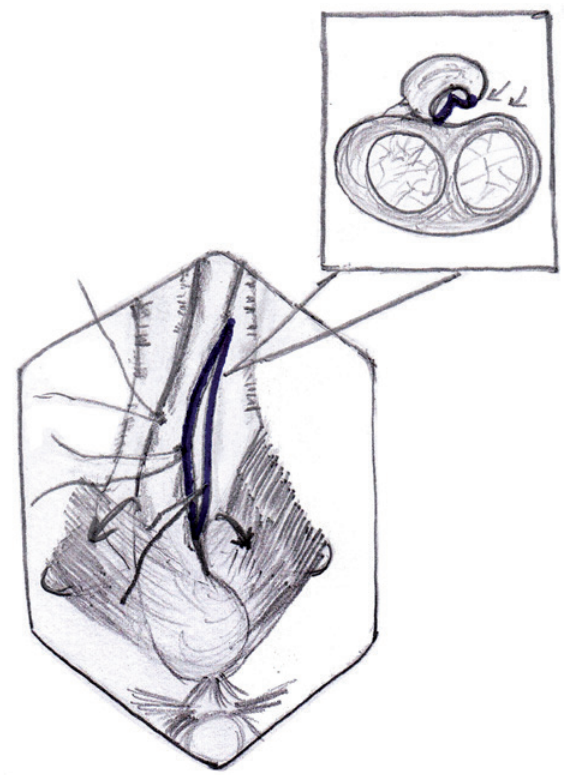
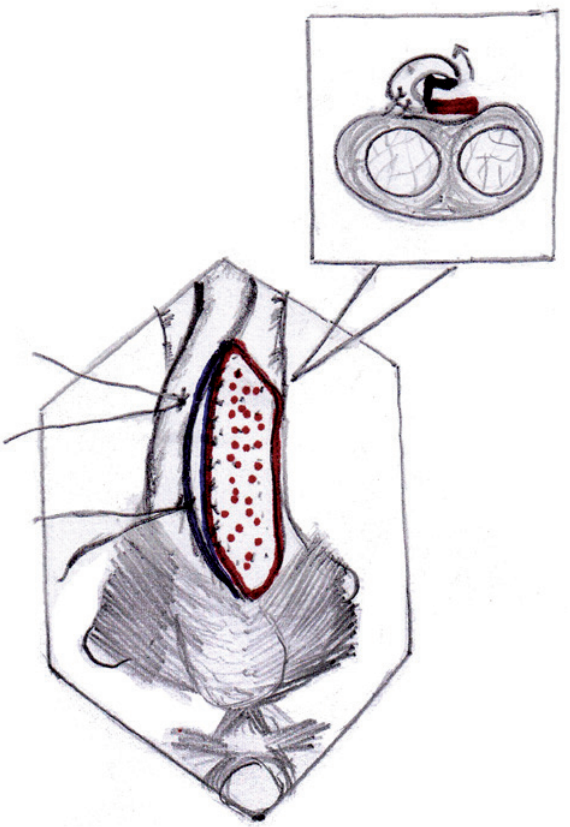


Figure 3a - Buccal mucosa graft placed in position by quilting over the tunica of corpora cavernosa.



tending up to the external urethral meatus, a dorsal meatotomy is performed from the meatus, through the urethra inside the glans, connecting it to the dorso-lateral incision in the distal penile urethra.

The buccal mucosa is harvested from the inner cheek (one or both sides, depending on the length required). The inner cheek from just inside the labial angle up to the retromolar trigone is marked, keeping 0.5cm away from the opening of the Stensen duct, to obtain a buccal graft of 2.5-3cm width and 6-7cm length. We use a 26 gauge needle to infiltrate dilute (1:200000) adrenaline under the marked portion of the mucosa. The edges are incised, 2 stay sutures are placed at the distal corners of the graft using 3-0 chromic catgut, for traction. Once the graft is harvested, the raw area is allowed to epithelize secondarily. The graft is defatted, trimmed to an appropriate shape and used as an onlay. We do not perform a primary closure of the mucosal defect.

The buccal mucosal graft is trimmed to an appropriate size and is spread and fixed (quilted) over the exposed half of the corpora. The edges of the graft are sutured to the corresponding edges of the opened urethral lumen using 4-0 polygalactin sutures (Figures 3a, 3b and 3c) over a 14Fr silicone Foley's catheter. In those cases with external urethral involvement, the dorsal meatotomy incision allowed us to widen the narrow meatus/fossa navicularis region and draw the graft in through the glans from the distal urethrotomy and place it right up to the tip of the external meatus (Figures 4a and 4b). After completion of anastomosis, the wound is closed in layers (Figure-5). The periurethral catheter is left in-situ for 3-4 weeks.

RESULTS

Twenty patients were included in the study (Table-1). Mean age of patients was 39±7.867 year

Figure 3b - Intra operative image showing placement of buccal mucosal graft.

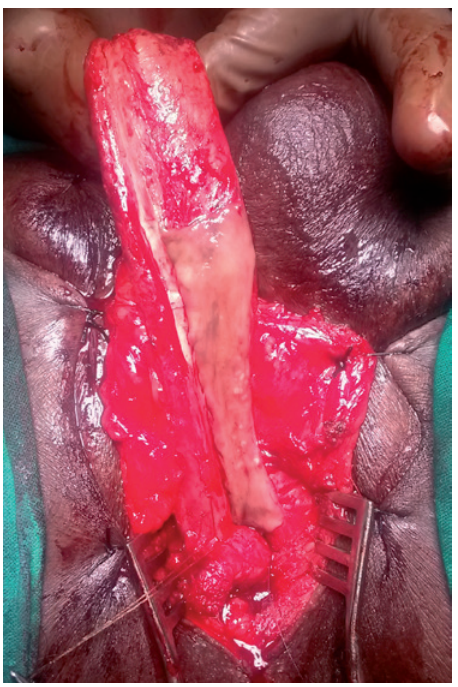


Figure 3c - Intra operative image showing completed graft placement. Note: Partial mobilization of corpus spongiosum.

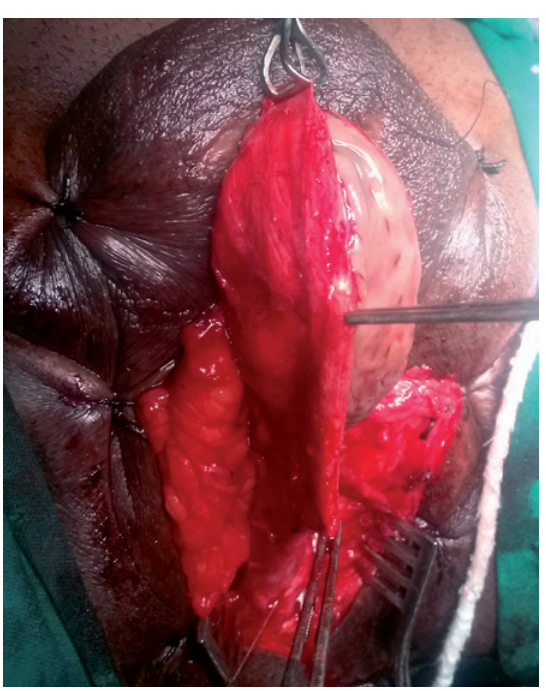


Figure 4a - Dorsal meatotomy and graft placement at the external urethral meatus.

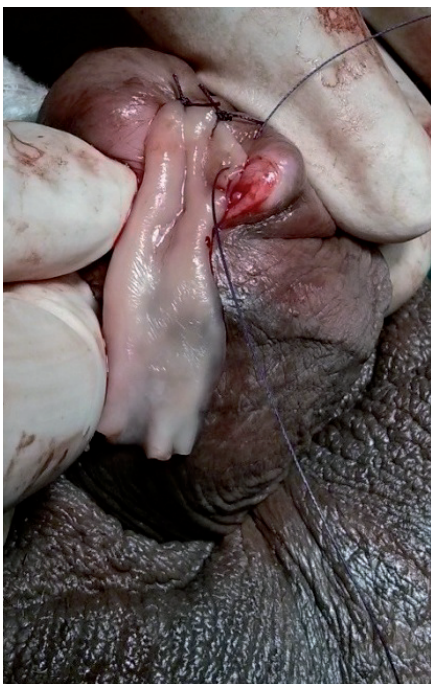


Figure 4b - Graft placement covering entire length of stricture and extending into fossa navicularis.

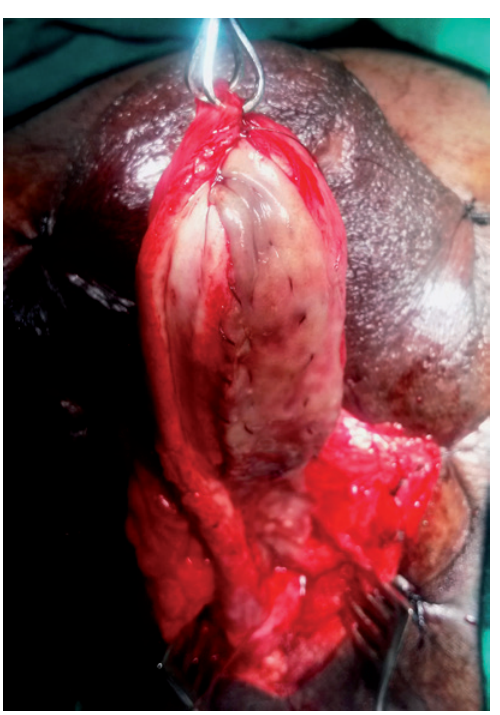
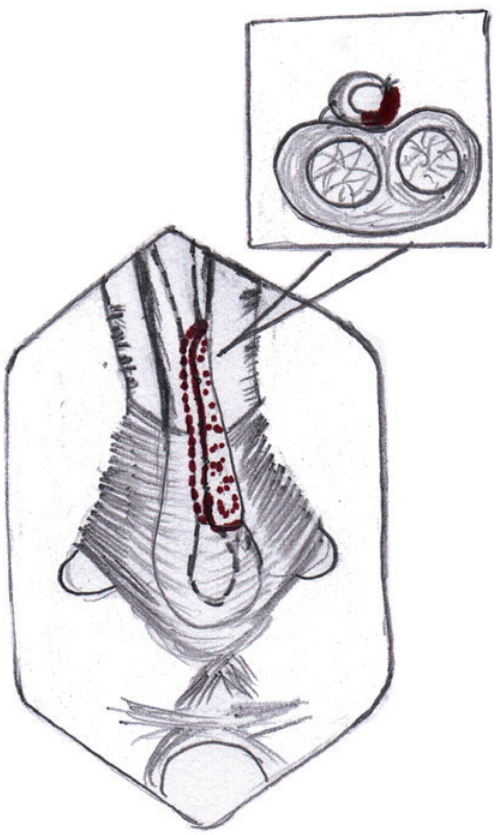


Figure 5 - Completed graft anastomosis.



(range 18 to 56 years). Mean stricture length was 8.5±1.395cm (range 4 to 12cm). Mean operative time was 140±11.337 min (range 120-180 min). The mean postoperative Qmax at the 12-month follow-up was 24±3.162mL/sec (range 18-32mL/sec). None of these patients had any significant post void residual urine. The mean hospital stay was 6.25±1.070 days (range 5-9 days). None of the patients required peri-operative blood transfusions.

Mean follow-up was 22.7±4.105 months (range 12 to 36 months). Treatment was successful in 17 (85%) and failed in 3 (15%). These 3 patients presented with decreased flow rates of<9mL/sec after 1-3 months. VCUG revealed a stricture at the proximal end of the graft in 1 (confirmed by urethroscopy), meatal stenosis in 1, and 1 had recurrent stricture along the whole length of the graft.

Recurrent stricture was treated by DVIU. Meatal stenosis was managed by a meatotomy. The patient who had recurrent stricture of the whole length was planned for revision urethroplasty but he lost follow-up.

Other complications included scrotal oedema in 3 (17.6%), 3 patients (17.6%) had brownish discharge through external meatus and 2 (10%) patients had wound infection (Figure-3). One of these patients of wound infection had an urethrocutaneous fistula, which presented to us 3 weeks after catheter removal. None of the patients in our study had postoperative chordee, diverticulum formation or post void dribble.

DISCUSSION

BMG augmentation urethroplasty has become the standard of care for long urethral strictures. Whether to place the graft dorsally, ventrally or laterally is controversial. Dorsal placement of graft has advantage of using corporal bodies to provide a secure well vascularized graft bed that helps to prevent protrusion of the graft

Table 1 - Patient demographics, operative and follow up data.

Total no of patients, *n* =20	Range	Mean ± standard deviation
Age, in years	18-56	39±7.867
Stricture length, in cm	4-12	8.5±1.395
Operative time, in min	120-180	140±11.337
Hospital stay, in days	5-9	6.25±1.070
Post-operative Qmax (12 month), in mL/sec	18-32	24±3.162
Follow-up, in months	12-36	22.7±4.105

with resulting pseudo-diverticulum formation. In addition, this spread BMG fixation preserves graft width and hence urethral caliber (10). On the other hand ventral location provides the advantage of ease of exposure and good vascular supply by avoiding circumferential rotation of urethra. Ventral urethrotomy allows the lumen to be clearly delineated, thus enabling the surgeon to identify mucosal edges, measure the size of the plate, carry out water tight anastomosis and if necessary, excise a portion of the stricture and perform dorsal re-anastomosis (3, 11). Barbagli et al., in 2005 published a retrospective study of 50 cases with bulbar urethral stricture where buccal mucosa graft urethroplasty was done. Grafts were placed as ventral, dorsal and lateral onlay in 17, 27 and 6 patients respectively. After a mean follow-up of 42 months, placement of graft into ventral, dorsal or lateral surface of the bulbar urethra showed similar results (12).

Later in 2008, Barbagli et al. showed that the dorsal urethral surface could be easily approached leaving the bulbospongiosum muscle and central tendon of the perineum intact, thus preserving the branches of perineal nerves from surgical injury. The bulbospongiosum muscle is primarily responsible for ejaculation because of its rhythmic contractions with other perineal muscles to expel semen from the urethra. It may also have an important role in expelling urine (8).

Kulkarni et al. published their series of 24 patients in 2009, wherein they described a new technique of one-sided anterior dorsal oral mucosal graft urethroplasty while preserving the lateral vascular supply to the urethra, the central tendon of the perineum, the bulbospongiosum muscle and its perineal innervation and showed a success rate of 92%. They also reported that the factors such as age, cause of stricture, length and prior instrumentation previously said to have influence on any kind of urethroplasty have no effect on the success rate, suggesting that other factors (possibly vascular and neurogenic injury) may play an important role in determining stricture recurrence (9).

In our series of 20 patients overall success was 85%, in a mean follow-up of 22.7 months. We feel that with a single perineal incision and invagination of the penis, adequate exposure of the whole anterior urethra is possible. This approach avoids a separate penile skin incision, making it more cosmetic and also reduces the chances of development of urethrocutaneous fistulas. One-sided dissection of the anterior urethra from the corpora cavernosa allowed us to visualize the urethral lumen with minimal rotation of the urethra. Also, placement of a guide wire/urethral catheter in the urethral lumen acts as a valuable guide while incising the urethra. We were able to avoid creating false passages, especially in very narrow or scarred portions of the stricture by this maneuver. None of the patients on our series had post void dribble following the procedure.

All 3 failures occurred in the early days of the study period. The patient who developed meatal stenosis had a Lichen sclerosus stricture involving the external meatus. The dorsal meatotomy incision that we used in such cases for laying the buccal mucosa on the glans portion of the distal urethra was probably of insufficient depth/width. He was treated by a simple meatotomy, which was sufficient. The cause for stricture at the proximal anastomotic site was similarly due to a failure to achieve mucosa-to-mucosa approximation of the graft and healthy urethra. This was managed by DVIU and the patient remained symptom free till the end of follow-up period. The patient with recurrent pan-urethral stricture was a chronic tobacco chewer and had to quit only 2 months prior to surgery. This could have resulted in a sub-optimal buccal mucosa graft.

Scrotal oedema in 3 (17.6%) was managed conservatively with scrotal support, and oral serratiopeptidase twice a day for 3 days. Three patients (17.6%) had brownish discharge through external meatus that was managed by gently squeezing the shaft from penoscrotal region till the meatus, which subsided in 3 days. This discharge was probably the collected blood that was retained in urethra during dissection. Two patients (10%) had wound infection and they were managed by regular dressings. One of these patients of wound infection had an urethrocutaneous fistula, which presented to us 3 weeks after catheter removal. He underwent reinsertion of suprapubic catheter & regular dressings. A VCUG done 3 weeks later showed resolution of

the fistula tract, so the suprapubic catheter was removed. These patients of wound infection had prolonged hospital stay.

Our results are comparable with those published by Kulkarni et al. in 2009, using the same technique (9). Limitations of our study are small number of patients and a short follow-up period of 22.7 months.

CONCLUSIONS

Dorsolateral placement of buccal mucosa graft for long anterior strictures is minimally invasive, safe and has good outcomes with short to intermediate length of follow-up. Further studies on larger series of patients are necessary to confirm that preservation of the one-sided lateral vascular supply to the urethra and its entire muscular and neurogenic support reduces the incidence of stricture recurrence, post void dribble and ejaculatory dysfunction.

ACKNOWLEDGEMENTS

Ethical Approval of the study was not required as we followed the standard operating procedures of our Hospital. However, we had a discussion in one of our IEC which also had the opinion that approval was not required.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Are patients with lichen planus really prone to urolithiasis? Lichen planus and urolithiasis

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ABSTRACT

Purpose: to investigate whether patients with lichen planus (LP) are really prone to urolithiasis or not.
Patients and Methods: We performed a prospective analysis of 40 patients diagnosed with lichen planus (LP) (group I), and 40 volunteers did not have LP before (group II). Participants were all checked for urolithiasis by radiological investigations. Blood samples were analyzed for biochemistry parameters including calcium and uric acid. 24-h urine samples were analyzed to investigate oxalate, citrate calcium, uric acid, magnesium, sodium and creatinine.
Results: Men/women ratio and mean age were similar between group I and II ($p>0.05$). A presence or history of urolithiasis was detected in 8 (20%) and 2 (%5) patients in group I and II, respectively ($p<0.05$). Hypocitraturia was the most common anomaly with 35% (n:14) in group I. The rate of hypocitraturia in group II was 12.5% (n:5) and the difference was statistically significantly different ($p=0.036$). In group I, hyperuricosuria and hyperoxaluria followed with rates of 27.5% (n:11) and 25% (n:10), respectively. The rate of hyperuricosuria and hyperoxaluria were both 5% (n:2) in group II and the differences were significant ($p<0.05$). Hyperuricemia was another important finding in the patients with LP. It was detected in 13 (32.5%) patients in group I and in 1 (2.5%) participant in group II ($p=0.001$).
Conclusion: According to our results, metabolic disorders of urolithiasis were highly detected in the patients with LP. However, similar to the etiology of LP, the exact reasons for these metabolic abnormalities in LP remain a mystery.

ARTICLE INFO

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Lichen Planus, Oral; Urolithiasis; Skin Diseases, Papulosquamous; Metabolic Diseases

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INTRODUCTION

Lichen planus (LP) is a common papulosquamous inflammatory skin disease, the etiology of which is unclear. It is estimated that the disease affects 0.5% to 2.0% of the general population. The disease is more common in females than males and is mostly detected in middle-aged patients 30-60 years of age (1). The cutaneous lesions are flat-topped, polygonal, shiny pinkish-purple papules and plaques and are faintly erythematous to violaceous. The disease is defined as unpredictable and continues approximately for 1 to 2 years. However, it is a chronic disease. It may present

with exacerbations or be quiescenct for many years. The duration and response to therapy varies according to the subtype of the LP (2).

Importantly, some diseases, such as hepatitis, anxiety, hypertension, diabetes mellitus or urolithiasis, can accompany LP (3-8). According to the results of a limited number of articles, urolithiasis is a common disease in patients with LP, although its cause and etiology are unknown. It was shown that some metabolic disorders associated with urolithiasis are more common in LP. However, on the other hand, it is not known if the LP is the causative factor or result of urolithiasis. Because there is limited literature about the association of urolithiasis and LP, we aimed to investigate if patients with LP are really prone to urolithiasis and if urolithiasis is a concern in this population.

MATERIAL AND METHODS

Patients

After obtaining approval of the Institutional Ethics Committee, we performed a prospective analysis of 40 patients diagnosed with LP and 40 participants without any prior skin disease such as LP. We created two groups for our study. Group-I was 40 patients with LP. Group-II was the control group of 40 volunteers without LP.

Patients with anatomic predisposing factors to urolithiasis, such as a horseshoe kidney, polycystic renal disease, malrotated or ectopic kidney, ureteropelvic junction obstruction were excluded. Patients with proteinuria, glomerular or tubular renal disease, chronic renal insufficiency and uncontrolled diabetes mellitus were also excluded. Volunteers in the control group were recruited from the patients who visited the urology or dermatology outpatient clinic for any reason and did not exhibit LP or any skin disease at the time of enrollment or before.

All the patients gave a detailed history including family history of urolithiasis, prior urolithiasis history, medications, additional comorbidities and dietary habits. The patients were all routinely evaluated using a plain abdominal X-ray and ultrasonography. Computed tomography (CT) or intravenous urography was used for patients with non-opaque stones. LP was easily diagnosed by clinically visualizing the lesions in 35 (87.5%) patients. Five (12.5%) patients required punch biopsies for the diagnosis.

One (2.5%) individual in the control group had a history of urolithiasis, and 1 (2.5%) individual had a kidney stone detected that was 2mm in diameter. The 24-h urine analysis results of the patient and control groups were compared in the present study. Spot urine samples were analyzed to detect an infection. A metabolic evaluation was postponed when a urinary system infection or hematuria was detected. Blood samples were analyzed for biochemistry parameters including calcium and uric acid. Oxalate, citrate, calcium, uric acid, magnesium, sodium and creatinine were analyzed in the 24-h urine samples.

The normal constituent values of a 24-h sample are <300mg/day for calcium; <750mg/day for uric acid; <44mg/day (man) and <31mg/day (woman) for oxalate; >320mg/day for citrate; <73mg/day for magnesium; <220mg/day for sodium; between 600-1600mg/day for creatinine; and >1200mL/day for urine volume.

Before the metabolic evaluation, participants were asked not to change their dietary habits. Medications that could affect the urinary excretion rates of stone forming substances were stopped at least 1 week prior to metabolic evaluation.

Statistical analysis

All statistical analyses were performed using SPSS, version 20.0. Statistical significance was considered at $p<0.05$. As a supplementary statistic, frequency (percent) for the variables obtained by counting and mean$\pm$standard deviation and median (minimum and maximum) values for the variables obtained by measuring were used. A Chi-square analysis was used for the variables obtained by counting.

RESULTS

The men/women ratio was approximately 3/2 in both groups I and II ($p>0.05$). The mean ages were 46.2 years (22-77 years) and 40.8 years (21-71 years) for groups I and II, respectively ($p>0.05$).

Dietary habbits that could affect the results (vegetarian, meat-based, too salty, etc.) were not detected in the individuals. The presence or history of urolithiasis was detected in 8 (20%) patients with LP. A renal calculus smaller than 3mm was detected in 2 (5%) of the patients at the time of LP presentation. Six (15%) of the patients had a history of previous spontaneous calculus passage. In the control group (group-II), 1 (2.5%) individual had a history of urolithiasis, and a kidney stone 2mm in diameter was detected in 1 (2.5%) individual. We could not assess any results of the patient's calculus analyses.

A family history of urolithiasis was highly detected in group-I. Thirteen (32.5%) individuals in group-I and 3 (7.5%) individuals in group-II had a family history of urolithiasis ($p<0.05$).

The additional comorbidities detected in groups I and II were hypertension (4 versus 4), diabetes mellitus (4 versus 2) and malignancy (0 versus 1). One patient in group-II had a history of a partial nephrectomy due to an exophytic right renal mass 2cm in diameter approximately 10 years ago. After a curative treatment, no recurrence was detected, and his renal function was completely normal (Table-1).

Hypocitraturia was the most common anomaly with 35% (n: 14) in group-I. The rate of hypocitraturia in group-II was 12.5% (n: 5). The difference between the two groups was statistically significantly different ($p=0.036$) (Table-2).

In group-I hyperuricosuria and hyperoxaluria followed with rates of 27.5% (n: 11) and 25% (n: 10), respectively. The rates of hyperuricosuria and hyperoxaluria were both 5% (n: 2) in group--II. The differences between the groups were significant ($p<0.05$) (Table-2).

Hypercalciuria was detected in 6 (15%) and 7 (17.5%), hypernatriuria in 12 (30%) and 10 (25%), hypomagnesiuria in 11 (27.5%) and 6 (15%), and low urine volume in 5 (12.5%) and 6 (15%) of the individuals in groups I and II, respectively. These findings were statistically similar between the patient and control groups ($p>0.05$).

Hyperuricemia was another important finding in patients with LP. It was detected in 13 (32.5%) patients in group I and in 1 (2.5%) participant in group-II ($p=0.001$). Three (7.5%) patient's in group-I and 1 (2.5%) participant in group-II had hypercalcemia, which was not significant ($p>0.05$). The metabolic analysis results of the groups are detailed in Table-2.

DISCUSSION

Lichen planus (LP) is an inflammatory disease that can occur on the skin, nails, hair or mucosal membranes. The incidence of the disease is unclear, but it is thought that approximately 1% of the general population are effected by the disease (9, 10). The cutaneous lesions are flat-topped, polygonal and shiny pinkish-purple papules and plaques. Reticulated whitish punctate networks called Wickham striae that can typically be seen over most of the papules is a characteristic finding of the disease (9, 11). While LP can be diagnosed by easily visualizing the lesions, a punch biopsy can be required to diagnose LP in some patients.

Although the etiology is unknown, immunologic mechanisms are known to be responsible for the formation of the lesions. When the phenotype of inflammatory infiltration was investigated, increased $CD4^+$ and particularly $CD8^+$ T-cells were observed within the epithelium and around the damaged basal keratinocytes. Following the antigen recognition that activates the T-cells, cytokines and chemokines, such as interferon-γ, tumor necrosis factor-α, transforming growth factor-β1, interleukin-2, interleukin-4 and interleukin-10, are released. Severity of the disease is based on the balance between the two extremes of lymphocytic activation and down regulation (9, 12).

LP can accompany some different illnesses. Gavic et al. (8) showed that LP is associated with anxiety and depression. However, in contrast, Hirota et al. (13) presented that there was no correlation between anxiety and LP. Some articles have investigated the coexistence of LP and hepatitis, hypertension, diabetes mellitus and urolithiasis. However, the relationship of these diseases were not identified (3-7).

Urolithiasis is a common disease that effects approximately 11% of the adult population. To date, a limited number of studies have evaluated the association of urolithiasis and LP (6, 14-16). Halevy et al. reported the coexistence of

Table 1 - The distribution of comorbid conditions, family history of urolithiasis and prior stone history.

			Group I		Group II		All		Chi-square test	
			n	%	n	%	n	%	Chi-square	p
Family history of urolithiasis		absent	27	67.5	37	92.5	64	80.0	6.328	**0.012**
		existence	13	32.5	3	7.5	16	20.0		
		all	40	100.0	40	100.0	80	100.0		
Prior stone history		absent	34	85.0	39	97.5	73	91.2	Fisher's Exact	0.108
		existence	6	15.0	1	2.5	7	8.8		
		all	40	100.0	40	100.0	80	100.0		
The presence or history of urolithiasis		absent	32	80.0	38	95.0	70	87.5	2.857	0.091
		existence	8	20.0	2	5.0	10	12.5		
		all	40	100.0	40	100.0	80	100.0		
Comorbidities	**Hypertension**	absent	36	90.0	36	90.0	72	90.0	Fisher's Exact	1
		existence	4	10.0	4	10.0	8	10.0		
		all	40	100.0	40	100.0	76	100.0		
	Diabetes Mellitus	absent	36	90.0	38	95.0	74	92.5	Fisher's Exact	0.675
		existence	4	10.0	2	5.0	6	7.5		
		all	40	100.0	40	100.0	76	100.0		
	Malignancy	absent	40	100.0	39	97.5	79	98.8	Fisher's Exact	1
		existence	0	0.0	1	2.5	1	1.2		
		all	40	100.0	40	100.0	80	100.0		

LP and urolithiasis for the first time in 1983 (15) From medical records and anamnesis, they found that 14.6% of 130 patients with LP had a history of urolithiasis. They claimed that this incidence was higher than the population of their community. In 1990, Halevy and Feuerman evaluated 42 patients with lichen planus with a biochemical analysis and 24-h urine results (16). At least one of the abnormalities, including hyperuricemia, hyperuricosuria or hypercalciuria, was detected in 9 (21%) patients. According to their results, they concluded that there could be involvement of metabolic disorders in LP. The last article on this topic was published by Kumar et al. in 1999 (6) and included 75 patients with LP and 62 healthy individuals. Nine (12%) of those patients had a history of urolithiasis. They checked the patients for urinary system stones with ultrasonography. Three (4%) of the patients had kidney stones detected at the time of presentation. They used blood samples to analyze biochemical parameters, including calcium and uric acid, and a 24 hours urine collection to analyze calcium, uric acid, phosphorus, urea and creatinine. Unlike previous literature (16), their results were similar between the patient and control groups. The authors concluded that the only noticeable result of their study was that the serum uric acid and urine calcium levels and prior history of urolithiasis were significantly higher in the patients with LP compared to the control group (6). We think an important limitation of their study was that they did not investigate other lithogenic factors, such as urine oxalate, citrate, magnesium or sodium levels, which can be considered important risk factors for urolithiasis (17).

Table 2 - The distribution of metabolic analysis results.

		Group I		Group II		All		Chi-square test	
		n	%	n	%	n	%	Chi-square	p
	absent	34	85	33	82.5	67	83.75		
Hypercalciuria	existence	6	15	7	17.5	13	16.25	0.000	1.000
	all	40	100.0	40	100.0	80	100.0		
	absent	29	72.5	38	95	67	83.75		
Hyperuricosuria	existence	11	27.5	2	5	13	16.25	5.878	0.015
	all	40	100.0	40	100.0	80	100.0		
	absent	30	75	38	95	68	85		
Hyperoxaluria	existence	10	25	2	5	12	15	4.804	0.028
	all	40	100.0	40	100.0	80	100.0		
	absent	26	65	35	87.5	61	76.25		
Hypocitraturia	existence	14	35	5	12.5	19	23.75	4.418	0.036
	all	40	100.0	40	100.0	76	100.0		
	absent	29	72.5	34	85	63	78.75		
Hypomagnesiuria	existence	11	27.5	6	15	17	21.25	1.195	0.274
	all	40	100.0	40	100.0	76	100.0		
	absent	28	70	30	75	58	72.5		
Hypernatriuria	existence	12	30	10	25	22	27.5	0.063	0.802
	all	40	100.0	40	100.0	80	100.0		
	absent	35	87.5	34	85	69	86.25		
Low urine volume	existence	5	12.5	6	15	11	13.75	0.000	1.000
	all	40	100.0	40	100.0	80	100.0		
	absent	37	92.5	39	97.5	76	95		
Hypercalcemia	existence	3	7.5	1	2.5	4	5	Fisher's Exact	0.615
	all	40	100.0	40	100.0	80	100.0		
	absent	27	67.5	39	97.5	66	82.5		
Hyperuricemia	existence	13	32.5	1	2.5	14	17.5	10.476	0.001
	all	40	100	40	100	80	100		

Our results demonstrated a 20% prevalence of urolithiasis in patients with LP, which can be considered similar to previous studies (6, 15). In 5% of the patients, a renal calculus at the time of presentation was detected. Fifteen percent of the patients had a previous history of spontaneous calculus passage. In the control group, 5% of the participants had urolithiasis or a history of urolithiasis. Although it seems to be high in the patient group, it was not statistically significant, perhaps due to the low number of the patients (p: 0.09). None of the patients had the results of their calculus analyzed.

Hyperuricemia was detected in 32.5%, hyperuricosuria in 27.5%, hyperoxaluria in 25%, hypocitraturia in 35% of the patients. These findings were significantly higher than the control group ($p<0.05$).

We hypothesize that the turn-over around the lesions could be mainly associated with the increased rate of hyperuricosuria and hyperuricemia. The high incidence of hyperoxaluria and hypocitraturia was revealed for the first time by our study. However, it is unclear why these metabolic abnormalities occur in LP. Although patients with LP seem to be prone to urolithiasis due to the metabolic disorders mentioned above and have a high incidence of a history of urolithiasis, none of the patients had a history of staghorn calculus or stone surgeries. The 3mm diameter calculuses diagnosed at the time of presentation in 2 patients were clinically insignificant. On the other hand, a history of urolithiasis was mostly experienced before the LP disease, which is similar to the literature (6, 15).

In addition, our results demonstrated a high rate of family history of urolithiasis in patients with LP (32.5% group-I versus 7.5% group--II). This finding led us to uncertainty about which was the reason and which was the result.

According to our results, the metabolic disorders of urolithiasis were highly detected in the patients with LP. However, the main reason for the metabolic abnormalities remains a mystery in LP, similar to the etiology of LP.

We acknowledge that CT was not routinely used to avoid radiation exposure when detecting the urinary system stones and was an important limitation within our study. However, the study was designed as a prospective study. The patients were all evaluated using plain abdominal X-ray and ultrasonography to avoid radiation exposure. A CT was required only in the patients with a history of non-opaque stones. In addition, we did not routinely use punch biopsies to diagnose the disease. LP is diagnosed by visualizing typical lesions, and a punch biopsy is required only in patient's with a suspicious diagnosis. The low number of patients could also be considered another limitation of the study. Despite these shortcomings, this is an important study because there are limited numbers of studies about this topic.

CONCLUSIONS

According to our results, metabolic disorders of urolithiasis were highly detected in the patient's with LP. However, there were no mortality or morbidity consequences of the urolithiasis disease to the patient's. Similar to the etiology of LP, the exact reasons for these metabolic abnormalities in LP remain a mystery. Further studies are necessary to clarify this mystery.

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The study was performed after having obtained approval of Institutional Ethics Committee. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Prophylactic effects of alpha-blockers, Tamsulosin and Alfuzosin, on postoperative urinary retention in male patients undergoing urologic surgery under spinal anaesthesia

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ABSTRACT

Purpose: Postoperative urinary retention (POUR) is one of the most common complications after surgical procedures under spinal anaesthesia. Recent studies have shown the beneficial effects of alpha-adrenergic blockers in preventing POUR. The aim of this prospective study was to investigate and compare the prophylactic effects of tamsulosin and alfuzosin on POUR after urologic surgical procedures under spinal anaesthesia.
Materials and Methods: A total of 180 males who underwent elective urologic surgery were included in this study. The patients were randomly allocated into three Groups. The Group I received placebo. Patients in Group II were given 0.4mg of tamsulosin orally 14 and 2 hours before surgery. Patients in Group III were given 10mg of alfuzosin ER orally 10 and 2 hours before surgery. All patients were closely followed for 24 hours postoperatively and their episodes of urinary retentions were recorded.
Results: There were 60 patients in each Group. Their mean age was 35.95±15.16 years. Fifteen patients in Group I (25%), 3 patients in Group II (5%) and 4 patients in Group III (6.7%) required catheterization because of urinary retention. In tamsulosin group and alfuzosin group, there were a significantly lower proportion of patients with POUR compared with the placebo Group (p=0.002 and p=0.006). The beneficial effects of tamsulosin and alfuzosin on POUR were similar between both Groups (p=0.697).
Conclusion: This study suggests that the use of prophylactic tamsulosin or alfuzosin can reduce the incidence of urinary retention and the need for catheterization after urologic surgical procedures under spinal anaesthesia.

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INTRODUCTION

Spinal anaesthesia is a common regional anaesthesia technique performed by anaesthesiologists since 1898 (1). It has some complications such as hypotension, bradycardia, cardiac arrest, nausea-vomiting, transient neurologic problems, headache, pruritus and urinary retention (2).

Postoperative urinary retention (POUR) has generally been defined as the inability to pass any urine in the presence of a percussible or palpable bladder after surgery, but the definition varies

widely. POUR is common and represents between 5% to 70% of all surgeries (3). It occurs more frequently in lower urinary tract, perineal, inguinal, orthopaedic, gynecologic, and anorectal surgeries after spinal anaesthesia.

Urethral catheterization, a mainstay of initial management for patients with POUR, is associated with some complications and increases in cost of care (3, 4). Both the health and financial costs of retention are considerable, because it can cause urinary tract infections and necessitate catheterization, which can in turn result in urethral strictures, prolonged hospital stays, and additional operations. Therefore, pharmacological therapy is viewed as an interesting option for patients developing urinary retention following surgery.

Urinary retention in the postoperative period has two main causes. The first is mechanical obstruction of lower urinary tract and the second is altered neural control of the bladder and detrusor mechanism, most commonly due to analgesic drugs (5). Additionally, high sympathetic activity increases the risk of urinary retention. Therefore, inhibition of alpha-adrenergic receptors located on the bladder neck and proximal urethra may prevent POUR (3). Tamsulosin and alfuzosin are safe selective alpha1-adrenergic receptor blockers characterized by their favorable side effect profiles (6, 7). There is currently little published data on the incidence and treatment of urinary retention after spinal anaesthesia in urologic surgery procedures. We think that prophylactic effects of alpha-blockers on POUR after urologic surgical procedures under spinal anaesthesia have not been investigated adequately.

The aim of the present study was to investigate the prophylactic effects of tamsulosin and alfuzosin on the prevention of urinary retention in male patients after spinal anaesthesia in urologic surgery procedures.

MATERIALS AND METHODS

From January 2010 through October 2014, a total of 180 male patients aged 18 to 69 years who underwent elective inguinal, penile, scrotal and perineal surgery under spinal anesthesia were included in this study. The study was performed in accordance with the Declaration of Helsinki and approved by the local ethics committee of Diyarbakir Training and Research Hospital. All patients provided informed consent.

The exclusion criteria were patients who had severe lower urinary tract symptoms before surgery (according to AUA-American Urological Association-symptom score), active urinary tract infection, medications that could affect voiding function such as alpha-agonists/antagonists and cholinergic/anti-cholinergic drugs, urinary incontinency, previous history of lower urinary tract surgery and history of neurological, urological or systemic disease (such as multiple sclerosis, prostate cancer, diabetes mellitus).

The patients were submitted to physical examination, blood analysis, electrocardiogram, chest X-ray, urinalysis, uroflowmetry and ultrasonographic investigation (measurement of prostatic volume and postvoid residual urine volume). The patients were randomly allocated into three Groups. In Group I (placebo), the patients were given two doses of placebo orally 2 and 12 hours before surgery. The patients in Group II (Tamsulosin) were given 0.4mg of tamsulosin orally 14 and 2 hours before surgery. The patients in Group III (Alfuzosin) were given 10mg of alfuzosin ER (extended release) orally 10 and 2 hours before surgery. The whole patients voided before transfer to the operating area. Ringer's lactate solution was infused at a rate of 10mL/kg/h during surgery and 30mL/kg/24h after operation. Surgery was performed under spinal anesthesia using 14-20mg bupivacaine. The patients were followed for 24 hours postoperatively. Nonsteroidal anti-inflammatory drugs were ordered for postoperative analgesia. Opioid analgesics were not applied to any patient in the postoperative period. The diagnosis of POUR was proved when the patient had a painful and palpable mass in suprapubic area, and was unable to void during the first 12 hours after surgery. It was confirmed by emptying of more than 500mL of urine by catheterization. A 14-French Foley catheter was placed to decompress the bladder of patients who could not urinate after surgery. Operation times, patient's age, urinary symptom scores of patients and urinary retentions were recorded and parameters were compared among three Groups.

All statistical evaluations were performed by the Statistical Package for Social Sciences (SPSS) software for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). Statistical analysis was accomplished by use of ANOVA (Analysis of variance), chi-square and Mann-Whitney U tests with a p-value of less than 0.05 considered significant.

RESULTS

A total of 180 patients who were assigned to placebo Group (Group I, n=60), tamsulosine Group (Group II, n=60) and alfuzosin Group (Group III, n=60) were included in the analysis. Inguinal surgery (especially varicocelectomy, n=89) was the most frequent surgery in all Groups. The other types of surgical procedures were hydrocelectomy (n=29), spermatocelectomy (n=8), epididymal cyst excision (n=6), scrotal orchiectomy (n=14), inguinal orchiectomy (n=7), orchiopexy (n=8), peyronie's disease and congenital penile curvature surgery (n=15), perineal ectopic testis surgery (n=1), perineal mass surgery (n=1), lymphangioma circumscriptum surgery (inguinal and perineal, n=2). The mean age of patients was 35.95±15.16. No statistically significant differences were found among three Groups in terms of age (p=0.819), duration of surgery (p=0.10) and severity of preoperative urinary symptom scores (p=0.995). In Group one, 15 patients required catheterization with a mean urine volume of 670mL at catheterization. In Group two, 3 patients required catheterization with a 650mL mean urine volume. In Group three, 4 patients required catheterization with a 720mL mean urine volume. Thus, 25% of patients in Group I, 5% of patients in Group II and 6.7% of patients in Group III had urinary retention. In tamsulosin Group, there was a significantly lower proportion of patients with POUR compared with the placebo Group (p=0.002). In alfuzosin Group, there was a significantly lower proportion of patients with POUR compared with the placebo Group, too (p=0.006). The beneficial effects of tamsulosin and alfuzosin on POUR were similar in both Groups (p=0.697) (Table-1). Two patients in tamsulosin Group and one patient in alfuzosin Group showed some side effects at 24 hours follow-up. All three patient's experienced vomiting and dizziness. Side effects were mild and did not lead to exclusion of patients from the study.

There was no statistically significant difference in age, IPSS (International Prostate Symptom Score) and operation time between patients who developed urinary retention and those who did not (Table-2).

DISCUSSION

POUR is a common complication after spinal anaesthesia in urologic and other surgical procedures. It is a medical emergency requiring prompt action. The incidence of urinary retention after spinal anaesthesia ranges from 0% to 69% (8). The data on regional anesthesia and its effect on POUR is more consistent in other fields. Spinal anesthesia has been shown to increase rates of urinary retention in orthopaedic, podiatric, and hernia surgery (9). POUR causes pain and discomfort after surgery and catheterization for resolving it, may lead to urethral injury or stricture or urinary tract infection and increase cost and work load and hospitalization period (10).

Three methods have been used to diagnose POUR: History and physical examination, ultrasonographic imaging of bladder and bladder catheterization (11). We used two practical methods for diagnose of POUR: 1-History and physical examination (lower abdominal pain and discomfort and palpation or percussion of bladder in suprapubic area); 2-Bladder catheterization. Many studies indicate that urine retention can be diagnosed when the patient cannot urinate at bladder volumes above 400–600mL (12, 13). The average urine volumes were above 500mL in all of our patients with POUR. We think that diagnosis of POUR by history and physical examination instead of ultrasonography was one of the limitation of this study.

Disturbances of micturition are common in the first 24 hours after spinal anesthesia. There is a higher frequency of these disturbances after bupivacaine than lidocaine spinal anesthesia (2, 14). After administration of spinal anesthesia with bupivacaine or tetracaine, the micturition

Table 1 - Clinical features and demographic characteristics of patients in three groups and comparison of all groups in term of POUR.

	Group I (Placebo)	Group II (Tamsulosin)	Group III (Alfuzosin)	ANOVA F Test (F) or chi-square test (X^2)	p value
Number of patients	60	60	60		
Mean age±SD (year)	34.95±15.21 (18-67)	36.30±15.22 (18-69)	36.60±15.26 (18-68)	F=0.200	0.819
Pre-operative urinary				X^2=0.196	0.995
Symptoms*	37 (61.6%)	38 (63.3%)	39 (65%)		
No	16 (26.7%)	15 (25%)	15 (25%)		
Mild Moderate	7 (11.7%)	7 (11.7%)	6 (10%)		
Region of surgery					
Inguinal	34 (56.7%)	36 (60%)	34 (56.7%)		
Penile	6 (10%)	4 (6.7%)	5 (8.3%)		
Scrotal	18 (30%)	19 (31.6%)	20 (33.3%)		
Perineal	2 (3.3%)	1 (1.7%)	1 (1.7%)		
Mean operation time±SD (minute)	48.58±12.69 (27-78)	52.28±13.34 (29-85)	53.63±13.72 (28-84)	F=2.333	0.100
Number of patients with POUR	15(25%)	3(5%)	4(6.7%)		
Comparison of Group I and Group II in term of POUR				X^2=9.412	0.002
Comparison of Group I and Group III in term of POUR				X^2=7.566	0.006
Comparison of Group II and Group III in term of POUR				X^2=1.52	0.694

*According to AUA (American Urological Association) symptom score.

Table 2 - Demographic data and clinical features of the all patients who developed POUR and those who did not.

	POUR (+) (n=22)	POUR (-) (n=158)	Z Score	p Value
Mean Age±SD (years)	38.86±14.558	35.54±15.243	-1.137	0.256
Mean IPSS±SD	3.23±3.161	2.80±4.638	-1.499	0.134
Mean Operation Time±SD (minute)	49.23±11.467	51.82±13±597	-0.798	0.425

reflex is very rapidly eliminated. Detrusor muscle contraction is restored to normal 7-8 hours after the spinal injection. On average, patients recover enough motor function to be mobilized 1–2 hours before the micturition reflex returns (2). Kamphius et al. found that motor blockade following bupivicaine spinals lasted 148±76 minutes compared to detrusor blockade of 462±61 minutes (15).

Many factors contribute to the development of POUR. These include history of underlying disease, the direct effects of anesthetic agents on the bladder, excessive perioperative fluid intake, traumatic instrumentation, pelvic dissection, diminished awareness of bladder sensation, increased outlet resistance, immobilization after the surgery, postoperative pain and use of narcotics, type of anesthesia, duration of surgery,

gender and age (3, 11). The stress response to surgery and especially postoperative pain increase sympathetic tone. When ephinephrine is injected intraperitoneally in rats, the intravesical pressure increases without raising urine output, suggesting that ephinephrine increases internal urethral sphincter tone by acting on alpha receptors in the bladder neck (16). So, the sympathetic stimulation influence the relaxation of the detrusor and close the internal urethral sphincter. The resultant stimulation of the alpha receptors in the internal urethral sphincter leads to increased pressure on the bladder neck and potentially to POUR (3). Micturition reflex might be inhibited by the high sympathetic activity after surgery. Alpha-blocker premedication might have inhibitory effect on the elevated sympathetic activity and therefore, prevent acute urinary retention after surgery.

Petros and colleagues reviewed 295 inguinal herniorrhaphies in men. They found use of spinal anesthesia, age less than 53 years, and perioperative fluid less than 1200mL all significantly reduced the incidence of POUR (17). Lee and colleagues declared that POUR increases with age, with the risk increasing by 2.4 to 2.8 times in patients over 50 years of age (18). Although some studies have reported higher incidence of POUR in men compared with women, some studies have reported that there isn't significant difference between men and women (3, 19). In our study, only men were included due to type of surgeries and limited number of female patients. The other limitation of our study was that we did not record perioperative fluid intakes of the patient's.

There are various methods for prevention of POUR, such as induction of local instead of regional or general anesthesia, restriction of preoperative fluid intake, use of short acting anesthesia agent, early ambulation of patient's after surgery, use of warm compress in suprapubic area and use of parasympathomimetic or α-adrenergic blockers (3, 4). In a review article published in 2010 to investigate the most effective drug for the treatment of POUR in adults, the authors concluded that no statistically significant associations were reported between successful treatment or any other outcome and alpha-blockers, cholinergic agents and sedatives as monotherapies. A statistically significant association between intravesically administered prostaglandin and successful voiding was detected. A statistically significant association was detected between cholinergic agents combined with sedative and an improved likelihood of spontaneous voiding compared with placebo (20).

The purpose of pharmacologic prevention of POUR is the increase of detrusor contractility or bladder neck and proximal urethral relaxation. Alpha-adrenergic receptors are found in trigone, prostatic urethra and ureters. These receptors cause contraction of the smooth muscles in these regions (21). Alpha-adrenergic blockers decrease bladder outlet resistance and facilitate micturation. Several studies found that prophylactic administration of alpha-blockers such as phenoxybenzamine and prazosin significantly decreases the incidence of POUR (10). Although all alpha-blocking compounds show similar levels of efficacy for lower urinary tract symptoms treatment, third generation alpha-blockers such as alfuzosin and tamsulosin tend to demonstrate improved selectivity for the prostate and bladder (22). Another advantage of tamsulosin and alfuzosin in the management of acute urinary retention is that a therapeutic dose can be administered at the onset of acute urinary retention (23). The mean time to peak serum concentration (Tmax) of alfuzosin and tamsulosin are 8 hours and 4-5 hours after an oral dose, respectively. Alfuzosin and tamsulosin have a serum half-life ($T_{1/2}$) of 5 hours and 14-15 hours after oral administration, respectively (24). Madani et al. assessed preventive effect of tamsulosin on POUR after spinal anesthesia. In this randomized study, 118 patients received 0.4mg tamsulosin 14 and 2 hours before and 10 hours after surgery and 114 patients received placebo. They concluded perioperative administration of tamsulosin reduced the risk of POUR from 21.1% to 5.9% (10). In our study, tamsulosin 0.4mg were given orally 14 and 2 hours before surgery and alfuzosin 10mg were given orally 10 and 2 hours before surgery. The effectiveness of both of them on POUR had equal degree.

In the present study, 15 of 60 patients (25%) in the placebo Group had urinary retention. 3 of 60 patients (5%) in the tamsulosin Group and 4 of 60 patients (6.7%) in the alfuzosin Group had urinary retention and required catheterization. The incidence of POUR was significantly greater in men who did not receive tamsulosin or alfuzosin before surgery. The beneficial effects of tamsulosin and alfuzosin on POUR were similar.

CONCLUSIONS

This study suggests that preoperative tamsulosin or alfuzosin administration reduces the incidence of postoperative urinary retention and the need for catheterization after surgeries under spinal anaesthesia. Therefore, the use of preoperative tamsulosin or alfuzosin can be recommended in adult male patients who will undergo urologic surgery under spinal anaesthesia.

CONFLICT OF INTEREST

None declared.

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Host inflammatory response to polypropylene implants: insights from a quantitative immunohistochemical and birefringence analysis in a rat subcutaneous model

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ABSTRACT

Objectives: To describe acute and sub acute aspects of histological and immunohistochemical response to PP implant in a rat subcutaneous model based on objective methods.
Materials and Methods: Thirty rats had a PP mesh subcutaneously implanted and the same dissection on the other side of abdomen but without mesh (sham). The animals were euthanized after 4 and 30 days. Six slides were prepared using the tissue removed: one stained with hematoxylin-eosin (inflammation assessment); one unstained (birefringence evaluation) and four slides for immunohistochemical processing: IL-1 and TNF-α (pro-inflammatory cytokines), MMP-2 (collagen metabolism) and CD-31 (angiogenesis). The area of inflammation, the birefringence index, the area of immunoreactivity and the number of vessels were objectively measured.
Results: A larger area of inflammatory reaction was observed in PP compared to sham on the 4th and on the 30th day (p=0.0002). After 4 days, PP presented higher TNF (p=0.0001) immunoreactivity than sham and no differences were observed in MMP-2 (p=0.06) and IL-1 (p=0.08). After 30 days, a reduction of IL-1 (p=0.010) and TNF (p=0.016) for PP and of IL-1 (p=0.010) for sham were observed. Moreover, area of MMP-2 immunoreactivity decreased over time for PP group (p=0.018). Birefringence index and vessel counting showed no differences between PP and sham (p=0.27 and p=0.58, respectively).
Conclusions: The implantation of monofilament and macroporous polypropylene in the subcutaneous of rats resulted in increased inflammatory activity and higher TNF production in the early post implant phase. After 30 days, PP has similar cytokines immunoreactivity, vessel density and extracellular matrix organization.

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Keywords:
urinary incontinence, pelvic organ prolapse, polypropylenes, graft versus host reaction, foreign body reaction, immunohistochemistry

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INTRODUCTION

Since the introduction of synthetic mesh implants for tissue reinforcement, surgical treatment of urinary incontinence pelvic floor prolapse has changed. Success rates have increased and became long lasting, however, harmful events related to biomaterials integration have been observed, even for organic or synthetic meshes (1-4). Adverse reactions related to synthetic mesh implants include chronic pain, dyspareunia, urinary or vaginal erosion of the mesh as well as lower urinary tract symptoms (5, 6).

Polypropylene (PP) is currently the most common material used in pelvic floor reconstructive surgery and stress urinary incontinence treatment. It is a hydrophobic and non-hydrolyzable polymer derived from oil refining. Sterilization is undertaken by either heat or radiation thus promoting molecular structural changes of the original polymer. Therefore, the biological response is not only a consequence of the contact between host and polymer, but is also a result of chemical changes in the preparation process (7). Several mechanical and histological characteristics secondary to PP implants in living organisms have been demonstrated (8-10). Most of the histological and immunohistochemical evaluations are based on the description of cellular types and/or semi-quantitative measurements of their distribution in randomized samples (11, 12). There is no standard way to study these implants. It should include objective, reliable and reproducible techniques that consider histological, cellular, molecular and even genetic aspects of this host response.

The aim of the present study was to describe acute and sub-acute aspects of histological and immunohistochemical response to PP implant in a rat subcutaneous model based on objective quantification methods.

MATERIALS AND METHODS

The study followed the ethical principles for animal experiments adopted by the Brazilian College of Animal Experiments and was carried out after approval by the Ethics Committee for Animal Experiments of the Institute of Biology of the University of Campinas, Brazil (protocol 2400-1).

The mesh used in this study is made of monofilament type I polypropylene with an original weight: 44g/m^2 and pores of 1mm and was the same as that included in NAZCA TC™ and Calistar A™ sets (Promedon™-Cordoba, Argentina), currently commercially available. Meshes were provided by the company in single sterilized packs and were sterilized using ethylene oxide.

Surgical procedure and tissue preparation

Thirty female, eight week old Wistar rats, weighing between 150 and 200g, received on one side of their abdominal wall an implant of a 10x10mm monofilament PP mesh.

After anesthesia with sodium pentobarbital 3% (0.15mg/g), a 2-cm cross-sectional incision was made in the lower abdominal region. The mesh was implanted in the animal in a standardized manner on one side of the abdominal wall between the hypodermis and the anterior fascia of the abdominal musculature. A similar dissection was then carried out on the other abdominal side but without mesh implant (sham). The animals were divided into two groups of 15 animals which were euthanized on the 4th and the 30th day after mesh implantation with a lethal dose of sodium pentobarbital 3%.

The whole abdominal wall was immediately removed for analysis and the sham areas and those with the implants were fixed (formalin 10% for 24 hours). Three consecutive sections of 5µm thickness were then placed on each of six slides; one stained slide with hematoxylin-eosin for optical microscopy (inflammation assessment); one unstained slide for polarization microscopy analysis (collagen fibers birefringence evaluation) and four slides for immunohistochemical processing with the following antibodies: anti-CD-31 (angiogenesis), anti-interleukin 1(anti-IL-1) and anti-tumor necrosis factor (anti-TNF-α) (inflammation and cytotoxicity) and anti-metalloproteinasis-2 (anti-MMP-2) (collagen metabolism).

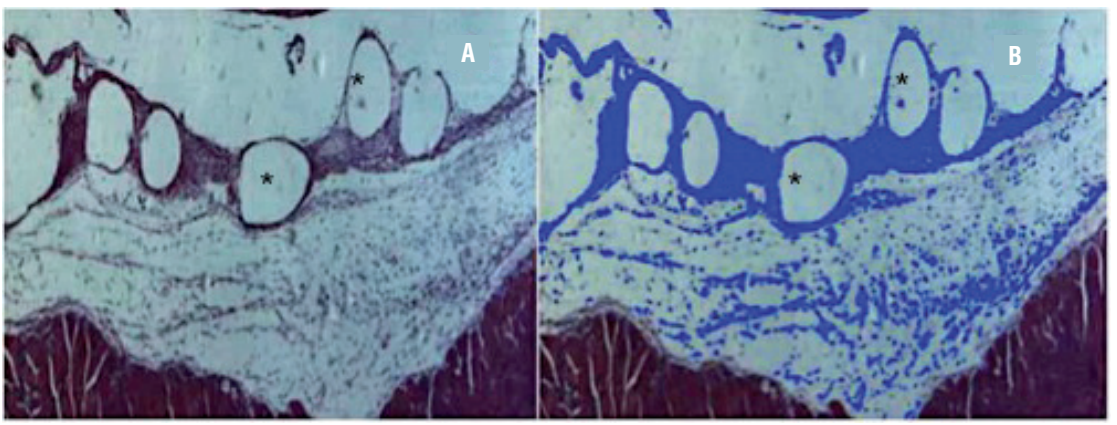
Histologic evaluation

Inflammatory reaction (hematoxylin-eosin staining) was studied on the 4th and 30th days post implant. The same researcher analyzed all slides, although he had not had knowledge of what animal or fragment was evaluating. On each slide, three photomicrograms (200x magnification) of the implant site were recorded. Axio Vision™ V 4.8.0.0 software (Karl Zeiss, Jena, Germany) was used to select and measure the areas of inflammatory reaction around the polypropylene filaments, as showed in Figure-1.

Birefringence analysis

The analysis of the direction and packing of collagen fibers was performed by polarizing microscopy, but only for those animals euthanized at

Figure 1 - Evaluation of the inflammatory reaction. (A) Inflammatory tissue around the PP filaments (rounded blank areas-*)-HE/100x; (B) Blue marks represent inflammatory reaction after processing by Axiovision software™-HE/100x



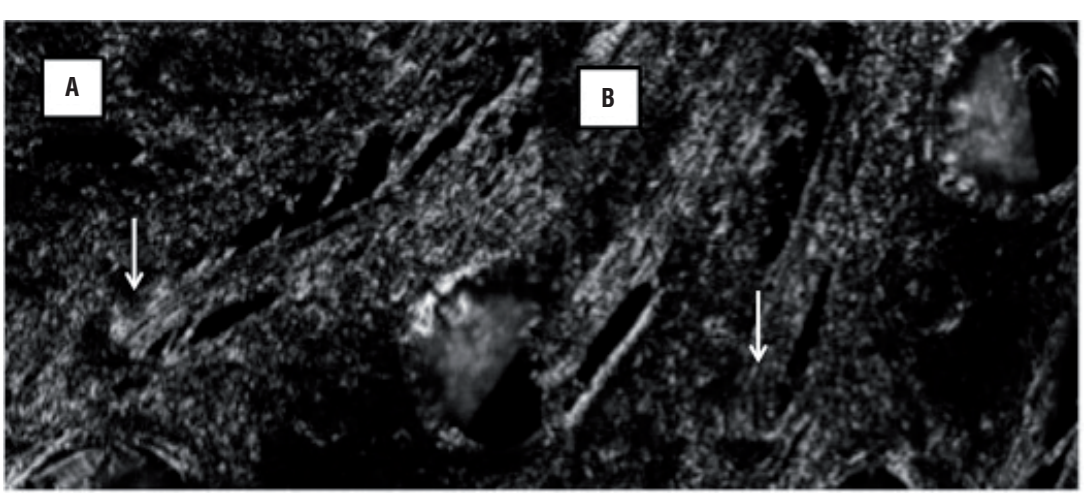
30 days due to the time necessary for the growth of the host collagen fibers. In each selected image (200x magnification), two records were obtained by rotating the microscope stage at approximately 45º in each field, to obtain the maximum polarization effect (called positions A and B), in order to demonstrate the group of fibers with the same or opposite orientation (Figure-2).

A ratio was calculated using the percent area of fibers from the same field, identified as birefringence index. This was obtained by dividing the percent birefringent area measured in the position A by the percent birefringent area measured in the position B (index A/B). Low ratios, close to 1 (one), indicate fibers with a similar birefringence in the two positions, reflecting a disorderly orientation. Therefore, the higher the index A/B, the higher the organization of collagen fibers in the same direction. The intensity of brightness (pixel/µm^2) emitted by collagen fibers was also evaluated, in order to estimate collagen density and packing.

Immunohistochemical analysis

Tissue specimens fixed in 10% formalin and embedded in paraffin were sectioned and placed on silanized slides. After initial

Figure 2 - Evaluation of collagen fibers birefringence in polarization microscopy. (A) The collagen fibers bright on the dark background. (B) The same area after 45o rotation of the polarization microscope stage. White arrow indicates the same fiber package in opposite arrangement (200x).



processing, sections were incubated at room temperature for 30 min and then overnight at 8°C with mouse monoclonal antibodies to CD31 (clone JC/70A, ab 9498, Abcam™, diluted 1/100) and polyclonal antibodies to IL-1 (ab106035, Abcam™,diluted 1/1000), TNF Receptor I (ab19139, Abcam™,diluted 1/1000) and MMP2 (ab37150, Abcam™,diluted 1/250). All antibodies were diluted with Dako Antibody Diluent (S3022, Dako™). Antigen-antibody binding was detected using the Advance system (K4068, AdvanceHPR, Dako™), and immunostaining was achieved using diaminobenzidine (K3468, Liquid DAB+substrate Dako™). Internal positive controls, as well as positive cases were previously used. Negative controls were represented by the same tissue sample used for positive control, in which the primary antibody was omitted.

The immunohistochemical analysis was carried out using specific antibodies to evaluate: (a) pro-inflammatory cytokines (interleukin-1–IL-1 and tumour necrosis factor-alpha-TNF-α); (b) collagen metabolism (metalloproteinase 2-MMP-2) and (c) angiogenesis (surface antigen CD-31).

A Primo Star™ Zeiss microscope (Carl Zeiss Microscopy, Jena, Germany) was used for histological evaluation. The entire slide was scanned using a 200x magnification (400x for vessel density), and three fields for each slide were randomly selected for subsequent image acquisition using a Zeiss AxioCam camera ICC1™. Objective analysis of immunoreaction (percentage area of immunoreactivity and vessel density) was carried out with AxioVision V 4.8.0.0 Software Microscope (Karl Zeiss-Germany) (Figure-3).

Statistical Tests

The Kruskal-Wallis test was performed for comparisons between periods and the Wilcoxon test for comparisons between groups. For repeated measures the ANOVA was used for comparisons of groups and periods. A 5% significance level was adopted for all statistical tests ($p<0.05$).

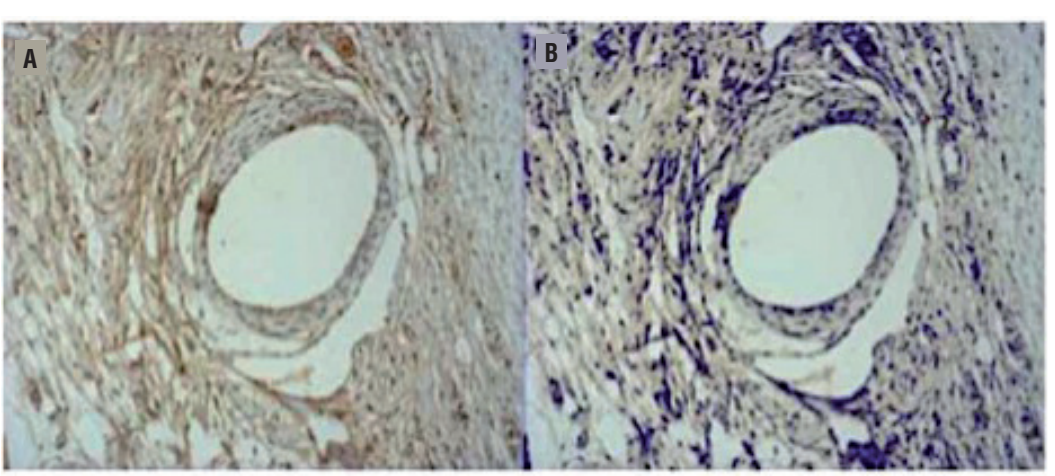
RESULTS

All rats survived and no complications were observed during the post implant period. In addition, no dehiscence or mesh exposure at the implant site was observed.

Histological analysis

Histological analysis of implantation site showed an expected pattern of acute inflammatory reaction at four days based on macrophages and polymorphonuclear infiltrate with few fibroblasts and edema. However, on the 30th day post implant, a foreign body reaction based on histiocytes and giant cells was the predominant pattern around

Figure 3 - Example of MMP2 immunoreactivity in an implant sample. Blank rounded area indicates the PP filament. (A) Before software selection. (B) After selection, note MMP2 immunoreactivity colored in blue (200x).



the PP filaments, combined with many fibroblasts with intense production of collagen resulting in a compact tissue. A larger area of inflammatory reaction was observed in the PP group compared to sham on the 4th and also on the 30th day (11.36% (PP) x 5.19% (sham) and 11.06% (PP) x 5.73% (sham) for 4 and 30 days respectively, p=0.0002) but no differences were observed when comparing the different times (4 and 30 days) in each one (sham and PP groups) (Table-1).

Birefringence analysis

The analysis of the organization of collagen fibers, represented by the birefringence index (index A/B), showed no differences between PP and sham (1.29 (PP) x 1.43 (sham), p=0.27). The collagen density (which estimates the intensity of tissue compaction) also showed no differences between the groups after 30 days post implantation (Table-2) (Figure-2).

IL-1

A reduction of IL-1 immunoreactivity was observed after 30 days post implant when compared with 4 days for both groups (50.07% (4 days) x 25.66% (30 days) and 32.36% (4 days) x 27.09% (30days), for PP and sham respectively, p=0.010) (Figure-4). On the 4th day, PP presented a slightly higher but not significant level of IL-1 immunoreactivity than the sham (p=0.08).

TNF-α

A higher TNF-α immunoreactivity in PP group was observed when compared with sham on the 4th day (56.42% (PP) x 31.98% (sham), p<0.0001). Comparing the features on the 4th and the 30th day for each group, there was a similar TNF-α immunoreactivity over time in sham group and it was observed a reduction over time in PP group (56.42% (4 days) x 40.65% (30days), p=0.0161) (Table-3).

MMP-2

PP group presented a higher MMP-2 immunoreactivity after 4 days compared to 30 days while sham presented similar levels over time (55.19% (4 days) x 29.98% (30 days), p=0.018) (Table-3). Sham presented higher MMP-2 immunoreactivity on the 30th day (31.65% (4 days) x 44.57% (30 days), p=0.024) however no difference was observed in comparison to PP group on the 4th day (p=0.066).

Table 1 - Inflammatory reaction (mean percent area).

	PP (SD)	Sham (SD)
4 days*	11.36 (6.94)	5.19 (1.68)
30 days*	11.06 (6.85)	5.73 (1.97)

***p** = 0.0002 (sham x pp)
SD = Standard deviation

Table 2 - Birefringence analysis of collagen fibers.

	Position A			Position B			Index A/B		
	PP (SD)	Sham (SD)	p	PP (SD)	Sham (SD)	p	PP (SD)	Sham (SD)	p
Collagen fibers area (mean percent area)	8.37 (5.32)	10.65 (4.63)	0.24	7.78 (5.18)	11.60 (7.67)	0.24	1.29 (0.24)	1.43 (0.33)	0.27
Collagen density (mean pixel/μm²)	73.58 (48.32)	48.37 (4.42)	1	79.15 (56.35)	50.44 (5.17)	0.73	-	-	

SD = Standard deviation

Figure 4 - Example of Il-1 immunoreactivity (Brown area) after 4 days (A) and 30 days (B)–(200x). Note a higher brown intensity and extension in A.

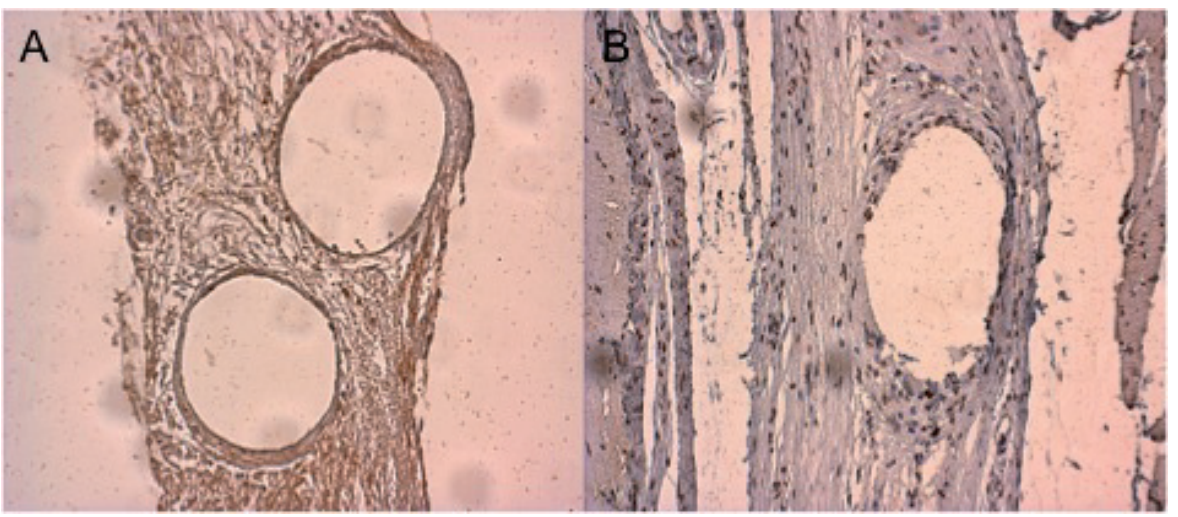


Table 3 - Immunohistochemistry analysis of angiogenesis, inflammation and collagen metabolism.

	IL-1*			TNF*			MMP-2*			CD-31**	
	PP (SD)	SHAM (SD)	p	PP (SD)	SHAM (SD)	P	PP (SD)	SHAM (SD)	p	PP (SD)	SHAM (SD)
4 days	50.07 (13.47)	32.36 (20.31)	0.08	56.42 (7.61)	31.98 (11.92)	<0.0001	54.19 (25.24)	31.65 (9.07)	0.066	N/A	N/A
30 days	25.66 (14.41)	27.09 (18.84)	0.08	40.65 (15.49)	34.39 (11.92)	0.420	29.98 (14.77)	44.57 (14.53)	0.024	19.64 (9.43)	16.54 (7.94)
p	0.010	0.010		0.0161	0.523		0.018	0.058		PP x SHAM	0.587

*Mean percentage of the area marked by the antibody relative to the field** Average number of vessels per field
SD = Standard deviation

CD-31

There were no differences in the average number of vessels per field between PP and sham at 30 days (19.64 (PP) x 16.54 (sham), p=0.587) (Table-3).

DISCUSSION

In addition to this study, several others, albeit using different methods, have described histological and molecular changes after the implantation of biomaterials, in particular, polypropylene (8, 9, 11, 13). An inflammatory response to macroporous monofilament PP was demonstrated in explanted meshes from humans one year after implantation and it was observed that this material had little long-term influence on the extracellular matrix composition, represented by the fraction of collagen and elastin in the tissue. However, consistent high concentrations of mast cells and macrophages were observed, which may suggest the perpetuation of a mild inflammatory foreign body reaction (14). Vandervord et al. implanted four types of biological meshes in subcutaneous of mice and found that, after a period of 12 weeks, the swine intestinal submucosa (SIS) presented a more effective integration represented by a significantly thicker inflammatory capsule with increased angiogenesis. The authors concluded that the control of inflammatory reaction and angiogene-

sis are the basis for effective tissue integration of the implant (15). In this present study, inflammatory reaction, elicited by PP implant, although higher than sham, did not differ significantly over time. Moreover, both groups presented a similar number of vessels after 30 days.

The impact of changes on the weight of the PP mesh and its combination with polyglactin in the inflammatory reaction were tested in a macrophage culture. In spite of demonstrating higher apoptosis levels than those of sham, no differences in the apoptosis index were found between the meshes. Furthermore, a higher rate of cell proliferation in mesh samples was observed than in those of sham (16). The present study, using histological samples, also found a higher cell proliferation rate (higher inflammatory reaction area) in PP group than sham. These findings, as well as others in vivo (17) and in vitro (18), suggest that mesh composition in addition to its surface features might be as important (or even more important) than its weight as a foreign body reaction drive.

Comparing PP and xenogeneic dermal collagen meshes, Zheng et al. found that the production of anti-inflammatory cytokines after the PP implant, such as interleukin-10 (IL-10) and tumor growth factor (TGF), was lower than the collagen group. An increased release of pro-inflammatory cytokines was also identified, such as interferon (IFN) and tumor necrosis factor (TNF-α) in PP meshes after the first week of implant, followed by a marked reduction over time and reaching the basal levels after thirty days (19). Moreover, when compared with sham (surgery without mesh), PP expressed a higher TNF-α level 24 hours after implantation (20). In the present study, a similar behaviour was observed in respect to pro-inflammatory cytokines (IL-1 and TNF-α) in the PP group. This may explain an increased inflammatory reaction area observed in the PP group. In another study, human blood samples showed a significant, although heterogeneous, increase of TNF levels after contact with PP meshes. Therefore, personal differences in TNF expression among patients may explain why women who undergo a surgical procedure under similar conditions can present different outcomes, such as a higher incidence and severity of mesh integration defects (21).

A reduced collagen deposition was observed 21 days after subcutaneous PP implantation in TNF-knockout rats when compared to control (22). This finding is consistent with the larger capsule thickness observed in the present study after PP implantation compared to sham, since the increased production of TNF may rise the proliferation and activation of fibroblasts and thus augment the collagen deposition (22, 23). Wu et al. analysed the MMP-2 gene activity and identified a higher gene expression in fibroblasts in contact with the mesh when compared with that found in the tissues far from the implant. According to these authors, at the beginning of the inflammatory process, remodelling of the extracellular matrix is essential for the migration and activation of inflammatory cells (24). Therefore, the production of matrix metalloproteinases (MMPs) by fibroblasts is an indicator of early inflammatory activity. During the implant integration, MMPs seem to be important in the tissue remodelling process as well as in the permanent mild foreign body reaction elicited by the presence of a no absorbable implant (24, 25). During the integration process, a progressive reduction in MMP-2 activity is generally expected in the same proportion as the body's adaptation to the biomaterial. This was the case in the present study. A higher MMP-2 immunoreactivity was observed in the tissue around the mesh filaments after 4 days when compared to 30 days of implantation. Furthermore, the PP presented a lower MMP-2 immunoreactivity than sham at 30 days, which may indicate a trend of acceleration of the extracellular matrix remodelling.

The variety and concentration of cytokines, cells and collagen fibers at the surgical site during the healing process determines which type of scar tissue will emerge in the implant area. A previous study has shown that the amount and organization of extracellular tissue can establish relationship between the scar pattern around the implant and its biomechanical properties, as tensile strength and stiffness (8). In the present study, we proposed the use of the birefringence index for the assessment of the organization of collagen fibers. Birefringence is an important property of some synthetic and natural macromolecules. In

the field of cell biology, birefringence is an important and reliable instrument for the analysis of collagen supra molecular properties (26). No differences in birefringence index between PP and sham were found. The collagen density analysis, which indicates tissue compression, also showed no difference between the groups 30 days after implantation. Therefore, in the present study, the PP elicited a similar quality and organization of extracellular matrix and did not stimulate an over production of collagen tissue in comparison to the regular healing process. In another sham-controlled study of subcutaneous implanted collagen coated versus uncoated PP meshes, the authors, although using semi quantitative methods, also observed a higher fibroplasia and no differences in angiogenesis or collagen fiber organization were observed between sham and PP (12).

Pierce et al. implanted meshes (PP and swine dermis) in the abdomen and vagina of rabbits and found that vaginal tissues demonstrated higher rates of inflammation; higher neovascularization but lower fibroblast proliferation than the abdomen independent of which mesh was being studied. Moreover, the same proportional difference between meshes was found in the vagina and the abdomen (27).

Despite advances in the understanding of the molecular process and histological response to mesh implant, their clinical translation requires further evidence. Rechberger et al. measured cytokines in the blood of patients undergoing sling surgery and found no differences between patients with or without mesh vaginal exposure during the follow-up. Only IFN, measured preoperatively, was higher among patients with exposed meshes. Therefore, the authors suggested that some blood tests could be used as complication predictors (28).

The upside of this study was to confirm previous data regarding the histological and molecular pattern of biological response to PP, based on objective and original methods for quantitative measurements (15). There are, however, downsides, since the methods did not allow the differentiation of cell types in each phase of the inflammatory process or the consideration of the long term aspects since the last measurement occurred at 30th day. Moreover, we did not completely avoid a systemic bias once we have used the same animal to both groups (sham and implant). There is also a lack of quantitative measurement of anti-inflammatory cytokines or an evaluation of mesh shrinkage or contraction and its relations with the inflammatory reaction that should be added in future studies.

CONCLUSIONS

The implantation of monofilament and macroporous polypropylene in the subcutaneous of rats resulted in increased inflammatory activity and higher TNF production in the early post implant phase. After 30 days, PP has similar cytokines immunoreactivity, vessel density and extracellular matrix organization, in addition to lower MMP-2 expression than sham. The evaluation of inflammatory reaction after mesh implant should be based on objective standardized methods.

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CONFLICT OF INTEREST

None declared.

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The influence of distal colon irritation on the changes of cystometry parameters to esophagus and colon distentions

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ABSTRACT

The co-occurrence of multiple pathologies in the pelvic viscera in the same patient, such as, irritable bowel syndrome and interstitial cystitis, indicates the complexity of viscero-visceral interactions and the necessity to study these interactions under multiple pathological conditions. In the present study, the effect of distal colon irritation (DCI) on the urinary bladder interaction with distal esophagus distention (DED), distal colon distention (DCD), and electrical stimulation of the abdominal branches of vagus nerve (abd-vagus) were investigated using cystometry parameters. The DCI significantly decreased the intercontraction time (ICT) by decreasing the storage time (ST); nonetheless, DED and Abd-vagus were still able to significantly decrease the ICT and ST following DCI. However, DCD had no effect on ICT following the DCI. The DCI, also, significantly decreased the Intravesical pressure amplitude (P-amplitude) by increasing the resting pressure (RP). Although DED has no effect on the P-amplitude, both in the intact and the irritated animals, the abd-vagus significantly increased the P-amplitude following DCI by increasing the maximum pressure (MP). In the contrary, 3mL DCD significantly increased the P-amplitude by increasing the MP and lost that effect following the DCI. Concerning the pressure threshold (PT), none of the stimuli had any significant changes in the intact animals. However, DCI significantly decreased the PT, also, the abd-vagus and 3mL DCD significantly decreased the PT. The results of this study indicate that chemical irritation of colon complicates the effects of mechanical irritation of esophagus and colon on urinary bladder function.

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INTRODUCTION

Due to viscero-visceral interactions, many inflammatory conditions have manifestations affecting not only the pathological organ but extends onto other viscera within the same vicinity or even further away. The spread of the symptoms onto other viscera complicates the pathological condition and make it more difficult to diagnose and manage. For example, chronic pelvic pain could be attributed to many conditions affecting urinary bladder/interstitial cystitis, gastrointestinal tract/irritable bowel syndrome, prostate gland/prostatitis or any other pelvic organ pathology (1).

Urinary bladder function can be affected by stimuli from other viscera. For example, colon inflammation in rats was shown to increase urinary bladder frequency (2). In addition, esophagus distention and electrical stimulation of vagus nerve, in rats, increased urinary bladder contraction frequency (3). In humans, patients

with irritable bowel syndrome showed symptoms of urinary bladder dysfunction, such as, an increase in urination frequency, as well as an increase in residual volume (4). Moreover, patients with interstitial cystitis showed higher incidence of irritable bowel syndrome and other systemic diseases compared to controls (5).

The complexity of the viscero-visceral interactions requires the study of these interactions under different pathological conditions. Most studies were designed to show the simple viscero-visceral interaction between viscera or the direct effect of a pathological condition of one viscera on the function of another; however, it is rare to find a study on how a pathological condition of one viscera can affect the viscero-visceral interaction of other viscera. In the present study, the influence of distal colon chemical irritation on the interaction of urinary bladder with distal colon and distal esophagus distentions was investigated.

MATERIALS AND METHODS

Animals

Eighteen male Wistar rats (300-350g) were used in the present study. Ten of these animals had distal colon irritation and the other eight animals remained intact. Animals were purchased and housed under standard conditions in the animal house at The Hashemite University. All experimental methods were approved by the Hashemite University Institutional Board and Animal Ethical Committee, which meet the requirements of the National Institute of Health (NIH, USA) guide for the use and care of laboratory animals.

Methods

At the day of experiment, each rat was anesthetized with urethane (1.2g/kg of 50% urethane in water); the anesthetic solution was divided into two halves, of which, one half was administered intraperitoneally and the other was given subcutaneously (6). Urethane was obtained from Sigma (St. Louis, Missouri, USA). The carotid artery and jugular vein at the left side were cannulated, in each animal, for blood pressure monitoring and anesthetic supplementation, respectively.

Continuous cystometry

An abdominal incision was made, in each animal, in order to expose the urinary bladder and ureters. A 20-gauge needle was introduced into the dome of the urinary bladder and connected to a programmable pump (AL-1000; World Precision Instrument, Sarasota, FL). Cystometry was done by bumping normal saline at a rate of 0.25mL/min to the urinary bladder. Intravesical pressure was monitored using a pressure monitor (BP-1; World Precision Instrument, Sarasota, FL) that was connected to the needle through a pressure transducer. The temperature and hydration of the urinary bladder were preserved throughout the experiment by surrounding the urinary bladder with cotton pallets that were soaked in a warm normal saline. The ureters were tied proximal to the urinary bladder, then ureters were cut and drained distal to it.

Distal colon distention

Distal colon distention was done by a 10mm long balloon, which was made from latex material and attached to a 25GX¾" catheter (7). The colon balloon was inserted about 10cm from the anus and was taped to the base of the tale to prevent movement. Colon balloon was connected to a 3mL syringe filled with normal saline. Distal colon distention was done manually by infusing the balloon with three increasing increments of normal saline (1mL, 2mL, and then 3mL). Last increment (3mL) produced greater-than or equal to 70mm Hg pressure, which is reported to be a noxious stimulus (8, 9).

Distal esophagus distention

Distal esophagus distention was done by balloon, similar to the distal colon balloon. The esophagus balloon was inserted about 7cm from the upper incisors, intra-orally, to the distal esophagus (10). The balloon was connected to 1mL syringe. Esophagus distention was done by infusing the balloon with 0.5mL normal saline.

Vagus nerve stimulation

The abdominal branches of the vagus nerve were stimulated, at the level of the esophageal

opening of the diaphragm, using digital stimulator (PG 4000 A; Cygnus Technology, Inc., Delaware Water Gap, PA) and isolated using isolated current source (SIU 91; Cygnus Technology, Inc., Delaware Water Gap, PA) with isolation. The stimulation was done indirectly through the esophageal wall using a bipolar electrode that was introduced orally down to the esophagus. The stimulation was conducted at frequency of 1 train/sec with 100msec train duration. Each train was composed of 14 pulses (at 70pulses/sec). Each pulse intensity was set at 8mA with 2msec duration (11). This stimulus produced compound action potentials, which were recorded from the vagus nerve in the cervical region (12).

Distal colon irritation

Ten rats had distal colon chemical irritation. Chemical irritation of the distal colon was done in the anesthetized animals by infusing 1mL of 2% acetic acid into the distal colon through a catheter (comprised of PE 60 tubing attached to a syringe). A cotton pallet was attached to the distal end of the catheter by fixing part of it to the distal end of the catheter tub, while leaving the remaining free part in direct contact with colon mucosa. This procedure insures the localization of the irritant within the distal colon.

EXPERIMENT DESIGN

At the beginning of each experiment, normal cystometry recordings were performed for 30 minutes. After that, cystometry recordings were done for another 30 minutes following the infusion of the irritant (in the irritated animals). Then, cystometry recordings were done for 10 minutes with esophagus distention, followed by 10 minutes recordings without esophagus distention. In the same way, cystometry recordings for another 10 minutes were done with vagal nerve stimulation, followed by normal recordings for 10 minutes. At the end, cystometry recordings were done for 30 minutes with distal colon distentions (10 minutes for each increment of distal colon distentions; 1mL, 2mL and 3mL). Cystometry was recorded for 10 more minutes following colon balloon deflation.

All data obtained from the pressure monitor were amplified and recorded on a computer using data acquisition system (National Instruments®, www.ni.com). Cystometrograms were recorded using a BioBench software program (National Instruments®, www.ni.com). The micturition cycle timing parameters, intercontraction time (the whole micturition cycle time) (ICT); the time of the voiding phase (VT); and the time of the storage phase (ST), and the intravesical pressure parameters, resting pressure (RP); pressure threshold (PT); maximum pressure (MP); and pressure amplitude (P-amplitude; the deference between MP and RP) were measured, offline, for statistical analysis.

Statistical analysis

All the parameters of the micturition cycles in ten minutes after each stimulus and the micturition cycles in the last ten minutes preceded the stimulus from each animal were considered for statistical analysis for each stimulus. The measurements of micturition cycles parameters preceded the stimulus were considered as control for the measurements following the stimulus. Statistical analysis was performed using two tailed, unpaired student t-test (t). Results were considered significant when $P<0.05$. All data are presented as mean$\pm$standard error.

RESULTS

Effect of Colon irritation on micturition cycle timing's parameters

Distal colon irritation significantly increased the ICT. In addition, DCI significantly increased the ST, however, there was no significant changes to the VT following distal colon irritation. Compared to intact animals (3), in the irritated animals, distal esophagus distention and electrical stimulation of the abdominal branches of the vagus nerve were still able to significantly decrease the ICT and ST of the micturition cycles without any significant effect on the VT. On the other hand, following distal colon irritation, all three distention increments (1mL, 2mL, and 3mL) of distal colon had no significant effect on the ICT, ST, or VT, and so, all significant effects of distal colon distention on these parameters in the intact animals (under publication) disappeared following

distal colon irritation. The effect of esophagus, vagal, and distal colon stimuli on the ICT are presented in Figure-1. All data for VT and ST of the micturition cycles are presented in Table-1.

Effect of colon irritation on intravesical pressure's parameters

In the intact animals, distal esophagus distention and electrical stimulation of the abdominal branches of vagus nerve didn't have any significant effect on the intravesical pressure parameters (RP, PT, MP, or P-amplitude), except for a significant increase in the RP to vagal stimulation. At the same time, only 3mL distal colon distention significantly increased the MP and the P-amplitude, without any significant effect on the RP or PT. Distal colon distention with 1mL and 2mL didn't have any significant effects on the intravesical pressure.

In the irritated animals, irritation of distal colon significantly increased the RP, while significantly decreased the PT and P-amplitude. However, Irritation of distal colon had no significant effect on the MP. Following distal colon irritation, distal esophagus distention still had no significant effect on the intravesical pressure parameters. Simultaneously, distal colon distention almost had no significant effect on the intravesical pressure parameters following distal colon irritation, except for a significant increase in the PT with 3mL distal colon distention. However, in the irritated animals, electrical stimulation of the vagus nerve significantly decreased the PT, though, significantly increased the MP and P-amplitude. Vagal stimulation had no significant effect on the RP. The effect of esophagus, vagal, and distal colon stimuli on the P-amplitude are presented in Figure-2. All data for RP, PT, and MP are presented in Table-2.

DISCUSSION

The results of this study shows how the changes of the urinary bladder function in response to mechanical stimuli from other viscera, either in the same region (distal colon distention) or in another region (esophagus distention), can be affected by chemical irritation to the distal colon.

The chemical irritation of the distal colon significantly increased the urinary bladder frequency. The increase in bladder frequency was attributed by the significant decrease in the storage time of the micturition cycle, where the voiding time did not have any significant changes. Since the storage phase is mainly a spinally mediated reflex (13), these results may indicate that the

Figure 1 - Effect of different visceral stimuli on the intercontraction time (ICT) in the intact and the irritated animals. In the intact animals, distal esophagus distention and electrical stimulation of abdominal branches of vagus nerve significantly ($P < 0.01$ and $P < 0.05$ respectively) decreased the ICT (data published (3)), however, distal colon distention with 3 ml significantly ($P < 0.04$) increased the ICT (under publication). In irritated animals, chemical irritation of the distal colon significantly ($P < 0.001$) decreased the ICT; distal esophagus distention and vagal stimulation significantly ($P < 0.03$) decreased ICT; distal colon distention had no significant effect. Vertical bars represent standard error of the mean.

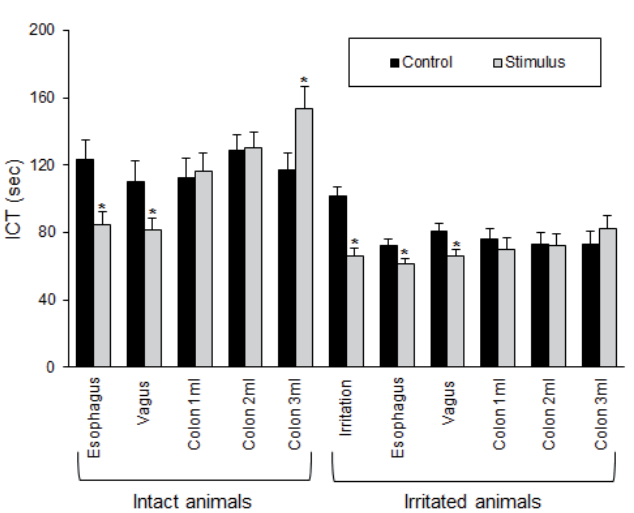


Table 1 - Effect of Different Visceral Stimuli on the Micturition Cycle Phases with and without Distal Colon Irritation.

	ST (sec)	VT (sec)
Intact animals		
Control	101.6±11.2	23.0±1.9
Distal Esophagus	59.9±6.3*	25.1±3.2
Control	84.2±10.6	25.8±2.3
Abd-vagus	56.8±6.1**	24.8±1.6
Control	85.0±11.1	27.4±1.8
Distal colon (1mL)	80.8±9.4	35.3±3.7
Control	98.4±9.2	30.4±1.3
Distal colon (2mL)	93.2±8.7	36.8±1.6***
Control	86.7±9.7	30.1±2.2
Distal colon (3mL)	103.4±13.0	45.0±5.0*
Irritated animals		
Control	80.5±4.6	21.5±1.0
Colon Irritation	46.9±3.7****	19.3±0.9
Control	52.4±3.0	20.2±0.9
Distal Esophagus	42.5±2.9*****	19.0±0.8
Control	60.0±4.5	20.7±0.9
Abd-vagus	46.8±3.4*****	19.3±0.7
Control	58.4±5.8	17.5±0.7
Distal colon (1mL)	53.1±6.2	17.2±1.2
Control	55.2±6.5	17.7±1.2
Distal colon (2mL)	53.0±6.6	19.3±1.5
Control	54.7±6.9	18.7±1.5
Distal colon (3mL)	63.4±7.4	19.0±1.7

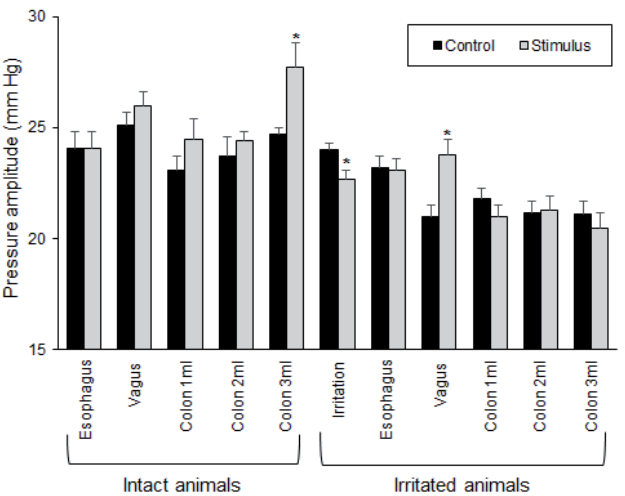
Abd-vagus, electrical stimulation of the abdominal branches of the vagus nerve; distal esophagus, distal esophagus distention; distal colon, distal colon distention; colon irritation, chemical irritation of distal colon.

*P<0.002, **P<0.02, ***P<0.004, ****P<0.001, *****P<0.03

effect of distal colon irritation on the urinary bladder mainly occur at the spinal level. The increase of bladder frequency in response to colon irritation could be explained by neuronal sensitization. Colon irritation is proved to sensitize neurons that receive convergent inputs from colon and urinary bladder both at the dorsal root ganglion (14) and lumbosacral spinal segments (15, 16). These results are consistent with other studies, where there was an increase of bladder activity in response to colon inflammation both in rats (2) and mice (17).

The neuronal sensitization can also explain the effect of distal colon irritation on intravesical pressure, where colon irritation significantly decreased the pressure amplitude by significantly increasing the resting pressure. In addition, distal colon irritation significantly decreased the pressure threshold. The effect of colon irritation on pressure threshold could be related to sensitization of the urinary bladder afferents as well. Ustinova et al. (18) demonstrated that colon irritation in rats sensitizes urinary bladder afferents to bladder

Figure 2 - The effect of different visceral stimuli on the pressure amplitude in the intact and the irritated animals. In the intact animals, distal colon distention significantly ($P < 0.02$) increased the pressure amplitude. In the irritated animals, distal colon irritation significantly ($P < 0.01$) decreased the pressure amplitude, whereas, vagal stimulation significantly ($P < 0.003$) increased the pressure amplitude. Vertical bars represent standard error of the mean.



distention. Also, the decrease in pressure threshold could be related to the sensitization of the spinal neurons receiving bladder inputs. It was shown that the volume of urinary bladder distention necessary to excite the lumbosacral neurons decreased significantly following colon inflammation in rats (15). All these effects of colon irritation on the cystometry parameters reflect an increase of bladder activity.

All the same, distal colon irritation had an influence on the bladder responses to the distal colon distention and distal esophagus distention, as well as to electrical stimulation of the abdominal branches of vagus nerve. Following distal colon irritation, the distal esophagus distention and electrical stimulation of vagus nerve were still able to significantly increase the bladder frequency as it did in the intact animals. This increase in the bladder urinary frequency is still attributed to the decrease in the storage time as well (3). So, despite that colon irritation itself increased the activity of the urinary bladder, it didn't attenuate the effect of distal esophagus and vagal stimulation on the urinary bladder activity. These results indicate that colon irritation sensitized the neural circuitries controlling the effect of esophagus and vagal stimuli to bladder activity. This sensitization is also reflected on the significant decrease of the pressure threshold by vagal stimulation in the irritated animals but not in the intact ones. The sensitization of the neural circuitries could be spinally mediated through the sensitization of the spinal part of the neural circuit that control the effect of the esophageal distention and vagal stimulation on the bladder activity, as mentioned above, or it could be directly through sensitizing the vagal afferents itself. It was shown through a neuronal tracing technique that distal colon is innervated by vagal afferents, in addition, it was shown in the same study that some nodose ganglion neurons innervate both the distal colon and urinary bladder (19).

On the other hand, following distal colon irritation, distal colon distention didn't have any significant effect on bladder frequency, which means that distal colon distention lost its inhibitory effect on the bladder function. On the opposite, 3mL distal colon distention significantly decreased the pressure threshold following colon irritation. The ability of colon irritation to sensitize the convergent neurons for urinary bladder and colon again can explain

Table 2 - Effect of Different Visceral Stimuli on the Intra-vesical Pressure during Micturition Cycle with and without Distal Colon Irritation.

	RP (mm Hg)	PT (mm Hg)	MP (mm Hg)
Intact animals			
Control	4.6±0.2	10.8±0.8	28.7±0.6
Distal Esophagus	4.7±0.2	9.3±0.5	28.8±0.7
Control	3.8±0.3	9.1±0.5	28.9±0.6
Abd-vagus	4.7±0.2*	8.8±0.4	30.7±0.6
Control	4.1±0.3	9.8±0.6	27.1±0.6
Distal colon (1mL)	4.2±0.4	9.1±0.6	28.7±0.8
Control	3.9±0.5	9.4±0.8	27.6±0.6
Distal colon (2mL)	4.0±0.6	9.5±0.6	28.3±0.7
Control	5.6±0.3	10.7±0.6	30.3±0.4
Distal colon (3mL)	5.3±0.3	11.1±0.8	33.0±1.1**
Irritated animals			
Control	3.7±0.2	9.0±0.3	27.5±0.5
Colon Irritation	4.5±0.1***	7.5±0.2***	27.0±0.4
Control	4.2±0.2	7.4±0.2	27.1±0.7
Distal Esophagus	4.8±0.3	7.4±0.3	27.5±0.8
Control	4.4±0.3	8.3±0.3	25.1±0.8
Abd-vagus	4.3±0.2	6.9±0.3****	27.6±0.9**
Control	4.6±0.4	8.7±0.3	25.9±0.9
Distal colon (1mL)	4.8±0.4	8.1±0.3	25.3±0.9
Control	5.0±0.4	8.1±0.3	25.6±0.9
Distal colon (2mL)	4.7±0.4	8.4±0.3	25.5±1.0
Control	4.8±0.4	8.5±0.3	25.5±1.0
Distal colon (3mL)	4.0±0.4	7.5±0.3*	24.0±1.0

Abd-vagus, electrical stimulation of the abdominal branches of the vagus nerve; distal esophagus, distal esophagus distention; distal colon, distal colon distention; colon irritation, chemical irritation of distal colon.

*P<0.02, **P<0.05, ***P<0.001, ****P<0.005

these results. Wang et al. (20) showed that colon inflammation increased the response of the lumbosacral neurons that have long discharge "sustained neurons" following colorectal distention in the lumbosacral segments. In another study, the convergent lumbosacral neurons for colon and urinary bladder inputs showed a significant increase in their response to bladder and colon distention following colon inflammation (15). The disappearance of the inhibitory reflex of distal colon distention on the urinary bladder might be due to the sensitization of the same neuronal circuits that relays the colon irritation effects, which means that the sensitization of the colon irritation overcomes the inhibition of the colon distention or even revers it.

Finally, the setup of the present study has some limitations, mainly related to the distal colon irritation and the conscious level of

the animals. More studies must be done about chronic irritation of the colon to resemble more the real pathological conditions. In addition, these experiments could be done in conscious animals, in order to exclude the effect of anesthesia on the viscero-visceral interactions. Moreover, electrophysiological studies must be carried on, in order to elaborate the changes in the neural circuitries that control the viscero--visceral interactions.

In conclusion, the results of the present study demonstrate that viscero-visceral interaction effects on the urinary bladder function depends on the variability of the mechanical and chemical stimuli from other viscera and the degree of neural overlapping that controls the different viscero-visceral interactions. The results of this study also indicate the necessity of taking in consideration the different nociceptive stimuli from other viscera in managing pathological conditions affecting certain visceral organ such as urinary bladder.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Effects of L-Glutamine oral supplementation on prostate of irradiated rats

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ABSTRACT

Objectives: To investigate the protective effect of L-Glutamine in animals undergone to ventral radiation when the target organ is not the prostate.
Materials and Methods: Wistar rats were divided into groups of 10 animals each: Controls (C), maintained under standard conditions and not exposed to radiation, Radiated group (R) undergone to abdominal radiation only and Radiated plus supplemented by L-glutamine group (R+G). The animals of group R+G were supplemented with L--glutamine at the beginning of the experiment until death in the 22nd day. The ventral prostate was dissected and processed for morphometrical analysis. The epithelial height, collagen density and acinar area were objectively assessed in histological sections.
Results: Epithelial height was significantly reduced in R group in comparison to C group (p= 0.005). However, there was no statistical difference between the C and R+G groups. Collagen surface density in the C and R groups were not statistically different, but a significant difference was observed when comparing groups R+G and R (p= 0.040). The R+G group values did not differ significantly from C group. The acinar prostate area of group R was similar to that of C (p= 0.971), but in R+G it was significantly reduced when compared with the C (p= 0.038) and R (p= 0.001) groups.
Conclusions: Pelvic radiation promotes structural modifications in ventral prostate of rats, which can be reduced by L-Glutamine.

ARTICLE INFO

Keywords:
L-glutamine 2-deoxy-scyllo-inososse aminotransferase [Supplementary Concept]; Prostate; Rats

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INTRODUCTION

Ionizing radiation, when used to destroy tumor cells in pelvic organs, always affect the normal cells of the target and surrounding organs leading to important side effects. Despite its negative aspects, pelvic radiotherapy is increasingly used for treatment of bladder and rectum cancer. As the consequence, there is a growing incidence of acute and chronic radiation-related lesions in pelvic organs, including the prostate (1).

The L-Glutamine is considered a non-essential amino acid in homeostatic situations but becomes essential in catabolic circumstances such as trauma and sepsis (2, 3). L-Glutamine is metabolized to glutathione that protects tissues against oxidative damage, and acts as a nitrogen conductor between cells and may be precursor for nucleotides and glucose (4). Supplementation with this amino acid prevents bacterial translocation from the intestinal mucosa, reduces the infection rate, hospitalization time and mortality in critically ill patients (4, 5).

Diestel et al. (6) suggests that the L-Glutamine supplementation assists the colonic wall repair in rat's after radiation. Radiotherapy toxic effects are extended when L-glutamine levels are low (7). Possibly the L-glutamine deficiency may limit both the protein production in inflammatory response and glutathione synthesis compromising the body antioxidant defenses (8).

The aim of the present work is to investigate the effects of radiation over a nonneoplasic prostate and the protective effect of L-Glutamine in this radiated organ.

MATERIAL AND METHODS

In the present study thirty adult male Wistar rats (90 days old, 350grams of body weight) were kept in a room with controlled temperature (25±1°C), artificial dark-light cycle (lights on from 7:00 am to 7:00 pm) and fed standard rat chow and water ad libitum.

The rats were randomly allocated into three groups: Control group (C) was maintained under standard conditions and was not exposed to radiation (n=10). Radiated group (R) undergone pelvic radiation (n=10) at the eighth day of the experiment. Supplemented and radiated group (R+G) undergone pelvic radiation plus L-glutamine supplementation (n=10). This group (R+G) was also exposed to radiation at the eighth day of the experiment and was supplemented with L-glutamine (Resource Glutamine, Novartis, Rio de Janeiro, Brazil) from the beginning of the experiment (day 0) until death. L-Glutamine was administered by gavage at a dose of 0.2g/Kg of body weight diluted in distilled water (6).

The animals of the R and R+G groups received a unique dose of abdominal radiation of 1164cGy. All rats were maintained in a dorsal position inside small plastic cages, avoiding movements during pelvic radiation. A linear accelerator of 06 MeV (model Clinac 2100®–Varian®) liberated the radiation with a speed of 240cGy/min, in a font-skin distance of 100cm, in a 6x4cm field over the lower abdomen. The head, thorax and members were excluded of the radiation field.

During all experiment stages, the animals were observed for signs of toxicity such as lack of appetite, weight loss, piloerection, hyper or hypo activity.

All animals were submitted to euthanasia by an overdose of sodium thiopental on the 22nd day (14 days after radiation exposure).

Prostate was dissected under magnification, and its ventral lobe was fixed in 4% buffered formaldehyde. The specimens were processed for paraffin embedding and sections of 5µm thickness were obtained. Samples were stained by hematoxylin and eosin to study acinar structures and Picrosirius red for collagen analysis.

Micrographs were captured by a digital camera (DP70-Olympus®) coupled to a light microscope (BX51-Olympus®). All analyses were performed on random fields with the software ImageJ® (National Institute of Health, USA).

After calibration, the area of the prostatic acini and epithelium height were measured with "freehand selections" and "straight line selections" tools respectively.

For collagen analysis, a 100 points grid was superimposed over the images, and the point counting method (9, 10) was used to objectively determinate collagen surface density, expressed as percentage.

For parametric values, analysis of variance (ANOVA) followed by Student t test were used. For nonparametric data Kruskal-Wallis test, followed by Mann-Whitney test were used. The GraphPad Prism 5.0 software was used for statistical analysis. The significance level for rejecting the null hypothesis was 5% ($p \leq 0.05$).

This research was approved by the Institutional Animal Bioethics Committee of the Biological Sciences Center, State University of Rio de Janeiro (protocol number: CEA/224/2008).

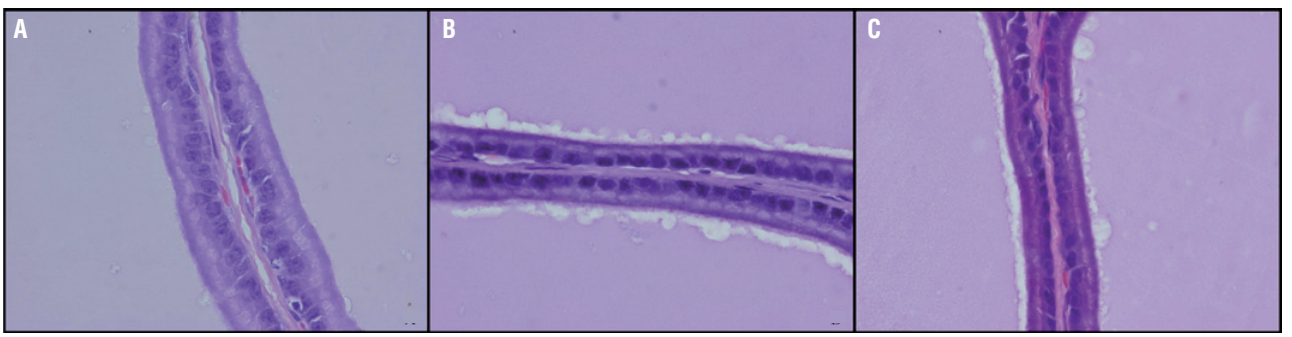
RESULTS

After radiation exposure, all animals presented diarrhea. No other toxicity sign was observed.

Epithelial height was significantly reduced in group R in comparison to group C ($p<0.01$). In the group R+G the epithelial height was similar to the C group (Table-1, Figure-1).

The collagen density between C and R groups showed no statistical difference ($p=0.16$).

Figure 1 - Epithelial height in the ventral prostate. a: Control; b: Irradiated ; c: Irradiated+L-glutamine. HE. X 1000.



Collagen increased significantly in the group R+G when compared with group R (p=0.04). The R+G group values did not differ significantly from C group (p=0.37) (Table-1).

The prostate acinar area of group R was similar to that of C group (p=0.97). The R+G group had a statistical decrease when compared with C group (p=0.03) and R groups (p<0.01) (Table-1).

According to data, the effect of radiation on the prostate of the rat affected the height of the epithelium significantly. In radiated rats and after supplementation with L-glutamine, it was observed a significant increase in the amount of collagen and a significant decrease in the size of acini (Table-1, Figure-1).

DISCUSSION

The pelvic radiation is well-recognized to produce major side effects contributing to morbidity of oncologic patients. Most of these effects occur in consequence of radiation to organs without cancer. This can begin immediately after the tissue exposition but the histological modification may take some weeks to occur (1, 11, 12).

In the present study, the tissue modifications after two weeks from radiation were evaluated. This period was determined taking into account that rat's tissue metabolism is faster when compared with humans. Despite the anatomical differences between human and rodents prostate, there are many similarities that allow the use of the latter as an experimental model, especially in regard to the acinar epithelium (13). Also, the choice of the ventral lobe to be analyzed comes from the statement that this tissue is the most similar to the human prostate (14, 15).

One of the consequences of the radiation--matter interaction on cell's structures is the production of reactive oxygen species and oxidative damage (16). The immediate radiation effects can be easily observed in tissues with great proliferative capability, such as the epithelium, leading to vascular injuries, hypoxia, and cell death (11).

Radiation promoted a significant change in the prostate acinar epithelium height, decreasing

Table-1 - Morphometric data of ventral prostate from control, radiated and radiated+L-glutamine supplementation rats.

	Control	Radiated	Radiated+Glutamine
Epithelial height (μm)	18.31±1.9	11.59±0.8[a]	13.14±1.4
Acinar area ($\mu m^2.10^3$)	78.3±5.2	78.6±2.8	64.1±3.6[a,b]
Collagen density (%)	8.14±0.6	7.00±0.5	9.13±0.8b

Values are presented as mean±SD; **a**: statistically different from Control group; **b**: statistically different from Radiated group.

it in approximately 36%, when compared to control animals. This modification corroborates with what was previously pointed out by Stone et al. (11).

Studies in rats showed that L-Glutamine aids in colonic wall healing after radiation (17, 18). However, there is a lack of information regarding L-glutamine in preserving and maintaining the integrity of the prostate after pelvic radiotherapy. The present study establishes through quantitative methods the effects of oral supplementation with L-glutamine for protecting the prostate from radiation.

A study concerning morphometric evaluation of ventral prostate cells of rats growth in primary cultures, determined that L-Glutamine supplemented cultures had a faster cellular growth (19). Actually, L-Glutamine acts on epithelial cells providing an adequate environment for its development. In the present study L-Glutamine was effective in restoring normal epithelium after pelvic radiation.

No significant change was observed on the total area of the acini after radiation. However, in the group supplemented with L--glutamine a 18% reduction in the size of acini was observed. This decrease could be explained by protein synthesis and muscle tissue development stimulated by L-glutamine (20). When muscle matrix density rises, the parenchyma reorganizes and, as a consequence, the acinar size reduces.

L-Glutamine supplementation is involved in extracellular matrix remodeling, influencing the rising collagen synthesis from fibroblasts, myofibroblasts and muscle cells. These cells, when activated act as collagen primary producers and others extracellular matrix components (6). The data presented show that L-Glutamine has a protective effect over prostate extracellular matrix, maintaining normal collagen levels.

One limitation of the present work is the short-term analysis after radiation treatment. It is possible that an analysis after longer period from pelvic radiation could show a more severe change than those observed in this work.

CONCLUSIONS

Pelvic radiation promotes structural modifications on ventral prostate of rats. These modifications can be reduced by oral supplementation with L-Glutamine.

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CONFLICT OF INTEREST

None declared.

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Can intraurethral stimulation inhibit micturition reflex in normal female rats?

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ABSTRACT

Objective: The study was designed to determine the effect of low frequency (2.5Hz) intraurethral electrical stimulation on bladder capacity and maximum voiding pressures.
Materials and Methods: The experiments were conducted in 15 virgin female Sprague--Dawley rats (220–250g). The animals were anesthetized by intraperitoneal injection of urethane (1.5g/kg). Animal care and experimental procedures were reviewed and approved by the Institutional Animal Care and Use Committee of Antwerp University (code: 2013-50). Unipolar square pulses of 0.06mA were used to stimulate urethra at frequency of 2.5Hz (0.2ms pulse width) in order to evaluate the ability of intraurethral stimulation to inhibit bladder contractions. Continuous stimulation and intermittent stimulation with 5sec ''on'' and 5sec ''off'' duty cycle were applied during repeated saline cystometrograms (CMGs). Maximum voiding pressures (MVP) and bladder capacity were investigated to determine the inhibitory effect on bladder contraction induced by intraurethral stimulation.
Results: The continuous stimulation and intermittent stimulation significantly ($p<0.05$) decreased MVP and increased bladder capacity. There was no significant difference in MVP and bladder capacity between continuous and intermittent stimulation group.
Conclusions: The present results suggest that 2.5Hz continuous and intermittent intraurethral stimulation can inhibit micturition reflex, decrease MVP and increase bladder capacity. There was no significant difference in MVP and bladder capacity between continuous and intermittent stimulation group.

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INTRODUCTION

Neurogenic bladder (NB) dysfunction results from spinal cord injury (SCI), and is associated with neurogenic detrusor overactivity and detrusor sphincter dyssynergia. Complications secondary to urinary dysfunction, e.g. frequent urinary tract infections, vesicoureteral reflux, can lead to upper urinary tract damage, and ultimately to renal failure (1). Currently, clean intermittent catheterization with concomitant anticholinergic medication is the most common therapy of bladder management for most individuals with SCI (2). However, anticholinergic side effects include dry mouth, constipation, blurred vision and drowsiness. Anticholinergic medication also has a possibility to cross the blood–brain barrier and impair cognitive function (3).

It is known that electrical stimulation of the pudendal nerve is an alternative approach to restore urinary function. Electrical stimulation of the pudendal nerve at 3-15Hz (4, 5) results in a robust inhibition of detrusor activity in persons with SCI. While high frequency stimulation (20-50Hz) (6) facilitates reflex bladder contractions. It is also known that activation of afferents in the sensory pudendal nerve can reflexively induce efferent firing in the pudendal nerve to elicit sphincter muscle contractions that in turn can induce pudendal afferent firing via a motor–sensory coupling (7).

Therefore, it seems logical to hypothesize that intraurethral stimulation, by electrical stimulation of the pudendal nerve, will inhibit the micturition reflex by activation of the pudendal afferent and efferent pathways. Therefore, two metal rings can be arranged on the catheter which is used thrice or more in one day to treat NB. However, to our knowledge this electrically evoked urethrovesical inhibitory reflex mechanism has never been examined in female rat. The experiments revealed an urethrovesical reflex that inhibits bladder contractions and increases bladder capacity. In the present study, we determined the effect of low frequency intraurethral electrical stimulation on bladder capacity and maximum voiding pressures. The outcome of intermittent and continuous stimulation was compared. This reflex could be evoked by devices used for neuromodulation to benefit a large population of patients suffering from NB or overactive bladder.

MATERIALS AND METHODS

The experiments were conducted in 15 virgin female Sprague-Dawley rats (220-250g). The animals were anesthetized by intraperitoneal injection of urethane (1.5g/kg). Animal care and experimental procedures were reviewed and approved by the Institutional Animal Care and Use Committee of Antwerp University (code: 2013-50). A ventral midline abdominal incision was made, and the bladder was catheterized via bladder dome with PE-50 polyethylene catheter (Clay-Adams, Parsippany, New Jersey). The catheter was connected by a three-way valve to both a pressure transducer (Emka technologies) connected to a NE-1000 syringe pump (New Era Pump Systems, Farmingdale, New York), and an exit port to empty bladder. A BD Insyte-WTM intravenous catheter (20 gauges) was inserted transurethrally. Two coated platinum wires were fully inserted into the catheter. The wires were hold in place securely and the catheter was pulled away from the urethra. The anode and the cathode were longer than the catheter 10mm and 8mm, respectively. The urethral meatus was tied around the wires (silk 3/0) to prevent leakage and firm the electrodes.

Based on a previous study (8) and our preliminary test, unipolar square pulses of 0.06mA were used to stimulate urethra at frequency of 2.5Hz (0.2ms pulse width) to value the ability of intraurethral stimulation to inhibit bladder contractions. Three control cystometrograms (CMGs) were performed during saline infusion without stimulation to obtain the control/baseline bladder capacity and evaluate reproducibility. Then continuous stimulation and intermittent stimulation with 5sec ''on'' and 5sec ''off'' duty cycle were applied during repeated saline CMGs, generated by an ISO-STIM 01DPI stimulator (Tamm, Germany). The continuous stimulation and intermittent stimulation started from filling to voiding contraction (greater than 25cm H_2O) finished.

Bladder activity was recorded by a pressure transducer-1290C, Hewlett-Packard GMBH, Boeblingen, Germany, an amplifier-monitor (Emka technologies) and WINDAQ® DI-710 data acquisition. The bladder was emptied after each CMG and a 5–10 min rest period was respected between CMGs to allow the bladder reflexes to recover. The rats were sacrificed by urethane overdose.

Statistical analysis was performed using SPSS software (version 16.0 for Windows, SPSS, Chicago, IL, USA). Maximum voiding pressures (MVP) and bladder capacity were investigated during CMGs with or without 2.5Hz stimulation to determine the inhibitory effect on bladder contraction induced by intraurethral stimulation. Repeated measurements in the same animal during the same experiment were averaged to avoid the large variation caused by individual animal differences. All reported values are means±SD. One-way Anova followed SNK-q was used to detect statistical significance. For all statistical tests, $P<0.05$ was considered significant.

RESULTS

Continuous stimulation and intermittent stimulation significantly ($p<0.05$) decreased MVP from 36.2±8.5cmH_2O to 30.0±5.6cmH_2O and 30.4±6.2cmH_2O, respectively (Figures 1 and 2a).

Bladder capacity was maximally increased to 116±8.5% of the control/baseline capacity (0.438±0.074mL) during continuous stimulation. Intermittent stimulation with 5sec ''on'' and 5sec ''off'' duty cycle significantly increased bladder capacity to 123±12% of the control/baseline capacity (Figures 1 and 2b).

There was no significant difference in MVP and bladder capacity between continuous and intermittent stimulation groups (Figure-2).

DISCUSSION

In the supra-SCI patients, control function in the cerebrum and the pons is blocked. Loss of supraspinal control leads to involuntary, reflexive bladder contractions and impaired coordination of the detrusor and sphincter system which can result in elevated bladder pressure during micturition and lead to structural damage of the bladder,

Figure 1 - The continuous stimulation and intermittent stimulation (5sec on/5sec off) decreased maximum voiding pressure. Bladder capacity was increased by continuous stimulation and intermittent stimulation (5sec on/5sec off). The black bars under the traces indicate the stimulation duration. Infusion rate: 0.09mL/min.

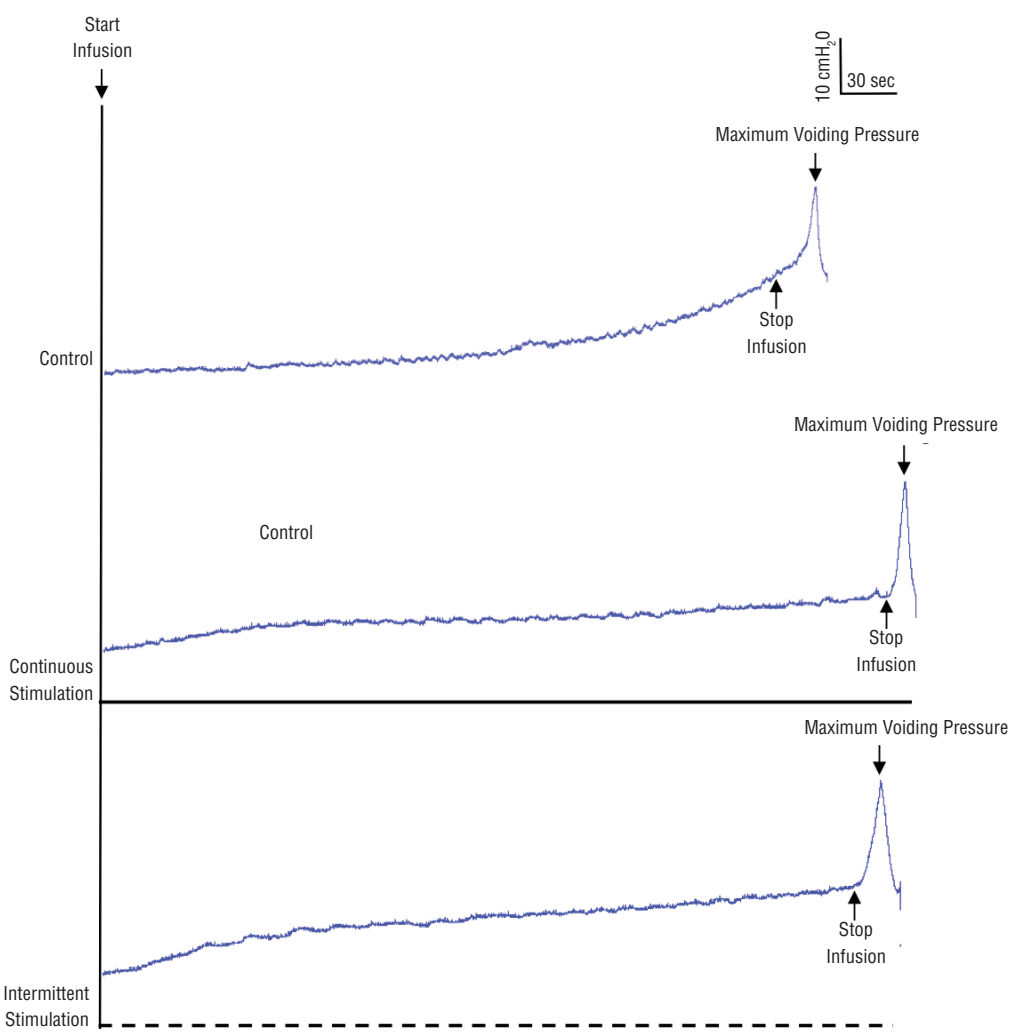
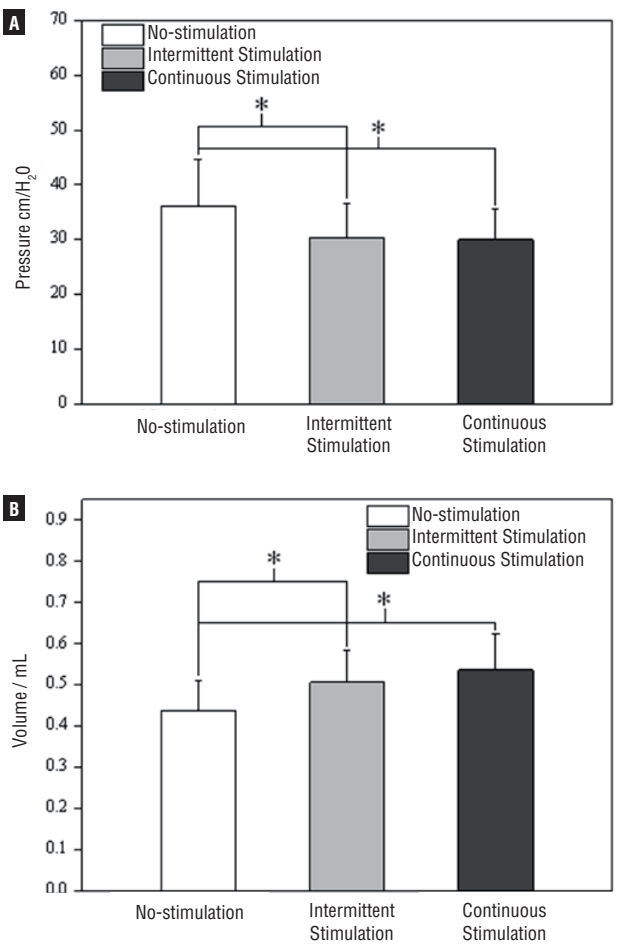


Figure 2 - MVP (a) was significantly decreased (p<0.05) in continuous and intermittent stimulation (5sec on/5sec off) in 15 female rats when compared with no-stimulation group. Bladder capacity (b) was significantly increased by continuous stimulation and intermittent stimulation. There was no significant difference in MVP and bladder capacity between continuous stimulation group and intermittent stimulation group (a, b).



*Significantly (p<0.05) different from control.

vesicoureteral reflux, and renal insufficiency. Treatment for neurogenic bladder in SCI patients should fulfill three main objectives: low-pressure urine storage, low-pressure voiding, and adequate urine drainage. Clean intermittent catheterization with concomitant anticholinergic medication is currently the most common therapy of bladder management for most individuals with SCI (2). However, these drugs have dose-limiting side effects and may be insufficiently effective to restore continence in patients with severe hyperreflexia. When medical treatment is not satisfactory, surgical operations can be tried to increase the bladder capacity and compliance. The side-effects of medications and surgical complications have prompted us to seek new treatment modalities.

A relatively new alternative treatment is to activate the pudendal nerve after SCI, which can improve urine storage (9). Intraurethral stimulation not only activates the pudendal nerve, but also has advantages with its local effect and minimal invasion, which eliminates the systemic side effects caused by medication.

The afferent innervation of the lower urinary tract is carried in three sets of nerves: the pelvic and hypogastric nerves, which innervate the urinary bladder and proximal urethra, and the pudendal nerves, which innervate the mid-distal urethra and the external urethral sphincter (EUS) (10). The urethral length measured from the ureteral orifice to urethral meatus was 13.0 to 15.8mm in virgin female Sprague-Dawley rats (170-200g). The most proximal part of the striated muscle area was located 5.0 to 8.1mm from the ureteral orifice (11). The distance from the anode to the urethral meatus was 10mm in our experiments, meaning that the electrodes are positioned in the striated muscle area. The urethra was also dissected to confirm the position of electrodes in 3 rats in a preliminary test. So, the pudendal nerve could be directly modulated by intraurethral stimulation.

Previous studies proposed three possible mechanisms for the decrease of MVP and the increase of capacity evoked by intraurethral stimulation. The first proposal suggests that electrical stimulation of these somatic afferent fibers influence continence reflex pathways in the central nervous system (12). Secondly, low-frequency pudendal--afferent stimulation can evoke a robust reflex activation of hypogastric efferents (13). Therefore, low-frequency intraurethral stimulation suppresses bladder contractions that may arise from the activation of hypogastric efferent neurons, and subsequent synaptic and ganglionic inhibition of the parasympathetic-efferent neurons. Previous studies in the rat showed that pudendal sensory branch transection reduced bladder MVP (14), so the third possible mechanism can be the modula-

tion of urethral afferent activity, which augments maximum bladder pressure and voiding efficiency.

This study provided pre-clinical evidence for designing a stimulator to stimulate the urethra intermittently instead of continuously while still achieving an inhibitory effect on bladder activity. Intermittent stimulation can reduce battery power consumption. In this study, at 5sec ''on'' and 5sec ''off'' ratio the inhibitory effect was also significantly ($P<0.05$) reduced when compared to the continuous stimulation. Thus, there is a trade-off between reducing the ''on/off'' ratio and maintaining the inhibitory effect.

The control experiments performed after short-time electrical stimulation reached baseline activity measured before electrical stimulation. This suggests the stimulation time can be extended to evaluate if it has a long-lasting post-stimulation inhibition function. In addition, the possible effects on delaying the progress of bladder fibrosis should be explored in SCI rat in our next study. Previous researches have demonstrated that somatic nerves stimulation increase bladder capacity in neurogenic bladder in animals and patients (14, 15), however, it was not clear if somatic nerves stimulation can decrease MVP.

Although clinical trials showed that the optimal stimulus parameters for neuromodulation therapy in human subjects are probably different from what was obtained in this animal study, the testing protocol and the results of this pre-clinical study will still provide very useful information for the design of a clinical trial that will use an intermittent stimulation strategy. Two Teflon wrapped metal rings can be arranged on the catheter which is used to drain urine from bladder every day in SCI patients to decrease bladder pressure or delay progress of bladder fibrosis (will be evaluated in next step). NB can be treated when intermittent catheterization is performed. Improving neuromodulation technology will benefit a large population of patients suffering from NB.

The present results suggest that 2.5Hz continues and intermittent intraurethral stimulation can inhibit micturition reflex, decrease MVP and increase bladder capacity. There was no significant difference in MVP and bladder capacity between continuous and intermittent stimulation group.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Nitric oxide and asymmetric dimethyl arginine (ADMA) levels in an experimental hydronephrotic kidney caused by unilateral partial ureteral obstruction

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ABSTRACT

Aim: Our aim is to measure asymmetric dimethyl arginine and nitric oxide levels in rats with induced unilateral acute ureteral obstruction to research the effects on the kidney.

Material and Methods: The study included 21 adolescent (average age 6 weeks) Sprague-Dawley male rats weighing between 240-290g divided at random into 3 groups. Group-1: Control group (n=6): underwent no procedures. Group-2: Sham group (n=6): underwent the same procedures as the experimental group without ureter and psoas muscle dissection. Group-3: Group with induced partial unilateral ureteral obstruction (n=9). All rats were sacrificed after 12 weeks. Superoxide dismutase enzyme activity and nitrite and nitrate salt levels were measured in renal tissue. Plasma nitrite-nitrate and ADMA levels were examined.

Results: In the experimental group histopathological changes observed included renal pelvis dilatation, flattened papillae, sclerotic glomerulus and fibrosis. In the experimental group tissue SOD and blood ADMA levels were higher than the control and sham groups ($p<0.05$) while tissue NO and plasma NO values were lower than in the sham and control groups ($p<0.05$).

Conclusion: Oxidative stress and disruption of NO synthesis play an important role in renal function and histopathological changes after obstructive renal disease. To prevent renal complications developing after obstructive nephropathy we believe that a new strategy may be research on reducing ADMA.

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Keywords:
Ureteral Obstruction; Nitric Oxide; Rats; Superoxide Dismutase

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INTRODUCTION

Ureteral obstructions are frequently observed in urology practice and without early diagnosis and treatment it may cause some serious complications (1-4). Many experimental studies have shown that retrograde glomerular reflux developing due to ureteral obstruction disrupts NO synthesis and in parallel affects renal function (5-8). However, how and by which mechanism NO synthesis is disrupted is still not fully known.

Asymmetric dimethyl arginine (ADMA) is a nitric oxide synthesis (NOS) inhibitor (9). The function of NOS in the body is provided by NO synthesis from L-arginine. In this reaction, occurring in the vascular endothelium, ADMA inhibits NOS activity by preventing L-arginine uptake into cells. In other words ADMA regulates the rate of

NO formation (9). Impaired endothelium vasodilation, increased aggregation of platelets and increased monocyte adhesion provide endothelial dysfunction that increase ADMA (10). During ureteral obstruction, inflammatory mediators in renal parenchyma have been shown to increase due to retrograde glomerular reflux. This situation increases ADMA synthesis causing NO synthesis disruption, which causes an effect on renal function. In one study, 221 chronic renal failure patient's serum ADMA levels were shown to be increased (11).

The aim of the study was to induce unilateral acute ureteral obstruction in rat models to measure ADMA and NO levels to research the effect on the kidney.

MATERIAL AND METHODS

Experimental Animals and Study Groups

This study began after permission was granted by Canakkale Onsekiz Mart University Animal Experiments Ethics Committee. The study used 21 adolescent (average 6 weeks) Sprague-Dawley male rats weighing from 240-290g. The animals were kept in standard laboratory conditions with stable temperature (18-21°C) and humidity, 12 hours of light and 12 hours of darkness, with 3-4 rats in each cage fed with rat food and tap water.

The rats were randomly divided into 3 groups. Group-1: Control group (n=6): underwent no procedures. Group-2: Sham group (n=6): underwent the same procedures as the experimental group (the ureter and psoas muscle were palpated and left on their own anatomical position). Group-3: Experimental group: induced partial unilateral ureteral obstruction (PUUO) (n=9).

Surgical Procedure

Rats used for partial unilateral ureteral obstruction (PUUO) and rats undergoing the sham operation were starved for 6 hours before the operation and only allowed water. The rats, in accordance with antiseptic rules, were operated on under laboratory conditions maintaining body temperature. All rats were anesthetized with intramuscular 50mg/kg ketamine hydrochloride (Ketalar, Eczacibasi) and then a 2cm area was shaved on bilateral abdominal wall and 10% Povidone iodine was used to clean the field.

Partial unilateral ureteral obstruction (PUUO) model: A 2cm incision was performed at the anterior abdomen region. Skin above the linea alba, subdermis, abdominal anterior wall and peritoneum was incised to reach abdominal cavity and the left kidney was located. Fat and connective tissues were dissected to reveal the left ureter and psoas muscle. For PUUO rats, similar to the technique of Ulm and Miller (12), the psoas muscle under the left ureter was longitudinally dissected to form a groove (~15mm) and a small part of the left ureter was placed into the groove. Later the edges of the psoas muscle were fixed above the ureter with 5/0 silk suture. Thus the ureter was enclosed in a tunnel (Figure-1). In the sham model rats after the left ureter and psoas muscle were located, the procedure was completed without ureter and psoas muscle dissection. Later 3/0 catgut and 3/0 silk suture were used to close the abdomen in 2 layers. All rats were sacrificed after 12 weeks.

Biochemical Tests

The kidney was dissected and excised and then stored at-80°C. To test for biochemical changes, the levels of superoxide dismutase (SOD) enzyme activity and nitrite and nitrate salts which are end--products of NO were measured. To investigate the nitrite-nitrate and ADMA levels in plasma, 5cc blood samples from the ventricle of rats were centrifuged for 10 minutes at 3000rpm and the separated samples were stored at-40°C until analysis.

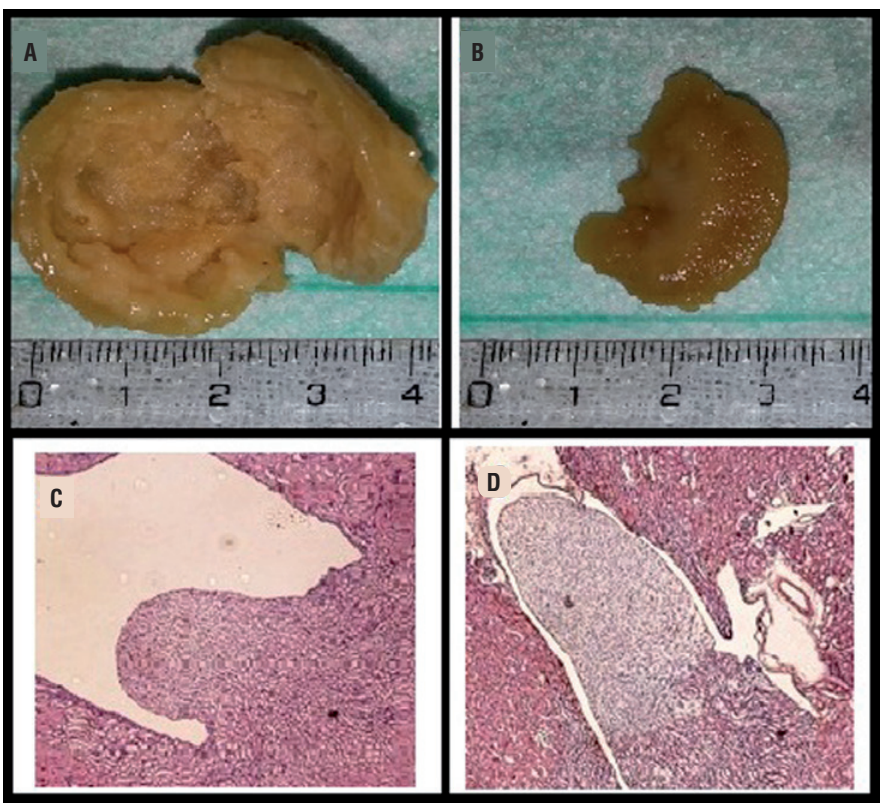
Tissue Homogenization

After tissue samples were weighed, for assay of total nitrite/nitrate and SOD samples, they were homogenized in 0.9% NaCl and 10% homogenates were prepared. For assay of total nitrite/nitrate and SOD, the prepared homogenates were centrifuged for 15 minutes at 15000rpm. Both assays were completed using samples of the supernatant liquid.

Nitrite/nitrate

For measurement a "nitric oxide colorimetric assay" kit (Boehringer Mannheim) was used to evaluate at 540nm.

Figure 1 - a) Macroscopic view of kidney tissue of experimental group; b) Macroscopic view of kidney tissue of control group; c) Hematoxilin and eosin (H&E) stained histopathological images of kidney tissue of experimental group; renal pelvis dilatation and flattening; d) Hematoxilin and eosin stained histopathological images of kidney tissue of control group; there was no pathological findings on renal papilla, cortex and medulla.



Tissue SOD Activity Assay

Tissue SOD activity was measured at 560nm by modifying the method determined by Sun et al. (13).

ADMA

ADMA levels in serum were measured by using a kit from BioVendor Research and Diagnostic Products (Cat. No: REA 201/96) manufactured by DLD Diagnostica GMBH (Germany). Results were determined by the ELISA method and reported as nanogram per millilitre (ng/mL).

Histopathological Investigation

After tissue samples were cleaned with saline they were immediately fixed in 10% formaldehyde solution at room temperature for 72 hours and prepared for routine light microscope examination. The tissue samples were dehydrated with alcohol and cleaned with xylene before being immersed in paraffin.

Five-micrometer slices of the tissues were made. The tissues were stained with hematoxyline-eosine (H&E) and periodic acid-Schiff (PAS) and the sections were examined and photographed with a light microscope.

Statistical Evaluation

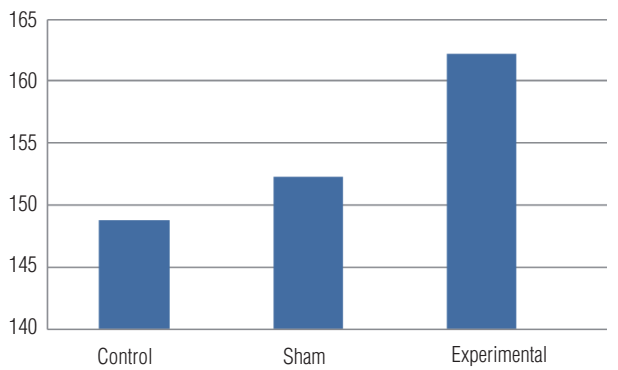
The Statistical Package for the Social Sciences 20.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. All values were given as mean±standard deviation. Kruskal-Wallis test was used for variance analyses. Mann-Whitney U test was used for dual comparisons between groups. Statistical significance was accepted as $p<0.05$.

RESULTS

While there was no pathological changes in the kidney sections from the control group and sham group, in the experimental group induced PUUO, on histopathological examination of the H&E dyed kidney fibrosis, inflammation, flattening of the renal papillae and dilatation of the renal pelvis were observed with varying degrees On kidney sections stained with PAS sclerotic glomerular changes, inflammation and fibrotic changes were observed (Figure-1).

Linked to increased oxidative stress the tissue SOD values, the enzyme with primary antioxidant properties, are summarized in Table-1.

Figure 2 - SOD values measured in tissue samples of the groups (µmoL/g tissue).



(p=0.004)

Table-1 - Biochemical results of the three groups.

	Control		Sham		Experimental		
	median	ss(±)	median	ss(±)	median	ss(±)	p
Tissue nitrate	0.45	0.04	0.33	0.06	0.28	0.02	0.0003
Plasma nitrate	31.72	2.36	21.28	3.16	16.86	0.57	0.0003
SOD	148.82	3.5	152.28	3.9	162.27	4.5	0.001
ADMA	0.82	0.14	0.92	0.82	2.7	0.59	0.001

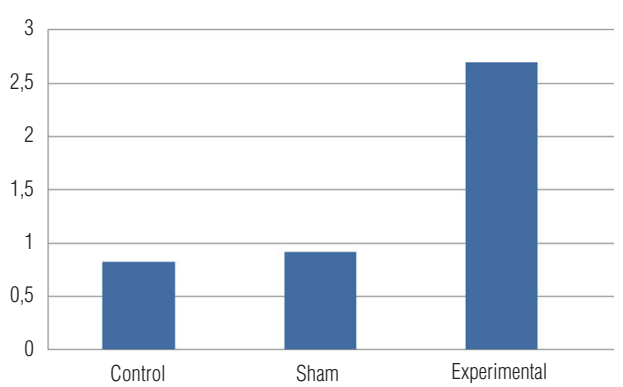
In the experimental group with induced PUUO, tissue levels of SOD were higher than in the sham and control groups (p=0.001) (Figure-2). Comparing the groups, there were differences between the experimental and control groups (p=0.001) and between the experimental and sham groups (p=0.003) (Table-1).

There was a clear increase in ADMA values measured in blood in the experimental group compared to the control and sham groups (p=0.001) (Figure-3). In the sham group there were higher levels of ADMA than in the control group (Table-1).

Nitrite/nitrate levels, end products of NO, were identified in both renal tissue and in plasma. The nitrite/nitrate values in tissue were lower in the PUUO induced experimental group compared to the sham and control groups (p=0.0003) (Figure-4) (Table-1).

Assay results of plasma nitrite/nitrate levels are shown in Figure-5. These results show

Figure 3 - ADMA values measured in blood samples of the groups (ng/mL).



(p=0.004)

the lowest plasma levels were found in the experimental group, followed by the sham group and the highest levels were in the control group. There was a significant difference between the groups (p=0.0003) (Table-1).

Figure 4 - Nitrite/nitrate levels measured in tissue samples of the groups (µmoL/g tissue).

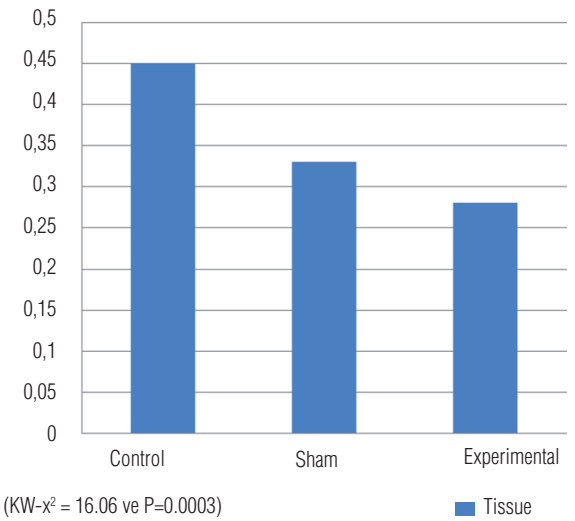
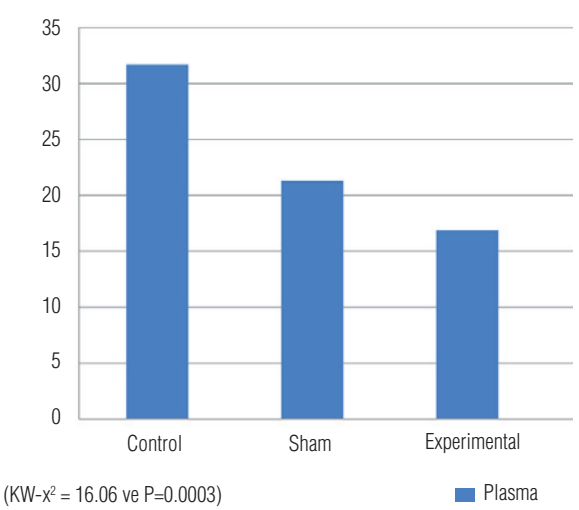


Figure 5 - Nitrite/nitrate levels measured in blood samples of the groups (µmol/L).



DISCUSSION

Different etiologic factors such as urinary tract stones, ureteropelvic junction or ureterovesical junction stenosis, tumors and iatrogenic factors lead to upper uriner tract obstruction that can cause organ failure in urology practice. Treatment planning is depend on duration, degree and level of obstruction. Upper urinary tract patologies have a broad treatment spectrum. The primary aim of treatment is to protect or recover the functional reserve of kidneys by relieving the obstruction. In case of prolonged obstruction, functional reserve of kidney can decrease so much that nephrectomy is required to prevent morbidities of dysfunctional kidney.

Fibrosis, collagen and extracellular matrix components accumulation are the most leading interstitial changes in upper urinary tract obsruction. Besides cellular composition changes of interstitium, many biologically active molecules changes occur with interstitial fibrosis. It is considered that obliteration of tubules and interstitial capillaries due to interstitial fibrosis are the major determinants of renal function failure in kidney disease. Claesson et al. (14) induced left chronic partial ureteral obstruction in newborn rats. After two weeks they began to observe histopathological changes from ureteral obstruction and they reported that primarily papilla deformation occurred. In our study the rats with induced PUUO were sacrificed after 12 weeks. In the hydronephrotic kidney, histopathological changes observed included renal pelvis dilatation, flattened papillae, sclerotic glomerulus and fibrosis.

In upper urinary tract obstructions, increased ureteral pressure is the first stage of damage that leads to renal blood flow reduction resulting in tissue ischemia, cellular atrophy and eventually necrosis. TNF-α is a potent proinflammatory cytokine that is capable of stimulating renal tubular cell apoptosis and infiltration of inflammatory cells during ischemic renal injury. After the development of obstructive nephropathy, it is reported that there is a role of factors such as prostaglandins (PG), angiotensin (ANG) II, growth factors and NO in the accumulation of free oxygen radicals and leukocyte infiltration (15). ROS may release vasoconstrictor bioactive lipids such as prostaglandin, thromboxane and platelet activating factors and inactivate NO inducing a reduction in glomerular blood flow and glomerular infiltration rate (16, 17). Ricardo et al. (18) after inducing a unilateral ureteral obstruction model in rats reported that ROS and overproduction of tubular irregular antioxidant enzymes cause increased intrarenal oxidative stress, leading to fibrogenesis, over expression of fibrogenic cytokines and loss of tubular shape. Kinter et al. (19) in a UUO model found

high levels of antioxidant enzymes (catalase, SOD, glutathione peroxidase) which can protect against the harmful effects of ROS. After UUO, ROS production was greater than the protective capacity of the antioxidant enzymes increasing renal damage with tubular atrophy and interstitial fibrosis observed. In our study a marker of oxidative stress (SOD level in tissue) was higher in the experimental group compared to the sham and control groups (p=0.001 and p=0.003). It was shown our study that upper urinary tract obstruction led to oxidative stress with disturbance of NO synthesis, creating fibrosis which could lead to renal damage.

Asymmetric dimethylarginine (ADMA) is an amino acid, like arginine, found in plasma, urine and tissue. In 1992, Vallance et al. (4) identified ADMA in human plasma and urine endothelial tissue as endogenous inhibitors of endothelial nitric oxide synthase (eNOS). It was the first time that the importance of ADMA as endogenous inhibitör of NOS in patient with end stage renal failure was cited by Vallance et al. (1). In these patients, increased plasma ADMA levels were reduced by dialysis with improvement of endothelial function. Later studies showed many times the relationship between increased ADMA levels and endothelial vasodilator dysfunction. In the endothelium NO is produced from L-arginine via the endothelial isoform (eNOS) of nitric oxide synthase. In humans NO synthesis may be disrupted by asymmetric dimethylarginine (ADMA), removing the endogenically-formed compound L-arginine from substrate linking points inhibiting NOS activity. An infusion of ADMA disrupts vasodilation in the endothelium. Increased ADMA levels in plasma are not only linked to endothelial dysfunction, but also related to increased oxidative stress (20). Boger et al. (21) found that oxidative stress damaged the cystein aminoacid in the active region of the DDAH enzyme responsible for ADMA catabolism reducing enzyme activity and thus reducing the ADMA disintegration. As a result of increasing oxidative stress in many degenerative diseases, ADMA levels were found to be high. In ureter obstruction, free oxygen radicals increase, as shown by many studies mentioned above (18, 19, 22). In our study, the findings are in accordance with these studies. Plasma ADMA levels in the experimental group were higher than in the sham and control groups (p=0.001 and p=0.001, respectively). ADMA inhibits NOS activity causing a reduction in NO levels, and as a result, disruption of endothelial function. Lin et al. (10) showed increased ADMA concentration in endothelial dysfunction was related to increased ROS production in plasma. In addition Takiuchi et al. (23) showed that endothelial dysfunction in coronary and peripheral vein diseases was linked to increased ADMA levels in plasma. The findings of our study are consistent with all these studies. When compared the experimental group to control and sham groups, we found increased both ADMA and SOD levels ($p<0.05$).

Nitric oxide is used in mitochondrial respiration, membrane transport and cellular energy stages, with a role in glomerular hemodynamic regulation, tubular transport and tubule-glomerular reabsorption and as a result is reported to play an important role in kidney physiology and pathology (24). Cherla and Jaimes (25) showed that when given the NO percursor, arginine, the synthesized NO had a protective effect against kidney damage. The reduction in the amount of NO in the kidney was an important effect on the progression of renal damage, and they reported that NOS inhibition led to hypertension and sodium retention (24). Many studies have examined the role of NO in the hemodynamic response to UUO. Lanzone et al. (6) found L-NMMA administration before UUO reduced the first increase in renal blood flow. When L-NMMA infusion was discontinued the renal blood flow increase resolved within 10 minutes. These findings prove the role of NO in pre-glomerular vascular resistance reduction after ureteral occlusion. Another study on NO created by eNOS in the kidney found that it played a basic role in protecting against renal fibrosis developing as a response to UUO (7). The reduction in biological effectiveness of NO increases oxidative stress (8). In our study the products of NO, nitrite and nitrate, were examined in tissue and plasma. The nitrite/nitrate levels in tissue and plasma were lower in the experimental group compared to the control and sham groups (p=0.0003 and p=0.0003). This situation is an indirect indicator of decreased NO levels in upper urinary tract obstruction model. According to our findings, reduction of NO depended on both increase in ADMA levels and oxidative stress.

CONCLUSIONS

Oxidative stress and disruption of NO synthesis play an important role in renal function and histopathological changes after obstructive uropathy. ADMA is an endogenous inhibitor of NOS. Increased ADMA levels show the inhibitor effect on NOS, causing a fall in NO levels in the kidney. We believe that methods to reduce ADMA may be a new strategy to prevent renal complications that develop after obstructive nephropathy.

CONFLICT OF INTEREST

None declared.

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RADIOLOGY PAGE

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Obstructive uropathy secondary to bilateral ureteroinguinoscrotal herniation

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CASE PRESENTATION

A 55 year old man presented with acute renal failure. He was grossly overweight with a BMI of 48 and had a past history of sleep apnoea, chronic lymphoedema and left ventricular dysfunction. Physical examination revealed a pendulous abdomen which extended to his knees and bilateral, irreducible inguinoscrotal hernias. Blood samples on admission revealed a serum creatinine of 187umol/l and an eGFR of 33ml/min. CT urogram demonstrated bilateral hydronephroureter to the level of the vesico-ureteric junction. The ureters were found to be tortuous and appeared to extend below the bladder before looping back up into the bladder. The absence of contrast within the ureters made the position of the lower ureter difficult to determine. Subsequent MAG-3 renogram showed a split function of 39/61% with a right sided preponderance. Both kidneys were slow to peak and showed negligible drainage. Intraoperative retrograde pyelograghy showed the ureters to be grossly elongated, looping down bilaterally through the hernial sacs within the scrotum before returning up to the kidneys (Figure-1). Conventional double pig tail ureteric stents were found to be not long enough to span the distance between the bladder and renal pelvis and 75cm-long ileal conduit stents were used successfully (Figure 2 and 3).

Figure 1 - Retrograde pyelograph showing the lower ends of both ureters looping below the pubic arch before ascending towards the kidneys.

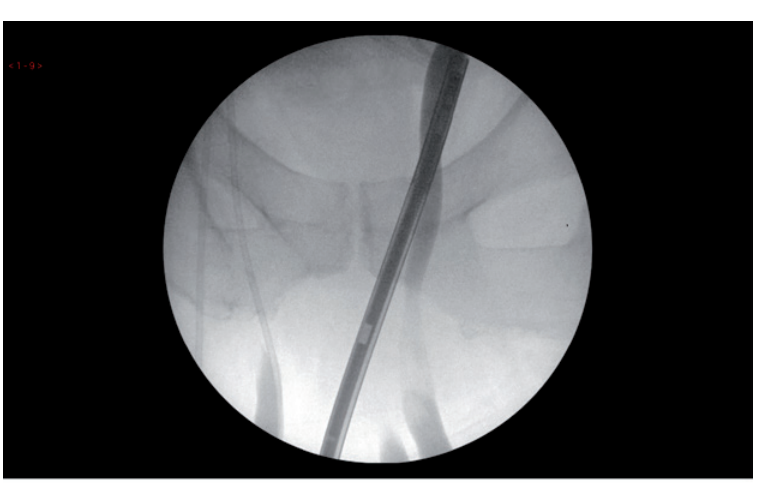


Figure 2 - CT-KUB scout film. The stents outline the unusual anatomical passage of both ureters. The upper coil of the stents shows the renal pelvises have been pulled down to L4/L5vertebral level.

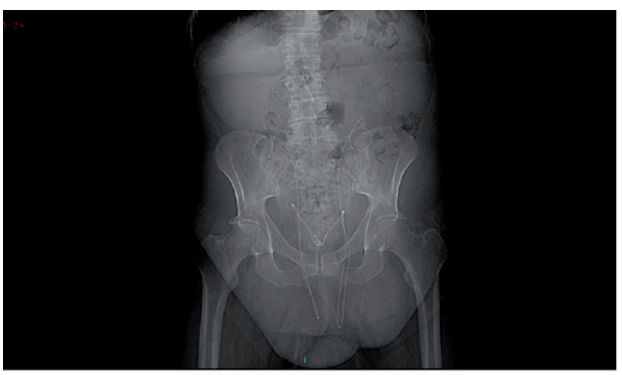
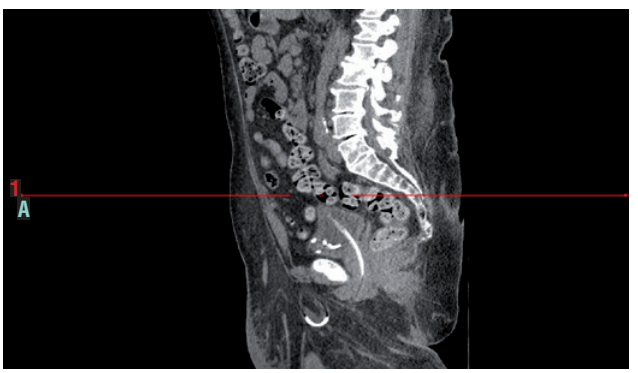


Figure 3 - In this sagittal section of the CT-KUB, the left ureter, as outlined by the stent, can be seen passing through the neck of the hernia sac.



DISCUSSION

Sliding inguinal hernias which contain the ureter have been reported in the literature (1, 2). Case reports also exist of associated ureteric obstruction and with resultant ureterohydronephrosis (3-5). Definitive management involves repair of the hernia with care taken to preserve the ureters. These patients are usually morbidly obese (6) and are likely to have co-morbidities that make surgery a high risk (3-5).

CONFLICT OF INTEREST

None declared.

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Robotic pyelolithotomy for staghorn nephrolithiasis during partial nephrectomy

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INTRODUCTION

Although the incidences of kidney cancer and urolithiasis are increasing (1, 2) the discovery of both pathologies in the same patient is uncommon. This video demonstrates the simultaneous management of a staghorn calculus and an ipsilateral renal mass using the robotic platform.

CASE

A 68-year-old woman was diagnosed with a 3.9cm left partial staghorn calculus and a 3.0x2.7cm left upper pole renal mass after an acute left flank pain episode. The patient had a history of hypertension, hyperlipidemia, coronary artery disease, asthma, hypothyroidism and obesity (BMI 39Kg/m^2).

Intraoperatively after colon mobilization and hilum dissection, the Gerota's fascia was incised and the entire surface of the kidney was exposed. The ureter was carefully dissected up to the renal pelvis. Intraoperative ultrasound identified the stone location and delineated the tumor borders. A posterior pyelotomy was performed using cold scissors and the stone removed in its entirety. A double J stent was inserted in an anterograde manner followed by the pyelotomy closure. The partial nephrectomy was then performed using our standard technique (3).

RESULTS

The operative time was 240 minutes and the estimated blood loss was 150ml. There were no intra or postoperative complications. Final histopathology showed a T1a renal cell carcinoma, clear cell papillary type with a negative surgical margin. The double J stent was removed after 4 weeks and the patient remains asymptomatic at 3 months postoperatively.

CONCLUSIONS

Simultaneous robotic pyelolithotomy and partial nephrectomy is a safe and feasible treatment for this uncommon presentation.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

Simultaneous robot-assisted laparoscopic pyelolithotomy and partial nephrectomy is a reasonable approach for patients suffering from renal stones that are diagnosed with renal cancer (1). In this video, the authors presented a successful procedure for stone and tumor removal through the same surgical access (2-3). This minimally invasive surgery combines the advantages of a laparoscopic pyelolithotomy over a percutaneous nephrolithotomy (lower incidence of bleeding and higher stone-free rate) with the benefits of a robotic procedure for the treatment of a renal cancer (lower warm ischemia time). This surgical approach should be considered as an alternative when treating patients with this uncommon presentation.

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EDITORIAL COMMENT

Management of a kidney containing both an enhancing renal mass and a partial staghorn calculus presents several dilemmas. As an alternative to radical nephrectomy, most urologists would likely perform staged procedures typically involving percutaneous nephrolithotomy and partial nephrectomy. While robotic assisted partial nephrectomy is well accepted for management of the renal mass, robotic lithotomy is infrequently performed for the removal of large stones (1-3). This video by Andrade et al from the Cleveland Clinic nicely demonstrates a robotic pyelolithotomy for a large stone at the time of robotic partial nephrectomy. Though this may be an uncommon situation, the video clearly shows the feasibility and safety of this combined procedure, at least in expert hands. This case avoided multiple surgeries and allowed for complete stone removal and tumor resection while maintaining renal function.

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VIDEO SECTION

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Transmesenteric robot-assisted pyeloplasty for ureteropelvic junction obstruction in horseshoe kidney

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INTRODUCTION

Transmesenteric laparoscopic pyeloplasty has previously been reported in two pediatric patients. To our knowledge, there has yet to be a report of a robotic-assisted transmesenteric pyeloplasty. We sought to present a video display and step-by-step demonstration of this approach.

CASE

The patient is a 28-year old female with an obstructed ureteropelvic junction (UPJ) of the left moiety of a horseshoe kidney. The Da Vinci S robotic platform was used. After transperitoneal access was obtained, a window in the mesentery was identified, and the renal pelvis was exposed. A dismembered, spatulated pyeloplasty was performed with transposition of the UPJ to a more dependent portion of the renal pelvis. A ureteral stent and closed surgical drain were placed.

RESULTS

The case was completed without complications. Operative time was 207 minutes. Foley catheter and drain were removed on postoperative days 1 and 2, respectively. The patient was discharged home on postoperative day 2, and the ureteral stent was removed after 8 weeks. Her diuretic T1/2 improved from 39 to 16 minutes. The differential function of the left moiety improved from 31% to 42%.

CONCLUSIONS

Robot-assisted transmesenteric pyeloplasty is safe and feasible for the management of UPJ obstruction in select patients with a horseshoe kidney. Future study of its use in a larger number of patients is necessary to define its role in this unique population.

CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

This is a well-done video that adds to the literature in the fledgling field of minimally-invasive reconstructive urology. This video should encourage urologists to counsel their patients that this procedure can be performed safely using minimally-invasive techniques with good outcomes. The difficulty with laparoscopic and/or robotic approaches to upper ureteric strictures is when direct visualization shows that the fibrosis extends beyond what was thought preoperatively. In this situation, the surgeon is faced with the choice of trying to reposition the patient for minimally-invasive psoas hitch/Boari flap, opening, or trying to obtain more length of ureter or bridge a gap that may cause undue tension. While the outcome here is excellent, proper patient selection is key.

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LETTER TO THE EDITOR

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RE: A Novel method of ensuring safe and accurate dilatation during percutaneous nephrolithotomy

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Int Braz J Urol. 2015;41:1014-9.

To the editor,

We have read the technique titled "A novel method of ensuring safe and accurate dilatation during percutaneous nephrolithotomy" by Javali et al (1) with great interest. We compliment the authors on this novel technique of placing guide wire in difficult situation.

We would like to draw the attention of the authors to a few points and make a few comments.

A well-placed guide wire is a corner stone to the success of percutaneous access. Failure of guide-wire access may result in potential complications such as loss of tract, bleeding due to parenchymal injury that might lead to abandonment of procedure (2). Although wire down the ureter in every case would be ideal, but it is not necessary to be very rigid about that. We feel adequate and secure length of the wire in the pelvi-calyceal system is all that is needed for a satisfactory and safe tract making.

The common causes of guide-wire not going up the renal pelvis or down the ureter (3) are:

- Large calculus occupying and/or blocking the calyx or infundibulum,
- Puncture of the anterior calyx instead of the posterior calyx.

If a large obstructing calculus is the cause of wire not progressing, there may be a need to fragment the calculus to create space for the wire to proceed. The authors have not mentioned any incidence of need for fragmentation in this large series.

The lower pole calyces usually have a complex arrangement. The typical anterior and posterior arrangement of calyces is seen only in 58% of cases in the lower pole (3). Eisner et al have found that in 31% of cases, the arrangement of calyces in the lower pole is such that no calyx is truly posterior. In such kidneys both the calices in the lower pole are anterior with one of the calyx being less anterior as compared to the other (4). If the anterior calyx is punctured then the glide wire would have difficulty in entering the pelvis (2). In this situation, gaining access to renal pelvis and upper ureter using an ureteroscope would torque the lower pole. This can be traumatic.

In a lower calyx tract (51 out of 85) it would be very difficult even under ureteroscopic vision to make the wire go down the ureter. The angle between the lower calyx infundibulum and the upper ureter would make entry of the wire across pelvi-ureteric junction difficult (5). In this situation placing the wire in upper calyx would be far easier.

The authors have passed a 6-7.5 Fr semi-rigid ureteroscope between two terumo guide-wires and have managed to keep the two guide-wires always in vision. This would be very difficult in patients with prior history of renal surgery (12 in this series). Posterior strong muscular support with

retractile property of muscles would increase this difficult. There is a chance of perforation of the calyceal system especially with semi-rigid ureteroscope. There are reports of use of flexible ureteroscopes (6, 7) for antegrade ureteroscopic assistance in percutaneous nephrolithotomy to prevent these potential damages.

This technique needs use of three guide-wires in addition to the use of the ureteroscope. There is a potential for damage to the optics of the telescope especially in patients with large stone burden with impacted calculi. All these aspects would increase the cost of the procedure. Is this escalated cost really necessary and justified?

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