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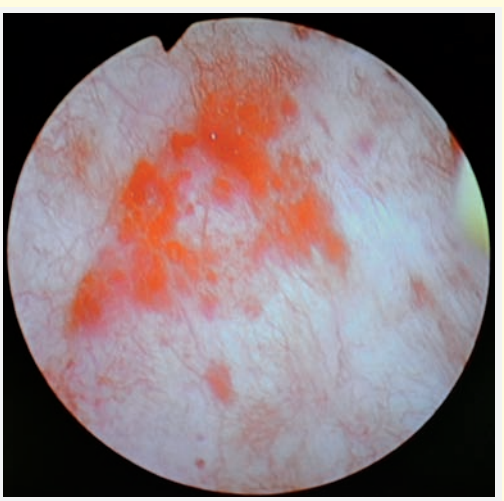

While the drip fusion was suspended, acute inflammation of parietal tunica was demonstrated. (Page 387)

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EDITOR'S COMMENT

Volume 40 | number 3 | May . June, 2014 | INT BRAZ J UROL

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Models for investigation in Urology: Rats, Pigs and Dogs. Importance of basic research in penile reconstruction and bladder overactivity.

The May-June 2014 issue of the International Braz J Urol presents original contributions with a lot papers in different fields. The papers come from many different countries such as Brazil, USA, China, Italy, Korea, Germany, Greece, Iran and Turkey, and as usual the editor´s comment highlights some papers. In this number we can observe some papers about basic research in Peyronie's disease and bladder overactivity. Several medical treatments are suggested to Peyronie's disease and overactive bladder. A lot of surgical techniques exist for the treatment of Peyronie's disease and penile reconstruction but the best surgical treatment still is under discussion. These two diseases still represent a clinical challenge for the urologist. We summarize three interesting papers about basic research in these topics below.

Doctor Salehipour and collegues, from the Departments of Urology, from the Shiraz university from Shiraz, Iran performed on page 105 an interesting study to evaluate the efficacy of human amniotic membrane (AM) grafting in the canine penile tunica albuginea defect; the authors developed an animal model as the first step toward an innovating new method for the treatment of Peyronie's disease. The authors concluded that the amniotic membrane can be used as a suitable substitution for tunica albuginea. It is safe, inexpensive, biodegradable, and available and may be used for the treatment of Peyronie's disease, penile cancers, congenital penile deformities, and penile reconstructive surgery.

Doctor Dambros and collegues from the department of urology of the University Hospital Maastricht and the School of medicine Sao Leopoldo, Sao Paulo, Brazil performed on page 113 a elegant study about the involuntary detrusor contractions. The authors studied the possibility to induce the muscle overactivity with oxidative stress using hypochlorous acid (HOCl). The authors concluded that an oxidative stressor, like HOCl, is capable of inducing smooth muscle overactivity. This model can be used for the development and testing of new treatment modalities for the overactive detrusor. Furthermore, this study provides evidence for a causal relationship between oxidative stress and detrusor overactivity.

Doctor Zhang and collegues from the department of urology and Pathology from Shandong Tumor Hospital, Jinan, performed on page 119 a study about a model for establishment and evaluation of detrusor overac- tivity in female Wistar rats. The authors ligated the perineal urethra of female Wistar rats and then performed filling cystometry. They observed that bladder weight increased significantly in detrusor overactivity rats and concluded that ligating perineal urethra and filling cystometry with intra-urethral cannula approach is a simple and easily reproducible method to establish and evaluate the model of detrusor overactivity in rats.

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REVIEW ARTICLE

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Is there a role for hyberbaric oxygen as primary treatment for grade IV radiation-induced haemorrhagic cystitis? a prospective pilot-feasibility study and review of literature

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ABSTRACT

Purpose: To examine the safety and efficacy of hyperbaric oxygen as the primary treatment for Grade IV radiation-induced haemorrhagic cystitis.
Materials and Methods: Hyperbaric oxygen was prospectively applied as a primary treatment option in 11 patients with Grade IV radiation cystitis. Primary endpoint was the incidence of complete and partial response to treatment. Secondary endpoints included the duration of response, the correlation of treatment success-rate to the interval between the onset of haematuria and initiation of therapy, blood transfusion need and total radiation dose, the number of sessions to success, the avoidance of surgery and the overall survival.
Results: All patients completed therapy without complications for a mean follow-up of 17.82 months (range 3 to 34). Mean number of sessions needed was 32.8 (range 27 to 44). Complete and partial response rate was 81.8% and 18.2%, respectively. However, in three patients the first treatment session was not either sufficient or durable giving a 72.7% rate of durable effect. Interestingly, all 9 patients with complete response received therapy within 6 months of the haematuria onset compared to the two patients with partial response who received therapy at 8 and 10 months from the haematuria onset, respectively ($p = 0.018$). The need for blood transfusion ($p = 0.491$) and the total radiation dose ($p = 0.259$) were not correlated to success-rate. One patient needed cystectomy, while all patients were alive at the end of follow-up.
*Conclusions: E*arly primary use of hyperbaric oxygen to treat radiation-induced grade IV cystitis is an effective and safe treatment option.

ARTICLE INFO

Key words:
Hyperbaric Oxygenation; Radiation; Cystitis

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INTRODUCTION

The inhalation of oxygen in high percentages and under high pressure has been extensively applied to the prevention and treatment of complications after radiation therapy (1). Recently, the European Society for Therapeutic Radiotherapy and Oncology and the European Committee for Hyberbaric Medicine underlined the indications of hyberbaric oxygen therapy (HBO) in the treatment of radio-induced lesions in normal tissue (1), including the prevention of osteoradionecrosis after dental extraction, the treatment of mandibular osteoradionecrosis in combination with surgery and the treatment of

haemorrhagic cystitis resistant to conventional treatments. All studies published on HBO therapy for radiation cystitis are not randomized or controlled. The majority constitutes retrospective reviews and case series (2-13), with only one study being prospective in nature (14). In all these studies HBO was used as a secondary treatment option. However, experimental (15-17) and clinical studies (2-13) indicate that HBO may correct the underlying pathophysiology of radiocystitis, leading to permanent cure. We present the first prospective series on hyberbaric oxygen therapy of radiation cystitis in patients who have not received any previous treatment.

MATERIALS AND METHODS

Inclusion/Exclusion criteria

Since September 2007 we have prospectively enrolled 11 patients with grade IV post-radiation haematuria morbidity, according to the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) acute and late radiation morbidity scoring criteria for radiation-induced haemorrhagic cystitis (Table-1) (18). As a consequence, all patients suffered from severe haemorrhagic cystitis with haematuria requiring transfusion. Furthermore, we have prospectively classified our cases into two groups according to transfusion needs prior to HBO treatment; the first group included patients who required 1-6 units of packed red cells and the second included patients who required more than 6 units of packed red cells, respectively. All patients should have not had any prior treatment of the radiation cystitis, apart from bladder irrigation. Patients with severe emphysema or other severe chronic obstructed airway disease, a history of spontaneous pneumothorax, a history of tympanic membrane spontaneous perforation or otological reconstruction were excluded from the current study. Moreover, patients with active viral infection, history of treatment with cisplatin or doxorubicin, active bladder malignancy and uncorrected bleeding disorders were not considered eligible for our study.

Evaluation and Treatment

On admission to hospital all patients underwent full blood count and complete clotting and biochemistry profile measurements. Urine samples for common urinalysis, culture and cytology were also sent to laboratory. Computed tomography (CT) or Magnetic Resonance Imaging (MRI) of the abdomen was scheduled for all patients to access the status of the underlying malignancy and to exclude other bladder pathology. All patients underwent cystoscopy under anesthesia

Table 1 - Classification of haematuria events for both acute and late radiation morbidity scoring criteria for radiation-induced haemorrhagic cystitis.

	Radiation morbidity	
Haematuria morbidity	Acute* (RTOG**)	Late* (RTOG/EORTC***)
Grade I	NA	Minor telangiectasia (microscopic haematuria)
Grade II	NA	Generalized telangiectasia (macroscopic haematuria)
Grade III	Gross haematuria with or without clot passage	Severe generalized telangiectasia (frequent macroscopic haematuria)
Grade IV	Haematuria requiring transfusion	Severe haemorrhagic cystitis
Grade V	Death from uncontrolled haematuria	Death from uncontrolled haematuria

* Acute morbidity defined as treatment related complications occurring within 90 days from first radiotherapy session
** RTOG: Radiation Therapy Oncology Group
*** EORTC: European Organization for Research and Treatment of Cancer

and bladder biopsies were taken by one surgeon to confirm histological changes consistent with radiation cystitis and to exclude bladder malignancy.

Based on the results of previous studies (2-14), all patients were initially scheduled to receive 30 HBO sessions in a walk-in multiplace hyberbaric chamber with intend to increase them up to 45 until the haematuria resolved. Patient would receive 100% oxygen at a 1.8 atmospheres absolute pressure per session for 90 minutes per day, five days a week- Monday to Friday, schedule which is compatible with the definition of HBO therapy according to the Undersea and Hyberbaric Medicine Society (19). When complete response to HBO was reached the treatment was ceased. In case of improvement only or relapse of haematuria during follow-up, therapy was planned to re-initiate under the same schedule. In case no benefit was gained from the initial treatment, more than 45 treatments needed, severe complications occurred, or the patient declined further therapy, HBO was considered as a failure and the plan was to refer the patient for having another treatment, either conservative or surgical. During treatment all patients were closely monitored. Serum glucose measurements were planned as needed in diabetic patients to exclude hypoglycemia.

Within 4 weeks of treatment completion, all patients underwent cystoscopy under anesthesia and bladder biopsy by the same surgeon to confirm treatment result and/or to compare with the pre-treatment status.

Study endpoints

Primary endpoint was the success rate measured by the incidence of complete and partial response to treatment. Complete response was defined as the complete cessation of bleeding and the lack of need for transfusion in combination with the disappearance of endoscopic findings and concomitant normal bladder findings in repeat biopsies. Partial response was defined as a decrease in the grade of RTOG/EORTC scoring criteria mainly the existence of microscopic haematuria or the persistence of mild macroscopic haematuria not requiring transfusion or other urgent treatment. Secondary endpoints included the duration of HBO response without need for further treatment, the correlation of the time interval between initiation of HBO therapy and the onset of haematuria to the success rate of HBO therapy, the correlation of blood transfusion need to HBO success rate, the correlation of total Gys received to the HBO success rate, the number of sessions needed to achieve success, the avoidance of surgery and the overall survival.

Statistical analysis

Descriptive statistics and comparisons were made using the SPSS 12 statistical package with $p < 0.05$ being significant. Statistical analysis was performed using the chi-square and t test, as appropriate.

RESULTS

Since September 2007 ten men and one woman were enrolled in our study. Mean patient age was 71.7 years (range 56 to 82). Indications for radiation therapy included prostate cancer for all male patients and bladder cancer for the female patient. Mean radiation dose was 74.45 Gy (range 66 to 80). Mean interval between completion of radiation therapy and onset of haematuria was 9.8 months (range 4 to 14). Mean interval between completion of radiation therapy and the onset of HBO therapy was 13.11 months (range 6 to 22 months). Mean transfusion need prior to and during the treatment was 8.18 red blood cells packs (range 3 to 16). More specifically 4 patients have been transfused with ≤ 6 units and 7 patients with > 6 units.

Pretreatment patient evaluation revealed no bladder infection or tumor. Bladder biopsy revealed diffuse mucosal edema, vascular telangiectasia, submucosal haemmorhage, interstitial fibrosis and fibrosis of smooth muscle, histological findings consistent with post-radiation cystitis. Severe ischemia of the bladder wall, a result of obliterative endarteritis, was also present.

All eleven patients completed HBO therapy without suffering any complications and were followed up for a mean period of 17.82 months (range 3 to 34). Mean HBO therapy sessions were 32 (range 27 to 44). Nine men had complete response while the last man and the woman experi-

enced partial response with marked improvement in their haematuria (grade II). One patient from the complete response group had a recurrence of grade II haematuria at 6 months of follow-up and received 18 additional HBO treatments. All these patients remained with complete response for the rest of the follow-up. The male patient with the partial response received 35 additional treatments and he has not had haematuria since then. The female patient experienced severe haematuria 6 months after the end of HBO therapy and following a full consent she chose cystectomy and urinary diversion for her treatment.

Post-hyberbaric treatment cystoscopy revealed a subjectively normal bladder mucosa in all men, which was confirmed by a histologically normal mucosa in only the 7 patients who had complete response. The male and the female with partial response showed improved but persistent findings of radiation cystitis. Cystectomy specimen revealed a T2G3N0M0 transitional cell carcinoma of the bladder.

Regarding our study endpoints, complete response rate was 81.8% and partial response rate was 18.2%, giving an overall success rate of primary therapy, as defined in our study, of 100%. However, as mentioned above, in three patients the first treatment session was not either sufficient or durable giving a 72.7% rate of durable effect. Interestingly, all 9 patients with complete response received HBO therapy within 6 months of the haematuria onset compared to the two patients with partial response who received HBO therapy at 8 and 10 months from the haematuria onset, respectively ($p < 0.018$). The need for blood transfusion was not correlated to the complete or partial response to HBO ($p = 0.491$). Total radiation dose was not correlated to complete or partial responses to HBO therapy ($p = 0.259$). All patients were alive at the end of follow-up.

DISCUSSION

Bladder complications may occur within 2 months to > 20 years following completion of pelvic radiotherapy (1,14). Their incidence ranges from 5 to 12%, with haemorrhage presenting in up to 9% of cases (1). Severe RTOG/EORCT grade III or worse bladder morbidity has been reported at 1% at 5 years, 1.4% at 10 years and 2.3% at 20 years following radiotherapy for cervical cancer (20). Radiation for prostate cancer may lead to moderate or severe haematuria in 3-5% of cases (10,12).

Traditionally, severe radiation cystitis has been treated in various ways (1). Bladder irrigation almost always constitutes the first-line treatment. Intravesical instillations with alum, silver nitrate, phenol or formalin have been used as a second-line treatment. Several oral and intravenous agents are administered either concomitantly or as a third-line option. Among them the most commonly applied are aminocaproic acid, traxenamic acid, corticosteroids, estrogens, antibiotics, prostaglandins and sodium pentosanpolysulphate. However, these treatments do not cure the radiation-induced cystitis, nor prevent recurrence of severe haematuria. Moreover, some of them may have serious systematic side effects or may exacerbate bladder fibrosis which was initiated by radiation treatment, leading to a small-capacity bladder (1,2-14). A recent Cochrane Database systematic literature review on non-surgical interventions for late radiation cystitis in patients who have received radical radiotherapy to the pelvis concluded that in the absence of randomized controlled studies it is impossible to set definitive rules for treatment (21). In case of intractable haemorrhage arterial embolization or ligation and/or cystectomy represent definitive treatment, at the cost of increased morbidity.

Pelvic radiotherapy initially causes mucosal edema and inflammation. Telangiectasia, submucosal haemorrhage and interstitial fibrosis follow. Obliterative endarteritis of small blood vessels leads to acute and chronic ischemia of the bladder wall and eventually to smooth muscle fibrosis due to cellular hypoxia (22). Hyperbaria related to HBO therapy increases bladder's tissue oxygen tension (14). Hyperoxia enhances neovascularization and growth of normal tissue (6,10,15,17). Angiogenesis is stimulated by tissue macrophages responding to the steep oxygen gradient (15). Tissue oxygen remains near normal levels for many years following HBO therapy, implying that the angiogenesis is essentially permanent (10). Vasoconstriction and cease of bleeding and improvements of tissue healing and immune function constitute ad-

ditional beneficial effects of HBO (6,12,15-17). For these reasons, HBO is the only treatment which is believed to reverse the vascular radiation-induced pathophysiology (15,22).

Several series of radiation-induced haemorrhagic cystitis treated with HBO have been reported (2-14). Tables 2 and 3 present indications and results for most of them. The vast majority are retrospective in nature. Endpoints have been set prospectively in only one study (14). These included recurrence of severe haematuria, cystectomy, or death. Forty patients were recruited, all of which had had previous unsuccessful treatments for radiation cystitis. In addition, although a mean transfusion need of 8.2 units per patient was reported, a specific classification system of haematuria morbidity was not used and patients presented with various haematuria grades according to RTOG/EORTC criteria, leading to a diversity of results. Similar to our study, a classification of the severity of haematuria according to transfusion needs was used. However, no statistical analysis was provided and HBO failure was seen only in 3 patients with a mean transfusion need of 25.7 units. Finally, neither the total Gys received nor the time interval elapsed from initiation of HBO therapy to onset of haematuria, were correlated to HBO success rate. Overall, haematuria disappeared completely or improved in 37 patients (92.5%). With a median follow-up of 23 months, in 9 patients haematuria recurred, representing a recurrence rate of 0.12/year (14). Bladder preservation was achieved in 36 of patients. Based on their results the authors inferred in their conclusion that HBO should not be reserved only for severely affected and conventional therapy-resistant patients.

The retrospective study with the most significant numbers included 62 patients, with a follow-up of 10-120 months (10). Among these patients, all had previous treatments while only 8 (13%) required pre-hyperbaric oxygen blood transfusion. Of the 57 patients to be evaluated, 49 (86%) presented with a complete disappearance or a notable improvement of their haematuria. Again, based on their results the authors inferred in their conclusion that early HBO should be considered before repeated instillations of chemicals leave the bladder fibrotic, contracted and non-compliant. Another important retrospective study on 60 patients with intractable to other conservative treatments radiation cystitis, showed an overall 80% complete or partial response to HBO after 12 months of follow-up (11). Having used similar response criteria to our study, the authors showed that HBO success rate has not been impaired by the modality and timing of pelvic radiotherapy or by previous intravesical treatment. Younger age, higher radiation dose and treatment within 6 months from the onset of haematuria were associated with a favorable HBO outcome. The later, also having been shown retrospectively in other studies (8), was confirmed in our study, in a prospective manner. Tables 2 and 3 summarize data and results for the most of the rest large retrospective studies. All these studies have confirmed the efficacy and safety of HBO therapy.

Our study has several drawbacks. First of all, it is neither randomized nor controlled. However, as cystectomy represents the alternative definitive treatment for radiation cystitis we believe it will be difficult for urologists to randomize patients. Secondly, due to strict inclusion criteria, the number of patients enrolled in our study is small and conclusions should be made with caution. Thirdly, the follow-up in our series is considered short. Although durable results up to 10-years have been published (6), HBO success rate may drop from 73% to 27% as follow-up increases from 2.5 years to 5 years (7). As our study is still ongoing, we believe these drawbacks will become weaker upon time.

Taking into consideration the aforementioned drawbacks, current study remains important for several reasons. It is the second prospective study in literature and the first on only haematuria grade IV patients. It is the first study using HBO as primary therapy to radiation-induced cystitis and the first in which post-treatment cystoscopic and histologic findings were included to study's endpoints and were documented for all patients. Several conclusions can carefully be drawn from the current study. Primary treatment of severe post-radiation haemorrhagic cystitis with HBO has proved to be effective and safe both for the bladder structure itself and for patients. Initiation of therapy within 6-months of haematuria onset will be of patient's benefit. HBO's success

Table 2 - Material and methods of studies on hyperbaric therapy in the treatment of radiation-induced bladder complications.

Series (Reference)	No. patients	Prospective /Retrospective	Mean Radiation dose (range) (Gy)	Symptoms / Grade of Haematuria (n = number of patients)	Number of patients transfused	Average Blood units per patient (range)	Mean (range) interval from radiation to symptoms (months)	Mean (range) interval from radiation to HBO therapy (months)	Mean (range) interval from haematuria to HBO therapy (months)
Nakada (3)	6	Retrospective	60 ± 4.3	Haemorrhagic cystitis	NA	NA	NA	20.8±3.6	NA
Norkool (4)	14	Retrospective	66.82 (45-100)	Haemorrhagic cystitis	1	3	NA	NA	NA
Lee (5)	20	Retrospective	62 (52-90)	Haemorrhagic cystitis n = 19 Frequency, urgency n = 1	NA	NA	114 (24-312)	NA	NA
Weiss (6)	13	Retrospective	46.87 (40-69.74)	Haemorrhagic cystitis	9	2.7 (2-7)	NA	69.23 (12-216)	NA
Del Pizzo (7)	11	Retrospective	75 (60-96)	Intractable haematuria n = 11 Pain n = 2 Urgency/ Incontinence n = 1	11	3.3 (2-15)	84 (16-144)	NA	NA
Mathews (8)	17	Retrospective	66	Haemorrhagic cystitis	8	NA	NA, (2-180)	NA	≤ 2 n=11 > 2 n=6
[3]Mayer (9)	11	Retrospective	[4]69.27 (66-70)	[2]Grade 2 n = 2 Grade 3 n = 6 Grade 4 n = 2	2	NA	[5]15.84	52.1 (11.1-145.3)	NA

Corman (10)	62	Retrospective	NA	[1]Haemorrhagic cystitis	8	4 (1-7)	48 (0-355)	63 (2-360)	NA
Chong (11)	60	Retrospective	NA	[2]Grade 1-2 n=16 Grade 3-4 n=44	NA	NA	NA	NA	≤ 6 n=28 > 6 n=32
Neheman (12)	7	Retrospective	64	[1]Haemorrhagic cystitis	NA	NA	NA	NA, (3-180)	NA
Yoshida (13)	8	Retrospective	56.6 (42-70)	Haemorrhagic cystitis	3	NA	NA	NA	8.9 (3-34)
Bevers (14)	40	Prospective	61.05	Haemorrhagic cystitis	30	8.2 (0-36)	53.1 (4-253)	NA	NA
Present study	11	Prospective	74.45 (66-80)	[2]Grade IV n=11	11	8.18 (3-16)	9.8 (4-14)	13.11 (6-22)	3.36 (1-10)

[1] = No specific symptoms; number of blood transfusions not mentioned; no grade of haematuria morbidity
[2] = RTOG/EORTC haematuria morbidity grades
[3] = Three patients had combined proctitis and cystitis
[4] = Refers to the mean and range of maximum dose of radiation
[5] = Median value
NA = Not Available

Table 3 - Results of studies on hyperbaric therapy in the treatment of radiation-induced bladder complications.

Series (Reference)	Mean (range) of HBO treatments	Mode of HBO sessions (absolute atmospheres/ Minutes per session/ Sessions per week	Criteria for response	Complete Response (patients/ %)	Partial response (patients / %)	Recurrence after complete response (patients, %)	Cystez	Mean (range) Follow-up (months)
Nakada (3)	45 (20-61)	2/90-120/7	Complete or partial improvement of haematuria and cystoscopic findings	5 (83.3%)	-	0 (0%)	0 (0%)	12 ± 1.2******
Norkool (4)	28 (9-58)	2.4/90/5-6	Complete or partial improvement of haematuria	8 (57%)	2 (14%)	1 (12.5%)	1 (7.1%)	19.07 (10-42)
Lee (5)	44 (10-87)	2.5/100	Complete or partial improvement of haematuria, frequency, urgency Changes in cystoscopic findings	16(80%)	2 (10%)	0 (0%)	1 (5%)	14 (5-41)
Weiss (6)	55.38 (34-60)	2/120/7	Complete or partial improvement of haematuria	12 (92.3%)	-	2 (15.38%)	1 (7.7%)	30 (4-102)
Del Pizzo (7)	40 (28-64)	2/90/5	Presence or absence of haematuria, urgency and pain	3 (27.2%)***	5 (45.4%)****	1 (33.3%)***	8 (72.7%)***	5.1***** (3.2-8.5)
Mathews (8)	14 (NA)	2-2.5/90/5	Complete or partial improvement of haematuria	13 (75%)	2 (11%)	NA	NA	21 (9-60)
Mayer (9)	26.5 (18-31)	2.2-2.4/60/7	RTOG/EORTC Haematuria morbidity grades	6 (54.5)	3 (27.27)	NA	1 (9%)	17.7 (2.2-51.6)
Corman (10)**	33 (9-68)	2.4/90/5-7	Complete or partial improvement of haematuria	21 (34%)	28 (45%)	6 (10.5%)*	0 (0%)	NA

Chong (11)	NA	2.36/90/5	**Complete response:** Absence of haematuria **Partial response:** Reduction in RTOG/EORTC grade	44 (73.35)	4 (10%)	NA	NA	At least 12 (NA)
Neheman (12)	30 (18-57)	2/90/5	Complete or partial improvement of haematuria	100%*	100%*	2 (28.55) *	0 (0%)	24 (3-53)
Yoshida (13)	19 (10-42)	2/90/5	Complete or partial response of haematuria	6 (75%)	0 (0%)	1 (12.5%)	2 (25%)	15.5 (2-31)
Bevers (14)	20 (NA)	3/90/5-6	Recurrence of severe haematuria, Cystectomy, death	30 (75%)	7 (17.5%)	3 (10%)	5 (12.5%)	23 (1-74)
Present study	32.8 (27-44)	1.8/90/5	**Complete response:** No haematuria, Normal cystoscopy Normal histology **Partial Response:** Reduction in RTOG/EORTC Grade No urgent treatment	9 (81.8%)	2 (18.2%)	1 (11.1%)	1 (9%)	17.82 (3-34)

* Results refer to complete and partial response in combination
** Data available on 57 out of 62 patients
*** Data refer to 5.1 years median follow-up
**** Data refer to 2.5 years median follow-up
***** Median value
****** ± Standard error
NA = Data not available

rate is not correlated to the degree of blood transfusion need or radiation dose. Finally, we support the findings of previous series (2,4), indicating that when HBO fails, the urologist should think of other underlying causes such as malignancy.

CONCLUSIONS

Early primary use of hyperbaric oxygen to treat radiation-induced grade IV haematuria is an effective and safe treatment option. Increase in patient recruitment and longer follow-up is warranted to extract permanent conclusions. Prospective randomized controlled trials will eventually provide information of high-level of evidence.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Radical prostatectomy and positive surgical margins: relationship with prostate cancer outcome

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ABSTRACT

Introduction: Positive surgical margins (PSMs) are an adverse factor that may predict a worse outcome in patients submitted to radical prostatectomy (RP). However, not all of these cases will evolve to biochemical (BCR) or clinical (CR) recurrence, therefore relationship between PSMs and these recurrent events has to be correlated with other clinical and pathologic findings to indicate complementary treatment for selected patients.

Materials and Methods: Of 1250 patients submitted to open retropubic radical prostatectomy (RRP), between March 1991 and June 2008, the outcome of 161 patients with PSMs and of 67 without PSMs as a control group, comprising a total of 228 cases were retrospectively reviewed. A minimum follow-up time of 2 years after surgery was considered. BCR was determined when PSA ≥ 0.2ng/mL. CR was determined whenever there was clinical evidence of tumor. Chi-square test was used to correlate clinical and pathologic variables with PSMs. Time interval to biochemical recurrence was analyzed by the Kaplan-Meier product limit analysis using the log-rank test for comparison between groups. Univariate and multivariate Cox stepwise logistic regression models were used to identify significant predictors of risk of shorter intervals to BCR.

Results: Prostate circumference margin was the most common site with 78 cases (48.44%). Regarding the outcome of 228 cases from both groups, BCR occurred in 68 patients (29.82%), and CR in 10 (4.38%). Univariate analysis showed statistically significant associations ($p < 0.001$) between presence of PSMs with BCR, but not with CR ($p = 0.05$). At follow-up of the 161 patients with PSMs, only 61(37.8%) presented BCR, while 100 (62.8%) did not. BCR correlated with pathologic stage; Gleason score; preoperative PSA; tumor volume in the specimen; capsular and perineural invasion; presence and number of PSMs. CR correlated only with angiolymphatic invasion and Gleason score. Considering univariate analysis of clinical and pathologic factors predicting progression-free survival at 5 years, prostate weight; preoperative PSA; Gleason score; pathologic stage; tumor volume; PSMs; capsular and perineural invasion were correlated with BCR. At multivariate analysis, only Gleason score and percentage of tumor volume correlated as significant independent predictors of BCR.

Conclusion: At univariate analysis, presence, number and location of PSMs have consistent correlation with BCR after RRP, but at follow-up BCR occurred only in 37.8% of patients with PSMs. However at multivariate analysis, the significant risk factors for BCR were percentage of tumor volume ($p = 0.022$) and Gleason score ($p < 0.005$) in the surgical specimen. Angiolymphatic invasion and Gleason score were significantly correlated with CR.

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INTRODUCTION

The finding of positive surgical margins (PSMs) after radical prostatectomy (RP) implies that cancer resection was not complete leading the surgeon to decide between complementary treatments such as: active surveillance, adjuvant radiotherapy or androgen-deprivation therapy. Many studies report that PSM represents an independent predictor of biochemical recurrence (BCR) after RP. Furthermore, these studies have also shown that most men with PSMs do not develop BCR (1-3). At multivariate analysis, Gleason score of specimen, pathologic stage, percentage of tumor volume in the surgical specimen and PSMs were all significant risk factors for BCR. Each of these factors has previously been associated with BCR (4). Another study shows that PSM is an independent predictor of BCR after RP, where BCR rates were similar for cases with unifocal and multifocal PSMs, and the risk of BCR was highly dependent on the PSM location. Cases of base and anterior margins of the prostate have a worse prognosis and should be considered candidates for adjuvant treatment due to the very high likelihood of BCR. Although PSMs are more common on the apex, posterior and posterolateral sites, they are associated with lower BCR rates (5). To verify the relationship between PSMs and BCR, we retrospectively analyzed the outcome of a group of patients submitted to RRP, for clinically localized prostate adenocarcinoma with PSMs, and studied the correlations of these results with clinical and pathologic variants.

MATERIALS AND METHODS

From a total of 1250 patients submitted to RRP to cure a clinically localized Prostate Cancer, by the team of the Division of Urology, Pelvic Surgery Department, A.C. Camargo Cancer Center, between March 1991 and June 2008, we retrospectively studied the outcome of 161 patients with PSMs, compared to a control group of 67 patients without PSMs, in a total of 228 cases. Our total number of patients with PSMs was of 298 cases (23.84%). We excluded from the study patients who received hormone therapy or radiotherapy before the surgery, 56 patients who have PSMs and involvement of seminal vesicles and/or inguinal or pelvic lymph nodes or stage T4 disease, and 81 patients who have PSMs with incomplete or missing follow-ups. Based upon their preoperative PSA, rectal digital examination, transrectal ultrasound, pelvic computerized tomography or nuclear magnetic resonance (high risk cases) results and the pathologic study from their prostate biopsies, all patients were considered bearers of organ-confined disease. We recorded patient age, race, preoperative PSA, clinical and pathologic stage, prostate surgical specimen weight, percentage of tumor volume, perineural and/or angiolymphatic invasion, capsular and extracapsular involvement, the number and site (urethral, bladder neck, prostate circumference) of PSMs in the surgical specimens. These were staged according to the 1997 American Joint Committee on Cancer System and graded using the Gleason system. All cases underwent the same protocol for pathologic evaluation, the prostate being analyzed as a whole. After removal of the seminal vesicles, surgical specimens were step sectioned at a constant interval obtaining variable number of transverse sections according to the prostate size. Each transverse section of the prostate was subdivided into 2 anterolateral and 2 posterolateral quadrants. From each quadrant it was obtained one slide unless too large to need a second slide. A visual estimate was used to evaluate tumor extent. After analysis of each quadrant a percentage was reached for the total tumor volume. Extraprostatic extension was evaluated whenever cancer was seen in adipose tissue being considered either focal or extensive. Surgical margins were considered positive when the tumor could be seen on the inked surface of the surgical specimen (6). Serum PSA levels after RRP were measured every 4 months for 2 years and then every 6 months for 2 more years and annually thereafter. BCR was considered when the PSA reached a level $\geq$ 0.2ng/mL. Thereupon the patient was referred for external pelvic and prostatic bed radiotherapy or radiation plus hormone therapy in selected cases with worse prognosis. CR was determined when clinical evidence of tumor was seen as a metastatic disease, or when PSA rose despite radiotherapy, hormone, or chemotherapy treatments. Minimum follow-up time was of 2 ye-

ars after surgery. The time interval to biochemical recurrence was analyzed by the Kaplan-Meier product limit analysis using the log-rank test for comparison between groups. The univariate and multivariate Cox stepwise logistic regression models were used to identify significant predictors of risk of shorter intervals to BCR. The Kaplan-Meier method was used to calculate the curves of biochemical-recurrence free survival (from the date of RRP until date of the first PSA measurement > 0.2ng/mL or to the date of the last follow-up) and clinical-recurrence free survival (from the date of the RRP until the date of detection of local or distant disease or until date of the last follow--up). The Chi-square test was used to correlate clinical and pathologic variables with PSMs. Time interval to biochemical recurrence was analyzed by the Kaplan-Meier product limit analysis using the log-rank test for comparison between groups. Univariate and multivariate Cox stepwise logistic regression models were used to identify significant predictors of risk of shorter intervals to BCR. All statistical tests were performed with $p < 0.05$ to indicate statistical significance with R free statistical software (www.r-project.org).

RESULTS

For the 228 patients, follow-up ≥ 5 years was available in 93 patients and ≤ 5 years in 135 patients. Minimum follow-up time after surgery was of 2 years, median follow-up 6.2 years (range 2-15 years). At diagnosis median age of patients was 64.5 years (range 43-81 years), race was 68.42% white, 19.29% black, and 12.29% mulatto, median preoperative PSA level was 8.47ng/mL (range 1.3-78.8ng/mL).

Prostate specimen weight ranged from 10 to 167g (mean 44.77g), and tumor volume was estimated as ranging from 0.5% to 100% of total prostate volume (mean 12.82%). Prostate capsule invasion (focal and extracapsular) was present in 123 cases and absent in 105, perineural invasion was present in 162 cases and absent in 66, angiolymphatic invasion was present in 18 cases and absent in 210.

Table-1 shows demographic, clinical and pathologic parameters correlated with presence of PSMs, age, preoperative PSA, specimen Gleason score, weight, pathologic stage, percentage of tumor volume, capsular and perineural invasion. Clinical stage and angiolymphatic invasion were not correlated. Patients younger than 50 and older than 70 years of age showed higher incidence of PSMs. Pre-treatment PSA ≥ 10ng/mL, specimen Gleason score ≥ 7, pathologic stage ≥ T2b, tumor volume ≥ 10% of specimen's total volume and presence of capsular and perineural invasion showed statistically significant associations with occurrence of PSMs.

Conversely, when weight of the prostate was ≤ than 60g it was more correlated with PSMs. From the total of 228 patients, 161 (71%) had PSMs, while 67 (29%) had negative surgical margins (NSMs). Of those with PSMs, 106 cases (46%) showed one margin, 44 (19%) two margins, and 11 (5%) three margins. The prostate circumference site was the most common PSM (48.44%) followed by prostatic+urethral (apical) (17.39%), urethral (apical) (13.66%), and bladder neck (6.21%) (Table-2).

Of the 228 patients BCR occurred in 68 (30%), and did not in 160 (70%), whereas clinical recurrence (CR) occurred in 10 (4%) and did not in 218 (96%).

Univariate analysis showed statistically significant ($p < 0.001$) association between presence of PSMs and BCR, however not with CR ($p = 0.06$).

BCR was found in 68 patients, wherein those with no PSMs corresponded to 7 (10.5%) cases, while PSMs were present in 61 (89.5%) cases.

Among 161 patients with PSMs, 61 (37.88%) presented BCR, while 100 (62.12%) did not (Table-3). COX univariate analysis of pathologic factors predicting progression-free survival of BCR and CR in 5 years after RRP (Table-4) correlated BCR progression-free survival with pathologic stage, Gleason score, pre-treatment PSA, tumor volume in specimen, capsular and perineural invasion, presence and number of PSMs.

Interestingly, the progression-free survival time for CR was correlated only with angiolymphatic invasion and Gleason score.

Table-5 shows univariate and multivariate regression analysis of clinical and pathologic

Table 1 - Demographic, clinical, and pathologic variables correlated with PSMs.

Variables	Categories	Negative PSMs N (%)	PSMs N (%)	p
Age (years)	40-50	2 (13)	13 (87)	< 0.001
	50-60	35 (43)	46 (57)	
	60-70	23 (22)	82 (78)	
	> 70	7 (26)	20 (74)	
Pre-operative PSA (ng/mL)	≤ 10	60 (34)	114 (66)	< 0.01
	10-20	5 (14)	32 (86)	
	> 20	1 (8)	12 (92)	
Specimen Gleason score	2-6	51 (40)	75 (60)	< 0.001
	7	11 (16)	59 (84)	
	8-10	5 (16)	27 (84)	
Clinical stage	< T2b	65 (31)	145 (69)	0.02
	≥ T2b	4 (22)	14 (78)	
Pathologic stage TNM	< T2b	63 (91)	6 (9)	< 0.001
	≥ T2b	4 (3)	155 (97)	
Tumor volume (% specimen)	≤ 10	65 (49)	68 (51)	< 0.001
	10-20	2 (4)	43 (96)	
	20-40	0 (0)	36 (100)	
	> 40	0 (0)	10 (100)	
Weight of specimen (g)	< 40	27 (23)	89 (77)	< 0.001
	40-60	22 (27)	59 (73)	
	> 60	18 (58)	13 (42)	
Capsular invasion	No	59 (56)	46 (44)	< 0.001
	Yes	8 (7)	115 (93)	
Perineural invasion	No	40 (60)	27 (40)	< 0.001
	Yes	27 (17)	134 (83)	
Angiolymphatic invasion	No	65 (31)	145 (69)	0.11
	Yes	2 (11)	16 (89)	

Table 2 - Sites of PSMs in prostate surgical specimen.

Sites of PSMs	N = 161	(%)
Prostatic (circunferential)	78	48.44
Urethral (apex)	22	13.66
Bladder neck (base)	10	6.21
Prostatic+urethral	28	17.39
Prostatic+bladder neck	6	3.72
Urethral+baldder neck	9	5.59
Prostatic+urethral+bladder neck	8	4.96

specimen Gleason score ≥ 7, smaller glands with weight ≤ 40g, pathologic stage ≥ pT2b, percentage of tumor volume higher than 10% of surgical specimen, capsular and perineural invasion with occurrence of PSMs, in accordance with several authors (7-9).

PSMs point to a greater risk of biochemical progression. D'Amico et al. (8) found that after RP failure rates of 2-year PSA were of 45-55% in patients with PSMs, when compared to 15-25% of those with organ confined disease. Several factors have been assessed to verify whether it is possible to further stratify risk of recurrence in patients with PSMs. In virtually all studies, multiple PSMs have signaled a worse prognosis. Number of PSMs

Table 3 - Correlation between PSMs and BCR and CR

	Category	No PSMs N(%)	PSMs N(%)	p
Biochemical recurrence	No	60 (38)	100 (62)	<0.001
	Yes	7 (10)	61 (90)	
Clinical recurrence	No	67 (31)	151 (69)	0.06
	Yes	0 (0)	10 (100)	

factors predicting BCR at 5 years post-RRP. At univariate analysis, prostate weight, preoperative PSA, Gleason score, pathologic stage, tumor volume, PSMs, capsular involvement, and perineural invasion were statistically significant.

Multivariate analysis correlated BCR only with Gleason score and tumor volume in surgical specimen as statistically significant independent predictors ($p < 0.005$ and $p = 0.022$ respectively).

DISCUSSION

In contemporary series, PSMs are reported in 11-38% of patients undergoing RP. The prognostic factors pointing at the presence of PSMs are many ranging from pathologic characteristics to the surgeons' expertise and surgical techniques.

Our results correlate younger and older age, pre-treatment PSA higher than 10ng/mL, (single vs. multiple) showed that there was a statistically significant higher risk of recurrence in patients with more than one PSM, with a hazard ratio of 2.19 at the 95% CI (9).

A similar result was reported by Obek et al. (10), who showed that at a mean follow-up of 25 months, the recurrence rate in patients with multiple PSMs was of 43% vs. 24% in those with a single focus. Furthermore, patients with two or more PSMs were 2.5 times more likely to have recurrence in a shorter period.

In our study, only 61 (37.88%) out of 161 patients with PSMs presented BCR. As in literature, various PSMs sites, bladder neck and prostate circumference, lead to worse outcome. In our cases with no PSMs, BCR was only found in 7 patients (10.5%).

It is extremely difficult to predict PSM outcome, and as patients with PSMs are at higher risk

Table 4 - COX proportional hazard regression analyses of pathologic factors predicting BCR and CR progression-free survival in 5 years following RRP.

Variables	Cathegory	N	BCR	p	N	CR	p
Age (years)	40-50	15	0.71		15	1.00	
	50-60	81	0.77	0.33	81	0.97	0.44
	60-70	105	0.61		105	0.93	
	> 70	27	0.84		27	1.00	
Clinical stage	< T2b	210	0.69	0.3	210	0.96	0.02
	≥ T2b	12	0.75		12	0.76	
Pathologic stage	< T2b	69	0.86	< 0.001	69	1.00	0.08
	≥ T2b	159	0.64		159	0.94	
Gleason score	2-6	126	0.79		126	0.98	
	7	70	0.62	< 0.001	70	0.94	< 0.01
	8-10	32	0.46		32	0.88	
Pre-operative PSA (ng/mL)	≤ 10	174	0.77		174	0.94	
	10-20	37	0.53	< 0.001	37	1.00	0.27
	> 20	17	0.31		17	0.92	
Tumor volume (% from specimen)	≤ 10	133	0.80		133	0.98	
	10-20	45	0.71	< 0.001	45	0.95	0.05
	20-40	36	0.46		36	0.94	
	> 40	10	0.30		10	0.80	
Weight (g)	≤ 40	116	0.62		116	0.94	
	40-60	80	0.83	0.03	80	0.97	0.57
	> 60	32	0.65		32	0.96	
Capsular invasion	No	106	0.84	< 0.01	106	0.99	0.05
	Yes	122	0.60		122	0.93	
Perineural invasion	No	66	0.86	0.01	66	0.97	0.24
	Yes	162	0.64		162	0.95	
Angiolymphatic invasion	No	210	0.70	0.83	210	0.96	0.01
	Yes	18	0.65		18	0.88	
Margins	No	67	0.89	< 0.01	67	1.00	0.08
	Yes	161	0.64		161	0.94	
Margins	None	67	0.89		67	1.00	
	Unique	106	0.66	<0.01	106	0.92	0.05
	Multiple	55	0.60		55	0.98	
Number of margins	0	67	0.89		67	1.00	
	1	106	0.66	< 0.01	106	0.92	0.11
	2	44	0.65		44	0.98	
	3	11	0.41		11	1.00	

Table 5 - Univariate and multivariate analyses of clinical and pathologic factors predictors of BCR in 5 years.

Characteristic		Univariate				Multivariate			
	n	RR	IC(95%)		Pr(>|z|)	RR	IC(95%)		Pr(>|z|)
Prostate weight	228	0.98	0.96	0.99	0.013	0.99	0.97	1.01	0.187
Patient age	228	0.99	0.96	1.03	0.737	0.99	0.95	1.02	0.489
Pre-operative PSA	228	1.039	1.021	1.056	0.0008	1.018	0.992	1.044	0.18
Gleason score					7.9E-05				0.005
≤ 6	124	1.00				1.00			
7	71	1.88	1.07	3.31	0.029	1.37	0.75	2.50	0.301
≥ 8	33	4.02	2.14	7.54	1.5E-05	3.13	1.57	6.25	0.001
Tumor Volume	228	1.02	1.01	1.03	3.2E-05	1.02	1.00	1.03	0.022
Margins					0.003				0.653
Negatives	67	1.00				1.00			
Positives	161	3.51	1.51	8.13	0.003	1.47	0.27	7.96	0.653
Pathologic stage					0.005				0.759
≤ pT2a	68	1.00				1.00			
≥ pT2b	160	3.09	1.41	6.77	0.005	0.78	0.16	3.81	0.759
Perineural invasion					0.009				0.533
No	67	1.00				1.00			
Yes	151	3.24	1.47	7.12	0.003	1.62	0.67	3.90	0.284
Extense	10	4.60	1.34	15.72	0.015	1.92	0.49	7.48	0.346
Capsular invasion					0.002				0.279
No	105	1.00				1.00			
Yes focal	82	2.42	1.30	4.49	0.005	1.76	0.86	3.61	0.124
Extracapsular	41	3.23	1.64	6.38	0.001	1.76	0.78	3.98	0.173
Angiolymphatic invasion					0.540				0.666
No	210	1.00				1.00			
Yes	18	1.30	0.56	3.03	0.540	0.82	0.33	2.04	0.666

of progression, the ability to stratify this risk needs improvement along with other factors that may affect disease progression and survival (11). Focal capsular or extensive extracapsular involvement, were both correlated with BCR in our study. Other studies found that men with PSMs and no extracapsular spread had a lower rate of recurrence than men with extracapsular disease, but this was contradicted by the SEARCH database study group (12), who found that men with PSMs and no extracapsular spread had a recurrence risk similar to those with extracapsular disease regardless of margin status.

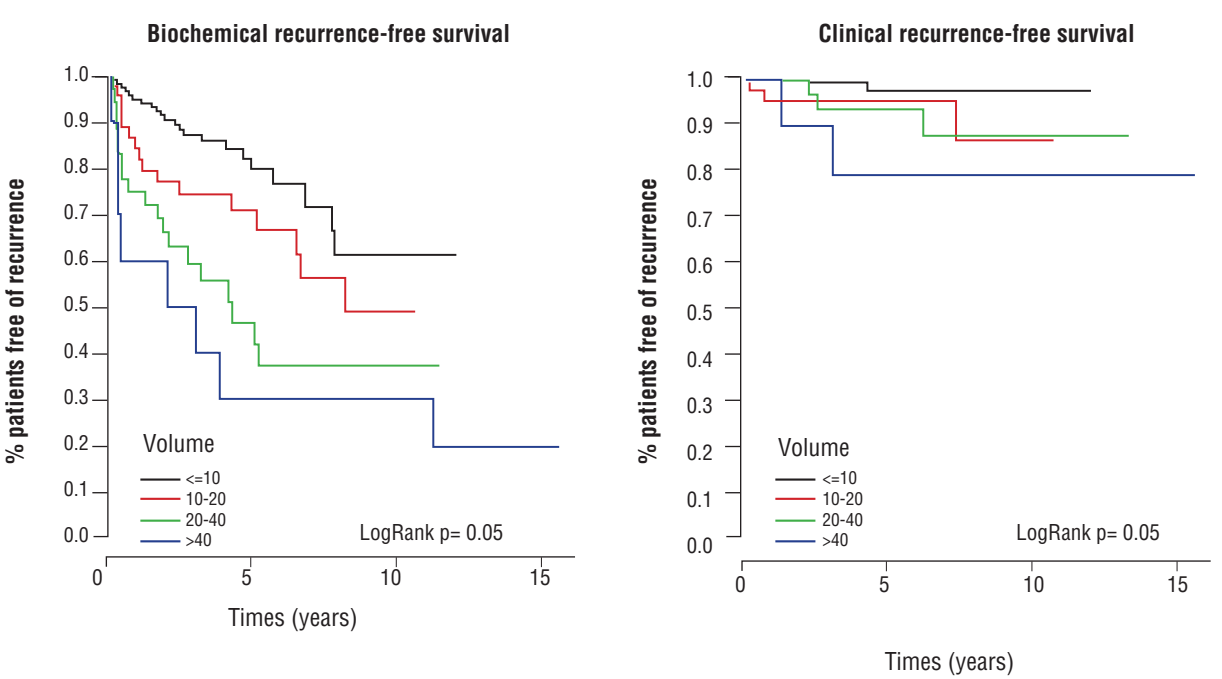
Similar to our results, Stephenson et al. (13) noted that 7-year progression-free probability was observed in 60% of patients with positive surgical margins. A positive surgical margin was significantly associated with biochemical recurrence (HR 2.3, $p < 0.001$) after adjustment of the following factors: age, prostate specific antigen, Gleason score, pathologic stage and year of surgery. An increased risk of biochemical recurrence was associated with multiple vs. single positive surgical margins (adjusted HR 1.4, $p = 0.002$) and extensive vs. focal positive surgical margins (adjusted HR 1.3, $p = 0.004$) at multivariate analysis. However, neither parameter improved the predictive accuracy of a nomogram compared to one in which surgical margin status was modeled as positive vs. negative (concordance index 0.851 vs.0.850 vs. 0.850).

In our results, at univariate analysis prostate weight, preoperative PSA, Gleason score, pathologic stage, tumor volume, PSMs, capsular and perineural invasion were correlated with BCR in full agreement with literature. Nevertheless at multivariate analysis only Gleason score and tumor volume were statistically significant independent predictors of BCR (Figure-1).

Guram et al. (14), conclude that patients with vascular invasion in the radical prostatectomy specimen are at high risk of recurrence after surgery, and that adjuvant systemic treatment should be considered for these patients. They further conclude that patients with negative surgical margins and no vascular invasion are likely to be cured by radical prostatectomy. Similarly, our results showed that angiolymphatic invasion and Gleason score were significantly correlated only with CR.

Gleason score reflects tumor aggressiveness, whereas cancer volume illustrates the extent of the lesion, as such it can be hypothesized that high-grade cancer volume and percentage simultaneously reflect cancer invasion ability to spread and their impact on outcome. Our results support the conclusions of other authors (15,16) that high-grade cancer volume had the highest impact on recurrence-free survival in patients with surgically treated and pathologicly organ-confined prostate cancer or that prostate volume has prognostic value in pathology T2 radical prostatectomy specimens (17). These facts highlight the importance of the percentage of tumor volume in the surgical specimen, rather than the presence of PSMs, as important predictor

Figure 1 - Probability of biochemical recurrence-free and clinical progression-free survival at 5-10 years according to percentage tumor volume in the specimen.



of BCR. Other studies, however, argued that tumor extent does not provide additional information beyond that of Gleason score and surgical margin status (18-20).

CONCLUSIONS

Our results agree with numerous previous reports that presence, number and site of PSMs have consistent correlation with BCR following RRP within other pathologic factors at univariate analysis. However, not all patients with PSMs will present tumor progression. As confirmed in our study, BCR occurred only in 37.8% of patients with PSMs. Overall, CR was very rare, as it represented 4% of the total number of cases (PSMs and no PSMs). At multivariate analysis, percentage of tumor volume ($p = 0.022$) and Gleason score ($p < 0.005$) in the surgical specimen were the independent significant prognostic risk factors for BCR, rather than the presence of PSMs, stressing the importance of these two pathologic factors. Furthermore, angiolymphatic invasion and Gleason score were significantly correlated only with CR.

ABBREVIATIONS

CaP = Prostate adenocarcinoma
PSMs = Positive surgical margins
RRP = Open retropubic radical prostatectomy
RP = Radical prostatectomy
BCR = Biochemical recurrence
CR = Clinical recurrence

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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A 10–year analysis of metastatic prostate cancer as an initial presentation in an underserved population

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ABSTRACT

Objective: To analyze patients from an underserved area who presented initially with metastatic prostate cancer in order to identify patients in our population who would suffer greatly if PSA screening was eliminated.
Materials and Methods: A prospectively maintained androgen deprivation therapy database from an inner city municipal hospital was queried to identify patients who presented with metastatic prostate cancer. We identified 129 individuals from 1999 to 2009 eligible for study. Those who underwent previous treatment for prostate cancer were excluded. We examined metastatic distribution and analyzed survival using Kaplan Meier probability curves.
Results: The median age of presentation was 68 with a median Gleason sum of 8 per prostate biopsy. Thirty-two patients presented with hydronephrosis with a median creatinine of 1.79, two of whom required emergent dialysis. Of those patients who underwent radiographic imaging at presentation, 35.5% (33/93) had lymphadenopathy suspicious for metastasis, 16.1% (15/93) had masses suspicious for visceral metastases. Of the patients who underwent a bone scan 93% (118/127) had positive findings with 7.9% (10/127) exhibiting signs of cord compression. The 2 and 5- year cancer specific survival was 92.1% and 65.6%, respectively.
Conclusions: In this study we have highlighted a group of men in an underserved community who presented with aggressive and morbid PCa despite widespread acceptance of PSA screening.

ARTICLE INFO

Key words:
Prostatic Neoplasms; Prostate-Specific Antigen; Mass Screening; Medically Underserved Area

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INTRODUCTION

Prostate cancer (PCa) remains among the most common causes of cancer related deaths in North American men with an estimated 28,170 deaths in 2012 (1). Since the inception of PSA screening in the early 1980's, a stage and grade migration towards diagnosing lower risk PCa has been identified. With this stage migration it was observed a lower incidence of metastatic disease and improved mortality rates (2). Etzioni et al. demonstrated a decrease in metastatic disease from 77 per 100,000 patients in1990 to 37 per 100,000 patients in 2000 (3).

Despite an overall trend towards organ confined, lower risk disease, the incidence and mortality rates of PCa in men of lower socioeconomic status (SES) and African American race has remained disproportionately high and relatively unchanged throughout the PSA screening era. A retrospective study looking at low income, uninsured men in California suggested that despite

widespread use of PSA screening, clinical T stage, Gleason scores, and rates of metastatic disease remained unchanged over time (4). Another study from Brazil investigated the impact of screening for PCa versus traditional referral for cancer treatment on clinical and pathological features, and found that cancers detected through screening proved to be significantly more favorable (5).

Race also appears to contribute to the disproportionate rates of incidence and mortality of PCa. Jemal et al. demonstrated that over a 5-year span African American men were 1.5 times more likely to be diagnosed with PCa and 2.4 times more likely to die from the disease than white men (6).

Considering recent controversies regarding PSA screening, we sought to identify patients in an underserved population who presented initially with metastatic prostate cancer (mPCa) to identify who would suffer if PSA screening was eliminated.

MATERIAL AND METHODS

After obtaining Institutional Review Board approval we queried a prospectively maintained androgen deprivation therapy database from an inner city municipal hospital to identify patients who at initial presentation were found to have a diagnosis of mPCa. All patients in our study had a prostate biopsy confirming the presence of cancer. mPCa was confirmed with either a bone scan that was positive for disease or a CT scan with evidence of visceral metastasis. Imaging was also used to evaluate lymph node status. A board certified Radiologist reviewed all images.

We identified 202 individuals from 1999 to 2009 with mPCa. Patients who had imaging studies performed within 30 days of PCa diagnosis were included in our study. Individuals who were previously treated for PCa were excluded. One hundred and twenty nine patients met our inclusion criteria and were included in our study.

We examined median age at diagnosis, Gleason score, PSA, creatinine level, hematocrit and the need for hemodialysis at the time of presentation. We examined the metastatic distribution in our patient population using nuclear bone imaging and CT scans. Unfortunately, the reporting system at our hospital does not give details such as percentage of PCa within fragment; we simply get a Gleason score. Also, many of the biopsies performed for men with mPCa upon presentation included only one or two cores in order to get a tissue diagnosis prior to starting systemic therapy. Therefore, all we have to report is the Gleason score, which is mentioned in the results section below.

All patients were treated with androgen deprivation initially with an androgen receptor blocker or ketoconazole for several weeks, which was given at the discretion of the treating physician. Following initial treatment, all patients were placed on an LHRH agonist. Biochemical failure was defined as a rise in serum PSA from nadir levels with a castrate testosterone level less than 50ng/mL. Individuals with evidence of biochemical failure were referred to medical oncology for initiation of secondary treatment. Secondary treatment was administered at the discretion of the treating medical oncologist.

Using SPSS 17.0 we constructed Kaplan Meier probability curves for overall survival and cancer specific survival.

RESULTS

Our patient population was predominantly African American (N = 126) with only two Hispanic and one Middle Eastern patient in our cohort. The median age at presentation was 68 years (IQR 63,75) with a median total Gleason sum of 8 (IQR 7.75,9). The median PSA level at presentation was 275ng/mL (IQR 132,88). The median creatinine level and hematocrit were 1.2mg/dL (IQR 1,1.6) and 37.9 (IQR 32.2,41.4), respectively (Table-1). The median follow-up was 26.6 months. The patients in this cohort presented over the course of 10 years (1999-2009), however our median follow-up time for these individuals was only 26.6 months.

Thirty-two patients presented with hydronephrosis with a median creatinine of 1.79ng/dL (IQR 1.04, 4.12), two of whom required emergent dialysis. Thirteen of the 32 patients (40.6%) who presented with hydronephrosis required intervention with either a percutaneous nephrostomy tube or ureteral stent placement. Intervention

Table 1 - Demographics and presenting laboratory values (median).

Age	68
PSA	275ng/mL
Race	
African American %	97.7
Other %	2.3
Gleason Sum	8
Creatinine	1.2mg/dL
Patients needing dialysis	2
Hematocrit %	37.9

was required because of intractable flank pain or evidence of acute renal failure.

Screening CT scans were performed in 93 patients. Of those patients who underwent imaging at presentation 33/93 (35.5%) were found to have lymphadenopathy suspicious for metastasis, 15/93 (16.1%) had masses suspicious for visceral metastasis with the predominant site being the liver or lungs. Positive bone scans were identified in 118/127 (93%) patients with 10/127 (7.9%) exhibiting suspicion of cord compression (Table-2).

Table 2 - Findings on imaging within 30 days of diagnosis (%).

Lymphadenopathy	65.5
Visceral metastases	16.1
Bone scan positive	93
Spinal Cord Compression	7.9

Six patients were lost to follow-up prior to obtaining the first post-treatment PSA level. Undetectable levels of PSA were achieved in 35/123 (28.4%) patients. The median time for the first PSA rise above initial treatment PSA, if it occurred, was 6.8 months (IQR 3.1,11.2). The median PSA at time of biochemical failure was 18.69ng/mL (IQR 2.1, 186.2).

The 2-year and 5-year cancer specific survival for our patient cohort was 89.4% and 62.7%, respectively (Figure-1). On univariate analysis creatinine at presentation ($p < 0.05$) and the presence of suspicious lymph nodes ($p = 0.012$) were independent predictors of PCa mortality. On multivariate analysis we were unable to identify any significant predictors of mortality. Using Kaplan-Meier survival analysis we compared the patients who presented with either lymphadenopathy or visceral metastasis to those who did not. The 5-year survival for patients with lymphadenopathy suspicious for metastatic disease on imaging compared to normal imaging was 42.5% and 75.4%, respectively ($p = 0.074$) (Figure-2). When comparing those patients with imaging findings suspicious for visceral metastasis to those with normal imaging we found a 5-year survival of 27.5% and 65.3% respectively ($p = 0.012$) (Figure-3).

Unfortunately, we did not have access to death certificates or actual cause of death for the vast majority of the patients in this database.

DISCUSSION

The findings reported in the present study provide additional insight into the severe morbidity and mortality associated with mPCa in an underserved, predominantly African American population despite widespread use of PSA screening. In our cohort we identified 202 patients, 129

Figure 1 - Kaplan-Meier Cancer Specific Survival Curve.

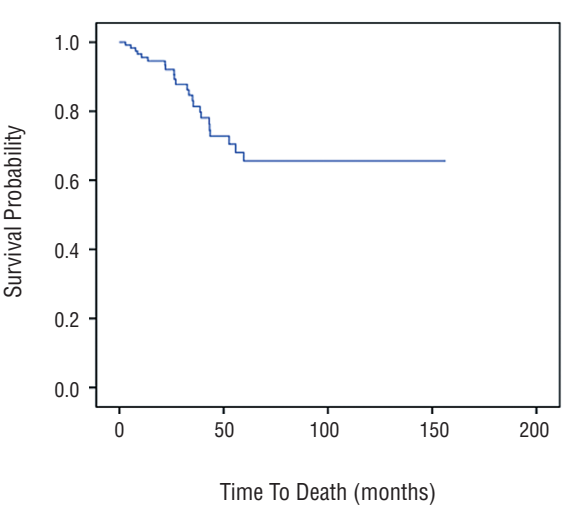


Figure 2 - Kaplan-Meier Survival Lymph Node Positive Disease Curve.

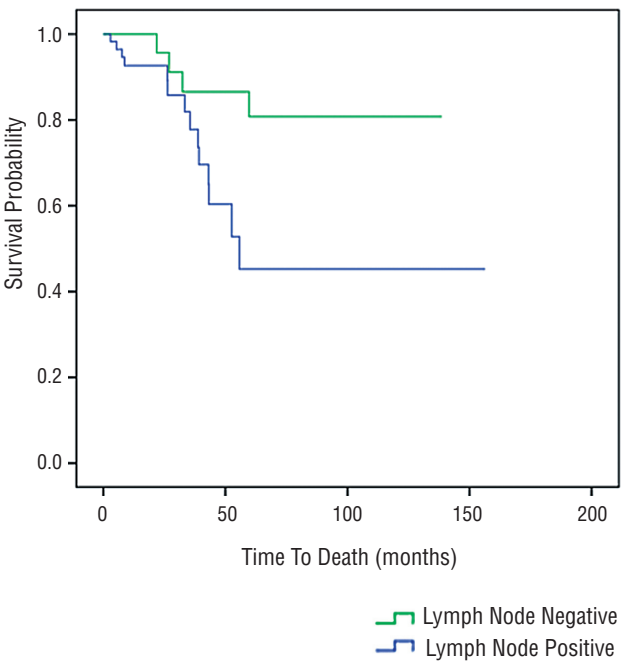
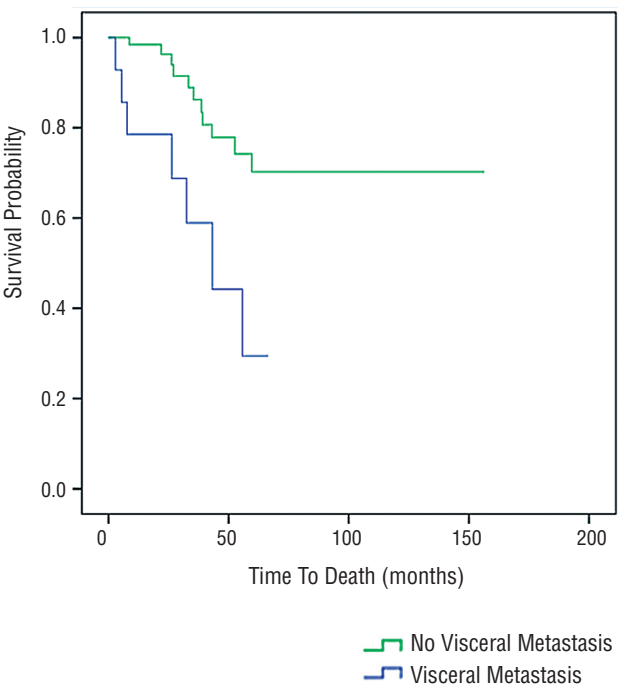


Figure 3 - Kaplan-Meier Survival Visceral Metastasis Curve.



evaluable based on our inclusion criteria, who were diagnosed with mPCa on initial presentation. The patients in this study were treated at an inner-city hospital that primarily serves individuals of lower SES often who have immigrated from third world countries in which PSA screening is largely unavailable. These patients presented with a significant cancer burden; 93% of which had skeletal metastases identified on bone scan, 65.5% had suspicious lymph nodes and 16.1% showing evidence of visceral metastasis on CT scan. Ten (7.9%) of these patients had radiological evidence of spinal cord compression, which is consistent with currently reported numbers in patients with mPCa (7-10). As expected, we also demonstrated that patients presenting with evidence of visceral metastases had a significantly higher mortality rate. While one can see a clear separation in mortality rates between patients with and without lymphadenopathy at presentation, this was not statistically significant ($p = 0.074$) likely due to the low number of patients in each group. In addition, imaging was only evaluated at time of presentation in these patients. Therefore, if our review was expanded we would have found higher rates of lymphadenopathy on later imaging, thus increasing the power of the analysis.

In previously reported studies with a more heterogeneous subset of patients, overall survival in men with metastatic disease was found to range from 5 to 7 years (11-14). Only 62.7% of our patient population was alive at 5 years. In spite of hormonal therapy, we demonstrated a median time to PSA rise above nadir of 6.8 months in this cohort. Ultimately, our findings reaffirm the notion that despite current therapies, those with distant metastases involving lymph nodes and/or visceral organs at the time of presentation have considerably poorer prognoses underscoring the importance of PSA screening in our male population.

Our patients in this study were predominately of African American descent, residing in an underserved area. In a SEER database study, Cheng et al. compared mortality rates from PCa based on SES and race. They demonstrated that higher SES is associated with a higher incidence of PCa but a lower mortality rate. Upon further analysis of patients with low SES they reported a higher mortality rate and when sub-stratified by

race they discovered that mortality rates from this disease were substantially higher among African-American men when compared to other racial/ethnic groups (15). The conclusions of this study in conjunction with our findings reinforce the potential danger of eliminating PSA screening in the general population but particularly in high-risk groups.

Despite the fact that overall rates of mPCa appear to be declining, our results and the conclusions of other recent studies reaffirm the notion that at risk populations would suffer greatly from the elimination of PCa screening (3,4,15-17). One such retrospective review, performed by Miller et al., examined 570 low-income uninsured men with the diagnosis of PCa. They demonstrated that 51% of these patients had a PSA greater than 10ng/mL, 50% had a Gleason score of 7 or greater, 43% had T2 or greater clinical stage, and 19% had metastatic disease at the time of diagnosis. They also showed that organ confined, low risk PCa did not increase over the 5-year period among these men (4). In our study we report a median PSA of 275ng/mL and a median Gleason sum of 8 from an underserved population of men who presented with mPCa. Clearly, PCa remains a significant public health concern, in particular in African-American men living in underserved areas. Therefore, we strongly feel that in order to diminish the racial and socioeconomic inequalities with regards to PCa morbidity and mortality, this high-risk population may benefit from a more comprehensive screening effort on behalf of primary care physicians and urologists alike.

There are several limitations of the present study. Despite being a prospectively maintained database, this was a strictly observational, retrospective analysis demonstrating the experience at a single institution. In addition, this cohort was homogeneous in its racial/ethnic breakdown therefore generalizations regarding the specific features of mPCa may not be extrapolated to the likes of the general population from this data alone.

CONCLUSIONS

We describe a cohort of men from an underserved area with mPCa on initial presentation in the PSA screening era. Our results underscore the notion that despite widespread use of PSA screening, aggressive, life-threatening PCa still exists. Additional studies should be performed focusing more specifically on the effect of PSA screening in an underserved population.

ABBREVIATIONS

PCa = prostate cancer
mPCa = metastatic prostate cancer
PSA = prostate specific antigen
SES = socioeconomic status
CT = computed tomography
LHRH = luteinizing hormone releasing hormone
IQR = interquartile range
SEER = surveillance, epidemiology and end-results
USPSTF = U.S. preventative services task force
PLCO = prostate, lung, colorectal and ovarian

CONFLICT OF INTEREST

None declared.

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Tailored treatment including radical prostatectomy and radiation therapy + androgen deprivation therapy versus exclusive radical prostatectomy in high-risk prostate cancer patients: results from a prospective study

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ABSTRACT

Purpose: To evaluate outcomes of patients with high risk prostate cancer (PCa) who underwent radical prostatectomy (RP) in a context of a multidisciplinary approach including adjuvant radiation (RT) + androgen deprivation therapy (ADT).

Matherials and Methods: 244 consecutive patients with high risk localized PCa underwent RP and bilateral extended pelvic lymph node dissection at our institution. Adjuvant RT + 24 months ADT was carried out in subjects with pathological stage ≥ T3N0 and/or positive surgical margins or in patients with local relapse.

Results: After a median follow-up was 54.17 months (range 5.4-117.16), 13 (5.3%) subjects had biochemical progression, 21 (8.6%) had clinical progression, 7 (2.9%) died due to prostate cancer and 15 (6.1%) died due to other causes. 136 (55.7%) patients did not receive any adjuvant treatment while 108 (44.3%) received respectively adjuvant or salvage RT+ADT. Multivariate Cox proportional hazard analysis showed that pre-operative PSA value at diagnosis is a significant predictive factor for BCR (HR: 1.04, $p < 0.05$) and that Gleason Score 8-10 (HR: 2.4; $p<0.05$) and PSMs (HR: 2.01; $p < 0.01$) were significant predictors for clinical progression.

Radical prostatectomy group was associated with BPFS, CPFS, CSS and OS at 5-years of 97%, 90%, 95% and 86% respectively, while adjuvant radiation + androgen deprivation therapy group was associated with a BPFS, CPFS and CSS at 5-years of 91%, 83%, 95% and 88%, without any statistical difference.

Conclusions: Multimodality tailored treatment based on RP and adjuvant therapy with RT+ADT achieve similar results in terms of OS after 5-years of follow-up.

ARTICLE INFO

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high-risk; prostate cancer; radical prostatectomy; androgen deprivation therapy; radiation therapy; multimodality

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INTRODUCTION

Prostate cancer (PCa) is the most commonly diagnosed non-dermatologic malignancy among American men, and it remains the second most fatal cancer. Similar incidence and mortality figures are reported by the European Association of Urology (EAU) (1).

The goal of PCa screening is to detect potential fatal cancers at a time when they may still be curable. The downside of screening is the diagnosis and overtreatment of tumours destined

to pose no threat to the man during his lifetime. The upside of screening is the detection of high-risk cancers while still clinically localized. In a heavily screened population, this "high-risk" group accounts for 15% of men with clinically localized disease and likely a higher percentage in less heavily screened population (2).

In the presence of adverse clinical or pathologic features connoting high-risk disease, results of local treatment alone are disappointing and there is increasing recognition of the need for a multimodal approach to treatment (3,4). The optimal sequence and constituents of such a strategy, however, remain controversial. The use of external-beam RT as primary therapy in conjunction with androgen-deprivation therapy (ADT) is supported by the results of several randomized controlled trials (RCTs) (5-8). Alternatively, surgery may be employed as the definitive initial treatment. While radical prostatectomy (RP) has not been traditionally recommended for high-risk disease in the past, its use in this setting is increasing, as evidenced by several large, modern, single-institution series (9-12). Currently, multimodality approaches, including surgery, adjuvant radiotherapy and androgen deprivation therapy are proposed for high risk prostate cancer.

The aim of this study is to evaluate outcomes of patients with high risk prostate cancer who underwent RP in a context of a multidisciplinary approach including surgery alone or adjuvant or salvage radiation therapy + androgen deprivation therapy.

MATERIAL AND METHODS

Study Population

From January 2003 to December 2006, 244 consecutive patients with high risk localized PCa (PSA greater than 20 ng/mL, and/or cT3-4 and/or biopsy Gleason Score 8-10) who underwent retropubic radical prostatectomy (RP) and bilateral extended pelvic lymph node dissection (eLND) at a single institution were enrolled in this prospective study.

The protocol was approved by the Internal Institutional Review Board and an informed written consent was obtained from each man before initiation of the study.

Clinical stage was assigned according to the 2002 TNM and prostate biopsy was performed under transperineal ultrasound guidance. Preoperative staging with CT and bone scan showed no signs of metastases. None of the patients received neoadjuvant ADT. All patients underwent extended lymph node dissection including bilateral dissection of the right and left common iliac vessels, the right and left internal iliac vessels, the right and left external iliac vessels, and the right and left obturator fossa (≥ 20 lymph node).

Follow-up included DRE and serum PSA every 3 months, CT and bone scan annually or when clinically appropriate; TRUS + biopsy of the prostatic bed when clinically required. The baseline information, Charlson Comorbidity Index (CCI), the pathologic Gleason score, surgical margin (SM) status, seminal vesicle invasion (SVI), and the follow-up information were recorded for each subject.

Postoperative therapy

Postoperative therapy was considered adjuvant therapy if it was begun before PSA or clinical progression. Patients with pathological pelvic lymph node metastases were excluded.

Adjuvant radiotherapy + 24 months ADT was carried out in subjects with pathological stage ≥ T3N0 and/or positive surgical margins at 4 to 6 weeks after surgery while salvage RT + 24 months ADT in patients with local relapse confirmed after biopsy of the prostatic bed. Radiotherapy was performed with intensity-modulated technique using 18-MV photons of an Elekta linear accelerator (Elekta AB, Crawley, UK) equipped with a multileaf collimator. The clinical target volume (CTV) consisted of the postoperative prostate and seminal vesicle bed. To create the planning target volume (PTV), an isotropic, 3-dimensional, 7-mm expansion of the CTV was performed. Treatment was delivered in 37 fractions with a median 76-Gy dose to the PTV (range: 70-79 Gy). ADT consisted of triptorelin 11.25 mg administered every 3 months as LHRH analogue.

Biochemical progression after surgery was defined as the first occurrence of two consecutive PSA levels above 0.2ng/mL at follow-up. Clinical progression was defined as either local recurrence or distant metastasis. Local recurrence was defined as histologically confirmed evidence of cancer cells

in targeted biopsies at the prostatic bed. Distant metastasis was defined as a positive finding on bone scan or imaging examination. Prostate Cancer Specific Mortality (PCSM) was defined as the time from RP to death for PCa or disease related complications while Other-Cause Mortality (OCM) as the time from RP to death not depending for PCa. Prostate Cancer-Specific Survival (PCSS) was defined as the time from RP to PCSM while overall survival (OS) was defined as the time from RP to death from any cause.

Statistical analysis

All statistical analyses were completed using *SPSS* v. 19 software (SPSS Inc, IBM Corp, Somers, NY, USA). Cox univariate and multivariate regression models were carried out to identify variables for predicting biochemical recurrence (BCR), clinical progression (CP), prostate cancer specific mortality (PCSM) and other-cause mortality (OCM) from preoperative variables including age, PSA levels, clinical T stage, biopsy Gleason score and from postoperative variables including pathological Gleason score, positive margin status, seminal vesicle invasions, and adjuvant treatment conditions. Biochemical progression-free survival (BPFS), clinical progression-free survival (CPFS), prostate cancer-specific survival (PCSS) and overall survival (OS) were determined using the Kaplan-Meier method and curves were tested with the log-rank test. Life-tables of each subgroup were analyzed using the Wilcoxon (Gehan) test. For all statistical comparisons significance was considered as $p < 0.05$.

RESULTS

Table-1 lists the baseline characteristics of the subjects included in this study. Median of pre-operative PSA level was 20ng/mL (range 1-82), median of age of patients was 68 (range 48-78) and CCI was respectively < 2 and ≥ 2 in 159 (65.2%) and 85 (34.8%) subjects. Upstaging and upgrading was found in 72 (29.1%) and 49 (20.08%) patients and median follow-up was 54.17 months (range 5.4-117.16), 13 (5.3%) subjects had biochemical progression, 21 (8.6%) had clinical progression, 7 (2.9%) died due to prostate cancer and 15 (6.1%) died due to other causes. 136 (55.7%) patients did not receive any adjuvant treatment while 108 (44.3%) received respectively adjuvant or salvage RT+ADT.

Multivariate Cox proportional hazard analysis showed that pre-operative PSA value at diagnosis is a significant predictive factor for BCR (HR: 1.04; $p < 0.05$) and that Gleason Score 8-10 (HR: 2.4; $p<0.05$) and PSMs (HR: 2.01 (0.75-3.12); $p < 0.01$) were significant predictors for clinical progression (Table-2). None of the pre-operative and post-operative variables were predictors of PCSM and OCM. Kaplan-Meier curves showed no significant differences between groups when considering BPFS, CPFS, CSS and OS. (Figure-1). The over-all 5-years BPFS, CPFS, PCSS and OS were respectively 94%, 85%, 95% and 87%. Radical prostatectomy alone was associated with BPFS, CPFS, CSS and OS at 5-years of 97%, 90%, 95% and 86% respectively, while adjuvant radiation + androgen deprivation therapy was associated with a BPFS, CPFS and CSS at 5-yr of 91%, 83%, 95% and 88% (Table-3).

DISCUSSION

In the past, RP was not considered an acceptable treatment in patients with high-risk prostate cancer. However, thanks to the improvements in surgical techniques and technologies, RP and adjuvant treatments are now increasingly being used in selected patients.

The exact definition of high risk is a matter of debate. High-risk, clinically localised disease was classically defined by D'Amico et al. as any combination of the following factors: a prostate-specific antigen (PSA) score > 20ng/mL, a Gleason score of 8-10, or clinical stage T2c or greater (13). More recently, the National Comprehensive Cancer Network and EAU have modified this definition to include any combination of a clinical T3, a PSA score > 20ng/mL, or a Gleason score of 8-10.

Several authors suggest the use of a combination of PSA, Gleason score, and clinical stage to predict outcomes after radical prostatectomy (RP) in patients with a PSA $\geq$ 20ng/mL, assuming that the use of a single criterion may overestimate the risk of recurrence and may not identify the

Table 1 - Clinical and pathological characteristics of patients.

	Overall (n = 244)	Exclusive RP (n = 136)	RT+ADT (n = 108)	p-value
Median (range) age, years	68 (48-78)	68 (53-78)	67 (48-78)	0.40
Median (range) PSA at baseline, ng/mL	20 (1-82)	14 (1-69)	21 (3-82)	0.03
CCI, n (%)				0.11
< 2	159 (65.2)	83 (61.0)	76 (70.4)	
≥ 2	85 (34.8)	53 (39.0)	32 (29.6)	
Clinical stage, n (%)				0.27
T1c	16 (6.6)	12 (8.8)	4 (3.7)	
T2	206 (84.4)	112 (82.4)	94 (87.0)	
T3a	22 (9.0)	12 (8.8)	10 (9.3)	
Biopsy Gleason score, n (%)				0.14
≤ 6	48 (19.7)	32 (23.5)	16 (14.8)	
7	43 (17.6)	20 (14.7)	23 (21.3)	
8-10	153 (62.7)	84 (61.8)	69 (63.9)	
Pathological Gleason score, n (%)				0.01
≤ 6	30 (12.3)	20 (14.7)	10 (9.3)	
7	105 (43.0)	66 (48.5)	39 (36.1)	
8-10	109 (44.7)	50 (36.8)	59 (54.6)	
Pathological stage, n (%)				< 0.01
pT2	80 (32.8)	64 (47.1)	16 (14.8)	
pT3a	104 (42.6)	46 (33.8)	58 (53.7)	
pT3b-4	60 (24.6)	26 (19.1)	34 (31.5)	
Upgrading, n (%)	49 (20.08)	25 (18.38)	24 (22.22)	0.09
Upstaging, n (%)	72 (29.1)	34 (25.0)	37 (34.26)	0.10
PSMs, n (%)	86 (35.2)	60 (55.6)	26 (19.1)	< 0.01
SVI, n (%)	65 (26.6)	0 (0.0)	28 (26.6)	< 0.01

true high-risk patient (14). In fact, men with a high level of PSA and a Gleason grade ≤ 7 had very low risk for cancer progression. Alternatively, men with multiple high-risk features (i.e., PSA > 20ng/mL, biopsy Gleason score 8-10, or clinical stage T3 disease) had poor outcomes despite surgery (15).

Data from the randomized controlled trial EORTC 22911 demonstrated that conventional postoperative irradiation significantly improves biochemical progression-free survival and local control compared with a wait-and-see policy at 5

Table 2 - Multivariate cox regression analysis of preoperative and pathological predictors of biochemical recurrence and clinical progression.

	Biochemical Recurrence		Clinical Progression	
	Multivariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Patient age, years	1.03 (0.89-1-19)	0.68	1.10 (0.94-1.28)	0.23
PSA level, ng/mL	1.04 (1.00-1.06)	0.04	0.68 (0.98-1.05)	0.68
Clinical T stage				
T1c	1.00 (Ref.)		1.00 (Ref.)	
T2	2.78 (0.10-4.63)	0.97	1.42 (0.1-6.69)	0.96
T3-4	4.00 (0.10-6.68)	0.96	2.97 (0.2-6.31)	0.97
Biopsy Gleason Score				
≤ 6	1.00 (Ref.)		1.00 (Ref.)	
7	3.07 (0.1-3.27)	0.95	3.14 (0.18-77.76)	0.48
8-10	6.57 (0.2-6.94)	0.95	4.25 (1.10-5.77)	0.38
Pathological Gleason Score				
≤ 6	1.00 (Ref.)		1.00 (Ref.)	
7	1.48 (0.50-4.80)	0.53	1.2 (1.1-1.4)	0.04
8-10	2.57 (0.48-4.22)	0.58	2.4 (1.0-2.8)	0.03
Pathological Stage				
T2	1.00 (Ref.)		1.00 (Ref.)	
T3a	1.44 (1.12-2.56)	0.55	2.36 (1.74-3.56)	0.50
T3b-T4	2.23 (0.32-15.54)	0.41	3.23 (2.02-4.50)	0.30
PSMs, yes vs. no	1.46 (0.84-1.98)	0.72	2.01 (0.75-3.12)	< 0.01
SVI, no vs. yes	0.87 (0.2-2.66)	0.74	0.83 (0.04-2.65)	0.64

and 10 years follow-up (16,17).

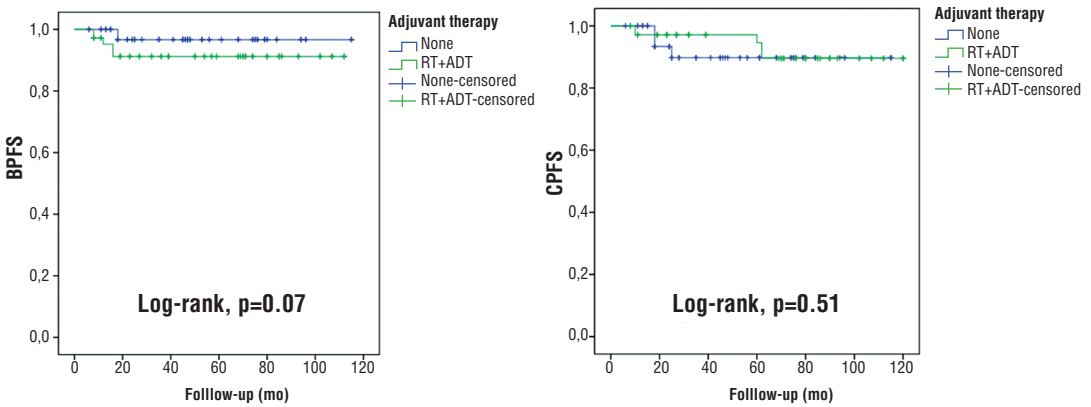
In addition, results from the SWOG 8794 showed that adjuvant radiotherapy within 18 weeks after radical prostatectomy in a men with pT3N0M0 prostate cancer significantly reduces the risk of PSA recurrence, metastasis and the need for hormonal therapy, and significantly increases survival (18).

More recently, in a retrospective study of Ost et al., it has been showed that adjuvant RT + ADT significantly improved biochemical and clinical progression rates after a median follow-up of 5 years in patients with unfavourable pathological findings (19,20).

In our study, good oncological outcomes seem to be obtained even in patients with worse pathological characteristics (i.e. pathological stage ≥ T3N0 and/or positive surgical margins) who needed adjuvant or salvage treatment like RT + ADT, with an estimated BPFS, CPFS, PCSS and OS of 94%, 85%, 95% and 87%respectively.

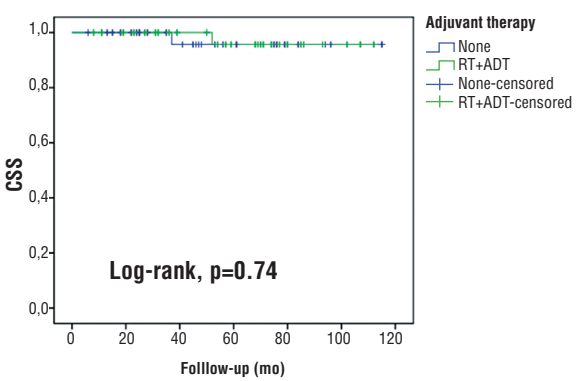
Androgen deprivation given in combi-

Figure 1 - Kaplan-Meier curve analysis of BFPS, CPFS, PCSS and OS between groups.

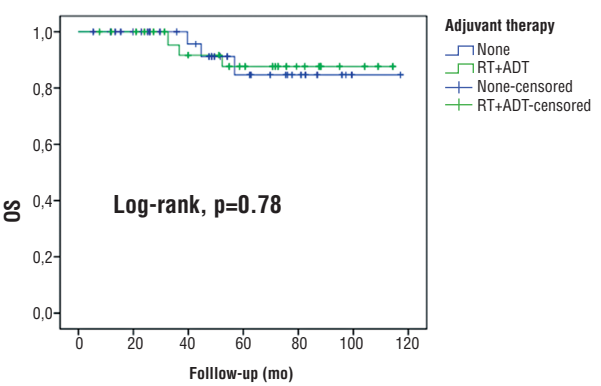


No. at risk	0 mo	36 mo	60 mo
None	132	76	26
RT+ADT	104	71	26

No. at risk	0 mo	36 mo	60 mo
None	136	76	26
RT+ADT	108	79	41



No. at risk	0 mo	36 mo	60 mo
None	136	80	26
RT+ADT	108	76	27



No. at risk	0 mo	36 mo	60 mo
None	136	89	26
RT+ADT	108	78	29

Table 3 - Life tables comparison of BPFS, CPFS, PCSS and OS between both groups.

	BPFS at 5-years		CPFS at 5-years		PCSS at 5-years		OS at 5-years	
	Cumulative Survival Rate	P-value	Cumulative Survival Rate	P-value	Cumulative Survival Rate	P-value	Cumulative Survival Rate	P-value
Adjuvant		0.20		0.64		0.83		0.90
Exclusive RP	97%		90%		94%		86%	
RT+ADT	90%		80%		94%		87%	

nation with RT in men with high risk prostate cancer demonstrates clinical benefits. The advantages appear to be related both to the ability of androgen deprivation to make prostate cancer more susceptible to radiation induced death and by killing or suppressing cancer cells that might have escaped from the prostate gland.

The role of lymph node dissection was addressed by Engel et al., who compared outcomes in LN positive patients with or without RP. They showed a survival benefit for local treatment even in positive lymph node disease, suggesting that RP may result in improved outcomes. However, these results must be viewed with caution given the greater proportion of prostatectomy abandonment in patients with unresectable and therefore more advanced disease (21). In our series, extended lymph node dissection was considered as integral part of the treatment.

Despite the different pathological characteristics of these patients, these tailored multimodality approach could offer benefits, with substantial survival gains of the RT+ADT group. In fact, we did not observe statistically differences in term of BPFS, CPFS, CSS and OS between groups. Certainly, the adjuvant or salvage therapy uniforms the survival rate to those patients who underwent exclusive RP.

However, the crucial question whether the optimum initial strategy should include radiation combined with androgen deprivation therapy at the time of RP, or surgery followed by selective radiation on the basis of pathological findings is still open (22).

Finally, to the best of our knowledge, this is the first study that report similar benefits in term of OS in high-risk prostate cancer patients who underwent a tailored treatment based on pathological features including RP alone and adjuvant or salvage therapy including RT+ADT when clinically required. However, our study contains potential limitations that need to be considered.

One possible limitation is the identification of high-risk prostate cancer patients based on D'Amico definition despite possible favorable features at pathological specimens after surgery.

Moreover, the short follow-up might have underestimated the overall risk of relapse and mortality, because it is well known that PCa progresses slowly and our median follow-up could be considered insufficient (23). Finally, recent observations demonstrated the importance of comorbidities, evaluated as Charlson Comorbidity Index (CCI), when showing long-term survival in high-risk prostate cancer patients (24). In this context, the role of radical prostatectomy even in patients with high risk prostate cancer should be cautious, due to the limited life expectancy. However, the small sample size and the impact of comorbidity on patient survival might have been underestimated in our analyses.

CONCLUSIONS

Although the heterogeneous pathological characteristics of our cohort of high-risk prostate cancer multimodality, tailored treatment based on RP and adjuvant or salvage therapy with RT+ADT achieved similar results in terms of BPFS, CPFS, CSS and OS after 5-years of follow-up.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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The cumulative analgesic consumption score (CACS): evaluation of a new score to describe postsurgical analgesic consumption as a surrogate parameter for postoperative pain and invasiveness of surgical procedures

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ABSTRACT

Objective: To validate and evaluate the applicability of a new score to describe postsurgical analgesic consumption in urological and surgical patients across different categories of pain medications and the invasiveness of medical interventions.
Materials and Methods: The cumulative analgesic consumption score (CACS) was determined for two cohorts of patients split into three groups with surgeries involving clinically distinct levels of invasiveness (n = 2 x 60). Nonparametric statistical analyses were performed to determine differences between the CACS among the different groups and to assess the correlation between CACS and numeric rating scale (NRS) values for pain intensity.
Results: The score was determined for postoperative days 1 and 2 and revealed median scores of 0 (0-11), 3 (0-22) and 10 (6-17) for UA (urological patients from group A), UB (group B) and UC (group C), respectively, and 4 (0-20), 8 (0-38) and 17 (7-68) for SA (surgical patients from group A, SB (group B) and SC (group C), respectively. CACS enabled reliable differentiation between groups involving different levels of invasiveness ($p < 0.001$). CACS and peak NRS values showed variable degrees of correlation, as expressed by levels of significance ranging from $p < 0.001$ to $p = 0.34$ (NS).
Conclusions: The CACS is a valid and easily applicable tool to describe postsurgical analgesic consumption in urological and surgical patients. It can be used as a surrogate parameter to assess postsurgical pain and the invasiveness of surgical procedures. These aspects may be measured to compare surgical procedures, in both clinical trials and clinical practice settings.

ARTICLE INFO

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Surgical Procedures, Operative; Analgesics; Postoperative Period

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INTRODUCTION

Following the development of minimally invasive surgery, measurements of invasiveness have become an issue of increasing scientific interest, particularly in parallel group trials comparing interventional and surgical treatments, such as laparoscopic and open surgery (1-4). Postoperative pain

correlates with the severity of impairment of bodily integrity, and hence with the invasiveness of surgical interventions. We hypothesize that pain and postoperative analgesic consumption (AC) constitute non-invasive measurement tools for surgical invasiveness when compared with other determinants of invasiveness such as inflammatory and immunologic markers (5).

Evaluation of pain is usually accomplished using numerical methods of pain measurement such as a visual analog scale (VAS) or a numeric rating scale (NRS). These have been widely accepted as patient-reported outcome (PRO) measurement tools and are commonly used in clinical trials and clinical practice settings to assess pain intensity (6-8). However, numerous confounding factors influence sensations of pain, and no agreement has been reached as to which is the gold standard method for assessing pain (9).

AC is a clinically reported outcome (CRO), which can be used as a surrogate parameter for postoperative pain (2) and analgesimetry (10,11). However, data establishing the validity of AC as a CRO in clinical trials on interventional and surgical treatments are scarce, and no generally applicable scheme has been established to evaluate AC (2). Comparisons in postoperative AC are usually conducted by counting doses of a defined drug (12,13), computed morphine equivalents (14) or patient-controlled analgesia (PCA) (15).

The cumulative analgesic consumption score (CACS) was developed in cooperation with the Department of Anesthesiology. It integrates a classification of AC by potency (qualitative) and by dose measurement (quantitative). The qualitative assessment is based on a modified version of the WHO pain relief ladder (WHO I - III) (16,17), which disregards the administration of any adjuvant medications. The quantitative assessment is carried out by summing up single administrations, but not individual doses, of a certain drug. Computed values for each WHO category are counted to obtain the CACS for an individual patient. As a mathematical formula the CACS may be expressed as:

An adequate timeframe must be defined, e.g., postoperative days 1 to 3 after minor surgery or postoperative days 1 to 8 after major surgery. The index is conceived as an open-ended scale that can be used for different timeframes.

MATERIALS AND METHODS

Informed consent requirements for this retrospective study were approved by the local ethics committee and were therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The CACS was determined for two cohorts of urological and surgical patients (n = 2 x 60). Each cohort was split into groups that received surgical treatments of different invasiveness from a clinical standpoint. Urological patients from group A (UA) had received interventions such as the insertion of an ureteral stent or a percutaneous nephrostomy tube; those of group B (UB) had undergone transurethral resection of the bladder or prostate, ureteroscopy or surgery of the external genitalia; and those of group C (UC) (18) had been treated by laparoscopic or open surgery of the kidney, bladder or prostate. Surgical patients from group A (SA) were those that had undergone minor surgery such as appendectomy or hernia repair; those of surgical group B (SB) were patients who had undergone medium scale surgical interventions such as cholecystectomy or thyroidectomy, and those of group C (SC) were patients who had undergone major surgery, e.g., hemihepatectomy or rectal resection. The timeframe for CACS determination was defined as the first two postoperative days, as this was the minimum duration of inpatient stay for all patients. Patients received preemptive/baseline and on-demand analgesic medications, according to standard protocols for medium or major surgery, or on-demand medications for minor interventions. Based on the WHO pain relief ladder (15,16), specified protocols for various surgical procedures included the following drugs: step 1 (non-opioids): acetaminophen, ibuprofen or metamizole; step 2 (opioids for mild to moderate pain): tramadole,

Σ = n x step of WHO pain relief ladder

e.g.: 2 x WHO step III + 3 x WHO step II + 5 x WHO step I = 6+6+5 = CACS 17

tilidine/naloxone; and step 3 (opioids for moderate to severe pain): piritramide, pethidine, oxycodone or morphine. Patients treated with PCA or regional anesthesia and patients on analgesic long-term medication were excluded from the study.

All patients were asked to indicate their subjective sense of pain on an NRS (ranging from 0 = "no pain" to 10 = "worst possible pain"). Pain was assessed three times a day at rest and (if possible) after mobilization for the first two postoperative days, and if the patient expressed extensive pain. NRS and CACS scores were retrospectively determined based on data obtained from the electronic patient records of our department.

The primary objective of the study was to confirm if there were significant differences in CACS values between groups SA, SB and SC and between groups UA, UB, UC (as assessed by the Kruskal-Wallis test and Mann-Whitney test). The secondary objective was to confirm if a high correlation existed between CACS (objective measurement of analgesic consumption) and NRS values (subjective pain sensation) for each group, using Spearman's rank-correlation test.

RESULTS

Review of patients' records enabled retrieval of all necessary values, with no missing data.

CACS values ranged from 0 to 11 (median 0) for group UA, from 0 to 22 (median 3) for group UB, and from 6 to 17 (median 10) for group UC; in the surgical cohort, values ranged from 0 to 20 (median 4) for group SA, from 0 to 38 (median 8) for group SB, and from 7 to 68 (median 17) for group SC. Statistical analysis confirmed the ability of CACS to differentiate reliably between groups involving different levels of invasiveness (p-values < 0.001). In contrast, this was not true in the same way for corresponding mean and peak NRS values for pain sensation (p-values ranging from "non significant" (NS) to < 0.005) (Table-1).

Comparison of CACS and peak NRS values revealed variable correlations, as expressed by levels of significance ranging from p < 0.001 for UA and UB to p = 0.21 (NS) for UC, and from p < 0.001 for groups SA and SB to p = 0.34 (NS) for group SC (Table-2).

DISCUSSION

The presented data demonstrate the clinical applicability of a newly developed score to determine postsurgical analgesic consumption. Given that pain and AC stand in a close correlation to the invasiveness of a specific procedure, our data suggest a stronger correlation between CACS values

Table 1 - CACS values and corresponding NRS values for pain (urological and surgical patients).

Patient group (3 x n = 20)	CACS (median, range)	NRS mean (median, range)	NRS peak (median, range)
UA (minor surgery)	0 (0 – 11)	0 (0 – 2.50)	0 (0 – 7)
UB (medium scale surgery)	3.00 (0 – 19)	1.0 (0 – 3.75)	2.0 (0 – 8)
UC (major surgery)	10.0 (6 – 17)	1.83 (0 – 3.15)	4.0 (0 – 6)
	P < 0.001	P < 0.005	P < 0.005
SA (minor surgery)	4.0 (0 – 20)	1.25 (1 – 5)	2.0 (1 – 8)
SB (medium scale surgery)	8.0 (0 – 38)	2.83 (0.5 – 6)	4.0 (1 – 10)
SC (major surgery)	17.0 (7 – 68)	3.01 (0 – 9)	6.0 (0 – 10)
	P < 0.001	P < 0.1 (n.s.)	P < 0.005

CACS values and corresponding **NRS** values for pain (mean, peak) for different types of urological (yellow field; group **UA =** minor, group **UB =** medium, group **UC =** major) and surgical interventions (red field; group **SA** = minor; group **SB =** medium; group **SC =** major) , levels of significance concerning the ability to differentiate surgical groups (using Kruskal-Wallis-test)

Table 2 - Correlation between CACS and peak NRS.

6 x n = 20 patients	Spearman's rank correlation coefficient	Significance (2-sid.)
UA	0.749	p < 0.001
UB	0.761	p < 0.001
UC	0.303	p = 0.21 (n.s.)
SA	0.797	p < 0.001
SB	0.901	p < 0.001
SC	0.226	p = 0.34 (n.s.)

Correlation between **CACS** and peak **NRS** for pain for different types of surgical and urological interventions (groups **SA/ UA =** minor surgery; groups **SB/ UB =** medium scale surgery; groups **SC/UC =** major surgery)

(AC) and invasiveness of different urological and surgical procedures than NRS pain scores.

In recent years, considerable efforts have been made to further minimize surgical trauma and reduce the adverse effects of surgery. Methods to determine the impact of different surgical approaches such as laparoscopic and open surgery include inflammatory and immunologic markers of invasiveness (5); clinical outcome parameters such as hematocrit drop, duration of surgery and postoperative pain (3,19); and social indicators like time of return to work and to full physical activity (20).

Postoperative pain correlates with the severity of impairment of bodily integrity, and hence with the invasiveness of surgical interventions, with a major impact on surgical site physiological function (21,22) and the patient's functional recovery (23).

However, numerous confounding factors influence the sensation of pain and there is no agreement regarding the best method of assessing pain scores, particularly regarding the timing and frequency of scoring, e.g., prescheduled determination of pain scores (three times a day), recording of peak pain levels, or the temporal context of administration and type of pain medication (9). Others have highlighted the distinction between "pain at rest" (PAR) and "movement-evoked pain" (MEP) and suggested that both PAR and MEP should be measured in postsurgical pain research (24).

In contrast, AC is a CRO (rather than a PRO) and can therefore be used as a surrogate parameter for postsurgical pain (2) and hence for surgical invasiveness. The CACS depicts AC as a non-invasive parameter, unlike the laboratory markers mentioned above.

There is a wealth of literature on AC as a method for measuring the analgesic efficacy of new drugs and other treatment modalities such as nerve blocks and transcutaneous electrical nerve stimulation, and for confirmation of new concepts such as pre-emptive analgesia (more than 600 trials have been performed) (10). However, postsurgical AC has been measured only rarely as a secondary outcome parameter in clinical trials and literature on this topic is scarce. Only one RCT on urolithiasis (25) described AC, stating whether "oral pain medication was used" and the mean duration of use (in days). In other fields, postoperative AC has been assessed as the cumulative dose of a specific drug (e.g., overall tramadole consumption in milligrams) (15,26-28). In a systematic review on predictors of postoperative pain and AC (2), Ip et al. identified a total of 42 studies from different surgical fields. All studies described pain intensity using a VAS or an NRS. Twenty-two other studies also commented on AC, with all describing cumulative doses of one specific drug or computed morphine equivalents. Others used a 5- or 7-point scale to discriminate between the efficacies of different analgesic drugs in the management of bone pain

(29,30). These scales were used over a treatment period of several months to evaluate the effect of bisphosphonates on pain reduction using the mean change from baseline to final assessment. Only one study describing an "analgesic score computed as a product of analgesic type and frequency of administration", could be identified, which had apparently been developed but not validated or published by the authors (31).

However, the use of both pain scores and analgesic consumption scores can be associated with significant potential problems. Indeed, numerous confounding factors influence the sensation of pain and the demand for medication, and therefore AC; these include individual sensitivity to pain medication, interference of non-analgesic effects, and patient and physician attitudes and behaviors, among others (2). An attempt has been made to overcome the covariation between pain intensity, AC and adverse drug effects by using a composite measure that combines pain intensity ratings and rescue medication use into a single score (9). However, this "integrated assessment" was proposed for use in studies of analgesic efficacy and does not seem to be an appropriate tool for assessing the postoperative course in clinical studies, because of its disproportion.

In addition to these inherent problems concerning pain scores and AC, there are additional methodological difficulties. Categorizing and quantifying the effects of different analgesic drugs can result in somewhat constructive vagueness. However, we found that the WHO pain relief ladder (16,17) simplified the potency-related classification of analgesic medication.

The WHO pain relief ladder was primarily conceived for use in the management of cancer pain relief, but is also used for the management of various other types of pain, e.g., postoperative analgesia. Because all types of drugs are to be considered, individual doses in milligrams cannot be calculated. However, assuming that single or combined administrations of analgesic drugs of the respective WHO categories are given at adequate doses (specified baseline or on demand medication), we hypothesized that the quantity (the overall dose of analgesic drugs) could be roughly estimated by counting single administrations of each drug during the pre-defined timeframe, and that the computed product of the frequency of "adequate" administrated single doses and the potency factor (WHO I – III) therefore could serve as a semi-quantitative assessment of overall AC.

The current study suggests a stronger correlation between CACS values and invasiveness of surgical procedures as compared to pain scores. It could be assumed that these findings reflect adequate analgesic therapy. This particularly applies to patients who undergo more invasive procedures; in these patients, good pain control will lead to lower pain scores in spite of higher invasiveness. This is consistent with our finding that correlation between CACS and mean and peak NRS values was significant in patients with minor or medium scale surgery but not in those who had major surgery. These data suggest that the CACS is a superior surrogate parameter to pain scores alone for measurement of the invasiveness of and pain after surgical procedures.

It is of note that in the setting of a specific study that will use CACS an appropriate time frame has to be defined in the study protocol (e.g. 2 days when comparing shock wave lithotripsy and ureteroscopy for stone therapy or 7 days when comparing laparoscopy and open surgery for prostate cancer).

Here, we intended to develop an easy-to-use score that could be applied in everyday clinical practice (e.g., if used as a secondary outcome parameter in clinical studies without specified analgesic regimens). Therefore, all available analgesic drugs had to be categorized using a simple system; the WHO pain relief ladder is a well-known and easily handled tool that can be used for this purpose.

This study had some limitations. The data where acquired retrospectively and the study included a rather small number of patients. However, taking into account that to date most clinical studies are of retrospective design, it may be assumed that the new score will most likely be applied in such a setting. In addition, for reasons described above, global scores are somewhat inaccurate. Furthermore, adjuvant medications (e.g.,

antidepressants, steroids) cannot be included in the CACS. PCA and other types of analgesic treatments, such as postoperative epidural analgesia, can be included in the score but were not considered in this study. It may be argued that patients on analgesic long-term medication will confound results of future clinical trials using CACS. This may be avoided by a prospective randomized design of high impact studies.

We believe that AC should be recorded as a clinical parameter to further describe patients' well-being after interventional or surgical therapies. Pain scores (as PROs) should be supplemented by related CROs (such as AC). The CACS can be used by clinical scientists to compare different surgical and interventional therapies (and even medical/oncological treatments) with respect to AC as a surrogate parameter for pain and invasiveness (surgical) or treatment success (medical/ oncological).

In summary, the CACS can be used to describe AC in many different clinical settings. It provides a semi-quantitative assessment of overall AC within a defined period of time, and as such can be used as a surrogate parameter for pain and the invasiveness of surgical procedures. Expressing AC as a figure on an open-ended scale will provide easy-to-use information to clinical scientists and treating physicians.

ABBREVIATIONS

AC = analgesic consumption
CACS = cumulative analgesic consumption score
CRO = clinically reported outcomes
NRS = numeric rating scale
PCA = patient-controlled analgesia
PRO = patient-reported outcomes
SA = surgical patients from group A
SB = surgical patients from group B
SC = surgical patients from group C
UA = urological patients from group A
UB = urological patients from group B
UC = urological patients from group C
VAS = visual analog scale

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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The efficacy of radiographic anatomical measurement methods in predicting success after extracorporeal shockwave lithotripsy for lower pole kidney stones

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ABSTRACT

Objectives: To assess the impact of lower pole calyceal anatomy on clearace of lower pole stones after extracorporeal shockwave lithotripsy (ESWL) by means of a new and previously defined radiographic measurement method.
Materials and Methods: Sixty-four patients with solitary radiopaque lower pole kidney stones were enrolled in the study. Infundibulopelvic angle (IPA), infundibulotransverse angle (ITA), infundibular lenght(IL), and infundibular width (IW) were measured on the intravenous urographies which were taken before the procedure.
Results: 48 of 64 patients (75%) were stone-free after a follow-up period of 3 months. The IPA,ITA,IL and IW were determined as statistically significant factors, while age,gender and stone area were found to have no impact on clearance.
Conclusion: By the help of radiographic measurement methods related to lower pole kidney anatomy, appropriate patient selection and increment in success after ESWL may be achieved.

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Lithotripsy; Calculi; Kidney

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INTRODUCTION

Urinary stone disease is a common urological problem with several treatment alternatives. Besides its high level of patient approval and low complication rates, the non-invasive nature and cost- effectiveness of extracorporeal shockwave lithotripsy (ESWL) have rendered this treatment modality a preferred option for most of the urinary calculi (1-5). It has been determined that many factors, including the size, composition and location of the stone and the infundibulopelvic anatomy of kidney are involved in the success of ESWL (6-8). The success rate of ESWL in the lower pole stones was reported to be the poorest when any other locations were taken into account (1,9). Gravity dependent position was thought to be a crucial factor in retention of the fragments rather than stone disintegration (9). Moreover particular spatial anatomical factors seem to be important in spite of the contradicting data.

The anatomical features of the lower pole collecting system and its possible effects on fragment passage were firstly investigated by Sampaio and Aragao (10). They concluded that the Infundibulopelvic angle (IPA) (Angle between the main lower infundibulum and renal pelvis), the lower infundibular diameters and the distribution of lower calices might be important in the clearance of disintegrated fragments of ESWL. After this study

many authors have defined and evaluated several methods to predict the success of ESWL in lower pole kidney stones. In the current study in addition to previous methods a new method utilizing the radiographic anatomy was evaluated in order to determine the influence of lower polar anatomy on success of ESWL.

MATERIAL AND METHODS

Patients, treated by ESWL with the diagnosis of lower pole kidney stones, between January 2004 and February 2008 were reviewed retrospectively. Cases with single radiopaque lower pole stones, 20mm. or less in size, were selected to comprise the study population. Radiolucent or multiple renal stones, abnormal renal or vertebral anatomy (rotation abnormalities, scoliosis, etc...), history of previous surgical intervention, severe hydronephrosis and follow-up less than 3 months were accepted as exclusion criteria.

Before ESWL all patients underwent renal ultrasonography and plain film of the urinary system in addition to intravenous urography (IVU). All IVUs were performed from 1m. distance by bolus radiopaque injection and without compression device application. Stone surface area was calculated on the anteroposterior plain film of IVU series, by multiplying the stone length by stone width in mm (11). IVU films taken at 10-15 minutes were utilized to measure IPA, infundibulotransvers angle (ITA), infundibular length (IL) and infundibular width (IW). Apart from the method of El-Bahnasy et al. (Figure-1), the method described by Sampaio et al. (Figure-2) was also used to measure the IPA (10,12). A line between the most distal point of the infundibulum containing the stone and midpoint at the lower lip of the renal pelvis was determined as IL. IW was measured at the narrowest point of infundibulum along the infundibulopelvic axis. ITA was described as the angle between the central axis of the lower pole infundibulum and a line, perpendicular to the midvertebral line (Figure-3).

A third-generation lithotripter, the electrohydraulic Stone Litho3pter (PCK, Ankara, Turkey) was used in the treatment of patients. All patients received diclofenac sodium preoperatively for the

Figure 1 - El-Bahnasy defined infundibulopelvic angle as the inner angle between the ureteropelvic axis (A line connecting the central point of the pelvis opposite the margins of superior and inferior renal sinuses to the central point of the ureter opposite the lower kidney pole) and central axis of lower pole infundibulum.

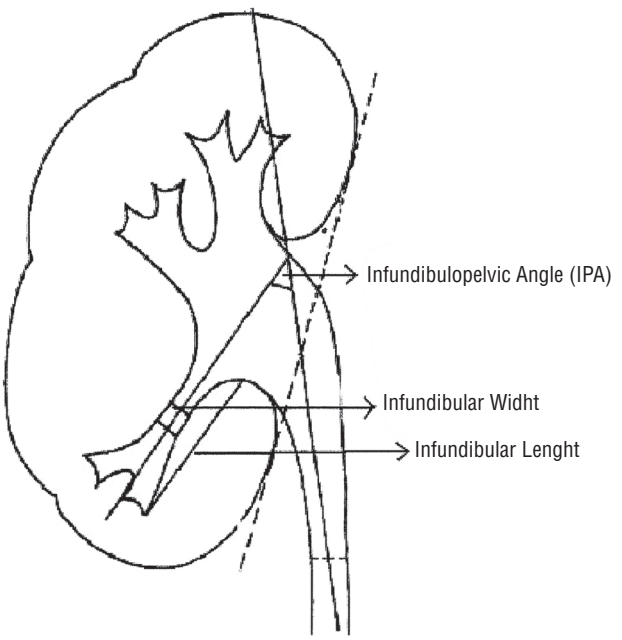


Figure 2 - Infundibulopelvic angle described by Sampaio et al. The angle formed by the central axis of the infundibulum containing the calculi and another axis connecting the central points of the ureter at the lower pole and ureteropelvic region.

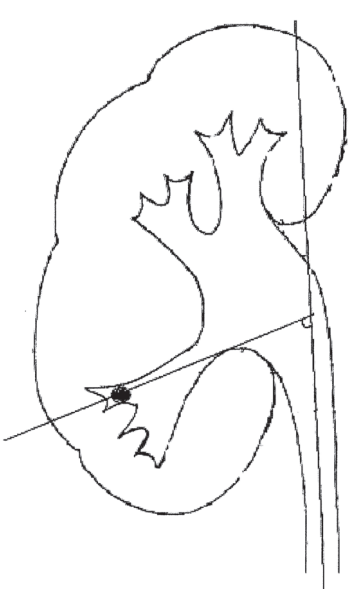
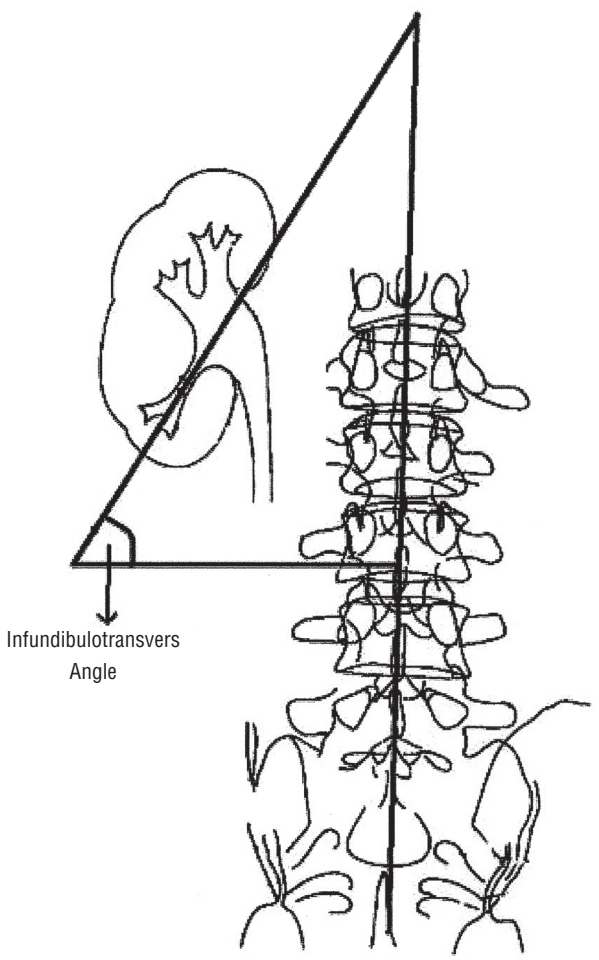


Figure 3 - Infundibulutransverse angle was described as the angle between the central axis of the lower pole infundibulum and a line which is obtained by drawing a perpendicular to midvertebral line (A line passing through the mid portions of vertebral bodies, connecting the spines).



pain management. That 1500-2000 shocks at 15-20kv. were delivered in every ESWL session was learned from patient charts. During ESWL and follow-up periods no postural drainage was performed and no additional medication was given.

According to routine follow-up procedures of the department, all patients were evaluated after every ESWL session with renal ultrasonography and plain films. Following the last ESWL session that resulted in residual fragments smaller than 4mm, the patients were monitored for 3 months to control the stone-free status.

No fragmentation of the kidney stones in three consecutive ESWL sessions or any residual stone fragment in any size after the end of 3-month follow-up were defined as treatment failure.

Patients were grouped according to the success of ESWL. Predictive value of all variables was tested by discriminant analysis and categorical data was compared by Chi-square test. P values < 0.05 were accepted as statistically significant. Chi-square test and discriminant analysis were performed by means of SPSS version 15 (SPSS Inc., Chicago, IL, USA) for Windows.

RESULTS

Sixty-four patients (32 female, 32 male patients with a mean age of 43) who had met the entry criteria were enrolled in the study. 48 patients (75%) were stone free after the follow-up period. Number of males and females were equal (50% male, 50% female). The age and gender differences of the patients had no significant influences on the success rate ($p < 0.05$). Mean IPA in the stone-free and the residual stone groups, measured with the methods of El-Bahnasy and Sampaio were 50.2 ± 9.82, 99.41 ± 18.3 and 37.75 ± 11.6, 69.43 ± 12.08 respectively. IL was 24.45 ± 4.18mm in the stone-free group and 31.81 ± 7.3mm. in the residual group. Mean values for the novel method, ITA, were 69.81 ± 22.26 and 50.22 ± 9.82 in residual and stone-free groups respectively. Detailed data of evaluated variables are presented in Table-1.

Statistical significance statuses of the variables are shown on Table-2. According to the discriminant analysis, statistically significant variables that could differentiate stone-free patients from those with residual stones were IPA (both Sampaio and El-Bahnasy), IL, IW, ITA. Stone area was found to be an insignificant factor.

Given the structure matrix analysis, presented in Table-3, IPA measured by Sampaio's method was found to have the highest power to discriminate the stone-free and residual stone groups. It was followed by IL and ITA.

To find the most effective cut off points of IPAs (measured by two methods) and ITA, sensitivity and specificity values of every angle between 20

Table 1 - Mean and standard deviation values of the variables.

Success	Mean	Std. Deviation	Valid N
Residual Stone			
IPA (El-Bahnasy) (degree)	37.75	11.61	16
IW (mm)	4.68	2.44	16
IL (mm)	31.81	7.34	16
Stone Area (mm^2)	127.68	132.6	16
IPA (Sampaio) (degree)	69.43	12.08	16
ITA (degree)	69.81	22.26	16
Number of Shocks	5975	569.8	16
Stone-free			
IPA (El-Bahnasy) (degree)	50.22	9.82	48
IW (mm)	6.66	2.92	48
IL (mm)	24.45	4.18	48
Stone Area (mm^2)	88.06	70.02	48
IPA (Sampaio) (degree)	99.41	18.3	48
ITA (degree)	51.22	10.55	48
Number of Shocks	3729.1	2645.6	48
Total			
IPA (El-Bahnasy) (degree)	47.1	11.56	64
IW (mm)	6.17	2.92	64
IL (mm)	26.29	6.01	64
Stone Area (mm^2)	97.96	90.24	64
IPA (Sampaio) (degree)	91.92	21.35	64
ITA (degree)	55.87	16.33	64
Number of Shocks	4290.6	2501.9	64

and 100 were calculated in 10 degree increments. The highest sensitivity rate with a reasonable specificity was obtained at 70 degrees for the IPA, measured by Sampaio's method. The probability of stone clearance was estimated to be 8.6 folds higher (Odd's ratio) at angles over 70 degrees (Table-4). The sensitivity and specificity rate of ITA at 60^o were found to be 83% and 50% respectively. Stone clearance rate was calculated to be 5 times higher at angles over 60^o for ITA.

Table 2 - Significance status of variables.

	Wilks' Lambda	F	Significance (p values)
IPA-1 (El-Bahnasy) (degree)	0.778	17.66	0.000
IW (mm)	0.913	5.92	0.018
IL (mm)	0.715	24.68	0.000
Stone Area (mm^2)	0.963	2.36	0.129
IPA-2 (Sampaio) (degree)	0.625	37.27	0.000
ITA (degree)	0.754	20.27	0.000
Number of Shocks	0.847	11.24	0.001
IPA-1 + IPA-2	0.624	37.4	0.000
IPA-1 + ITA	0.966	0.273	0.603
IPA-2 + ITA	0.998	0.146	0.703
IPA-1 + IPA-2 + ITA	0.798	15.65	0.000

The cut off points (IPA measured with El--Bahnasy's method and ITA) and their sensitivity and specificity rates are presented on Table-4.

Table 3 - Structure Matrix. Negative values indicates inverse relationship of variables with success.

	Function
	1
IPA-1 (Sampaio)	0.646
IL	-0.525
ITA	-0.476
IPA-2 (El-Bahnasy)	0.445
Number of Shocks	-0.355
IW	0.257
Stone Area	-0.163
IPA-1 + IPA-2	0.648
IPA-1 + ITA	0.055
IPA-2 + ITA	0.045
IPA-1 + IPA-2 + ITA	0.419

DISCUSSION

The ambiguity in determining a reliable factor for predicting the success of ESWL in lower pole kidney stones have resulted in several studies in which the significance of many anatomical factors have been investigated. After the study carried by Bagley and Rittenber (13) which analyzed the effect of lower pole infundibular length on the clearance of fragments after ureteroscopic intervention, the pioneer study about the spatial anatomy of lower pole was conducted by Sampaio and Aragao (10). The interrelationship was investigated by the help of 3-D polyester resin endocasts of collecting systems, which were procured from cadavers. Sampaio et al. concluded that IPA, diameter of lower pole infundibulum and inferior pole calyceal distribution may have played an important role in drainage of the lower pole collecting system (10). In a subsequent assessment of the same authors, the significance of the radiographic measurements was evaluated and previously determined factors were found to be important in the evacuation of fragments after ESWL (14).

Afterwards, in order to define more constant radiographic landmarks, a new method was suggested by El-Bahnasy et al. to measure the lo-

Table 4 - Sensitivity and specificity rates of IPAs (Sampaio and El- Bahnasy) and ITA when different angles were taken as cut off points.

IPA (Sampaio)	60º	70º	80º
Sensitivity	95%	89.5%	79.5%
Specificity	25%	50%	93.3%
ITA	50º	60º	70º
Sensitivity	48%	83%	100%
Specificity	75%	50%	31%
IPA (El-Bahnasy)	30º	40º	50º
Sensitivity	94%	81%	39.5%
Specificity	21%	62.5%	100%

wer pole IPA (12). The effect of infundibular width and length was investigated as well. All IPA, IW, IL were established as statistically significant factors that influence the clearance of stone fragments following ESWL (12). Keeley et al. suggested that IPA was the only factor associated with stone free status (15). Likewise Ghoneim et al. identified the lower pole IPA and IL as significant factors in stone clearance, however he found IW not to have significance on fragment evacuation (16). In several other studies investigating the significance of pelvicalyceal anatomy IW, IL and IPA, whether solely or together, were found to have impact on clearance of fragments (10,12,15-23) (Table-5).

Contradicting studies, investigating the importance of the lower pole kidney anatomy also exist in the literature. Madbouly et al., Sorensen et al. and Sahinkanat reported that they didn't observe any significant impact of the lower pole pelvicalyceal anatomy on the outcome after ESWL (24,25).

In our current study, methods of both Sampaio and El-Bahnasy were used to determine the IPA. In the final analysis, the angle was observed to be significantly obtuse in the stone-free patients regardless of the methods (p = 0.001). Although Sampaio's original study reported a critical angle of 90º as the most reasonable sensitivity and specificity rates (Table-4),

Table 5 - Results of some studies investigating the effect of IPA, IL and IW on success after ESWL.

	IPA	IL	IW
Sampaio, 1997 (10)	+	N/A	+
Sabnis, 1997 (17)	+	N/A	+
El- Bahnasy, 1998 (12)	+	+	+
Keeley, 1999 (15)	+	N/A	-
Madbouly, 2001 (24)	-	-	-
Sorensen, 2002 (11)	-	-	-
Sumino, 2002 (19)	-	-	+
Fong, 2004 (18)	-	+	+
Ruggera, 2005 (23)	+	+	+
Ghoneim, 2005 (16)	+	+	-
Talas, 2007 (20)	+	-	-
Tan, 2007 (21)	+	+	+
Sahinkanat, 2008 (31)	-	-	-
Lin, 2008 (22)	-	-	+

(+) = Denotes statistically significant factor; **(-) =** Denotes statistically insignificant factor; **N/A =** Not applicable; **IPA =** Infundibulopelvic angle; **IL =** Infundibular length; **IW =** Infundibular width.

we considered 70° to be the cut off point with the method of Sampaio. Additionally, IL and IW were other parameters that correlated with stone-free status (Table-2).

Stone size was reported to be one of the key elements, besides stone location (9,26-29). Sorensen et al. and Abala et al. indicated the negative correlation of stone burden with the stone free rate (11,30). However, in our study no significant relationship could be established between the outcome and the stone burden. From this aspect, our data collaborates with the findings of Ghoneim et al., Keeley et al., Madbouly et al., and Sahinkanat et al. (15,16,24,31). This may be ascribed to our small cohort. Besides, impact of stone size on clearance may not be accurately evaluated due to selection bias as patients with stones lower than 20mm comprise the cohort.

Due to the tortuosity or distortion of the proximal ureter while measuring the IPA, in some cases precise measurement may not be possible. In order to manage with this difficulty, Tuckey et al. proposed calyceal-pelvic height (CPH), which is defined as the distance between the highest point of the lower lip of renal pelvis and the deepest point of calyx encompassing the calculi (32). However the effectiveness of the CPH was not confirmed by some of the subsequent studies (19,25). Having mentioned the complexity of measurement methods Sahinkanat proposed another novel method, parenchyma-to-ureter distance (PUD) to estimate the success of ESWL in lower pole kidney stones. He reported PUD to be the only significant method in determining the stone-free status after ESWL for lower pole kidney stones (31).

By the same token, to provide a more dependable measurement and to eliminate the difficulties encountered on IVU, ITA has been suggested in the current study. Anatomic structures which seem to be more fixed were utilized in the formation of the method. ITA was demonstrated to be a statistically significant variable in the determination of the stone-free patients ($p < 0.01$). 60° may be taken as the critical angle when the sensitivity and the specificity values were regarded (Table-4). ITA also seems to be one of the superior methods among the others in terms of discriminating the stone-free patients from residual stone group (Table-2). It has the third highest power in estimation of the success following ESWL. We believe that the efficacy of the method needs to be investigated in different and larger cohorts.

As the three-dimensional structure of the lower pole pelvicalyceal anatomy and the stone size may not be evaluated precisely by the help of two-dimensional conventional methods, contradicting results are not surprising.

Body habitus, hydration condition and respiratory movements during radiographic procedures may be counted as other factors contributing to the equivocal results (16,24). The importance of positional chances was pointed out by Sengupta et al. (33). He reported the positional change of the body to be a significant factor that causes planar differences of kidneys. Kim et al. observed the motions of the abdominal organs by the means of four-dimensional CT and he reported cranio-caudal average movements of the right and left kidneys to be 14.3mm. and 12.3mm, respectively, in supine position and 12.1 and 12.6mm, respectively, in the prone position (34).

It is appropriate that applicability of the current methods to predict the success of ESWL in lower pole kidney stones should be investigated on 3 dimensional or 4-dimensional imaging technics. We also believe it is essential that a comparison of 2-dimensional and 3-dimensional modalities should be performed. Besides these, ultrasonographic parameters can also be evaluated.

Although there is not a standardized method of assessing the density of calculi currently, kidney stone density reported to be another factor influencing the success of ESWL (35). Combining the aforementioned anatomical factors, and stone morphology or density may increase our selectivity while deciding the appropriate modality of treatment.

CONCLUSIONS

Although IPA, IW and IL were found to be statistically significant 2-dimentional measurement methods in our study, debate on their reliability still exists. ITA seems to be a useful method but its validity should be confirmed by other studies. Novel 3-dimentional measurement

methods evaluating the lower pole calyceal anatomy may help us define accurate patients groups that will benefit from ESWL treatment.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Bipolar transurethral vaporization: a superior procedure in benign prostatic hyperplasia: a prospective randomized comparison with bipolar TURP

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ABSTRACT

Objective: To compare the outcomes of bipolar transurethral vaporization of the prostate (TUVP) with bipolar transurethral resection of the prostate (TURP).

Materials and Methods: In a prospective randomized trial, 88 patients with moderate to severe lower urinary tract symptoms secondary to benign prostatic hyperplasia (BPH) underwent bipolar TUVP (N = 39) or bipolar TURP (N = 49) from October 2010 to November 2011. The inclusion criteria were age > 50 years, prostate volume of 30-80mL, serum PSA < 4ng/mL, IPSS ≥ 20, Q_{max} ≤ 10mL/s and failed medical therapy. The perioperative and postoperative outcomes were evaluated and the IPSS and Q_{max} were assessed preoperatively and 3 months after procedure in all cases.

Results: Both groups were similar in patient age, prostate volume, preoperative IPSS and Q_{max}. The TUVP group had significantly lower mean values of operative time, hospital stay, catheterization period, irrigation fluid volume and serum hemoglobin, creatinine, sodium and potassium changes compared with TURP group. No significant differences were seen between two groups regarding complications (TUVP = 10.3%; TURP = 12.2%) and modified Clavien classification of complications. No TUR syndrome, obturator reflex or epididymitis occurred in both groups. Re-hospitalization and transfusion due to clot retention (N = 2) and urethral stricture (N = 1) were reported only in the TURP group. Three patients experienced urinary retention after catheter removal in the TUVP group. Two patients were re-catheterized temporarily and one patient required repeat bipolar TUVP. Three months after surgery, two groups had significant improvement in IPSS and Q_{max}. But the TUVP group had significantly lower IPSS and higher Q_{max} than TURP group.

Conclusions: Bipolar TUVP is a safe, effective and low cost procedure among minimally invasive surgeries of BPH. Compared with bipolar TURP, the bipolar TUVP had similar complications, better perioperative and postoperative outcomes, superior hemostasis and higher efficacy.

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INTRODUCTION

Benign prostatic enlargement is a common problem in the aging men (1-3) and may lead to lower urinary tract symptoms (LUTS) (2-6). Several endourologic minimally invasive procedures have been suggested and used for surgical treatment of moderate to severe LUTS related to benign prostatic hyperplasia (BPH) (3,6-11). Although conventional monopolar transurethral

resection (TUR) of the prostate (TURP) has been applied as a gold standard surgical modality in the recent decades (6-12), but its outcomes including patient discomfort, prolonged catheterization and hospitalization durations, need to transfusion and re-admission due to hemorrhage or clot retention, high volume of irrigation fluid, electrolyte imbalance and TUR syndrome, urinary retention, urethral stricture, incontinence, retrograde ejaculation or erectile dysfunction (6-8,13-20) elicited the tendency to the use of the newer technologies such as bipolar energy or laser energy for resection, vaporization, ablation or enucleation and changing the irrigation fluid from glycine to normal saline in the endoscopic management of BPH (6,8,13-15,20-26).

Bipolar technology using saline conductive medium accompanies with proper translucency, similar osmolality to the serum, minimal risk of dilutional hyponatremia and TUR syndrome, larger removal of prostate tissue, smaller coagulation depth, longer time for safe resection and coagulation, less tissue damage due to lower energy, and lower temperature and thermal damage (7,8,12,15,19,27,28). Nowadays, bipolar TURP is used in many centers due to several benefits and superior or similar results in comparison with monopolar TURP (8,14,23,29-31). Bipolar transurethral vaporization of the prostate (TUVP) in saline using hovering technique is an easy learning and low cost procedure in comparison to laser technique (12,14,20). Bipolar TUVP provides suitable depth of coagulation, high hemostasis and proper outcomes in comparison with monopolar TUVP and monopolar TURP (7,14,20,24,26,32-34).

In this study, we compared the perioperative and postoperative outcomes of bipolar TUVP and bipolar TURP in a prospective randomized trial in patients with moderate to severe LUTS secondary to BPH.

MATERIALS AND METHODS

From October 2010 to November 2011, 88 patients underwent bipolar TUVP (B-TUVP, N = 39) or bipolar TURP (B-TURP, N = 49) in a single-center prospective randomized trial who were referred for surgical management of moderate to severe LUTS secondary to BPH. All procedures were performed successfully by single surgeon under spinal anesthesia. Local ethical committee approved this research. Before operation, all patients were assessed by medical history, general physical and regional neurological examinations, digital rectal examination (DRE), laboratory tests (CBC, hemoglobin and hematocrit, coagulation tests, serum prostate specific antigen [PSA], ESR, BUN, serum creatinine and electrolytes [sodium, potassium], urine analysis, urine culture and sensitivity test), abdominal ultrasonography (including measurement of the prostate volume), international prostate symptom score (IPSS) questionnaire and uroflowmetry (measurement of maximum flow rate [Q_{max}]).

The inclusion criteria were age > 50 years, prostate volume of 30-80mL, serum PSA < 4ng/mL, IPSS ≥ 20, Q_{max} ≤ 10mL/s and failed BPH-related medical therapy. The exclusion criteria were abnormal DRE or ultrasonography with suspicion of prostate cancer, history of prostate cancer, serum PSA ≥ 4ng/mL, previous urethral or prostate surgery, urethral stricture, neurogenic bladder, bladder calculi, BPH-related hydronephrosis, anticoagulant therapy, coagulation disorders, renal insufficiency and severe co-morbidities or co-existing diseases.

The procedures were accomplished under direct sight by continuous flow irrigation with normal saline (0.9% NaCl), the Olympus bipolar generator (cutting: 280 W; coagulation: 125 W), the classical and traditional surgical steps of transurethral resection in saline (TURis) for TURP and hovering technique for TUVP. A standard resection loop and a "button-type" vaporization electrode were used for TURis and vaporization without resection respectively. In all patients, a 20-24Fr three-way Foley catheter was placed at the end of the procedure.

The parameters including operative time, irrigation fluid volume, catheterization period, postoperative hospital stay, complications and postoperative changes in hemoglobin, serum creatinine, sodium and potassium levels were assessed in all patients. Also three months after procedure, the IPSS and Q_{max} were measured for evaluation of efficacy in all cases.

Software SPSS version 16.0, independent t test, Mann-Whitney test, Chi-square test, Fisher Exact test and Wilcoxon test were applied for statistical analysis and P-value < 0.05 was considered significant.

RESULTS

The mean patients' age, values of prostate volume, IPSS and Q_{max} are mentioned in Table-1. The mean patients' age (70.97 ± 3.79 vs. 69.14 ± 4.09 years) and mean prostate volume (46.92 ± 4.67 vs. 47.14 ± 4.44mL) were similar between B-TUVP and B-TURP groups. No significant differences were seen in pre-operative IPSS (P = 0.545) and Q_{max} (P = 0.341) between B-TUVP (26.36 ± 1.96; 8.48 ± 1.04mL/s) and B-TURP (26.04 ± 3.02; 8.22 ± 1.21mL/s) groups. (Table-2).The mean values of operative time (25.92 ± 2.36 vs. 32.63 ± 2.87 minutes), postoperative hospital stay (1.89 ± 0.38 vs. 2.10 ± 0.51 days) (hospitalization was calculated by the time the patients were discharged after the operation), catheterization period (4.12 ± 0.33 vs. 4.77 ± 0.42 days) and irrigation fluid volume (10.74 ± 1.46 vs. 14.22 ± 1.04 liters) in the B-TUVP group were significantly (P < 0.05) lower than the B-TURP group. Compared with the B-TURP group, the mean hemoglobin drop (0.53 ± 0.29 vs. 1.39 ± 0.45g/dL) and the mean changes in serum creatinine, sodium and potassium levels were significantly (P < 0.05) lower for the B-TUVP group (Table-1).

Table 1 - Patient- and operation-related parameters in Bipolar TUVP and Bipolar TURP groups.

Parameter	Bipolar TUVP	Bipolar TURP	P-value
Patients, n	39	49	-
Mean Age (range; SE), year	70.97 ± 3.79 (65-79; 0.60)	69.14 ± 4.09 (62-77; 0.58)	0.053*
Mean Prostate Volume (SE), mL	46.92 ± 4.67 (0.74)	47.14 ± 4.44 (0.63)	0.888*
Mean Operative Time (range; SE), minute	25.92 ± 2.36 (22-35;0.37)	32.63 ± 2.87 (25-35; 0.41)	< 0.001*
Mean Irrigation Fluid Volume (range; SE), liter	10.74 ± 1.46 (8-13; 0.23)	14.22 ± 1.04 (12-15; 0.15)	< 0.001*
Mean Postoperative Hospital stay (range; SE), day	1.89 ± 0.38 (1-3; 0.06)	2.10 ± 0.51 (1-4; 0.07)	0.047*
Mean Postoperative Catheterization Period (range; SE), day	4.12 ± 0.33 (4-5; 0.05)	4.77 ± 0.42 (4-5; 0.06)	< 0.001*
Mean Hemoglobin Drop (range; SE), g/dL	0.53 ± 0.29 (0-1.4; 0.04)	1.39 ± 0.45 (0.5-3; 0.06)	< 0.001§
Mean Serum Creatinine Level Increase (range; SE), mg/dL	0.10 ± 0.08 (0-0.3; 0.01)	0.16 ± 0.33 (0-2; 0.04)	0.338*
Mean Serum Sodium (Na^+) Level Decrease (range; SE), meq/l	1.71 ± 0.19 (1.3-2.2; 0.03)	2.29 ± 0.15 (2-2.6; 0.02)	< 0.001§
Mean Serum Potassium (K^+) Level Increase (range; SE), meq/l	0.22 ± 0.20 (0-0.9; 0.03)	0.31 ± 0.13 (0-0.6; 0.02)	0.012§

SE = Standard error of mean; * = Mann-Whitney test; **§ =** Independent T test

Table 2 - IPSS and Qmax in Bipolar TUVP (B-TUVP) and Bipolar TURP (B-TURP) groups.

	Before Operation	After Operation	P-value
B-TUVP: mean IPSS (range; SE)	26.36 ± 1.96 (20-30; 0.31)	2.56 ± 2.58 (0-10; 0.41)	< 0.001*
B-TURP: mean IPSS (range; SE)	26.04 ± 3.02 (20-30; 0.43)	5.49 ± 3.40 (0-10; 0.48)	< 0.001*
P-value	0.545†	< 0.001†	-
B-TUVP: mean Qmax (range; SE), mL/s	8.48 ± 1.04 (7-10; 0.16)	23.23 ± 1.08 (18-24; 0.17)	< 0.001*
B-TURP: mean Qmax (range; SE), mL/s	8.22 ± 1.21 (6-10; 0.17)	20.79 ± 1.47 (18-22; 0.21)	< 0.001*
P-value	0.341†	< 0.001†	-

SE = Standard error of mean; * = Wilcoxon test; **† =** Mann-Whitney test

The overall complication rate was 10.3% in the B-TUVP group and 12.2% in the B-TURP group. No significant differences (P > 0.05) were seen in overall complications and modified Clavien classification of complications between the B-TUVP and the B-TURP groups. Low grade self-limited fever occurred in one patient (2.6%) of the B-TUVP group and in three patients (6.1%) of the B-TURP group and this difference was non-significant (P = 0.626). No TUR syndrome, obturator reflex or epididymitis were seen in both groups. Two patients (4.1%) experienced postoperative hematuria and clot retention during one week after B-TURP procedure and were re-hospitalized. These patients were treated by bladder fluid irrigation and required blood transfusion. Urinary retention occurred after catheter removal in the three patients who underwent B-TUVP. Two patients were re-catheterized for a short period and one patient re-treated with repeat B-TUVP. During a three month follow-up, urethral stricture occurred only in one patient following B-TURP who was treated by endoscopic urethral dilation (Table-3).

Three months after procedure, significant (P < 0.001) improvement in the mean values of IPSS and Q_{max} were seen in the B-TUVP and the B-TURP groups. But the B-TUVP had significantly higher efficacy compared with B-TURP. The B-TUVP group (2.56 ± 2.58) had significantly (P < 0.001) lower mean IPSS than the B-TURP group (5.49 ± 3.40). Also in the B-TUVP group (23.23 ± 1.08mL/s), mean Q_{max} was significantly (P < 0.001) higher than B-TURP group (20.79 ± 1.47mL/s) (Table-2).

DISCUSSION

The quality of life and health care cost may be affected in the aging males due to LUTS following benign progressive enlargement of the prostate gland (1-6,31,35). The monopolar TURP has been used as the traditional therapeutic procedure of LUTS/BPH for several decades (6-12,36,37). But for reducing adverse events such as bleeding and clot retention, TUR syndrome, damage of surrounding or deeper tissues, and urethral stricture, bipolar technology and conductive irrigation fluid of normal saline have been applied instead of monopolar energy and glycine nonconductive medium as the popular and the most important alternatives in the recent years (18,23,28,29,31,36). The bipolar TURP is a proper procedure with shorter learning curve (30), better outcomes concerning duration of irrigation and catheterization (31), depths of coagulation zone (28), decrease in serum sodium (15,29,31,38), occurrence of TUR syndrome (18,29,31,39) bleeding (23,28,38), clot retention (31,39) and re-admission (23), comparative efficacy and other similar results in comparison with M-TURP (15,23,29-31,38).

Increase in life expectancy and higher prevalence of surgical risk and comorbid diseases such as cardio-pulmonary diseases, coagulation disorders and anti-platelet or anticoagulant therapies in the

Table 3 - Complications in Bipolar TUVP and Bipolar TURP groups.

Parameter	Bipolar TUVP	Bipolar TURP	P-value
Complication, n (%)	4 (10.3%)	6 (12.2%)	1.000*
TUR syndrome, n (%)	0 (0%)	0 (0%)	-
Obturator Reflex, n (%)	0 (0%)	0 (0%)	-
Epididymitis, n (%)	0 (0%)	0 (0%)	-
Fever, n (%)	1 (2.6%)	3 (6.1%)	0.626*
Postoperative Hematuria, n (%)	0 (0%)	2 (4.1%)	0.501*
Transfusion, n (%)	0 (0%)	2 (4.1%)	0.501*
Clot Retention, n (%)	0 (0%)	2(4.1%)	0.501*
Re-hospitalization, n (%)	1 (2.6%)	2 (4.1%)	1.000*
Urinary Retention, n (%)	3 (7.7%)	0 (0%)	0.083*
Re-catheterization, n (%)	2 (5.1%)	0 (0%)	0.194*
Repeat Surgery, n (%)	1 (2.6%)	0 (0%)	0.443*
Urethral Stricture, n (%)	0 (0%)	1 (2.0%)	1.000*
Modified Clavien Classification of Complications			
Grade 0, n (%)	35 (89.7%)	43 (87.8%)	0.707†
Grade I, n (%)	1 (2.6%)	3 (6.1%)	
Grade II, n (%)	0 (0%)	0 (0%)	
Grade III, n (%)	3 (7.7%)	3 (6.1%)	
Grade IV, n (%)	0 (0%)	0 (0%)	
Grade V, n (%)	0 (0%)	0 (0%)	

* = Fisher Exact test; † = Chi-Square test

old patients may lead to the limitation in the use of bipolar TURP (3,18). Also fluid absorption betides in the bipolar TURP and volume overload may be problematic in patients with severe cardio-pulmonic disorders (23,27,31,36). In the last decade, laser energy has been applied with high safety and efficacy for vaporization or enucleation of hypertrophic large volume prostate (6,9,11-13,40-42). But laser therapy may be accompanied with the use of multiple techniques and different wattage, technical complexity, prolonged operative time, higher applied energy and re-operation rate in the larger prostate volume cases, high cost equipment and inaccessibility in many centers (6,9,11-13,40-42). Beside morbidity and complication, attention to other outcomes, prostate volume, anesthesia risk, patient satisfaction, cost-benefit or cost--effectiveness, learning curve, easy accessing and performing is important in the selection of preferable procedure.

The bipolar TUVP (including the plasmakinetic vaporization of the prostate [PKVP] using the Gyrus system and the technique of TU-Ris bipolar plasma vaporization using Olympus generator) profits by advantages of monopolar TURP and bipolar TURP and is devoid of their

limitations in the high risk patients (9,12,34,43). Also the bipolar TUVP can compete with TURP and laser-related techniques due to easy learning and lower cost procedure, superior hemostasis, decreased fluid absorption and TUR syndrome, low morbidity and comparative outcomes (9,12,14,34). In a prospective randomized trial, we compared the outcomes between bipolar TUVP and bipolar TURP in patients with moderate to severe LUTS/BPH. The mean values of pre- and postoperative hemoglobin were 13.8-14.3 and 12.7-13.1g/dL without transfusion requirement in two experiences about bipolar TUVP (B-TUVP) (12,20). Dunsmuir and co-workers reported similar postoperative hemoglobin between bipolar electrovaporization and TURP (16). But in Hon et al. study, bipolar PKVP (0.8g/dL) had significantly lower hemoglobin drop compared with standard TURP (1.39g/dL) (17). The mean hemoglobin drop in the B-TUVP (0.5g/dL) was significantly (P = 0.0001) lower than bipolar TURP (B-TURP) (1.2g/dL) and monopolar TURP (M-TURP) (1.6g/dL) in Geavlete et al. randomized comparison (34). Also in our trial, the B-TUVP had lesser mean hemoglobin drop than B-TURP (0.53 vs. 1.39g/dL) due to superior hemostasis and coagulation (12,34).

The published experiences reported the mean postoperative hospitalization and catheterization periods of 1.4-2.08 and 2.2-3.54 days for bipolar vaporization (12,20,44,45). No significant differences were seen in catheterization and hospitalization duration between bipolar electrovaporization (1193 minutes, 1.45 days) and TURP (1007 minutes, 1.5 days) in Dunsmuir and co-workers trial (16). But catheterization time was significantly shorter for vaporization compared with TURP in multiple studies (1.9 vs. 2.71 days (46). PKVP: 35 vs. 68 hours (47), bipolar plasmakinetic vaporization-resection: 2.3 vs. 3.8 days (19), B-TUVP: 1.3 vs. 2.8 days (14). Also vaporization had significantly shorter hospital stay than TURP (3.9 vs. 4.7 days (46), PKVP: 3.02 vs. 3.36 days (17)). The photoselective vaporization of the prostate (PVP) using laser energy and B-TURP had significantly shorter catheterization and hospitalization times compared with M-TURP in the different meta-analysis studies (6,22,31). In Geavlete et al. randomized comparison, the mean catheterization and hospitalization times were 23.5 hours and 1.9 days in the B-TUVP (the shortest), 46.3 hours and 3.1 days in the B--TURP, 72.8 hours and 4.2 days in the M-TURP (the longest) and these differences were significant (P = 0.0001) (34). Proper hemostasis, lower blood loss and hemorrhagic events and subsequent morbidities following B-TUVP can justify shorter postoperative hospitalization (1.89 vs. 2.10 days) and catheterization (4.12 vs. 4.77 days) in comparison with B-TURP in our results (12).

The operating time had the means of 61 and 63 minutes for B-TUVP and the median of 55 minutes for bipolar plasmakinetic electrovaporization in the published experiences (12,20,45). In Dunsmuir and co-workers trial, the bipolar electrovaporization and TURP had similar operation time (33 vs. 26 minutes, P = 0.78) (16). Hon et al. reported longer mean resection time for PKVP compared with standard TURP (32.6 vs. 28.5 minutes, P = 0.08) (17). But in other studies, the PKVP (40.3 vs. 55 minutes) (47) and bipolar plasmakinetic vaporization-resection (40.3 vs. 57.8 minutes, P < 0.01) (19) had shorter mean operative time than TURP. In the different meta-analysis studies, the operative time was similar between B-TURP and M-TURP (31) but the operative time in the PVP was longer than TURP (6). Ahyai et al. reported the shortest mean operation time (36 minutes) for B-TUVP among minimally invasive surgical therapies (14). Also in Geavlete et al. comparison, the mean operation time in the B-TUVP (39.7 minutes) was significantly (P = 0.0001) shorter than B-TURP (52.1 minutes) and M-TURP (55.6 minutes) (34). In our trial, B-TUVP had shorter mean operative time (25.92 vs. 32.63 minutes) compared with B-TURP. This result can be explained by easy performance, good hemostasis and coagulation, better sighting due to decreased hemorrhage, the lack of vacating resected samples and possible proper vaporization of prostatic tissue during moving of the electrode in the B-TUVP (12,34).

The mean values of pre- and postoperative serum sodium were 141.3 and 140.6mmol/L and no serum electrolyte abnormality occurred in Reich et al. experience in B-TUVP (12). In Otsuki et al. report the irrigation fluid volume was 22.9 liters and the B-TUVP had similar pre- and postoperative serum sodium level (20). Mamoulakis et al. reported signi-

ficantly higher sodium level for B-TURP compared with M-TURP (31). In Dunsmuir and co-workers trial, bipolar electrovaporization and TURP had similar postoperative serum sodium level (16). Also similar sodium changes and perioperative fluid absorption were reported for PKVP and TURP in Hon et al. study (17). The bipolar plasmakinetic vaporization-resection had significantly lower mean perioperative irrigation fluid volume compared with TURP (11.4 vs. 18.3 lit) in Tefekli et al. comparison (19). In our study, the mean values of irrigation fluid volume (10.74 vs. 14.22 lit), serum sodium (1.71 vs. 2.29meq/l) and potassium (0.22 vs. 0.31meq/l) changes in the B-TUVP were lower than B-TURP. Reduced hemorrhage, superior sight and performing the operation without resection and sampling, decrease irrigation fluid volume, subsequent fluid absorption and serum electrolytes changes in the B-TUVP compared with B-TURP (12,34).

The early postoperative complication rate in the bipolar plasmakinetic vaporization-resection was higher than TURP (16.3% vs. 8.5%, P = 0.0014) in Tefekli et al. (19) research, but the overall complication rate was similar (10.2% vs. 6.3%, P > 0.05) (19). In the meta-analysis from Ahyai et al., the B--TUVP (14%) and B-TURP (12%) had significantly lower perioperative complication rates compared with TURP (18.7%) (14). But the intraoperative, late and overall complication rates were similar (14). During our follow-up, no significant differences were seen between B-TUVP and B-TURP regarding overall complication rate (10.3% vs. 12.2%) and modified Clavien classification of complications.

The complications including gross hematuria requiring re-catheterization and bladder irrigation (4.7%) (20), transfusion (1.9%) (20), AUR requiring re-catheterization (5.7%) (20) transient incontinence (1.9%) (20), re-catheterization (13%) (12), bladder neck contracture (0.9%) (20), urethral stricture (7.5%, 4.7%) (20,44) and re-operation (3%, 0%) (12,20) were reported for bipolar vaporization in the published experiences. In Hammadeh and co-workers study, TUVP and TURP had similar results regarding re-operation, urethral stricture, impotency and retrograde ejaculation (48). In Kaya et al. research, PKVP (12%) had significantly higher re-operation rate than standard TURP (6.7%). But urethral stricture, erectile dysfunction and retrograde ejaculation were similar in both groups and no urinary incontinence or bladder neck stricture occurred (43). In Hon et al. (17) and Karaman et al. (47) studies, transfusion occurred only in the TURP group compared with PKVP. The bipolar electrovaporization had significantly higher rate of re-catheterization (30% vs. 5%) and lower rate of clot evacuation (0% vs. 19%) compared with TURP in Dunsmuir and co-workers trial (16). In Tefekli et al. comparison, the re-operation rate was 4.1% and 2.1% in the bipolar vaporization-resection and TURP groups (19). The re-catheterization rate was 4.1% for vaporization-resection (19). The bipolar vaporization-resection had higher rates of severe irritative symptoms (12.2% vs. 4.3%) and urethral stricture (6.1% vs. 2.1%, P = 0.002) (19). But both groups were similar in terms of transfusion, AUR and re-catheterization, and retrograde ejaculation (19). In the meta-analysis studies, the B-TURP had significantly lower rates of TUR syndrome (22,31) and clot retention (22,31) compared with M-TURP. But both techniques were similar regarding transfusion (22,31) AUR (31), re-operation (22), urethral stricture (31) and bladder neck contracture (31). Although the PVP had significantly lower rates of capsular perforation, TUR syndrome, transfusion and clot retention and higher re-operation rate than TURP in the meta-analysis, both procedures had similar results regarding AUR and urethral/bladder neck sclerosis (6). In the meta-analysis from Ahyai et al., the B-TUVP had higher rate of AUR and re-catheterization (8.2% vs. 3.6%, 4.5%), transient dysuria (2.9% vs. 0%, 0.8%) and re-intervention (2.4% vs. 0.2%, 0.5%) and lower rates of hematuria (0.0% vs. 1.0%, 3.5%) and transfusion (0.5% vs. 1.9%, 2.0%) compared with B-TURP and TURP (14). The urgency (2.2% vs. 0%, 0.2%), bladder neck stenosis (2% vs. 0.5%, 0.5%) and urethral stricture (4.1% vs. 1.9%, 2.4%) in the TURP were higher than B-TUVP and B-TURP (14). Bleeding, capsular perforation and TUR syndrome were reported following TURP and the three techniques had similar results regarding mucosal injury and conversion to TURP (14). In Geavlete et al. randomized comparison, the B-TUVP had significantly lower rates of intraoperative bleeding (1.8% vs. 8.2%, 13.5%), capsular perforation (1.2% vs. 7.1%, 9.4%), re-

-catheterization (1.8% vs. 5.9%, 7.1%), re-treatment (3.5% vs. 9.4%, 8.8%) and bladder neck sclerosis (0.6% vs. 3.5%, 4.1%) compared with B-TURP and M-TURP (34). Also postoperative hematuria (2.9%, 4.7% vs. 15.3%), transfusion (1.2%, 1.8% vs. 6.5%), clot retention (0.6%, 1.2% vs. 4.1%), TUR syndrome (0%, 0% vs. 1.8%) and re-hospitalization following hemorrhage (0.6%, 1.2% vs. 3.5%) in the B-TUVP and B-TURP were significantly lower than M-TURP (34). But the three groups had similar results regarding early irritative symptoms, urethral stricture and urinary incontinence (34). During our follow-up, no significant differences were seen between B-TUVP and B-TURP regarding TUR syndrome, re-hospitalization, repeat surgery and urethral stricture. Although postoperative hematuria, clot retention and transfusion occurred only in the B-TURP group and urinary retention and re-catheterization occurred only in the B-TUVP group, these differences were non-significant probably due to the small sample size.

The published studies have reported significant improvement in IPSS and Q_{max} with different follow-up durations for vaporization and vaporization-resection (including bipolar technology) in the case series (12,20,44,45) or in comparison with monopolar or bipolar TURP (19,34,43,46-48) and our results are similar to those. In the meta-analysis studies, the PVP and B-TURP had similar results with M-TURP regarding IPSS and Q_{max} especially in the short-term follow-up (6,14,22,31) Otsuki and co-workers reported significant improvement in IPSS between three months and one month after B-TUVP (8.8 vs. 11.1), but this matter wasn't proved about Q_{max} (15.2 vs. 15.1mL/s) (20). Karaman et al. reported significantly higher improvement of IPSS for PKVP compared with TURP on postoperative month 3 and both groups had similar Qmax values (47). In Tefekli et al. comparison, the bipolar plasmakinetic vaporization-resection had significantly higher improvement in Q_{max} (120.5% vs. 103.6%) compared with TURP at 12 months after operation (19). But both groups had similar improvement regarding IPSS (63% vs. 64.3%) (19). But in Kaya et al. comparison, the TURP had significantly better result of IPSS (5.2, 5.7 vs. 7.1, 7.6) and Q_{max} (20.8, 21.8 vs. 12.5, 14.4mL/s) than PKVP at 24 and 36 months after operation (43). Furthermore, no significant differences were seen in efficacy (based on IPSS and Q_{max}) between vaporization (including bipolar technology) and TURP in multiple studies (14,16,17,48). In Geavlete et al. trial, the B-TUVP had significantly better results of IPSS and Q_{max} compared with B--TURP and M-TURP during 18 months of follow-up (34). Also in our trial, the B-TUVP had significantly higher improvement in postoperative IPSS (2.56 vs. 5.49) and Q_{max} (23.23 vs. 20.79mL/s) compared with B-TURP. Proper visibility due to lesser bleeding and formation of suitable cavity with good margins and surface in the operated area can explain this result with B-TUVP (34). We believe that TUVP can be a good alternative for TURP or even laser, because of lesser bleeding during the surgery and low cost of the equipments.

CONCLUSIONS

Bipolar TUVP is a safe, effective and low cost procedure in the endoscopic minimally invasive surgical management of BPH. Compared with bipolar TURP, the bipolar TUVP had similar complications and significantly better perioperative and postoperative outcomes (including shorter operative time and postoperative hospitalization and catheterization periods, lower irrigation fluid volume and serum sodium and potassium changes), superior hemostasis (due to lower hemoglobin drop) and higher efficacy (because of superior improvement in postoperative IPSS and Q_{max}). However, more studies are needed with large amount of patients to corroborate our results.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Effects of prostatic inflammation on LUTS and alpha blocker treatment outcomes

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ABSTRACT

Purpose: To evaluate the association between prostatic inflammation and lower urinary tract symptoms (LUTS), and to identify the effects of prostatic inflammation on the treatment with an alpha blocker.
Materials and Methods: 111 Participants who were aged ≥ 50 years, the presence of LUTS (maximal flow rate < 20 m/s, IPSS ≥ 11), and an elevated PSA level (3-20ng/mL) were treated with tamsulosin 0.2mg once daily for 3 months after prostate biopsies. Prostatic inflammation was scored as none (0), mild (I), moderate (II), or marked (III). LUTS parameters including urine flow rates, IPSS, PSA, and prostate volume were evaluated.
Results: Inflammation grading resulted in 25, 60, and 26 patients that were grade 0, I, and II, respectively. Lower grade inflammation was related to higher urine flow rate at baseline. Patients with higher inflammation grades had larger prostate volumes, larger total and transitional zone volumes, and higher PSA levels. Overall, urine flow rates and residual urine volume were improved after 3 months of alpha blocker therapy. Eighty percent of patients with grade 0 inflammation, 73% of patients with grade I inflammation, and 92.3% of patients with grade II inflammation showed improvement of LUTS after treatment. Longer duration of treatment was related to a decreased chance of improvement of LUTS. Patients with increased IPSS voiding subscales could be predictive of improvement of LUTS.
Conclusions: Patients with high grade inflammation had lower flow rates and higher prostatic volumes than patients with low grade inflammation. Inflammation grade did not affect the outcomes of alpha blocker treatment.

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INTRODUCTION

Although the pathogenesis of benign prostatic hyperplasia (BPH) is not yet completely understood, there is some evidence that prostatic inflammation could be a key contributor to prostate enlargement and progression of BPH. The presence of chronic histologic inflammation is a common finding in prostatic tissue on biopsies of surgical specimens from patients with and without lower urinary tract symptoms (LUTS) or prostatitis (1-3). Although it is not yet defined when and why chronic inflammation occurs, it has been hypothesized that BPH is an immune-mediated inflammatory

disease (2,4,5). Various growth factors and cytokines including T and B lymphoid cells and macrophages have been shown to be involved in both the inflammatory process and in the interactions between epithelial and stromal prostatic cells (2).

Several studies have investigated the relationship between histologic prostatic inflammation and LUTS related BPH (6-8). Chronic prostate inflammatory infiltrates were at a higher risk of BPH progression and acute urinary retention when compared with patients without inflammatory infiltrates at baseline. Depending on the relationship between prostatic inflammation and LUTS, medications with anti-inflammatory effects could be a novel treatment option for the management of BPH related LUTS. We evaluated the association between prostatic inflammation and LUTS. We also characterized the effects of prostatic inflammation on the treatment of LUTS with an alpha blocker.

MATERIALS AND METHODS

Study participants

The protocol and procedures used in this study were approved by the Institutional Review Board at Ewha Medical Center. Data was retrospectively collected from 10 hospitals in Korea. Patients who met the following criteria were included in the study: (i) men, aged ≥ 50 years, (ii) total IPSS ≥ 11, (iii) maximum flow rate (MFR) < 20mL/sec. and voided volume ≥ 120mL, (iv) total prostate volume between 20 and 50g, (v) baseline serum prostate specific antigen (PSA) level between 3 and 20ng/mL, and (vi) pathologically confirmed BPH on tissue obtained via transrectal ultrasound-guided biopsy. Exclusion criteria for this study included: (i) history of 5-alpha reductase inhibitor or alpha1--blocker use or a history of surgical therapy for BPH within 6 months of this study, (ii) neurogenic bladder, (iii) known history of an urothelial tumor such as prostate cancer or bladder cancer, and history of a urethral stricture or bladder neck obstruction, (iv) history of orthostatic hypotension with syncope, (v) history of chronic prostatitis/chronic prostatic pain syndrome, (vi) history of acute bacterial prostatitis within 6 months of this study, (vii) history of acute urinary tract infection within 1 month of this study, and (viii) history of unstable angina, myocardial infarction, or cerebro-vascular disease within 6 months of this study.

Evaluations

All data included in this study were obtained from patients who underwent transrectal ultrasound-guided biopsy of the prostate to rule out prostate cancer. All patients were treated with tamsulosin 2mg once daily for 3 months post-biopsy. Inflammation grades were reviewed by a single pathologist. The pathologist assessed the prostatic strips throughout whole specimens. Inflammation was assessed across all cores. Scoring of inflammation was based on a histologic grading system as follows: (i) grade 0, no inflammation; (ii) grade I, scattered inflammatory cell infiltrate without nodules; (iii) grade II, no confluent lymphoid nodules; (iv) grade III, large inflammatory areas with confluence (9). We assessed all specimens for degree of inflammation according to the most frequent and most severe scores.

The primary endpoint was the difference in total IPSS according to the prostatic inflammation grade. Secondary endpoints were the differences in IPSS subscales and quality of life scores with respect to prostatic inflammation grade. Baseline LUTS parameters including uroflowmetry data, IPSS, PSA, and prostate volume were evaluated for an association with prostatic inflammation. Uroflowmetry data included voided volume, maximum flow rate, average flow rate, and post-void residual urine (PVR) volume. IPSS was evaluated using a total index score (items 1-7), storage subscale (items 2,4,7), voiding subscale (items 1,3,5,6), and a quality of life item. Total and transitional zone prostate volumes and serum PSA levels were analyzed according to the prostatic inflammation grade. The effect of alpha blocker therapy for LUTS was evaluated according to the inflammation grade. The changes in total IPSS and subscales in the storage and voiding domains, quality of life (QoL) index, MFR, AFR, and post-void residual urine volume were measured at baseline and at 3 months. Improvement was defined as an increase in maximum flow rate > 3m/s or > 25% improvement in total IPSS. Safety parameters monitored included changes in systolic and diastolic blood pressures, and serious adverse events were recorded.

Statistical analysis

We assessed differences in clinical parameters such as MFR, average flow rate (AFR), PVR, IPSS, prostate volume, and PSA level using paired t-tests or Wilcoxon signed-rank tests with Bonferroni correction. We analyzed differences in clinical parameters according to the inflammation grade using Kruskal-Wallis tests and Wilcoxon rank-sum tests with Bonferroni adjustment. All analyses were performed using SAS software version 9.1.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Participants

A total of 111 patients from 10 hospitals were included in this study. Inflammation grades were assigned based on the most frequent score, with 25 patients at grade 0, 60 at grade I, and 26 at grade II. The mean age of each group was 64.3 (grade 0), 65.6 (grade I), and 64.9 years (grade II). The duration of treatment for each group was 6.9, 5.6, and 4.5 months (grades 0, I, and II, respectively). There were no significant differences in demographic data between the groups (Table-1).

Baseline LUTS parameters and prostatic inflammation grades

Differences in baseline LUTS parameters according to inflammation grade were evaluated. The mean MFR of each group was 13.5 (grade 0), 11.9 (grade I), and 10 (grade II). The mean AFR of each group was 8 (grade 0), 6.2 (grade I), and 5.1 (grade II). Lower grade inflammation was associated with higher MFR and AFR ($p < 0.05$). Mean total prostate volume in each group was 36.3 (grade 0), 38.9

Table 1 - Demographic data of study participants (mean [SD], median [IQR]).

	Grade 0* (N = 25)	Grade I* (N = 60)	Grade II* (N = 26)	p-value**
Age				
Mean (SD)	64.3 (7.4)	65.6 (7)	64.9 (8)	0.658
Median (IQR)	64 (60,68)	66 (61,69.5)	68 (58,70)	
BMI				
Mean (SD)	23.8 (3.5)	23.5 (2.8)	24.9 (3.3)	0.265
Median (IQR)	23.5 (22.4,24.8)	23.4 (21.4,25.2)	24.4 (22.4, 27.7)	
Systolic BP				
Mean (SD)	123.4 (12.5)	123 (11.3)	124.6 (13.8)	0.983
Median (IQR)	125 (110,130)	120 (120,130)	121 (117,130)	
Diastolic BP				
Mean (SD)	78.1 (9.1)	77.3 (8.9)	77.3 (12)	0.832
Median (IQR)	80 (70,85)	78.5 (70,82)	80 (70,84)	
Treatment duration (months)				
Mean (SD)	6.9 (7.1)	5.6 (10.7)	4.5 (5)	0.092
Median (IQR)	4 (3,7)	3 (3,3.8)	3.3 (3,4)	
DM (n[%])	4 (16.0)	2 (3.3)	5 (19.2)	0.022
Hypertension (n[%])	8 (32.0)	11 (18.3)	3 (11.5)	0.170
CVA (n,[%])	3 (12.0)	2 (3.3)	0 (0)	0.121

SD = standard deviation; **IQR =** interquartile range. * Inflammation grade was based on the most frequent score assigned to prostate specimens. ** Statistical analysis using chi-squared tests.

(grade I), and 47.9 (grade II). Higher grade inflammation was associated with larger prostate volumes including total and transitional zone volumes ($p < 0.05$). Baseline IPSS and QoL scores were unrelated to prostatic inflammation grade. In terms of serum PSA, patients with higher inflammation grades had significantly higher PSA levels ($p < 0.05$) (Table-2).

Alpha blocker treatment effects according to inflammation grade

We evaluated changes in clinical parameters and symptom scores according to inflammation grade after 3 months of treatment with an alpha blocker (Table-3). Voided volume, MFR, AFR, and PVR improved after 3 months of alpha blocker therapy, although these changes were unrelated to inflammation grade ($p > 0.05$). Similarly, IPSS improved after alpha blocker treatment, independent of inflammation grade.

The association between inflammation grade and symptomatic improvement

We evaluated whether or not improvement of LUTS was related to inflammation grade. According to the most popular inflammation scoring system, 80% of patients with grade 0 prostatic inflammation experienced improvement in their LUTS. Seventy-three percent and 92.3% of patients with grade I and grade II inflammation, respectively, had improvement of LUTS. There was no significant difference in improvement rates among the three groups ($p = 0.1363$). According to the most stringent inflammation scoring system, 82% of patients who had grade 0 inflammation experienced improvement. Additionally, 72%, 83.7%, and 100% of patients with grade I, II, and III inflammation, respectively, had improvement of LUTS ($p = 0.3185$) (Table-4).

Predictive factors for treatment responses to alpha blockers

Factors that predicted symptomatic improvement as a result of alpha blocker therapy were evaluated using univariate and multivariate analysis. Longer duration of medication use was related to decreased symptomatic improvement (OR = 0.92, 95% CI 0.85 - 0.99). Increased IPSS voiding subscales were associated with an increase in symptomatic improvement (OR = 1.17, 95% CI 1.02 - 1.34). Thus, more severe symptoms, which were represented by high IPSS voiding scores, could be predictive of improvement of LUTS with alpha blocker therapy (Tables 5 and 6).

Safety

Systolic blood pressures were decreased by a mean of 4.3mmHg after 3 months of treatment with an alpha blocker compared to baseline, while diastolic blood pressures were decreased by a mean of 4.7mmHg. There were no serious adverse events related to treatment with tamsulosin.

DISCUSSION

The present study sought to evaluate whether there is a correlation between histologically graded prostatic inflammation and prostate-related lower urinary tract symptoms. Our data suggest that prostatic inflammation grades are associated with LUTS, and that high grade inflammation was associated with lower urine flow rates and higher prostate volumes than low grade inflammation.

Prostatic inflammation is gaining increasing attention as a potential etiologic factor in prostate cancer, benign prostatic hyperplasia, lower urinary tract symptoms, and chronic pelvic pain syndrome (CPPS). In a mouse model, acute bacterial inflammation of the prostate was associated with epithelial proliferation and reactive hyperplasia (10). This study concluded that transurethral inoculation of uropathogenic E.coli 1677 reliably infected the mouse prostate, produced a significant inflammatory response, and induced quantifiable epithelial proliferation and reactive hyperplasia.

Similar to the intestine and the lung, the prostate is considered to be an immune-competent organ. It is populated by a small number of inflammatory cells (leukocytes) that increase with age and consist of scattered stromal and intraepithelial T and B lymphocytes, macrophages, and mast cells. Several reports have evaluated the constituents of inflammatory infiltrates in patients with BPH. The REDUCE study reported that chronic inflammation is observed in 77.6% of patients with LUTS, and that the higher the average chronic inflammation score, the higher the IPSS. In the

Table 2 - Differences in baseline LUTS parameters according to inflammation grade.

	Grade 0 (N = 25)	Grade I (N = 60)	Grade II (N = 26)	p-value
Uroflowmetry				
Voided volume (mL)				
Mean (SD)	236.9 (108.3)	223 (85.4)	194.1 (106.3)	0.148
Median (IQR)	184.1 (160, 294)	196.5 (161, 269.7)	170.4 (129,217)	
Maximum flow rate (mL/s)				
Mean (SD)	13.5 (3.5)	11.9 (3.6)	10 (3.3)	0.005*
Median (IQR)	15 (10, 16.3)	11.9 (9.2,14.9)	10 (7,12.3)	
Average flow rate (mL/s)				
Mean (SD)	8 (2.9)	6.2 (2.8)	5.1 (2.2)	0.002*,†
Median (IQR)	8 (5.9,10.3)	5.5 (4.2,8)	4.8 (3.7,6.7)	
Post-void residual urine volume (mL)				
Mean (SD)	59.6 (55.2)	57.3 (56.5)	52.8 (50.3)	0.615
Median (IQR)	47 (25,80)	43 (18.5,79)	(31,20,87)	
IPSS				
Total index score				
Mean (SD)	14.8 (5.3)	17.2 (7)	17.4 (4.4)	0.088
Median (IQR)	14 (12,17)	15.5 (12,21)	16.5 (14, 21)	
Storage subscale				
Mean (SD)	5.9 (2.6)	6.8 (3.1)	7.2 (2.3)	0.160
Median (IQR)	6 (4, 7)	6 (5,8.5)	7 (6,8)	
Voiding subscale				
Mean (SD)	8.8 (3.9)	10.4 (4.8)	10.2 (4.4)	0.174
Median (IQR)	8 (7,9)	10 (7,14)	9.5 (7,14)	
Quality of life item				
Mean (SD)	3.2 (1.2)	3.5 (1.1)	3.6 (1.1)	0.391
Median (IQR)	3 (3,4)	4 (3,4)	4 (3, 4)	
Prostate volume				
Total volume (cc)				
Mean (SD)	36.3 (8.2)	38.9 (10.7)	47.9 (26.5)	0.018*, ‡
Median (IQR)	37 (32, 43)	38 (30.2, 46)	41.7 (31.3,57)	
Transitional zone volume (cc)				
Mean (SD)	15 (7.8)	19 (8.5)	27.3 (19.6)	0.001*,‡
Median (IQR)	11.1 (9.8, 19)	17.3 (12.6,25.7)	23 (13.9,37)	
PSA (ng/mL)				
Mean (SD)	6.3 (4.6)	7.6 (11.6)	8.4 (4.7)	0.027
Median (IQR)	4.4 (3.7,6)	5.3 (4.6,6.8)	8 (4.6,10.9)	

SD = standard deviation; **IQR =** interquartile range. *Significant difference between grades 0 and II, † significant difference between grades 0 and I, ‡ significant difference between grades I and II. Kruskal-Wallis tests using Wilcoxon rank-sum tests with Bonferroni adjustment.

Table 3 - Changes in clinical parameters and symptom scores according to inflammation grade after 3 months of alpha blocker treatment.

	Grade 0 (N = 25)		Grade I (N = 60)		Grade II (N = 26)		p-value
	3 months	Change from baseline to 3 months	3 months	Change from baseline to 3 months	3 months	Change from baseline to 3 months	
Uroflowmetry							
Voided volume (mL)							
Mean (SD)	243 (120.3)	6.2 (115.2)	258.4 (89.6)	33.2 (77.4)	217.5	23.4 (103.3)	0.301
Median (IQR)	192.4 (170, 340)	17 (-29,51)	243 (200,298.1)	35 (-7,69.5)	(89.2) 210 (160, 235)	27 (0, 59)	
Maximum flow rate (mL/s)							
Mean (SD)	16.4 (5.4)	2.9 (5)	15.1 (5.5)	3.2 (5.8)	13.9 (4.7)	3.9 (4.4)	0.423
Median (IQR)	16 (13,17.9)	3 (0.9,4.6)	14.8 (12.3,18.3)	2.8 (-0.9,6.4)	12.8 (11.3, 18.1)	4.6 (1.5, 6.3)	
Average flow rate (mL/s)							
Mean (SD)	10 (4)	1.9 (3.2)	8.4 (5.5)	2.2 (5.5)	6.8 (2.8)	1.7 (2.3)	0.899
Median (IQR)	10.5 (6.8,12)	2 (0.5,2.7)	7.6 (5.3,10)	1.6, (0,3.2)	6.3 (5.2, 8.4)	1.2 (0, 2.6)	
Post-void residual urine volume (mL)							
Mean (SD)	34.1 (19.5)	-25.6(50.1)	36 (29.5)	-22 (51.4)	37 (35.1)	-15.7 (39.2)	0.507
Median (IQR)	33 (20,45)	-18 (-32,-9)	33 (20,48)	-10 (-40,12)	27.5 (16.7, 41)	-5.5 (-24, 0)	
IPSS							

Total index score							
Mean (SD)	9.6 (3.6)	-5.1 (4)	11.4 (6.4)	-5.8 (6.9)	9.9 (5.7)	-7.5 (5)	0.232
Median (IQR)	9 (7,12)	-4 (-6,-2)	11 (6.5, 14)	-6 (-9.5, -0.5)	9 (6, 13)	-6 (-11, -4)	
Storage subscale							
Mean (SD)	4.4 (2.1)	-1.5 (2.2)	4.8 (2.7)	-2 (2.9)	4.2 (2.1)	-3 (2.5)	0.088
Median (IQR)	4 (3,5)	-1 (-2,0)	4 (3, 6)	-1.5 (-4,0)	4 (3, 6)	-2 (-5, -1)	
Voiding subscale							
Mean (SD)	5.2 (2.1)	-3.6 (3.2)	6.6 (4.2)	-3.9 (4.7)	5.7 (4)	-4.5 (4.1)	0.733
Median (IQR)	5 (4-7)	-3 (-5,-2)	6 (3,8)	-3 (-6,-1)	5 (2, 7)	-4 (-6, -2)	
Quality of life score							
Mean (SD)	2.2 (1)	-1.1 (1.3)	2.4 (1.3)	-1.1 (1.2)	2.5 (1)	-1.1 (1.1)	0.953
Median (IQR)	2 (2,2)	-1 (-2,0)	2 (2,3)	-1 (-2,0)	3 (2, 3)	-1 (-2, 0)	
PSA (ng/mL)							
Mean (SD)	6 (5.8)	-0.3 (3.9)	5.4 (3)	-2.3 (12)	6.9 (3.3)	-1.5 (3.9)	0.377
Median (IQR)	3.9 (3.3,5.4)	-0.3 (-0.7,0.2)	4.7 (3.5,6.4)	-0.6 (-1.8,0)	6.3 (4.2,10.1)	-0.9 (-3.1, 0.2)	

Kruskal-Wallis tests using Wilcoxon rank-sum tests with Bonferroni adjustment.

Table 4 - The association between inflammation grade and symptomatic improvement.

	Improvement	No improvement	p-value
Inflammation grade - most frequent			
0 [n, (%)]	20 (80)	5 (20)	0.1363
I [n, (%)]	44 (73.3)	16 (26.7)	
II [n, (%)]	24 (92.3)	2 (7.7)	
Inflammation grade – most severe			
0 [n, (%)]	9 (81.8)	2 (18.2)	0.3185
I [n, (%)]	32 (71.7)	13 (28.9)	
II [n, (%)]	41 (83.7)	8 (16.3)	
III [n, (%)]	6 (100.0)	0 (0)	

Table 5 - Predictive factors of symptomatic improvement after alpha blocker therapy on univariate analysis.

	Univariate analysis		
	OR	95% CI	p-value
Age (years)	0.97	0.91-1.04	0.432
BMI	1.12	0.95-1.31	0.173
Treatment duration (months)	0.92	0.86-0.99	0.023*
PSA (ng/mL)	1.08	0.94-1.24	0.268
Inflammation grade - most frequent	1.47	0.74-2.93	0.271
Inflammation grade - most severe	1.54	0.83-2.88	0.174
TRUS			
Total prostate volume (cc)	1.00	0.97-1.03	0.822
Transitional zone volume (cc)	1.03	0.99-1.09	0.167
IPSS			
Total index score	1.09	1.00-1.20	0.047*
Storage subscale	1.06	0.90-1.25	0.510
Voiding subscale	1.14	1.02-1.29	0.023*
Quality of life item	1.25	0.83-1.89	0.294
Uroflowmetry variables			
Voided volume (mL)	1.00	1.00-1.01	0.202
Maximum flow rate (mL/sec)	0.96	0.84-1.08	0.484
Average flow rate (mL/sec)	0.90	0.77-1.06	0.205
Post-void residual urine (mL)	1.00	0.99-1.00	0.224

Table 6 - Predictive factors of symptomatic improvement after alpha blocker therapy on multivariate analysis.

	Multivariate analysis		
	OR	95% CI	p-value
Age (years)	0.97	0.91-1.05	0.462
BMI	1.15	0.95-1.40	0.157
Treatment duration (months)	0.92	0.85-0.99	0.025*
PSA (ng/mL)	1.06	0.90-1.26	0.477
Inflammation grade - most frequent			
Grade I vs grade 0	0.44	0.12-1.65	0.223
Grade II vs grade 0	2.52	0.32-19.96	0.382
Total prostate volume (cc)	0.99	0.95-1.02	0.460
IPSS			
Storage subscale	0.98	0.79-1.21	0.826
Voiding subscale	1.17	1.02-1.34	0.024*

*$p<0.05$

REDUCE population, there was evidence of a weak relationship between the degree of LUTS and the degree of chronic inflammation (8). Collins et al. previously reported that prostatitis may be a risk factor for the development of pathologic prostatic hyperplasia into clinical prostatic hyperplasia (11). Additionally, inflammation detected on prostate biopsies performed during a baseline assessment in a subgroup of over 1000 patients enrolled in the MTOPS study predicted progression including symptom worsening, acute urinary retention, and the need for operative management in placebo--treated patients (12).

Basic and clinical research have sought to better elucidate the prostatic inflammation pathways and their relationship with BPH and prostate cancer, with a goal of identifying new therapeutic targets and strategies for reducing the risk of benign and malignant tumors of the prostate (13). Nickel raised the possibility of using anti--inflammatory agents as an additional treatment option for patients with BPH (6). Several reports have suggested that combination therapy of an alpha-blocker and an anti-inflammatory agent was more effective for treatment of BPH than monotherapy with an alpha blocker (14-16). Therefore, the management of intraprostatic inflammation plays an important role in the improvement of IPSS in patients with prostatic hyperplasia (17).

In this study, we found that lower grade inflammation was associated with higher MFR and AFR, and higher grade inflammation was related to larger prostate volume including total and transitional zone volume. As a result, higher grade inflammation may lead to increased prostate volume and subsequent increased severity of LUTS. However, caution must be taken in interpreting these results, as prostate volume itself had an association with LUTS. While greater prostate volume was associated with more severe LUTS, prostatic inflammation may also be an effect of the symptoms themselves, though it is difficult to distinguish direct and indirect causes of dysfunctional voiding. Furthermore, baseline IPSS and QoL scores were unrelated to prostatic inflammation grade. Similarly, Nickel et al. previously reported that higher average chronic inflammation scores were associated with higher IPSS, though there were no differences in IPSS or QoL scores prior to treatment among the three groups (8). Thus, subjective symptoms at baseline may not be associated with the degree of prostatic inflammation.

Regarding factors that were predictive of alpha blocker treatment outcomes, more severe symptoms and shorter duration of treatment predicted improvement of symptoms. This is likely because symptom severity may not be directly related to the duration of treatment. We were unable to demonstrate a relationship between improvement of symptoms after alpha blocker treatment and inflammation grade.

This study was inherently limited by its retrospective design, though data were collected from 10 different hospitals to decrease the risk of bias. We included patients with PSA levels of 3-20ng/mL and excluded one patient who was found to have prostate cancer on tissue biopsy. These inclusion criteria reflect those of a previous study by Kryvenko et al. That group analyzed the association between prostatic inflammation and pre-neoplastic lesions as risk factors for prostate cancer (18). They concluded that clinicians should consider patterns and extent of inflammation when managing high-risk patients with negative biopsy results. Therefore, the evaluation of pattern and extent of inflammation in prostate tissue has emerged as an important factor influencing treatment. Further studies will be required to confirm and extend these collective results.

CONCLUSIONS

Patients with high grade inflammation had lower urine flow rates and higher prostate volumes than patients with low grade inflammation. Prostatic inflammation grade did not affect outcomes of alpha blocker treatment. More severe symptoms, which were represented by high IPSS voiding scores, could be predictive of improvement of LUTS after treatment with an alpha blocker. Further studies will be required to investigate the causally related link between these findings.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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A short-term arm-crank exercise program improved testosterone deficiency in adults with chronic spinal cord injury

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ABSTRACT

Purpose: To determine the influence of arm-crank exercise in reproductive hormone levels in adults with chronic SCI. Further objectives were to assess the influence of arm-crank exercise on muscle strength and body composition.

Materials and Methods: Seventeen male adults with complete SCI at or below the 5th thoracic level (T5) volunteered for this study. Participants were randomly allocated to the intervention (n = 9) or control group (n = 8) using a concealed method. The participants in the intervention group performed a 12-week arm-crank exercise program, 3 sessions/week, consisting of warming-up (10-15 min) followed by a main part in arm--crank (20-30 min [increasing 2 min and 30 seconds each three weeks]) at a moderate work intensity of 50-65% of heart rate reserve (HRR) (starting at 50% and increasing 5% each three weeks) and by a cooling-down period (5-10 min). Serum follicle-stimulating hormone (FSH), luteinizing hormone (LH), testosterone and estradiol were determined by ELISA. Muscle strength (handgrip) and body composition (waist circumference [WC]) were assessed.

Results: After the completion of the training program, testosterone level was significantly increased (p = 0.0166;d = 1.14). Furthermore, maximal handgrip and WC were significantly improved. Lastly, a significant inverse correlation was found between WC and testosterone (r =- 0.35; p = 0.0377).

Conclusion: The arm-crank exercise improved reproductive hormone profile by increasing testosterone levels in adults with chronic SCI. A secondary finding was that it also significantly improved muscle strength and body composition in this group.

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Key words:
Spinal cord injury; Exercise; Testosterone; Abdominal obesity; Muscle strength

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INTRODUCTION

Several studies have reported that measuring serum total testosterone levels should be included in standard screenings for patients with SCI, particularly those with motor complete injuries, given their high prevalence of testosterone deficiency (1,2).

In fact, low levels of testosterone may further adversely affect metabolism and body

composition in this group (3). Similarly, a recent review reported it may also contribute to the impairment of semen quality in spinal cord injured men (4).

Therefore, testosterone deficiency has been reported as a target in the therapeutic approach of this entity. In this respect, results achieved by using testosterone replacement therapy both in animal research (5) and human studies (3) have been promising. To date, no studies have been focused on improving testosterone levels by performing an intervention program based on regular exercise in individuals with chronic SCI. However, a recent published trial has demonstrated that aerobic training at moderate intensity increased testosterone levels in abdominally obese, sedentary adults without SCI (6).

For the reasons already mentioned, this was the first study conducted to determine the influence of arm-crank exercise in reproductive hormone levels in adults with chronic SCI. Further objectives were to determine the influence of arm-crank exercise on muscle strength and body composition.

MATERIALS AND METHODS

Study population

A total of 17 male adults with complete SCI at or below the 5th thoracic level (T5) volunteered for this study from the community. The rationale of this sampling was that the work capacity of individuals with spinal cord injury at or above the 4th thoracic level (T4) is limited by reductions in cardiac output and circulation to the exercising musculature (7).

Injury level was determined from a motor and sensory physical examination using the International Standards for Neurological Classification of Spinal Injury written by the American Spinal Injury Association (ASIA) (8).

Inclusion criteria were defined as follows: man; aged 20-35 years-old; SCI below T5; all lesions were traumatic; 4-5 years post-injury; medical approval for physical activity participation.

On the other hand, exclusion criteria were: pressure ulcers and/or coexisting infections; toxic habits (smoking or alcohol); receiving medication that may interfere with their metabolism; participation in a training program in the 6 months prior to their participation in the trial; not-completing at least 90% of the training sessions; a concurrent medical condition that might impact on their ability to participate in an exercise program.

Ethics

This research has been conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki (version, 2002). Participants gave their written informed consent prior to study participation. Furthermore, the present protocol was approved by an Institutional Ethics Committee.

Intervention program

Participants were randomly allocated to the intervention (n = 9) or control group (n = 8) using a concealed method. Characteristics of participants at baseline are summarized in Table-1.

Subjects assigned to the intervention group performed a 12-week arm-crank exercise program 3 sessions per week, consisting of warming-up (10-15 min) followed by a main part in arm-crank (20-30 min [increasing 2 min and 30 seconds each three weeks]) at a moderate work intensity of 50-65% of heart rate reserve (HRR) (starting at 50% and increasing 5% each three weeks) and by a cooling-down period (5-10 min).

Heart rate reserve was obtained according to the following equation by Wilmore et al. (9):

$HRR = ((HRact - HRrest) \times (HR\ peak - HRrest)^{-1}) \times 100\%$.

The resting heart rate (HRrest) was measured on one occasion during rest early in the morning before the training program had started. The peak heart rate (HRpeak) was derived from the pre-test arm-cranking maximal ergometry.

Exercise duration and intensity were carefully monitored and gradually increased in order to guarantee long-term compliance and injury avoidance (7). In this respect, each training session was supervised by researchers to ensure training workload was appropriate. In addition, participants wore a wireless wearable heart rate monitor (Sport Tester PE3000, Polar Electro, Kempele, Finland).

Prior to testing, participants were asked to desist from eating for 4h. To perform each training

Table 1 - Participant´s characteristics at baseline in the intervention (n = 9) and control (n = 8) groups.

	Intervention group	Control group	p Value
Age (year)	29.6 ± 3.6	30.2 ± 3.8	> 0.05
Duration of injury (months)	54.8 ± 3.4	55.7 ± 3.6	> 0.05
WC (cm)	98.1 ± 6.6	98.4 ± 6.7	> 0.05
Maximal handgrip (Kg)	45.7 ± 7.2	46.3 ± 7.5	> 0.05

Note: Results expressed as mean ± sd; **WC =** Waist circumference.

session, they were placed on a chair that was connected to the arm-crank ergometer (Ergometrics 900 SH) with their legs and their hips fixed with belts for optimal stability. It should be pointed out the pedal axis was aligned with the participant's shoulder, and participants were positioned such that their elbows were slightly flexed at maximal reach. Their feet were placed on the floor such that the knees were bent at an angle of approximately 90º. Control group included 8 age, sex and injury level matched individuals who did not take part in any training program. Further, it should be pointed out that all participants underwent a pre-training period to be familiarized with the correct use of the arm-crank ergometer. In addition, they were also asked not to perform strenuous workouts before the testing session.

Muscle strength

The Jamar handgrip electronic dynamometer (Bolingbrook, Illinois, US) was used to assess maximal handgrip strength of the dominant hand, defined as the one preferred for daily activities. The standard testing position, approved by the American Society of Hand Therapists, was used (10). Three maximal attempts, separated each one by 90 second (maximal handgrip) and 20 min (peak torque) resting periods, were given by each subject. The highest value was considered for further analysis. Verbal encouragement was afforded to ensure maximal efforts. Furthermore, all participants included in the intervention and control group underwent a preliminary session to be familiar with the correct use of the dynamometer as well as to determine the handle position at which they achieved maximal grip strength (11).

Biochemical outcomes

Blood samples were collected from the antecubital vein puncture after a 12h fast and collected by using an evacuated tube containing EDTA. The whole blood was centrifuged at 3000 rpm for 10 minutes in a clinical centrifuge.

The plasma was separated and stored at -80º C until further analysis. Serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol and testosterone were determined by ELISA (Diagnostics Systems Laboratories Inc., Texas, USA).

Abdominal fat mass

Waist circumference (WC) was determined at minimal waist after normal expiration using an anthropometric measuring tape. It should be pointed out participants were placed in a sitting position.

Statistical analyses

The results were expressed as a mean (SD) and 95% confidence intervals (95%CI). The Shapiro-Wilk test was used to assess whether data were normally distributed. To compare the mean values, a one-way analysis of variance (ANOVA) with post-hoc Bonferroni correction to account for multiple tests was used. Pearson´s correlation coefficient (r) was used to determine potential associations among tested parameters. For all tests, statistical significance was set at an alpha level of 0.05. Finally, Cohen's d statistics were used for determining mean effect sizes that were considered to be small $d \geq 0.2$ and < 0.5, medium $d \geq 0.5$ and <0.8 or large $d \geq 0.8$ respectively.

RESULTS

After the completion of the training program, testosterone level had significantly increased (p = 0.0166; d = 1.14). Conversely, changes in levels of FSH and LH were not statistically significant in the intervention group. These results are detailed in Table-2.

Regarding muscle strength assessment, the maximal handgrip strength was significantly improved after the completion of the training program (45.7 ± 7.2 vs. 50.1 ± 6.9 Kg; p = 0.027; d = 0.76). Similarly, body composition was improved as WC was significantly reduced (97.7 ± 6.3 vs. 94.2 ± 6.2cm; p = 0.044; d = 0.82).

Lastly, a significant, negative, correlation was found between WC and testosterone levels (r =- 0.35; p = 0.0377) after being exercised. Similarly, testosterone concentration was significantly associated with handgrip strength (r = 0.31; p = 0.0412).

With respect to the control group, no significant changes in any of the tested parameters were found. Finally, neither sports-related injuries nor withdrawals from the program were reported during the entire study period in the intervention group.

DISCUSSION

To the best of our knowledge, this was the first study that demonstrated arm-crank exercise improved reproductive hormone profile, by increasing testosterone levels, in adults with chronic SCI. Our results are consistent with a previous study that reported aerobic training at moderate intensity increased testosterone levels in abdominally obese, sedentary adults without SCI (6). Similarly, a 12-week resistance training significantly increased sex hormone-binding globulin (SHBG) in overweight/obese, sedentary young men (12).

These findings are of particular interest given that considerable evidence had emphasized the role of testosterone in increasing and maintaining muscle mass leading to a better metabolic control and basal energy expenditure (13). Furthermore, low levels of androgens have been associated with cardiovascular disease progression, especially coronary artery disease, and increased mortality (14). The clinical relevance of the present study seem even more relevant given that morbidity and mortality from cardiovascular disease are greater and occur earlier among individuals with chronic SCI compared to able-bodied population (15).

The current results have also demonstrated that arm-crank exercise improved body composition, by reducing WC, in adults with SCI. Similarly, a 12-week mixed protocol based on resistance training using neuromuscular electrical stimulation (FES) + diet significantly reduced visceral adipose tissue in men with chronic SCI (15). It should be emphasized our protocol was based only on exercise so that it may facilitate participants´ compliance with the intervention. These findings are of particular interest given that abdominal obesity has a negative impact on reproductive hormone levels such as testosterone (17).

Table 2 - Reproductive hormone profiles in sedentary adults with chronic SCI enrolled in the intervention (n = 9) and control (n = 8) groups.

	INTERVENTION GROUP		CONTROL GROUP		
	Pre-test	Post-test	Baseline	Final	Cohen´s d
FSH	6.26 ± 1.76	6.45 ± 1.68	6.18 ± 1.72	6.17 ± 1.70	0.17
LH	4.62 ± 1.41	4.82 ± 1.37	4.54 ± 1.43	4.55 ± 1.43	0.19
Testosterone	216.6 ± 17.4	238.4 ± 15.7 [a,b]	212.2 ± 16.9	214.6 ± 17.0	1.4
Estradiol	59.0 ± 6.2	57.4 ± 5.7	58.2 ± 5.9	58.3 ± 6.0	0.15

Note: Results expressed as mean ± sd. FSH and LH expressed mIU/mL. Testosterone expressed as ng/dL. Estradiol expressed as pg/mL. **Ratio T/E:** Ratio testosterone/estradiol. [a]p < 0.05 versus pre-test; [b]p < 0.05 versus final

In a more detailed way, current evidence suggests excess adipose tissue results in increased conversion of testosterone to estradiol, which may lead to secondary hypogonadism through reproductive axis suppression (18).

Another challenge of the present trail was to identify significant associations between testosterone and abdominal obesity in order to provide an easier, quicker, cheaper and non-invasive assessment of this reproductive hormone. In this respect, a significant but negative correlation was found between WC and testosterone. Similarly, the significant inverse association between plasma levels of cytokines and testosterone suggests an important role of low-grade visceral fat inflammation in the testosterone deficiency (19).

Regarding muscle strength, a recent systematic review of the literature concluded that handgrip dynamometry has a great potential, and could be used more often in clinical practice in a wide range of medical conditions (20), including SCI (21). In the present study, it was shown that arm-crank exercise significantly improved handgrip strength in sedentary adults with chronic SCI. Despite functional outcomes were not included in the study, Larson et al. (22) reported that the use of hand-held dynamometry to predict postural muscle strength for maintaining upright sitting in individuals with SCI has high intrarater and interrater reliability.

In spite of individuals with SCI have to face many obstacles to exercise (23), the current results are strong arguments for strengthening the role of exercise as a preventive strategy. It may also reduce healthcare costs associated to secondary conditions in this group, given the longer life expectancy observed in the last decades (24).

Finally, despite our significant results, the present study had some limitations that should be considered. Since all patients volunteered for this study from the community, a selection bias might be considered given that participants were highly motivated to undergo and follow through the program. The short sample size may also limit the generalization of the results. Lastly, a major weakness was the relatively short duration of the exercise intervention so that testosterone levels still remain below normality limit in spite of they were significantly increased. Furthermore, there is a clear need for long-term, well-conducted studies to determine whether correction of reproductive hormone profile improves clinical outcomes of individuals with SCI.

On the other hand, strengths of the current study included the homogeneous sample size in contrast to previous studies that included males and females, tetra- and paraplegia, different etiologies for SCI, years since injury, etc... Furthermore, the presence of a control group consisting of age, sex and injury-level matched individuals may reduce the recruitment bias of able-bodied controls. Lastly, the excellent adherence rate suggested the training program was effective and easy to follow-up. In fact, testosterone may improve motivation and decrease fatigue and may therefore enable participants to better adhere to exercise (25). Furthermore, it may also give them the confidence to continue exercising after the trial finishes. It should be pointed out that erring on the conservative side of selected exercise durations and intensities are prudent and even more important for persons training with a disability than those without (7). Mainly, if we take into consideration that overuse injuries, joint dislocations and fractures have been reported as common and may ultimately compromise performance of essential daily activities, including wheelchair propulsion, weight relief, etc. in this group (26).

CONCLUSIONS

A short-term intervention program based on arm-crank exercise improved reproductive hormone profile by increasing testosterone levels in adults with chronic SCI. A secondary finding was that arm-crank exercise significantly improved muscle strength and body composition. In order to confirm and extend these preliminary findings, larger, randomized, controlled clinical trials are required.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Does sildenafil enhance the effect of tamsulosin in relieving acute urinary retention?

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ABSTRACT

Objective: To compare the safety and efficacy of combined therapy using sildenafil and tamsulosin for management of acute urinary retention (AUR) with tamsulosin alone in patients with benign prostate hyperplasia (BPH).

Materials and Methods: 101 patients were enrolled in a randomized placebo-controlled study from June 2009 to April 2012. Patients presenting with an initial episode of spontaneous AUR underwent urethral catheterization and then prospectively randomized to receive tamsulosin 0.4mg plus sildenafil 50mg in group A and tamsulosin 0.4mg plus placebo in group B for three days. Urethral catheter was removed three days after medical treatment and patient's ability to void assessed at the day after catheter removal and seven days later. Patients who voided successfully were followed at least for three months.

Results: Mean age of patients was 59.64 ± 3.84 years in group A and 60.56 ± 4.12 years in group B (p value = 0.92). Mean prostate volume and mean residual urine were comparable between both groups (p value = 0.74 and 0.42, respectively). Fifteen patients in group A (success rate: 70%) and nineteen patients in group B (success rate: 62.7%) had failed trial without catheter (TWOC) at 7th day following AUR (p value = 0.3). No significant difference was noted between both groups regarding the rate of repeated AUR at one month and three month follow-up period (p = 0.07 and p = 0.45, respectively).

Conclusion: It seems that combination therapy by using 5-phosphodiesterase inhibitor and tamsulosin has no significant advantages to improve urinary retention versus tamsulosin alone.

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INTRODUCTION

Acute urinary retention (AUR) is one of the most important complications following benign prostate hyperplasia (BPH) that may led to prostate surgery (1). Previous reports revealed that dynamic factors in bladder outlet have significant role in occurrence of AUR; thus α-blocker agents such as tamsulosin or alfuzosin-SR are administered as the mainstay treatment after catheterization and significantly reduce the need for prostate surgery (2-4).

There are some evidences about association between lower urinary tract symptoms (LUTS) and erectile dysfunction (5,6). Some previous studies confirmed that combination therapy with

5-phosphodiesterase inhibitors and α-adrenergic blockers resulted in significant improvement of LUTS (7-9). Recently, a meta-analysis of the cross sectional data from twelve articles depicted that 5-phosphodiesterase inhibitors can significantly improve LUTS secondary to BPH in patients with or without erectile dysfunction (10) but there is no obvious data about the role of 5-phosphodiesterase inhibitors in AUR when administered as combination therapy with α-blocker agents.

This randomized placebo-controlled study was conducted to evaluate the safety and efficacy of tamsulosin and sildenafil versus tamsulosin alone in patients presenting with an initial episode of AUR due to BPH.

MATERIALS AND METHODS

Patients younger than 65 years old presenting with an initial episode of spontaneous AUR secondary to BPH were included in this study. Written informed consent was obtained from all patients. Patients with history of urethral stricture, previous urologic surgeries, chronic renal failure, diabetes mellitus, bladder or prostate cancer, prolonged constipation, active urinary tract infection (fever and flank pain and/or nausea and vomiting), gross hematuria, nitrate consumption, addiction to opium and alcohol and residual urine greater than 1000mL were excluded from this study. Likewise, patients with previous use of α-blocker and 5α-reductase inhibitor were excluded.

Patients were divided into two groups according to a randomized study to assess the safety and efficacy of tamsulosin 0.4mg and sildenafil 50mg versus tamsulosin 0.4mg and placebo in improving the AUR.

We conducted this randomized study on 110 patients (55 men in each group) from June 2009 to March 2012. Patients presenting with an initial episode of spontaneous AUR underwent urethral catheterization and then prospectively randomized to receive tamsulosin 0.4mg plus sildenafil 50mg in group A and tamsulosin 0.4mg plus placebo in group B for three days. No antibiotics were administered to the patients. Urethral catheter was removed three days after medical treatment and patient's ability to void was assessed at the day after catheter removal and seven days later. The patients who voided successfully were followed at least for three months, while receiving administered medicine (combination therapy vs. monotherapy) unless another episode of AUR occur.

Prostate volume was measured by transrectal ultrasonography. Urinary retention that was refractory to medical therapy was considered an indication for surgical intervention. We had no detailed information about urodynamic parameters of patients because they had not followed their lower urinary tract symptoms previously.

Statistical analysis was performed by SPSS-19 software (Statistical Package for the Social Sciences). Baseline characteristics were compared using t-test and chi-square and Fisher exact tests. TWOC were compared using ANOVA test. $P < 0.05$ was considered as the critical point for significant results.

RESULTS

Two patients in group A and one patient in group B were lost during follow-up and were excluded from analysis. Three patients in group A due to blurred vision and vertigo and three patients in group B due to headache and orthostatic hypotension withdrew from the study. Thus, statistical analysis was done on 50 cases in group A and 51 cases in group B.

Mean age of patients was 59.64 ± 3.84 years in group A and 60.56 ± 4.12 years in group B (p value = 0.92). Mean prostate volume in group A and B was 54.86 ± 19.21 and 52.66 ± 15.48, respectively (p value = 0.74). Mean residual urine at initial presentation was 717.77 ± 129.75 cc in group A and 738.54 ± 120.83 in group B (p value = 0.42).

Forty one cases (82%) in group A and thirty seven cases (72.5%) in group B had successful trial without catheter (TWOC) after catheter removal during 24 hours after catheter removal. Successful rate of TWOC was significantly better in tamsulosin plus sildenafil group versus tamsulosin at this period (p value = 0.039).

At seven days after catheter removal, six new cases in group A and five new cases in group B had failed TWOC. Thus totally 15 patients in

group A and 19 patients in group B experienced repeated urinary catheterization.

Our findings at early period (after one week) after AUR revealed 70% (35/50) success rate of combination therapy in group A and 62.7% (32/51) success rate of monotherapy in group B. Even though, difference in success rate between these two groups was 8% this difference was not statistically significant (p value = 0.3).

Of 35 patients with successful TWOC in group A, three cases (3/35) at one month follow-up and 6 cases (6/32) at three month follow-up experienced repeated urinary retention. Of 32 cases with successful TWOC in group B, failure of spontaneous voiding was noted in four cases (4/32) at one month follow-up and four other cases (4/28) at three month follow-up. Analysis of these findings revealed no significant difference between groups A and B regarding repeated AUR at one month and three month follow-up period (p = 0.07 and p = 0.45, respectively). These results are listed in Table-1.

We found no significant difference regarding to mean prostate volume and successful or failed TWOC after three months of follow-up. Mean prostate volume in successfully TWOC group and failed TWOC group was 51.53 and 57.35, respectively (P = 0.647).

DISCUSSION

Forty three percent (43%) of men in their life experience LUTS secondary to BPH (11). Obstructive and/or irritative urinary symptoms may be progressed and resulted in occurrence of some adverse events such as renal failure, gross hematuria, bladder stone, urinary tract infection and acute urinary retention (12). Anyone can experience urinary retention, but it is most common in men (15% of men) in their fifties and sixties because of prostate enlargement (1). Painful overdistention of bladder due to bladder outlet obstruction (BOO) mandates emergent urethral catheterization. Following insertion of urethral catheter, medical treatment should be initiated and after a few days, the catheter is removed in order to attempt a trial of voiding without a catheter.

Different protocols of medical therapy have been recommended in the recent years for management of LUTS using different agents including alpha blockers, 5-alpha reductase inhibitors, phytotherapic agents, anti-muscarinic drugs and 5-phosphodiesterase inhibitors (13). Alpha adrenergic blockers are the mainstay for treatment of urinary symptoms secondary to BPH. Tamsulosin and alfuzosin SR have high affinity to alpha-1a receptor and do not require dose titration; so these agents are reasonable initial option for managing AUR (14). McNeill et al. revealed that alfuzosin 10mg once daily increases the successful TWOC in men with an initial episode of spontaneous AUR and recommended that this long-acting alpha blocker should be continued after the acute phase (3).

Previous studies evaluated the safety and efficacy of monotherapy with alpha blocker alone versus combination therapy using alpha blocker and 5-alpha reductase inhibitors or anti-muscarinic drugs or 5-phosphodiesterase inhibitors. Medical therapy of prostatic symptoms (MTOPS) study indicated that long-term use of combination therapy with doxazosin and finasteride has significantly greater decrease in LUTS and lowering the rate of

Table 1 - Three month follow-up period of patients after the first episode of spontaneous AUR.

Patients with successful TWOC	Combination therapy	Monotherapy	P value
During 24 hours after catheter removal	(41/50) 82%	(37/51) 72.5%	0.039
7th day after catheter removal	(35/50) 70%	(32/51) 62.7%	0.3
One month following first episode of AUR	(32/50) 64%	(28/51) 55%	0.07
Three months following first episode of AUR	(26/50) 52%	(24/51) 47%	0.45

clinical progression comparing to monotherapy with either drug alone (15). Another study confirmed the aforementioned findings of MTOPS study and revealed that combination therapy of tamsulosin and dutasteride reduced significantly the international prostate symptom score (IPSS) especially in patients with moderate to severe symptoms when compared with monotherapy (16). Likewise, antimuscarinic agents may be useful in combination therapy with alpha blocker in patients with symptoms of BOO and detrusor overactivity without concerns of AUR (17).

LUTS have two components including static and dynamic. Static component is related to the enlargement of prostate and dynamic element comes from contraction of smooth muscle of the prostate. AUR mainly occurs from dynamic component of prostate hyperplasia (18). In addition to corpus cavernosum, there is high expression of PDE-5 mRNA in the bladder and urethra and also a substantial gene expression of PDE-5 has been found in prostate tissue and its smooth muscle (19). Urkert et al. revealed the presence of PDE-5 (CGMP-PDE) mainly in glandular and periglandular areas in transition zone (20). Age-related changes in the nervous system and neuroregulatory factors such as nitric oxide (NO) and RhoA/Rho-kinase may contribute to the pathogenesis of LUTS due to BPH and erectile dysfunction (6). Previous study by Stothers et al. showed that NO may improve LUTS by reducing the smooth muscle tone of the prostate and relaxing the urethra (21). Theoretically, inhibition of 5-phosphodiesterase resulted in increasing of cyclic guanosine mono-phosphate (cGMP). Following accumulation of cGMP, hyperpolarization, rapid drop in intra-cytoplasmic calcium and finally relaxation of smooth muscle will happen (22,23). In vitro study showed that sildenafil inhibits the growth of prostatic smooth muscle cells (24). Inhibition of PDE-5 in the prostate may have a positive impact on dynamic component of LUTS by decreasing sympathetic tone (7). These findings are in favor of the hypothesis for the use of PDE inhibitors in the pharmacotherapy of LUTS and AUR secondary to BPH. Recently, Angulo et al. described that while tadalafil enhances the effects of sodium nitroprusside induced relaxation and accumulation of cGMP, combination of tadalafil and tamsulosin resulted in greater decrease in neurogenic contractions of human bladder neck and peripheral prostate (25). According to the aforementioned findings, it seems that PDE-5 inhibitor might act on smooth muscle tone, but cannot influence the bulking effect of the enlarged prostate.

Gacci and their colleagues compared the adverse events and efficacy of tamsulosin 0.4mg/day and vardenafil 10mg/day versus tamsulosin 0.4mg/day alone in reducing LUTS due to BPH in a 12 week follow-up. They concluded that patients in combination therapy group experienced no serious adverse events and this regimen was significantly more effective than tamsulosin alone in improving urinary symptoms (9). Another randomized parallel placebo controlled clinical trial confirmed that tadalafil or tamsulosin has significant and numerically similar effects on improvement of LUTS when comparing to placebo. Even though, only tadalafil was effective in patients with LUTS and erectile dysfunction (26). There are some previous reports regarding the safety and efficacy of sildenafil (25 or 50mg/day) in decreasing of IPSS as monotherapy or in combination with alpha blocker (7-9). A recent systematic review of the prospective and cross sectional studies on 3214 patients suggested that 5-phosphodiesterase inhibitors can significantly improve obstructive urinary symptoms secondary to BPH (10).

There are paradoxical reports regarding the impact of 5-phosphodiesterase inhibitors on maximum urinary flow rate (Q_{max}). Sairam et al. described that inhibition of 5-phosphodiesterase enzyme may increase the urinary flow rate by decreasing the smooth muscle tone of the prostate (27) but Madani et al. indicated that tadalafil improves quality of life and obstructive urinary symptoms (mean 4 scores drop after treatment) but has no significant effect on Q_{max} (28).

There is no clinical study regarding the assessment of efficacy of 5-phosphodiesterase inhibitors as monotherapy or in combination with other agents on AUR following BPH. An interesting double blind placebo controlled crossover study by Datta et al. on 20 women with complete retention or obstructed voiding showed no significant clinical improvement in this group of pa-

tients who had received sildenafil when compared with placebo (29). Some confounding factors that may have influenced the pure effect of 5-phosphodiesterase inhibitor in AUR secondary to BOO were excluded and finally our findings revealed that combination therapy with sildenafil and tamsulosin in patients with AUR has no significant advantages versus monotherapy with tamsulosin in improving retention.

The aim of this study was to assess the efficacy of 5-phosphodiesterase inhibitor as an additive agent to alpha blocker for management of AUR and no voiding diary or IPSS were recorded during follow-up period (early and short--term) and maybe this is the main limitation of our study.

CONCLUSIONS

It seems that combined therapy with 5-phosphodiesterase inhibitor and alpha-blocker has no significant synergistic effects in relieving acute urinary retention when compared with alpha blocker alone in early phase and in a short--term follow-up. Even though no significant side effects were noted, the administration of this agent has some limitations regarding the interference of 5-phosphodiesterase inhibitor with some co-morbidities in older patients with AUR.

CONFLICT OF INTEREST

None declared.

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Endoscopic treatment of vesicoureteral reflux with polyacrylate polyalcohol copolymer and dextranomer/hyaluronic acid in adults

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ABSTRACT

Purpose: Aim of this study is to examine the effectiveness of dextranomer/hyaluronic acid copolymer and polyacrylate polyalcohol copolymer in endoscopic treatment of vesicoureteral reflux disease in adult patients with and without chronic renal failure.
Materials and Methods: Thirty two patients (12 female, 20 male) with a total of 50 renal units were treated for vesicoureteral reflux. There were 26 (81%) chronic renal failure patients. The success of treatment was evaluated by voiding cystouretrography at 3rd and 12th months after subureteric injection. The persistence of reflux was considered as failure. Patients were divided into two groups according to injected material. Age, sex, grade of reflux and treatment results were recorded and evaluated.
Results: Reflux was scored as grade 1 in seven (14%), grade 2 in 16 (32%), grade 3 in 21 (42%) and grade 4 in six (12%) renal units. There was not patient with grade 5 reflux. Fourteen renal units (28%) were treated with dextranomer/hyaluronic acid copolymer (group 1) and 36 renal units (72%) were treated with polyacrylate polyalcohol copolymer (group 2). The overall treatment success was achieved at 40 renal units (80%). The treatment was successful at 11 renal units (79%) in group 1 and 29 renal units (81%) in group 2 (p = 0.71). There was not statistically significant difference between two groups with patients with chronic renal failure in terms of treatment success (p = 1.00).
Conclusions: The effectiveness of two bulking agents was similar in treatment of vesicoureteral reflux disease in adult patients and patients with chronic renal failure.

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INTRODUCTION

Treatment indications of vesicoureteral reflux (VUR) disease in children are well defined. In adult patients, American Urology Association (AUA) recommends surgical treatment for patients with grade 3 or higher reflux, recurrent pyelonephritis history and nephron loss (1,2). The recent surgical treatment modalities of VUR disease are open and endoscopic surgery. The endoscopic treatment may be chosen as an alternative to open surgery because of low morbidity and mortality rates, lower cost, short term of hospital stay, and similar results to open surgery (3).

Synthetic and absorbable dextranomer/hyaluronic acid (DxHA) copolymer is the only material approved by FDA (The Food and Drug Administration) which is used in treatment of VUR disease. Particle size is more than 80µm. This reduces migration probability and does not cause

allergic reactions. After two weeks of injection, hyaluronic acid is absorbed from the injection field and dextranomer microparticles are left (4). It is the most used material worldwide (5). Overall success rates are reported between 70% and 90% in all patient groups in different studies (6). The complications are minimal such as urinary obstruction (2.1%), macroscopic hematuria (12.5%), lumbar pain (6.2%) and urinary retention (4%) (7).

Synthetic and non-absorbable polyacrylate polyalcohol (PPC) copolymer is a new material. Sizes of particles are 320µm. A fibrotic capsule of 70µm remains after implantation. The bulging effect at ureteral orifice remains within years because it cannot be absorbed when it is injected to soft tissues. There is not foreign material reaction, cytotoxicity, necrosis and migration within a 1 year follow-up after injection of PPC in animal research models (8). The stability of fibrotic capsule and long time duration is an important advantage at long term success (8). The complication and success rates reported are similar to DxHA in pediatric population (8).

There are a lot of reports concerning treatment outcomes and comparison of materials used in endoscopic treatment of VUR in pediatric patients. Reports about endoscopic treatment of VUR in adult patients are limited (9,10).

The aim of this study is to examine the effectiveness of absorbable synthetic DxHA copolymer and non-absorbable PPC copolymer tissue injection materials in endoscopic treatment of VUR disease in adult patients and patients with chronic renal failure.

MATERIALS AND METHODS

Thirty two patients (12 female, 20 male) with a total of 50 renal units (RU) were treated for primary vesicoureteral reflux (VUR) between 2003 and 2010 in Kartal Training and Research Hospital, Turkey. The patients' data were collected retrospectively. There were bilateral VUR in 18 (56%) and unilateral VUR in 14 (44%) patients. There were 26 (81%) chronic renal failure patients who were candidates for renal transplantation.

The indication of treatment in patients with normal renal function was recurrent pyelonephritis. All of the patients were evaluated with urine culture, kidney ultrasonography and voiding cystouretrography (VCUG). Six patients who have not renal failure were additionally evaluated with static renal scintigraphy (DMSA). Large spectrum antibiotic therapy was used for prophylaxis in all of the patients.

Subureteric injection was performed by three surgeons after routine cystoscopy at dorsal lithotomy position under general anesthesia. 22 F cystoscope with 3-5 F polyethylene ureteral catheter and 18-23 gauge needle were used for injection. Injection was made at 6 o'clock position and 0.5 cm away from orifice. A second access to subureteric field was made if the bulging effect was not adequate particularly in high grade refluxing units with wide ureteral orifices. Needle was pulled from tissue one minute after injection. DxHA was used between 2003 and 2005 while PPC was used between 2005 and 2010 in our hospital. Patients were evaluated with ultrasonography for hydronephrosis after one month postoperatively.

The success of treatment was evaluated by VCUG at 3rd and 12th months after subureteric injection. The persistence of reflux was considered failure even if there was a reduction or not of the grade of reflux. Patients were divided into two groups according to injected material. One of the groups received DxHA (group 1) and the other PPC (group 2). Age, sex, grade of reflux and treatment results were recorded and evaluated. Mean follow-up time was 13.2 ± 0.5 months (12-15 months).

Exclusion criteria consisted of reflux secondary to other anatomical malformation of urinary tract (complete ureteral duplication, ureterocele), previous surgical or endoscopic treatment, neurogenic bladder, suspected or confirmed dysfunctional voiding and pediatric patients.

Data are presented as mean ± standard error of mean values. Statistical calculations were performed using the chi-square and unpaired t tests using Prizm 2.01 (GraphPad Software, San Diego, CA). $P < 0.05$ was considered significant.

RESULTS

Mean age of the patients was 35 ± 3.2 and 31.5 ± 2.3 years in group 1 and in group 2 respectively ($p = 0.29$). Grades of VUR according to

renal units, injection materials, rate of chronic renal failure and treatment success are presented in Table-1. According to International Reflux Classification, reflux was scored as grade 1 in 7 RU (14%), grade 2 in 16 RU (32%), grade 3 in 21 RU (42%) and grade 4 in 6 RU (12%). There was no patient with grade 5 reflux (Table-1).

Fourteen RU (28%) were treated with DxHA (group 1) and 36 RU (72%) were treated with PPC (group 2). Mean injected material volume was 1.8 ± 0.1mL in group 1, and 1.1 ± 0.06mL in group 2 (p = 0.04).

The overall treatment success was achieved in 40 RU units (80%). The treatment was successful in 11 RU units (79%) in group 1 and 29 RU (81%) in group 2 (p = 0.71). There were similar results for grade 1-2 VUR patients in DxHA and PPC groups. Total success rate for grade 3 and 4 in DxHA group was 57%, and 65% in PPC group (p = 1.00). Treatment success rate of patients with CRF was recorded as 76.9% in PPC group. There was no statistical difference among patients with CRF in Dx/HA group (p = 1.00).

DISCUSSION

A meta-analysis reported treatment success rates with DxHA in pediatric patient population as 78.5% in grade 1-2 VUR, 72.5% in grade 3 VUR, 63% in grade 4 VUR and 53% in grade 5 VUR (11). In a European multicentre trial, DxHA injection was performed in 284 pediatric patients with 424 RU. 79% RU success rates were reported between 6 months and 3 years follow-up (12).

Arce et al. reported treatment success rates as 69% in first injection, 81% in second injection by using DxHA in adult population and they found a decrease in success rates with increasing grades of reflux (9). In another study, 100% success rate was reported in low grades of reflux and 40-60% success rate in higher grades after repeated injections in adult patients (10). Moore and Bolduc reported higher success rates as 93% in adult patients. The cause of injection treatment failure was ureterocele in one patient and ureteral surgery history in two patients, but in this report, only one patient had grade 4 reflux (13). In a study with 19 adult female patients 79% success rates after first injection and 96% after repeated injections was reported (14). In 81 RU at 49 adult patients, polytetrafluoroethylene and DxHA were analyzed and 77.8% success rates with DxHA was reported (15). In another study with 21 adult renal transplant candidate patients, success rates after 1 year follow-up were reported as 82.7% in 29 RU (16). Again in study with adult CRF patients different types of injection materials were examined and success rate of DxHA injection was found as 61% in first injection and 65% when patients with decrease in grade of reflux was added. Grade of reflux did not seem to affect the treatment success (17).

In our study, DxHA injection was performed to 14 RU. We had a success rate of 79% at 1 year follow-up. No treatment success was found in grade 4 VUR disease. Our treatment and follow--up results were similar to other studies in literature but were not similar in grade 4 VUR patients because in all of these patients VUR recurred in

Table 1 - VUR grades of renal units, injection materials, rate of chronic renal failure and treatment success. CRF: chronic renal failure, DxHA: dextranomer/hyaluronic acid copolymer, PPC: polyacrylate polyalcohol copolymer.

VUR grade	Dx/HA n	CRF n (%)	Success n (%)	PPC n	CRF n (%)	Success n (%)
Grade 1	1	1 (100)	1 (100)	6	2 (33)	6 (100)
Grade 2	6	6 (100)	6 (100)	10	3 (30)	10 (100)
Grade 3	5	5 (100)	4 (80)	16	4 (25)	11 (69)
Grade 4	2	2 (100)	0 (0)	4	4 (100)	2 (50)
Total	14	14 (100)	11 (79)	36	13 (36)	29 (81)

our study. The cause of difference in success rate can be interpreted with not accepting a decrease in grade of reflux as success and not including the patients who had been treated after repeated injections to the study groups in our study. An important limitation of our study was the small number of patients in DxHA group. In addition, the number of patients with grade 4 VUR in this group was insufficient to make an accurate assessment of this issue. Another limitation can be the short follow-up period.

Studies with PPC are limited even in pediatric patient population. A multicenter trial in South America reported 2 year follow-up results of injection treatment at 82 pediatric primary VUR patients with 88 RU. They had 88.6% success rate (78 RU), 6.8% decrease in grade of VUR (6 RU) and 4.6% failure rate (4 RU) (18). Chertin et al. studied on 38 pediatric patients with 59 RU and reported a success rate of 95% in first 3 months of injection. In 21 patients the treatment was successful at the end of 1 year follow-up (19). In our study, 81% (29 RU) success rate was recorded by injection of PPC. Treatment success rates were found similar with other PPC injection studies with pediatric patients in literature. According to our knowledge this is the first study that compared PPC and DxHA in adults and patients with chronic renal failure.

When we compare treatment results of groups 1 and 2 in our study, overall success rates was similar. Treatment outcomes were similar in patients with CRF in both groups. There was a decrease in success rates in both groups with increasing grade of reflux.

CONCLUSIONS

In conclusion, the effectiveness of PPC and DxHA was similar in treatment of VUR disease in adult and chronic renal failure patients. According to our treatment results, both materials may be used as first choice in treatment of VUR disease in renal transplantation candidate patients and patients with chronic renal failure. More studies with large patient population and longer follow-up are needed for PPC usage in adult patients.

CONFLICT OF INTEREST

None declared.

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Minimal Hydrocelectomy with the aid of scrotoscope: a ten-year experience

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ABSTRACT

Background: Since hydrocelectomy remains the choice of surgical treatment of hydrocele and standard surgical procedures may cause postoperative discomfort and complications, a new minimal surgery procedure is needed. The scrotoscope was used for the diagnosis and treatment of intrascrotal lesions. The aim of the study is to illustrate a new minimal hydrocelectomy with the aid of scrotoscope, in an effort to decrease complications.

Materials and Methods: Between 2002 and 2012, 65 patients underwent hydrocelectomy with the aid of a scrotoscope. Before carrying out hydrocelectomy, the scrotoscopy was first used to examine the intrascrotal contents to exclude any pathological lesions. After determining the condition of testis, epididymis and spermatic cord and excluding any other secondary causes of hydrocele, a 2.0cm scrotal incision was performed. The parietal tunica vaginalis was then grasped out of scrotum, and the mobilized tunica was excised. The scrotoscopy was then performed again to inspect the intrascrotal contents.

Results: Mean operative time was 35.4 minutes. No major complications occurred during the post-operative follow-up period. Of these 65 patients, 61 underwent scrotoscopy and minimal hydrocelectomy, two patients underwent open hydrocelectomy because thickening of hydrocele wall was identified; two patients with acute inflammation only underwent scrotoscopy. Pathological changes were observed among eight patients. All patients were satisfied with the outcomes.

Conclusions: Minimal hydrocelectomy shows commendable results and fewer complications. The combination of minimal hydrocelectomy and scrotoscopy seems to be an encouraging technique. This novel surgical procedure proves to be a viable option for the diagnosis and treatment of hydrocele.

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INTRODUCTION

Hydrocele refers to a collection of fluid between the parietal and visceral layer of tunica vaginalis (1). Pathogenesis of hydrocele is based on an imbalance between the secretion and reabsorption of this fluid. It is one of the most common benign scrotal pathology that leads patients to visit urologists as outpatients. Acquired hydrocele affects approximately 1% of men and most of them are more than 40 years old (2).

Acquired hydrocele can occur secondary to intrascrotal infection, regional or systemic diseases, inguinal or scrotal surgery or neoplasm, but most hydroceles are commonly idiopathic in origin (3). To diagnose hydrocele, clinical examination and ultrasound are the first options. However, in certain situations, a definitive diagnosis

is not possible on the basis of the clinical and ultrasound findings. Muglia et al. found ultrasound to be inconclusive in 5.02% of their patients with scrotal disease (4). Endoscopy is an instrument used to detect and visualize the intrascrotal contents directly. Gerris J et al. first reported the use of scrotal endoscopy (5). Shafik et al. presented some further experience with scrotoscope in the diagnosis and treatment of intrascrotal lesions (6). Our previous study showed that scrotoscope was far more precise than B-ultrasonography in diagnosing intrascrotal lesions (7).

The conventional treatment of a symptomatic hydrocele is surgical and hydrocelectomy remains the most common method of treatment. Standard surgery brings about postoperative discomfort, a temporary limitation of normal activity and complications including prolonged pain, recurrence, hematoma, infection and injury to the scrotal contents (8). Various minimal invasive procedures including minimal access hydrocelectomy, fenestration, aspiration and sclerotherapy were described (9,10). However, all the minimal procedures were performed without the thorough observation of intrascrotal contents. Therefore, the surgery could be performed under the condition that other underlying intrascrotal pathology is missed, for preoperative clinical examination or ultrasound could misdiagnose these conditions.

We innovatively combined the scrotoscope and a minimal access hydrocelectomy for the first time. To our knowledge there are very few published reports on scrotoscope for intrascrotal diseases used as an operative instrument. This novel technique appeared to be feasible, effective, well tolerated and safe for acquired hydrocele.

MATERIALS AND METHODS

Patients

We obtained approval for this study from the Institutional Review Board of The Second Xiangya Hospital, Central South University. Informed consent was obtained from all patients in the study. The informed consent was written and specified in the operative consent. All the participants were informed of the risks and benefits and completed the informed consent process.

Between April 2002 and December 2012, a total of 65 patients, aged 19-67 years (mean age 50.8 years) presenting with non-septated hydroceles underwent our novel surgical treatment. Before undergoing the surgery, all patients were evaluated with history and clinical examination followed by scrotal ultrasound to determine the nature of the hydrocele and to rule out any other intrascrotal pathological conditions including testicular malignancy, infection and hernia. Patients who were diagnosed as non-septated hydrocele were included in this study. Exclusion criteria included patients with a multiseptated hydrocele, communicating hydrocele or other scrotal abnormalities, such as tumor, infection, spermatocele or hernia.

Surgical technique

The patients received general anesthesia, spinal anesthesia, or caudal anesthesia. With the patients in lithotomy position, the scrotal skin was thoroughly examined and sterilized with povidone-iodine. A small scrotal incision of about 1.0cm was performed. Bluntly dissection was then performed through the scrotal layer until the tunica sac was disclosed (Figure-1). Generally, the hydrocele fluid would flow out and a 50mL syringe was used to aspirate the fluid. The amount and appearance of the fluid were recorded and all of it was sent for bacterial culture to rule out any potential infection. Typically, the fluid was clear yellow in appearance and negative result in bacterial culture.

As no specialized scrotocrope exists, we used cystoscope or resectoscope as scrotoscope. The sheath of scrotoscope with the obturator was passed through the incision and tunica sac (Figure-2). Keeping the drip fusion of isotonic solution inflowing, the scrotum was maintained appropriate distended. The tunica sac wall including parietal and visceral tunica was checked thoroughly while the instrument was advanced. The testis, epididymis and spermatic cord were then examined from the anterior, posterior and both lateral aspects to find out any potential pathology. Biopsy of the suspicious lesions was performed when intrascrotal abnormalities were identified.

Figure 1 - A 1.0cm incision is made in the middle to lower part of the scrotum.

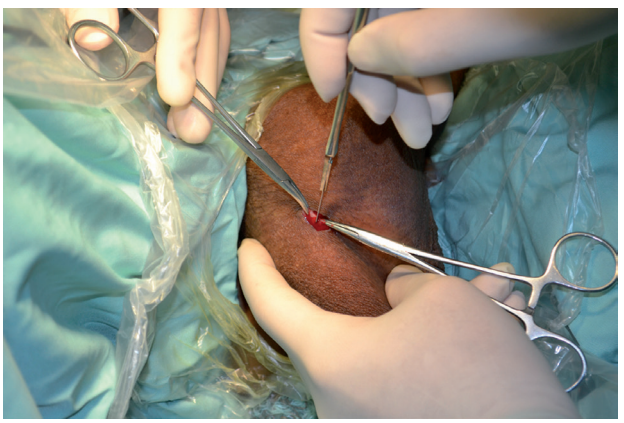
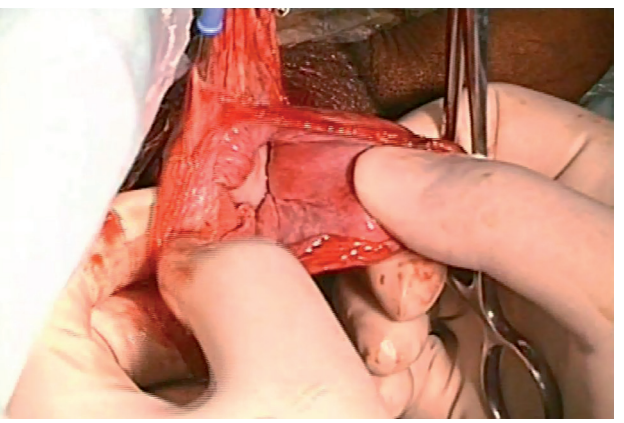
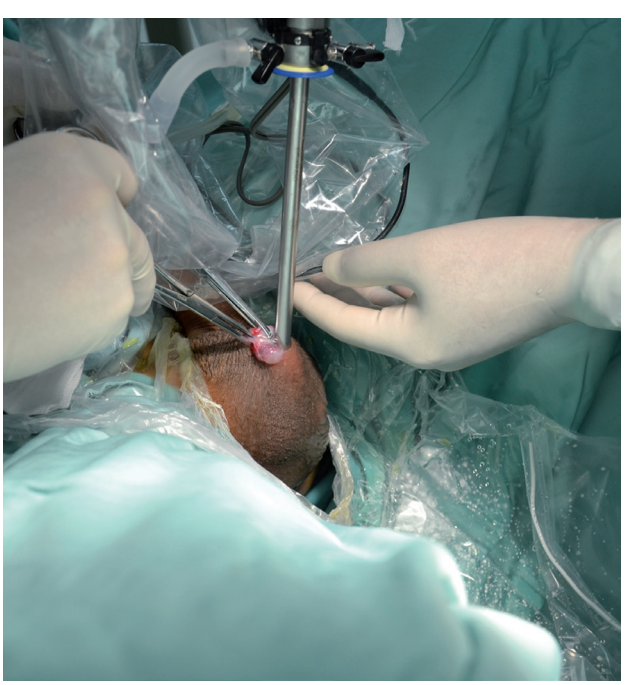


Figure 3 - Tunica vaginalis is grasped, bluntly dissected and gently pulled out of the scrotal incision.



The sheath was then removed and the incision was elongated to 2.0cm using a scalpel knife. With the aid of the index finger, the parietal tunica vaginalis was grasped and bluntly dissected from adherent tissues. Using Allis forceps, the sac was then gently pulled out of the scrotal incision (Figure-3). The mobilized tunica vaginalis was excised by electrocautery. Active bleeding was clamped and ligated. The remaining sac was replaced back in the scrotum. All excised tissue specimens were sent for pathological examination to rule out any epididymal or vasal structures in the specimen.

Figure 2 - A resectoscoope is used as scrotocrope and is placed into tunica sac through the 1.0cm incision.



The scrotoscopy was performed again to reexamine the intrascrotal contents to exclude any active bleeding or neglected lesion. The incision was then closed with an absorbable suture with placement of a rubber strip drain. All patients had the drains removed 24 hours after surgery. A wound dressing was applied with the scrotum elevated for 2-3 days. Antibiotics were administrated as anti-infective prophylactic therapy. Additional course of antibiotics were given depending on intrascrotal condition and the results of bacterial culture.

All patients were followed up in the outpatient office 4 weeks after the procedure. Subsequent follow-up was made in the outpatient or with a telephone call. All patients were followed at 6 months intervals for a mean of 26 months (range 12-30 months). The outcome criteria included: pain was assessed using visual analogue scale (VAS) of 10 ('0' meaning no pain at all and '10' meaning worst possible pain), and patient scoring 3 were considered to have pain; infection was defined as the presence of either positive microbial culture from wound discharge, or a combination of fever, pain, local erythema and discharge at the incision site. A patient was considered satisfied if the following criteria were met: decrease in pain; decrease in size of hydrocele; relief of any hydrocele-related disability; and satisfaction with overall

experience and results. Success was defined as no perceptible fluid, improvement in symptoms of pain or discomfort and patient satisfaction at the last follow-up. Criteria for failure were recurrence of the hydrocele and no improvement in symptoms including pain and discomfort.

RESULTS

A total of 65 patients aged 19-67 years old (mean age 50.8 years) from April 2002 to December 2012 were admitted to our hospital. Mean operative time was 35.4 minutes (range 25.4 to 38 minutes). Overall mean follow-up was 16 months (range 12 to 22 months). Mean volume of fluid aspirated during the procedure was 85mL (range 22 to 285mL). The color of aspirated fluid of 61 patients (61/65) was clear yellow, of two patients was turbid yellow and of 2 two patients was light red. All the bacterial cultures of fluids were negative. All the pathological examination of the resected tissue proved to be normal tunica.

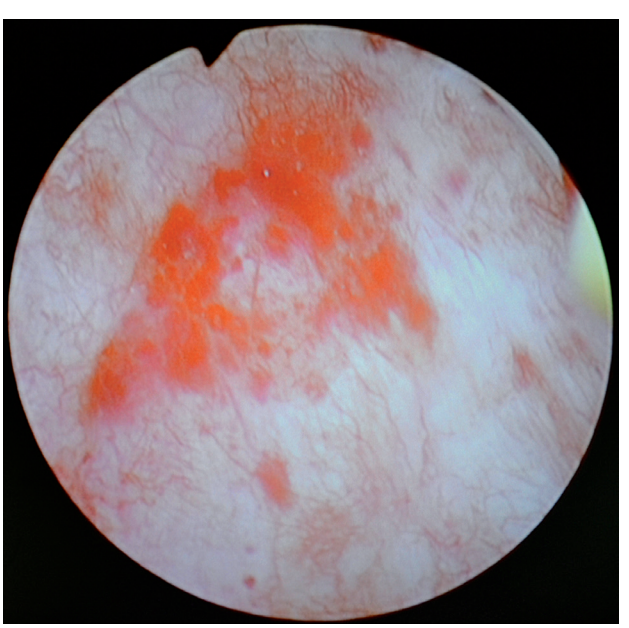
Of these 65 patients, 61 underwent scrotoscopy and minimal hydrocelectomy. Two patients underwent open hydrocelectomy following scrotosctopy because thickening of hydrocele wall was identified through scrotoscope and minimal hydrocelectomy was not suitable. Two patients only underwent scrotoscopy because acute inflammation was found through scrotoscope (Figure-4). Abnormalities were identified in eight patients of 65 and biopsies were then performed. These eight patients included two thickening of hydrocele wall, two acute inflammation and four chronic inflammation. Patients were able to resume usual daily activities an average of 4 days (range 2 to 7) after surgery.

The main complications included mild to moderate scrotal edema in four patients and two with moderate amount of postoperative pain. These two complications mostly resolved within 1-2 days without the need for pharmacologic treatment or surgical, endoscopic, and radiologic interventions. No other complications occurred. Complications of all patients were included into grade I in terms of Clavien-Dindo classification system. Intrascrotal acute inflammation was found through scrotoscope in these two patients and the hydroceletomy was not performed and the pain subsided five days later after surgery. No patients experienced postoperative hematoma or wound infection. Postoperative recurrence was not seen in any of these patients. All patients were satisfied with this procedure. The procedure was thought to be successful for all the patients (100%).

DISCUSSION

An acquired hydrocele is one of the most common benign scrotal pathological changes which affects approximately 1% of men and is mostly seen after age 40 years. Most acquired hydroceles are idiopathic in origin, but some may result from a reaction to tumors, infection or trauma. Pathogenesis of hydrocele is based on an imbalance between the secretion and reabsorption of the fluid (11). The standard hydroceletomy is a common surgical procedure, though various methods of treatment for acquired hydrocele were described, such as hydrocele aspiration and sclerotherapy, endoscopic hydrocele ablation (12,13). Hydroceletomy has advantages over these treatments in terms of the recurrence rate and patient satisfaction. Hydrocelectomy remains as the gold standard

Figure 4 - While the drip fusion was suspended, acute inflammation of parietal tunica was demonstrated.



modality for the treatment of hydrocele (14). But it has the disadvantages of discomfort and complications including mild to moderate incidence rate of recurrences, hematomas and infections; none of which had happened in our new surgery (8,15). New minimal hydrocelectomy are designed to overcome these disadvantages.

Some new minimal hydrocelectomy procedures were reported to excise hydrocele sacs through small incisions. The procedures showed minimal complications, decreased discomfort, and without recurrence. (9,10). They proved to be a viable and promising option for the surgical management of idiopathic hydrocele. But these procedures were performed without inspection of intrascrotal contents. Some pathological lesions resulting in hydroceles like infection, trauma or aseptic inflammation may be overlooked even when surgery was done. Though preoperative clinical examination and ultrasound can diagnose most of the intrascrotal lesions correctly, some pathological changes may still be missed.

Scrotal endoscopy was first reported in 1988 (5). It was used in the examination of intrascrotal contents and taking biopsies of pathological lesions (6). We started to utilize scrotoscopic technique to perform direct observation and biopsies of scrotal lesions and removal of lumps in 1990. We made a comparative study of the diagnostic preciseness of scrotoscope and B-ultrasonography on scrotal lesions. It showed that scrotoscope is far more precise than B-ultrasonography in the total diagnostic effectiveness (73.3% / 46.7%) and distinguishing a benign lump from a tumor (87.6% / 60%) (7).

In a study of endoscopic hydrocele ablation, electrocautery or laser were used to ablate tunica vaginalis endoscopically. In comparison with open hydrocelectomy, this approach appeared to be effective and well-tolerated with minimal postoperative discomfort. However, some drawbacks of this approach including need of extra trocar, risk of injuring the testis and fulguration of the testis or epididymis may limit its wide use in clinical practice (12). We started to utilize scrotoscope to treat hydrocele in 2002. Scrotoscope was used to inspect intrascrotal contents to rule out any pathological changes which could be missed by clinical examination and ultrasound. Minimal hydrocelectomy was then performed followed by second time scrotoscopy.

Mean operative time in our study was 35.4 minutes (range 25.4 to 40 minutes) which was longer than other minimally invasive procedures but was shorter than endoscopic hydrocele ablation and open hydrocelectomy (9,10,12). It was reasonable since extra scrotoscopy was performed. All patients were considered to be satisfied with their treatment. The most common complications were mild to moderate scrotal edema (4/65) and scrotal pain (2/65). Scrotal hematoma, severe scrotal edema, wound infection or recurrence was not seen in all cases. These values are comparable to other similar reports.

One advantage of this surgery procedure is the combination of scrotoscope with minimal hydrocelectomy. Because of the scrotoscopy performed, intrascrotal abnormalities which may be misdiagnosed by clinical examination and ultrasound could be detected. This study has showed that pathological changes have been identified in eight patients. The hydroceletomy was avoided in two patients with acute inflammation and open hydroceletomy was performed in two patients with thickening of tunica wall. These pathological changes would not be observed if minimal hydrocelectomy was completed alone.

Scrotoscope enables the surgeon to pick the most suitable surgery procedure for these patients. Comparing with standard hydrocelectomy, another advantage of this procedure is that the testis and spermatic cord are not handled and not removed out of the scrotum. Thus, there is fewer chance that spermatic cord or testicular torsion happen during and after operation. However, this procedure is not suitable for patients with septated hydroceles. For these patients, scrotoscopy is not recommended and open hydrocelectomy is necessary. One limitation of this study was that it was a retrospective and nonrandomized study in nature. To provide more accurate and convincing information, a prospective randomized trial is highly recommended and it is the next study we are working on.

CONCLUSIONS

The scrotoscope proves to be a safe and effective diagnostic and therapeutic technique. Our findings demonstrate that minimal hydrocelectomy with the aid of a scrotoscope has the advantages

of minimal incision, decreased complications and low rate of recurrence while clearly detecting intrascrotal contents.

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CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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PDE5 Inhibitor Treatment Persistence and Adherence in Brazilian Men: Post-hoc Analyses from a 6-Month, Prospective, Observational Study

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ABSTRACT

Purpose: Characterize persistence and adherence to phosphodiesterase type - 5 inhibitor (PDE5I) on-demand therapy over 6 months among Brazilian men in an observational, non-interventional study of Latin American men naïve to PDE5Is with erectile dysfunction (ED).

Materials and Methods: Men were prescribed PDE5Is per routine clinical practice. Persistence was defined as using ≥ 1 dose during the previous 4 - weeks, and adherence as following dosing instructions for the most recent dose, assessed using the Persistence and Adherence Questionnaire. Other measures included the Self - Esteem and Relationship (SEAR) Questionnaire, and International Index of Erectile Function (IIEF). Multivariate logistic regression was used to identify factors associated with persistence/adherence.

Results: 104 Brazilian men were enrolled; mean age by treatment was 53 to 59 years, and most presented with moderate ED (61.7%). The prescribed PDE5I was sildenafil citrate for 50 (48.1%), tadalafil for 36 (34.6%), vardenafil for 15 (14.4%), and lodenafil for 3 patients (2.9%). Overall treatment persistence was 69.2% and adherence was 70.2%; both were numerically higher with tadalafil (75.0%) versus sildenafil or vardenafil (range 60.0% to 68.0%). Potential associations of persistence and/or adherence were observed with education level, ED etiology, employment status, and coronary artery disease. Improvements in all IIEF domain scores, and both SEAR domain scores were observed for all treatments. Study limitations included the observational design, brief duration, dependence on patient self - reporting, and limited sample size.

Conclusion: Approximately two-thirds of PDE5I-naive, Brazilian men with ED were treatment persistent and adherent after 6 months. Further study is warranted to improve long-term outcomes of ED treatment.

ARTICLE INFO

Key words:
Advance Directive Adherence; Erectile Dysfunction; sildenafil [Supplementary Concept]; tadalafil [Supplementary Concept]; vardenafil [Supplementary Concept]

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INTRODUCTION

Erectile dysfunction (ED) is a common condition among men worldwide and has a negative impact on interpersonal relationships, overall self - esteem, sense of well-being, and quality of life for both men and women (1,2). In a 2001 survey of more than 1,200 men aged 40 to 70 years in 9 major cities across Brazil, 46.2% reported having ED of minimal or greater severity. The prevalence of ED increased with age, and several sociological, demographic, and medical variables were also correlated with increased ED prevalence (3).

Oral phosphodiesterase type - 5 inhibitors (PDE5Is) represent the first line of therapy for men with ED. While clinical studies have demonstrated that PDE5Is are efficacious, safe, and well tolerated, patient outcomes in clinical practice have been more variable due to a variety of factors including incorrect PDE5I administration and/or premature discontinuation of therapy (4,5). Given the contribution of successful PDE5I therapy to improvements in quality of life, confidence, and relationships (5-8), it is important to understand factors that may affect patients' continuation of therapy. Continuation itself may be considered based on two aspects - "persistence" (the patient's continuation of PDE5I therapy over a prolonged duration) and "adherence" (the patient's compliance with PDE5I dosing instructions).

Recent studies examining PDE5I persistence and adherence have demonstrated widely varying rates of persistence, ranging from 29% to 84% (9,10). Among non-persistent patients, commonly cited reasons for discontinuing PDE5I therapy have included the cost of medication, loss of interest in sex, loss of a sexual partner, lack of efficacy, or improvements in ED (10-12). Notably, a lack of efficacy may be due to either the drug or to improper use of the medication.

Given that effective PDE5I therapy requires both that patients continue to take medication and that they take it correctly, understanding factors affecting persistence and adherence in clinical practice is essential to the effective treatment of ED. In the current study, we assessed persistence and adherence to sildenafil, tadalafil, and vardenafil on-demand therapy in Brazilian men with ED and sought to identify characteristics associated with non-persistence and non-adherence. The impact of treatment on patients' ED and measures assessing satisfaction with their sexual relationships and with their ED treatment were also evaluated.

PATIENTS AND METHODS

Study Design

A 6-month, prospective, observational, non-interventional study was conducted in Brazil, Mexico, and Venezuela during the period from October 2009 through January 2011. Overall results and a detailed description of the study methods have been published previously (13). The present analysis was performed to characterize persistence and adherence specifically in the Brazilian men from that study.

In brief, sildenafil, tadalafil, vardenafil, or lodenafil on-demand dosing was prescribed to men by their clinician according to standard clinical practice. Changes to or discontinuation of the selected PDE5I treatment regimen were at the discretion of the patient and clinician. Evaluations were performed before the initiation of PDE5I therapy (baseline), and patients provided assessments of drug administration and dosing compliance, erectile function, sexual performance and satisfaction, and relationship status at 1, 3, and 6 months of treatment. The primary objective was to identify the persistence rate of prescribed PDE5I treatment at 6 months. Secondary objectives included identifying separate rates for each PDE5I and identifying factors that were associated with non-persistence and non-adherence.

Patients

Men from Brazil were eligible if they were ≥ 18 years of age, had been clinically diagnosed with ED (of any severity or etiology), were naive to PDE5I therapy, and agreed to be prescribed PDE5I on-demand therapy. All men provided written informed consent prior to initiating the study.

Outcomes Assessments

The Persistence and Adherence Questionnaire (PAQ) was administered at 1, 3, and 6 months. The PAQ asked patients if they had taken ≥ 1 dose of the originally prescribed PDE5I within the last 4 weeks (the persistence measure) and whether they had taken their most recent PDE5I dose according to their original treatment instructions (the adherence measure). Also administered at 1, 3, and 6 months postbaseline were the International Index of Erectile Function (IIEF) (14); the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS), a validated questionnaire (15) used to assess the patient's satisfaction with their current ED therapy; and the Self-Esteem And Relationship

(SEAR) Questionnaire, a 14 - item validated measure (16) assessing the sexual relationship and overall confidence of the patient. Data for these measures were summarized at 6 months only for this report.

Safety

This was an observational, non-interventional study; the safety of PDE5I on-demand therapy was monitored by each patient's physician, but safety measures were not collected and analyzed for this report.

Statistical analysis

Persistence and adherence were each treated as dichotomous outcome measures. Patients were considered persistent if they had taken ≥ 1 dose of their originally prescribed PDE5I within 4 weeks prior to a given study visit. Patients were considered adherent if they had followed treatment instructions for their most recent PDE5I dose. Patients who did not complete assessments were considered to be non-persistent and non-adherent for that visit. Patients were considered to be persistent or adherent if they met the criteria at all prior post-baseline assessments. Treatment groups correspond to the PDE5I initially prescribed.

Analyses were performed as described previously (13). The primary analysis was the calculation of the proportion of patients who met the criteria for persistence at 6 months. Persistence was also assessed at 3 months and adherence at 1, 3, and 6 months. Persistence and adherence rates were also calculated for each PDE5I (sildenafil, tadalafil, vardenafil, and lodenafil) as well as a corresponding 95% confidence interval (CI), which was calculated as an exact CI for the binomial proportion using the F distribution. To identify factors associated with persistence and adherence, a multivariate logistic regression model was used to analyze data for the complete study population from Brazil, Mexico and Venezuela. Factors significantly associated with outcomes at the 10% level were included in the model, with stepwise reduction to exclude factors with p value > 0.05. Identification of factors presented in this report was based on modeling from the overall study population applied to data for patients from Brazil only. The Spearman Rank correlation and Kruskal--Wallis test were used to investigate associations between patient characteristics and adherence/persistence.

Descriptive statistics (e.g., mean, standard deviation [SD], median, 95% CI) were used to summarize results from the IIEF, EDITS, and SEAR. Treatment groups correspond to the PDE5I initially prescribed. Findings were considered statistically significant if $p < 0.05$. Due to the small sample size, which limits statistical power, results with $p \geq 0.05$ and < 0.1 were considered of potential interest and reported here as "weakly significant."

RESULTS

Patients

A total of 104 Brazilian patients entered the study; the prescribed PDE5I was sildenafil citrate for 50 (48.1%); tadalafil for 36 (34.6%); vardenafil for 15 (14.4%), and lodenafil for 3 patients (2.9%). For lodenafil, data were generally presented in the tables but not discussed in comparison to other treatment groups due the lack of ability to draw inferences due to the very low sample size. Of all men, 90 (86.5%) completed treatment, with comparable rates of completion across the three commonly prescribed treatments (84.0 to 88.9%).

Patient characteristics are summarized by study treatment in Table-1. Mean (SD) ages ranged from 52.7 (17.9) to 58.7 (9.7) years, with an overall range of 26.0 to 79.0 years. Overall, most patients had ED of mixed (47.1%) or organic (36.3%) etiology, and for the majority (61.7%), ED severity was moderate. A slight majority of patients were diagnosed with hypertension (51.9%), 24% had diabetes mellitus, and 9.6% were obese.

Persistence and Adherence - Overall Study Population and Treatment Groups

Rates of treatment persistence and adherence are shown in Table-2, and treatment persistence is illustrated by treatment in Figure-1A. At 6 months, the overall rate of treatment persistence was 69.2%. Treatment persistence was highest with tadalafil (75.0%), but similar between sildenafil and vardenafil (64.0% and 66.7%, respectively). Persistence at

Table 1 - Demographics and Baseline Characteristics.

	Tadalafil (N = 36)	Sildenafil (N = 50)	Vardenafil (N = 15)	Lodenafil (N = 3)	Overall (N = 104)
Mean age (SD), years	58.7 (9.7)	58.3 (9.9)	55.3 (15.4)	52.7 (17.9)	57.8 (10.9)
Mean BMI (SD), kg/m^2	27.2 (4.2)	27.8 (5.5)	25.9 (6.0)	25.0 (2.8)	27.3 (5.1)
Education level, n (%)					
Primary education	13 (36.1)	13 (27.1)	7 (46.7)	1 (33.3)	34 (33.3)
Secondary education	13 (36.1)	19 (39.6)	5 (33.3)	0 (0)	37 (36.3)
Tertiary education	5 (13.9)	7 (14.6)	1 (6.7)	1 (33.3)	14 (13.7)
University education	4 (11.1)	8 (16.7)	1 (6.7)	1 (33.3)	14 (13.7)
Postgraduate education	1 (2.8)	1 (2.1)	0 (0)	0 (0)	2 (2.0)
Median ED duration, years (Q1, Q3)[a]	2.2 (1.3, 3.0)	3.0 (2.0, 3.1)	0.8 (0.6, 1.0)	0.8 (0.8, 0.8)	2.0 (1.1, 3.0)
ED Severity Categories, n (%)					
Mild	3 (9.1)	7 (16.3)	2 (13.3)	1 (33.3)	13 (13.8)
Moderate	18 (54.5)	28 (65.1)	10 (66.7)	2 (66.7)	58 (61.7)
Severe	12 (36.4)	8 (18.6)	3 (20.0)	0 (0)	23 (24.5)
ED Etiology, n (%)					
Mixed	19 (52.8)	21 (43.8)	8 (53.3)	0 (0)	48 (47.1)
Organic	13 (36.1)	17 (35.4)	6 (40.0)	1 (33.3)	37 (36.3)
Psychogenic	4 (11.1)	9 (18.8)	1 (6.7)	2 (66.7)	16 (15.7)
Pre-existing Conditions, n (%) yes					
Hypertension	19 (52.8)	25 (50.0)	8 (53.3)	2 (66.7)	54 (51.9)
Diabetes Mellitus	7 (19.4)	14 (28.0)	4 (26.7)	0 (0)	25 (24.0)
Obesity	6 (16.7)	3 (6.0)	1 (6.7)	0 (0)	10 (9.6)
Coronary Artery Disease	1 (2.8)	3 (6.0)	0 (0)	0 (0)	4 (3.8)
Benign Prostatic Hyperplasia	2 (5.6)	3 (6.0)	2 (13.3)	0 (0)	7 (6.7)
Lower Urinary Tract Symptoms	2 (5.6)	3 (6.0)	0 (0)	0 (0)	5 (4.8)
Hyperlipidemia	6 (16.7)	5(10.2)	2 (13.3)	0 (0)	13 (12.6)

BMI = body mass index; **ED =** erectile dysfunction; **N =** number of patients in treatment group; **n =** number of patients observed/reported; **SD =** standard deviation **Q =** quartile.

[a]**ED** duration data were available for: Tadalafil, n = 10; sildenafil, n = 18; vardenafil, n = 2; lodenafil, n = 1; overall, n = 31.

3 months was also highest with tadalafil (86.1%) but similar for sildenafil (70.0%) and vardenafil (73.3%).

Overall adherence was 70.2% at 6 months (Table-2). The rate of adherence was highest with tadalafil (75.0%), then sildenafil (68.0%) and vardenafil (60.0%) (Table-2, Figure-1B). At 1 and 3 months, adherence rates were also highest in tadalafil patients (Figure-1B).

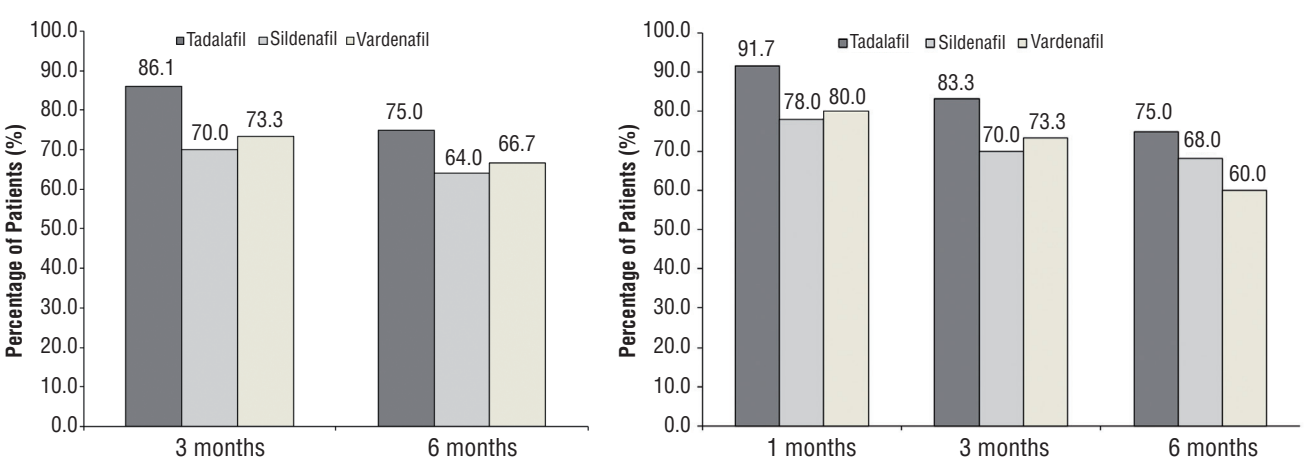
The differences in persistence and adherence estimates for the PDE5Is were not significant, as indicated by the overlapping 95% CIs.

Table 2 - Treatment Persistence and Adherence.

	Tadalafil (N = 36)		Sildenafil (N = 50)		Vardenafil (N = 15)		Lodenafil (N = 3)		Overall (N = 104)	
Parameter	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Persistence at 3 months	31	86.1 (70.5,95.3)	35	70.0 (55.4,82.1)	11	73.3 (44.9,92.2)	3	100 (29.2,100)	80	76.9 (67.6,84.6)
Persistence at 6 months	27	75.0 (57.8,87.9)	32	64.0 (49.2,77.1)	10	66.7 (38.4,88.2)	3	100 (29.2,100)	72	69.2 (59.4,77.9)
Adherence at 1 month	33	91.7 (77.5,98.2)	39	78.0 (64.0,88.5)	12	80.0 (51.9,95.7)	3	100 (29.2,100)	87	83.7 (75.1,90.2)
Adherence at 3 months	30	83.3 (67.2,93.6)	35	70.0 (55.4,82.1)	11	73.3 (44.9,92.2)	3	100 (29.2,100)	79	76.0 (66.6,83.8)
Adherence at 6 months	27	75.0 (57.8,87.9)	34	68.0 (53.3,80.5)	9	60.0 (32.3,83.7)	3	100 (29.2,100)	73	70.2 (60.4,78.8)

N = overall number of patients in treatment group; **n =** number of patients who met the criteria for indicated parameter.
Note: Additionally, persistent but not adherent patients at 3 months included 2 tadalafil, 3 sildenafil, and 1 vardenafil patient, and at 6 months included 2 tadalafil, 2 sildenafil, and 1 vardenafil patient.

Figure 1 - Treatment persistence and adherence by treatment group for sildenafil, tadalafil, and vardenafil. A) Treatment persistence by treatment group at 3 and 6 months, B) Treatment adherence at 1, 3, and 6 months.



Baseline Characteristics of Patients by 6-Month Persistence and Adherence Status

Men who were persistent at 6 months differed from men who were non-persistent in that on average they were slightly younger (mean age 57.0 [11.2] versus 59.5 [10.2] years) and had a shorter median duration of ED (2.0 versus 3.0 years; Table-3). As shown in Table-3, other factors that appeared to

Table 3 - Baseline Characteristics by 6-month Treatment Persistence and Adherence.

	Persistent (N = 72)	Non-Persistent (N = 32)	Adherent (N = 73)	Non-adherent (N = 31)
Mean age (SD), years	57.0 (11.2)	59.5 (10.2)	57.2 (10.9)	59.3 (11.0)
Education level, n (%)				
Primary education	21 (29.2)	13 (43.3)	22 (30.1)	12 (41.4)
Secondary education	25 (34.7)	12 (40.0)	24 (32.9)	13 (44.8)
Tertiary education	10 (13.9)	4 (13.3)	12 (16.4)	2 (6.9)
University education	14 (19.4)	0 (0)	13 (17.8)	1 (3.4)
Postgraduate education	2 (2.8)	0 (0)	2 (2.7)	0 (0)
Employment status, n (%)				
Full-time	44 (61.1)	11 (37.9)	45 (61.6)	10 (35.7)
Part-time	4 (5.6)	5 (17.2)	3 (4.1)	6 (21.4)
Retired	17 (23.6)	10 (34.5)	18 (24.7)	9 (32.1)
Unemployed	7 (9.7)	3 (10.3)	7 (9.6)	3 (10.7)
Race, n (%)				
Black or African America	8 (11.1)	6 (18.8)	8 (11.0)	6 (19.4)
White	64 (88.9)	26 (81.3)	65 (89.0)	25 (80.6)
Median ED duration, years (Q1, Q3)[a]	2.0 (1.1, 3.0)	3.0 (2.0, 4.0)	2.0 (1.1, 3.0)	3.0 (2.0, 4.0)
ED severity, n (%)				
Mild	11 (15.9)	2 (8.0)	10 (14.1)	3 (13.0)
Moderate	38 (55.1)	20 (80.0)	43 (60.6)	15 (65.2)
Severe	20 (29.0)	3 (12.0)	18 (25.4)	5 (21.7)
ED etiology, n (%)				
Mixed	30 (41.7)	18 (60.0)	30 (41.1)	18 (62.1)
Organic	26 (36.1)	11 (36.7)	27 (37.0)	10 (34.5)
Psychogenic	15 (20.8)	1 (3.3)	15 (20.5)	1 (3.4)
Comorbid conditions, n (%) yes				
Hypertension	34 (47.2)	20 (62.5)	36 (49.3)	18 (58.1)
Diabetes Mellitus	15 (20.8)	10 (31.3)	15 (20.5)	10 (32.3)
Coronary Artery Disease	1 (1.4)	3 (9.4)	0 (0)	4 (12.9)

ED = erectile dysfunction; **N =** number of patients in treatment group; **n =** number of patients observed/reported; **SD =** standard deviation.
[a]ED duration data were available for: Tadalafil, **n =** 10; sildenafil, **n =** 18; vardenafil, **n** = 2;

differ between persistent and non-persistent men included employment status, educational level, and the presence of diabetes mellitus, hypertension, and coronary artery disease. The severity of ED differed in that a greater proportion of men who were persistent (versus non-persistent) had severe ED (29.0% versus 12.0%) and a lower proportion had moderate ED (55.1% versus 80.0%). The etiology of ED also differed by up to 18.3% between persistent and non-persistent men. Characteristics associated with adherence versus non-adherence were generally closely comparable to those associated with persistence versus non-persistence.

Correlation Analysis of Factors Associated with 6-month Persistence and Adherence Status

Results of analyses of the correlation of various factors with persistence or adherence at 6-months are shown in Table-4. For persistence, no correlations achieved statistical significance; however, weakly significant p-values ($0.05 \leq p < 0.10$) were seen for education level ($p = 0.065$) and coronary artery disease ($p = 0.051$), while p-values for employment status ($p = 0.108$) and ED etiology ($p = 0.111$) approached this level.

Statistically significant associations with adherence were seen for employment status ($p = 0.022$) and for coronary artery disease ($p = 0.002$). Weak statistical significance was seen for education level ($p = 0.097$), while ED etiology approached weak statistical significance ($p = 0.103$).

Therapeutic Efficacy - Erectile Function, Sexual Performance, and Relationship Status

Sildenafil, tadalafil, and vardenafil on-demand dosing for 6 months were all effective in treating ED in Brazilian men, as baseline-to-endpoint improvements were observed for all treatments in

Table 4 - Correlation of Factors with Treatment Persistence and Adherence.

	Persistence		Adherence	
Factor	Correlation coefficient	P-value[a]	Correlation coefficient	P-value[a]
Age[a]	-0.110	0.268	-0.104	0.292
Marital status[b]	N/A	0.279	N/A	0.131
Education level[b]	N/A	0.065	N/A	0.097
Employment status[b]	N/A	0.108	N/A	0.022
Race[b]	N/A	0.294	N/A	0.253
ED severity[a]	0.076	0.464	0.020	0.848
ED etiology[b]	N/A	0.111	N/A	0.103
Duration of ED[a]	-0.234	0.205	-0.207	0.264
Diabetes mellitus[a]	-0.113	0.255	-0.125	0.205
Dyslipidemia[a]	0.058	0.559	-0.014	0.890
Hypertension[a]	-0.141	0.153	-0.080	0.419
Coronary artery disease[a]	-0.192	0.051	-0.307	0.002
Depression[a]	0.077	0.437	-0.018	0.860
Initial treatment[b]	N/A	0.465	N/A	0.474

ED = erectile dysfunction.

[a]Spearman correlation coefficient, used when both variables were continuous, binary or ordered categorical variables; bKruskal-Wallis test, used when one variable was a continuous, binary, or ordered categorical variable and another was not an ordered categorical variable.

all IIEF domain scores and both SEAR domain scores (Table-5). Patients also reported high levels of treatment satisfaction based on EDITS scores at 6 months ranging from 65.6% with vardenafil to 82.2% with tadalafil.

Safety

This was an observational, non-interventional study; therefore patient safety was monitored by physicians at each respective study site, but safety measures were not collected and analyzed for this report.

DISCUSSION

Among the 104 Brazilian men with ED who entered this study, 69.2% (n = 72) were persistent after 6 months of PDE5I therapy, while 70.2% (n = 73) were considered adherent through 6 months (Table-2). Patients in the tadalafil treatment group exhibited the highest rates of persistence and adherence through 6 months (75.0% for both), with somewhat lower rates for sildenafil and vardenafil (persistence, 64.0% - 66.7%; adherence, 60.0% - 68.0%).

Comparing baseline characteristics based on persistence and non-persistence at 6 months, men who were subsequently non-persistent were slightly younger, and had a shorter duration of ED. The proportion of patients with severe ED was greater, and the proportion with ED of moderate severity was lower, for persistent versus non-persistent men. Mixed etiology was more prevalent and psychogenic etiology less prevalent in persistent versus non-persistent men. Persistent men also had more full-time employment, higher average educational level, and a higher proportion had diabetes mellitus, hypertension, or coronary

Table 5 - Measures of Therapeutic Effectiveness - Results for IIEF, EDITS, and SEAR at Baseline and 6 Months.

Domain	Tadalafil		Sildenafil		Vardenafil		Lodenafil	
Parameter, mean (SD)	Baseline	Change from baseline[a]	Baseline	Change from baseline[a]	Baseline	Change from baseline[a]	Baseline	Change from baseline[a]
IIEF Erectile Function	12.5 (5.7)	10.1 (8.5)	13.4 (6.8)	8.4 (8.2)	11.5 (6.4)	8.4 (6.6)	19.3 (6.1)	7.7 (6.0)
IIEF Intercourse Satisfaction	5.3 (3.2)	4.8 (4.8)	6.2 (3.8)	3.2 (4.9)	5.5 (3.3)	3.5 (3.7)	9.3 (4.0)	2.7 (4.2)
IIEF Orgasmic Function	5.8 (3.8)	2.2 (3.7)	5.6 (3.4)	1.8 (3.3)	5.5 (3.5)	1.0 (3.3)	7.3 (2.1)	2.3 (2.5)
IIEF Sexual Desire	6.5 (1.8)	0.7 (2.3)	6.8 (2.3)	0.4 (2.3)	5.7 (2.1)	0.1 (2.2)	7.0 (2.0)	1.3 (1.2)
IIEF Overall Satisfaction	4.6 (2.0)	3.3 (2.4)	4.8 (2.3)	2.5 (3.3)	4.6 (2.1)	1.6 (2.1)	5.3 (2.3)	4.0 (2.7)
SEAR Sexual Relationship	41.9 (24.7)	31.2 (31.3)	51.7 (19.1)	21.3 (25.3)	44.8 (24.8)	19.2 (20.8)	67.7 (23.7)	20.8 (23.5)
SEAR Confidence	41.6 (22.4)	33.3 (31.6)	47.7 (22.8)	24.9 (28.2)	48.6 (18.9)	14.7 (18.9)	61.1 (18.8)	26.4 (23.0)
EDITS Total (Score)	N/A	82.2 (23.7)[a]	N/A	78.1 (22.9)[a]	N/A	65.6 (30.3)[a]	N/A	91.7 (8.0)[a]

EDITS = Erectile Dysfunction Inventory of Treatment Satisfaction; **IIEF =** International Index of Erectile Function; **SD =** standard deviation; **SEAR =** Self-Esteem and Relationship questionnaire. [a]Patients with data available both at baseline and 6 months only, except EDITS score; [b]As EDITS scores are not collected prior to treatment, data show scores at 6 months, rather than change from baseline.

artery disease. Findings for adherence were generally consistent with those for persistence.

Correlation analyses identified no statistically significant correlations with persistence; however, borderline/weakly significant correlations were observed for education level and coronary artery disease, while employment status and ED etiology had p-values just above the threshold to be considered weakly significant. Statistically significant correlations with adherence were seen for employment status and coronary artery disease, with a weakly significant correlation for education level, and ED etiology just above the threshold for weak significance. While borderline/weakly significant findings were not considered statistically significant, they could suggest areas of interest for future clinical studies or patient populations that may require additional care to improve treatment success in clinical practice.

Notably, rates of persistence and adherence were numerically higher with tadalafil versus sildenafil or vardenafil. While the reasons for this finding are unclear, there was numerically greater improvement observed with tadalafil than with sildenafil or vardenafil for most efficacy measures, including the SEAR relationship and self-confidence domains, and the various IIEF domains (including erectile function). Although modest differences in efficacy must be interpreted with caution, patients experiencing better results may have been more likely to continue therapy. However, baseline differences between patients receiving the various treatments could also have contributed to these findings.

The rates of persistence and adherence observed here are difficult to compare directly to some previous reports due to use of chart reviews, differences in follow-up times, or other methodological differences (9,11,17). Nonetheless, the findings are consistent with a persistence rate of 69% (per at least one prescription refill) through 6 months found in patients who began successful therapy with sildenafil (12), and perhaps with discontinuation rates of 47.6% and 45.4% among men previously treated and men naive to ED therapy, respectively, after a mean of 17-18 months follow-up (18), although higher persistence was reported at 6 and 12 months with tadalafil in one study (90% and 84%, respectively) (10).

In addition to the different numbers of patients assigned to each treatment and differences in some patient characteristics between treatments, other limitations of this study should be considered when interpreting these results. First, as a non-interventional, observational study, conditions of patient and treatment selection, and monitoring of follow-up were less stringent controlled than in a randomized clinical trial, and some factors influencing self-reporting could have differed between study sites. Second, some factors that could be associated with PDE5I persistence/adherence were not included in the analyses, such as the effects of concomitant medications. Third, the sample size was relatively limited, and may not be representative of Brazilian men seeking treatment for ED overall. Finally, the 6-month observational period for this study was relatively brief in comparison to other studies examining treatment compliance, which often have had observation periods ≥ 1 year; thus, the results may be less representative of prolonged PDE5I therapy. Additional study is warranted to further examine PDE5I persistence and adherence in Brazilian men, as well as to further investigate the predictive value of factors correlated with persistence and adherence. Future studies could include larger sample sizes, treatment randomization, regimented monitoring, and observational periods ≥ 1 year.

CONCLUSIONS

In this observational study, 69.2% of PDE5I-naive Brazilian men were treatment persistent with sildenafil, tadalafil, vardenafil, or lodenafil on-demand dosing after 6 months, while 70.2% were treatment adherent. Men who were initially prescribed tadalafil demonstrated somewhat, but not significantly, higher persistence and adherence rates than those who were prescribed sildenafil or vardenafil. Patient characteristics that showed some degree of association with higher persistence and/or adherence rates included higher education level, lack of coronary artery disease, full-time employment, ED of psychogenic origin, and ED of a shorter duration since diagnosis.

CONFLICT OF INTEREST

The study was funded by Eli Lilly and Company

Drs. Luis Antonio Reyes, Carsten Henneges and Sebastian Sorsaburu are employees of Eli Lilly and Company

Other authors have no conflict of interests

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ORIGINAL ARTICLE

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Application of Human Amniotic Membrane in Canine Penile Tunica Albuginea Defect: First Step toward an Innovating New Method for Treatment of Peyronie's Disease

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ABSTRACT

Purposes: To evaluate the efficacy of human amniotic membrane (AM) grafting in the canine penile tunica albuginea defect; we developed an animal model as the first step toward an innovating new method for the treatment of Peyronie's disease, penile cancers, and congenital deformities of the penis.

Material and Methods: From August to September 2011, ten healthy male dogs were selected. A rhomboid incision about 3x2cm over the tunica albuginea and its overlying squamous epithelium was made and then excised. The amniotic membrane was folded twice on itself and grafted on the defect. After 8 weeks, artificial erection was made for 5 dogs and for the other 5 dogs after 12 weeks. After artificial erection, partial penectomy was done and histopathological evaluation was performed on the grafts.

Results: Artificial erection performed successfully in all of the dogs. No infection or any other complication was seen. Histopathological examination showed complete re-epithelialization with squamous epithelium and collagen fiber deposition. Also, no dysplasia was seen.

Conclusions: The amniotic membrane can be used as a suitable substitution for tunica albuginea. It is safe, inexpensive, biodegradable, and available and may be used for the treatment of Peyronie's disease, penile cancers, congenital penile deformities, and penile reconstructive surgery.

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INTRODUCTION

Peyronie's disease, penile cancers, congenital deformities of the penis, and penile reconstructive surgery are conditions in which a suitable substitute for tunica albuginea is needed. Peyronie's disease is an acquired, localized fibrotic disorder of the tunica albuginea, resulting in penile deformity, pain, and in some men, erectile dysfunction. Several medical and surgical treatments are suggested for the Peyronie patients but all of them have their own advantages and disadvantages and none of them is an ideal choice for the treatment of the disease. Surgery is performed for the patients whose disease is stable and mature plaque is formed. Indications for surgery include deformity and/or erectile dysfunction that preclude intercourse. Excision and plication techniques have been frequently employed with different results. Also, biomaterial grafts of the dermis (1), cadaver pericardium (2), porcine small intestinal submucosa (3), tunica vaginalis (4), and temporalis fascia have

been used (5). Despite several surgical methods and biomaterials, it seems that none of them is an excellent choice and more studies could be logical and the matter is still under discussion. We herein report our experience in excising a part of canine penile tunica albuginea, grafting the human amniotic membrane, and evaluating artificial erection and histopathological changes of the specimens afterwards. We hope that success of this study could be first step toward an innovating new method for treatment of Peyronie's disease and other conditions mentioned above.

MATERIAL AND METHODS

This experiment was conducted on 10 male dogs from German race with an average age of 4 years (range = 2 to 6 years) and an average weight of 35kg in the Animal Laboratory of Shiraz University of Medical Sciences between August 2011 and September 2011. The procedures and the handling of the animals were reviewed and approved by the Research and Ethics Committee of Shiraz University of Medical Sciences in accordance with the 'principles of laboratory animal care', formulated by the National Society for Medical Research and the 'Guide for the Care and Use of Laboratory Animals', published by the National Institutes of Health (NIH publication 85-23, revised 1985). All the dogs were healthy and without any urogenital disease.

Also, human amniotic membranes, provided by Shiraz Ghotbedin Burns Hospital were kept in alcohol (95%) until application. (In this center, amniotic membranes are provided from delivery rooms and are used as a biological dressing in burn patients.)

Anesthesia was induced with thiopental intravenous administration (5mg/kg), and the dogs were thereafter intubated. Anesthesia was maintained with halothane and oxygen. The site of surgery was shaved and prepped with Betadine solution, and the rest of the body was covered with sterile drapes. A tourniquet was applied at the base of the penis. Then, by injecting 75-100cc (further injection was impossible) of sterile normal saline, artificial full rigid erection was made for evaluation of any deformity or chordee in the penis. Next, the penis was degloved by retracting the cutaneous sheath of the penis. A rhomboid incision, about 3x2cm in size, was made over the tunica albuginea and its overlying squamous epithelium before it was dissected from the underlying corpora cavernosa using Metzenbaum scissors. Any tear in the corpora cavernosa vessels was repaired with vicryl 5-0. Subsequently, a piece of amniotic membrane was selected, washed with normal saline, and folded twice on itself to increase its thickness and strength. The amniotic membrane graft with the same size as the defect was snuggly sutured to its edges with prolene 5-0, the tourniquet was removed, and any bleeding from the graft edges was controlled by over-sewing with prolene 5-0. At the end of the procedures, Ceftriaxone (1gr.) was injected intramuscularly.

All the animals were NPO for 6 hours postoperatively before the diet was started. The dogs were kept in a clean environment and separate cages and were followed up daily for two weeks and weekly after that.

After about 8 weeks, five dogs were operated on again under general anesthesia. First, a tourniquet was applied at the base of the penis and artificial full rigid erection was made by injection of 75-100ml (as maximum as possible) of normal saline into the corpus cavernosum. At this step more injection of more saline was impossible. Full erection of the penis was created for evaluation of any chordee or deformity in them. Then, the grafts, in addition to 5 millimeters of the normal margin, were removed and sent to the pathology ward for histopathological examination in formalin (10%) solution. Also, the operation was performed for the other 5 dogs in the same manner as was explained above, after about 12 weeks. Also, in this group, artificial rigid erection was made by injection of 75-100ml of normal saline into the corpus cavernosum. Samples of this group were sent for histopathological examination as well. In the pathology ward, the slides were made from samples and H&E, Masson's trichrome, and Verhoeff-van Gieson elastin staining were performed on the slides under 100x magnification.

RESULTS

The operations were performed successfully in all of the animals. No complications re-

lated to surgery like infection or bleeding were seen during intra or postoperatively. The mean operation time was about 30 minutes. Full artificial erection was created without any chordee or deformity in the penis, and no leakage or bulging in the area of the grafts was seen in all of the dogs. The grafted amniotic membrane became similar to the surrounding tissue, and only the line of non-absorbable sutures discriminated the border between the graft and normal tissue (Figure-1).

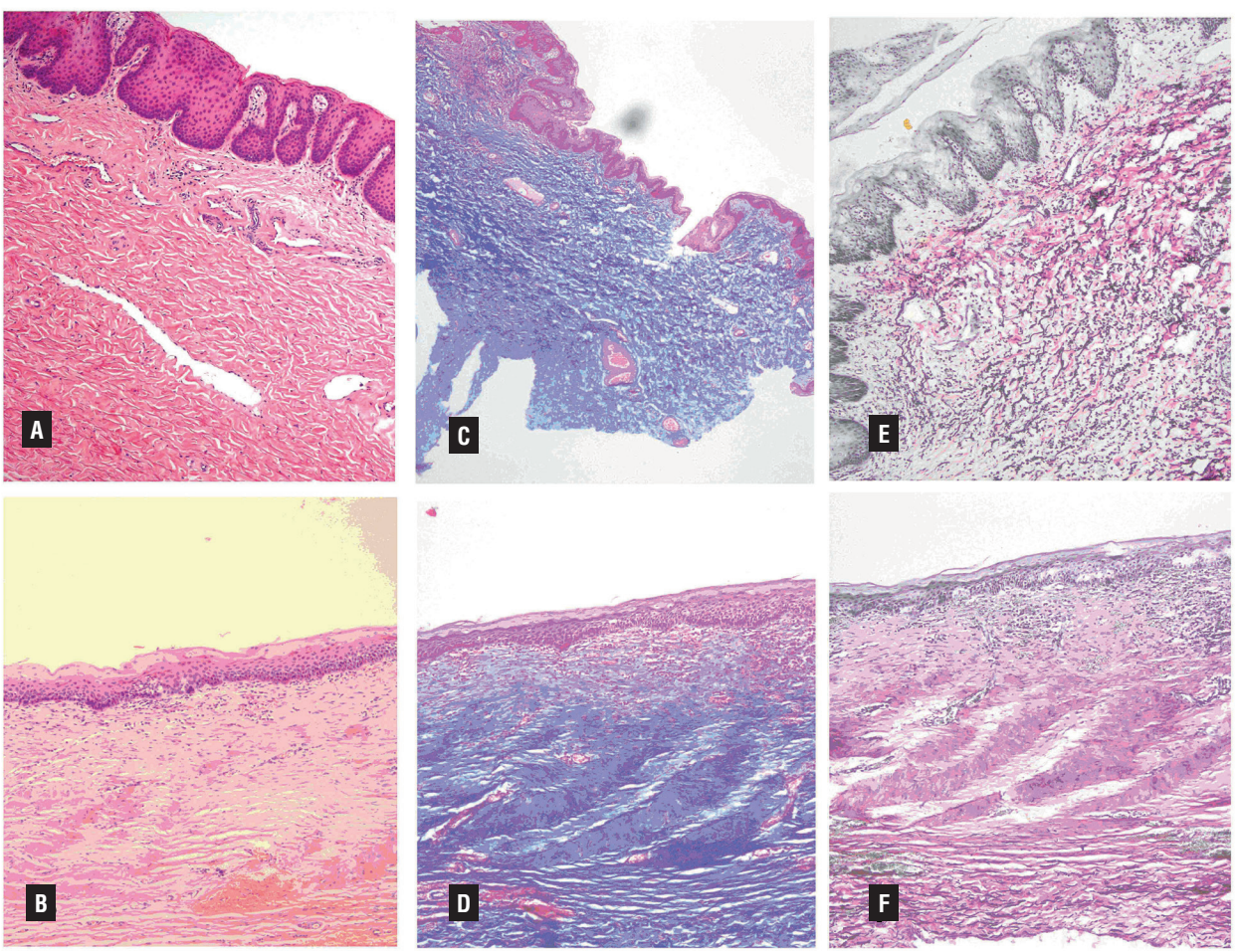
Histopathological evaluation revealed complete re-epithelialization of the epithelium with squamous layers. Also, scattered chronic inflammatory cells infiltration was seen but inflammation decreased significantly in the samples that were subjected to surgery after 12 weeks as compared to the other group. Moreover, increased collagen fiber deposition and decreased elastic fibers in the upper portion of the repaired area was seen (Figure-2). No dysplasia was detected.

DISCUSSION

The tunica albuginea is a bilaminar structure throughout most of its circumference. It is composed of an outer longitudinal layer and an inner circular layer and the corpora are separated by an incompetent septum. Nevertheless, on the ventrum, the longitudinal layer of the tunica albuginea is absent and this potentially allows dorsal buckling more easily; this can explain why most patients with Peyronie's disease demonstrate lesions dorsally. The etiology and risk factors of Peyronie's disease, however, are not known completely. Some factors such as β blockers, urethral instrumentation, certain human leukocyte antigen subtypes, TGF-β (6), downregulation of matrix metalloproteinase (7), reduction in α1-antitrypsin level (8), oxidative stress, and cytokine release may have a role in the pathogenesis of the disease. In most cases, there are two phases. The first one is the active phase and is usually associated with painful erections and changing deformity of the penis. The second quiescent phase is described by stabilization of the deformity and disappearance of painful erections. A wide spectrum of medical and surgical treatments has been suggested for Peyronie's disease but none of them is perfect. Vitamin E, colchicine, intralesional corticosteroids, and intralesional Verapamil are among the medications usually prescribed for

Figure 1 - The appearance of penile tunica albuginea before grafting (A) and 12 weeks after grafting (B).

Figure 2 - Histopathological examination of the normal tunica albuginea (A, C, and E) and repaired area (B, D, and F). In slide A (H&E), the section is from the normal area and shows the squamous epithelium with papillary structures. In slide B(H&E), the section is from the grafted area after 12 weeks and illustrates complete squamous re-epithelialization. However, the papillary structure of the epithelium became flattened to some extent. Also, scattered chronic inflammation was seen in this slide. In slide C, Masson's trichrom staining of the normal area was seen. In slide D, similar staining of the repaired area exhibits dense collagen fibers deposition 12 weeks after grafting. Slides E and F demonstrate Verhoeff-van Gieson elastin staining of the normal and repaired areas, respectively. The comparison between these two slides shows decreased elastin fibers after grafting (Magnification: 100).



the treatment. Some urologists prefer surgical correction for stable and mature disease. Reed Nesbit (9) corrected erectile deformities caused by congenital abnormalities by shortening the opposite side of the penis using plication or the excision of an ellipse of tunica albuginea. This technique was applied to Peyronie's disease by Pryor and Fitzpatrick (10), who made use of the classical elliptical excision of the tunica opposite side of the plaque. Plication of the opposite aspect of the corpora cavernosa without excising the plaque was performed by Lue and Gholami (11). Also Yachia (12) explained the corporoplasty technique of longitudinal incision in the opposite side of the tunica albuginea and transverse closure. Modifications of the Nesbit operation (tunical incision with plication, plication alone, or combinations with elliptical excision) are commonly used by urologists. Be that as it may, in all of these techniques, shortening of the penis occurred and many of the

patients did not accept this shortening. Austoni (13) showed high incidence of erectile dysfunction with plaque excision, when 20% of 418 patients developed postoperative erectile dysfunction. Penile prostheses are reserved for patients who also have an impaired erection or extensive disease. Several studies have shown that the satisfaction rates for the Nesbit Operation for Peyronie's disease are variable (Table-1) (14). Also, the results of plication techniques in different studies are available (Table-2) (14). Due to high failure rates, erectile dysfunction, penile shortening, recurrent deformity, and dissatisfaction of the patients, some physicians have searched for materials that can substitute the lesions. Excision of the plaque and closing the corporotomy defect with tunica vaginalis, as an island based on a dartos fascial and cremasteric flap, was described by Das and Amar (4). Also, Buncke (15) performed an experimental animal study, in which the lesion was excised and

Table 1 - Results of the Nesbit Operation for Peyronie's Disease (14).

Study group	Year	Number	Satisfaction (%)
Sulaiman and Gingell	1994	78	79
Poulsen and Kirkeby	1995	48	91
Ralph et al.	1995	359	82
Porst	1997	118	86
Savoca et al.	2000	157	88
Syed et al.	2003	42	79

Table 2 - Results of Penile Plication for Peyronie's Disease (14).

Study group	Year	Number	Satisfaction (%)	Recurrent deformity (%)
Nooter et al.	1994	33	64	5
Klevmark et al.	1994	51	82	5
Klummerling and Schubert	1995	54	89	10
Thiounn et al.	1998	29	62	20
Schulteiss et al.	2000	21	67	43
Chahal et al.	2001	69	52	14
Gholami and Lue	2002	116	93	15
Cormio et al.	2002	30	92	-
Van der Drift et al.	2002	31	58	47
Van der Horst et al.	2004	28	57	18
Greenfield et al.	2005	68	98	1.5

the defect was substituted with temporalis fascia as a microvascular free flap.

Utilization of de-epithelialized penile skin or other parts of the body has been suggested by many authors in the literature. Still, most urologists are unfamiliar with the skin de-epithelialization technique and as such tend to find it a difficult and time-consuming procedure. Incision in the plaque and patching the corporotomy defects with vein grafts is another technique. Grafts from the cadaver pericardium and porcine small intestinal submucosal graft have also been reported (2,3). Foreign material "grafts" (e.g. Silastic, Gore-Tex, and Dacron) have not had promising results thus far.

In addition to Peyronie's disease, there are other conditions whose treatment requires a substitution for tunica albuginea; these conditions include trauma, penile cancers, congenital curvatures, and reconstructive surgery of the penis. The amniotic membrane has been recently used widely and successfully in ophthalmology for corneal and conjunctival reconstructions (16), burn dressing (17), urethroplasty (18), vestibuloplasty (19), surgical dressings (20), myelomeningocele (21), long ureteral stricture construction (22), bladder reconstruction (23), and other modalities. The amniotic membrane is composed of the connective tissue with a significant collagen and extracellular matrix composition. It is resistant to infection and rejection. In addition, it is avascular and has anti--inflammatory and anti-scaring properties (24).

Artificial erection showed that the amniotic membrane changed from a delicate structure to firm adhesive fibrous material that can tolerate high intra-cavernosal pressure without leakage or bulging. Also during full rigid erection no chordee was seen and it showed amniotic membrane grafting is not only a fibrotic reaction; instead this biomaterial get host tissue properties like its distensibility and elasticity. Presence of elastin fibers in histopathologic evaluation confirms this. The capability of the amniotic membrane to achieve host tissue characters has been proved by several studies. It is a pluripotential tissue that can transform to the cornea, epidermis, dermis, transitional epithelium of the urethra and bladder, and others. We folded the amniotic membrane twice, and this may be responsible for the increased strength after the operation. In addition, we thought folding of the amniotic membrane helps us in suturing and handling of this delicate material.

A study by Dr. Khodadoust (25) showed that the basement membrane of the amnion promotes the migration of the epithelial cells and reinstitutes adhesion between the basement membrane and new epithelial cells. In addition, Kim (26) showed that the stromal matrix of the amniotic membrane contains proteinase inhibitors that promote healing of the epithelium and reduces inflammation of the host tissue stroma. In one study, reverse transcription-polymerase chain reaction analysis showed that human amniotic epithelial cells are capable to express albumin, alpha-1--antitrypsin and other hepatocyte-related genes; therefore, the amniotic membrane has the potency to produce alfa-1-antitrypsin (27). Furthermore, in organ culture, the amnion also secreted alpha-1--antitrypsin. On the other hand, alfa-1-antitrypsin deficiency is likely to play a role in the pathogenesis of Peyronie's disease (8); as a result, the production of this material from the amniotic membrane can help in Peyronie's disease treatment. A study by Del Carlo evaluated the role of matrix metalloproteinase in this abnormal scarring process. Matrix metalloproteinases are enzymes that are engaged in the remodeling of the extracellular matrix proteins; these remodeling enzymes are regulated by the tissue inhibitors of metalloproteinase. In the case of Peyronie's disease, matrix metalloproteinases are downregulated, acting as a possible mechanism for the scarring process in the pathogenesis of Peyronie's disease (7). In addition, immunohistochemistry studies performed on freshly prepared amniotic membrane confirmed that all the members of the tissue inhibitor of metalloproteinase (TIMP) family were present in the epithelial and mesenchymal cells and the compact layer of the amniotic stroma (24). So, the interaction between amniotic membrane TIMP and tunica albuginea must be studied further. The amniotic membrane contains several growth factors; it is avascular and has anti-inflammatory, anti-angiogenic, and anti-scarring effects. These properties make human amniotic membrane an ideal tissue graft for the surface reconstruction of different tissues. In contrast to the studies that have repor-

ted the anti-inflammatory effects of the amniotic membrane, we observed chronic inflammatory cells infiltration in the repaired area, although the inflammation decreased significantly in the dogs subjected to surgery after 12 weeks in comparison to the other group. Re-epithelialization occurred in all of the grafts in our study. Other studies have also demonstrated the great potential of re-epithelialization in amniotic membrane grafts. Although the dogs haven't Peyronie's disease, these results that showed tunica abuginea could be replaced by amniotic membrane are encouraging. Also longer follow-up in next studies is recommended for evaluation of late complications. It should be emphasized that although we hadn't any infection or unwanted reaction, allografts and synthetic materials carry the risk of tissue reaction and infection.

CONCLUSIONS

This study suggests that the amniotic membrane is a biodegradable graft with little antigenic effects and its grafting is economical and easy. The amniotic membrane may be an ideal substitution for tunica albuginea and treatment of Peyronie's disease, penile cancers, and congenital deformities and in penile reconstructive surgery. Although the situation might not be the same in human and the immunological reaction, the retraction rate and the function of the graft could be different but at this step the results are encouraging but more experimental studies are highly recommended for more accurate and reliable results, which hopefully would make it possible for the amniotic membrane to be used in human cases.

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ORIGINAL ARTICLE

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The use of Hypochlorous Acid as a Model for Investigating Bladder Overactivity

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ABSTRACT

Involuntary detrusor contractions play an important role in the development of urge incontinence. Also in an in-vitro situation contractions which develop spontaneously can be seen; a parallel with the in vivo observations is likely. In order to study this muscle overactivity we investigated the possibility to induce this phenomenon with oxidative stress using hypochlorous acid (HOCl).

Materials and Methods: Urinary bladder muscle strips from pigs were mounted in a custom made organ bath and incubated for 20 minutes in Krebs solution. Next HOCl (10µM) was added to the organ bath and the onset of overactive contractions was closely followed. Overactivity was defined as a development of more than 5 phasic detrusor contractions per minute without any other provocation in the 30 minutes following addition of HOCl to the organ bath.

Results: Of the 50 strips which were used 36 (72%) became overactive after exposure to HOCl during 30 minutes recording. In 76% of the overactive strips overactivity occurred within 5 minutes, in 19% between 5 and 15 minutes, and in 5% it took longer than 15 minutes. The overactivity could be stopped by washing out HOCl for 10 minutes after which still a significant contraction after EFS and ACh stimulation was seen.

Conclusions: It can be concluded that an oxidative stressor, like HOCl, is capable of inducing smooth muscle overactivity. This model can be used for the development and testing of new treatment modalities for the overactive detrusor. Furthermore, this study provides evidence for a causal relationship between oxidative stress and detrusor overactivity.

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INTRODUCTION

Overactivity bladder (OAB) has become the focus of intense interest because this term is used to describe the symptom complex of urinary urgency with or without urge incontinence, usually with frequency and nocturia (1). Drug treatment continues to have an important role of women with OAB.

Concerning the basic mechanisms of bladder overactivity, increasing evidence has shown that the generation of free radicals plays a role in the development of overactivity bladder (2).

Previous in vitro research showed that during low extracellular calcium concentrations a relatively fast rate of force development was observed (3,4). A similar rate of force development could be demonstrated in spontaneously generated contractions. Therefore it was hypothesized that spontaneously generated contractions might be more dependent upon calcium release from intracellular stores. At least these contractions were

evoked by a process with a fast pathway to the contractile units. From our previous study we could conclude that selective inhibition of the IP_3 pathway with the calcium blocking agent Xestospongin C significantly (P = 0.036) slowed down the rate of force development while still a significant (P = 0.003) contraction amplitude remained through the CICR pathway. We could assume that the IP_3 pathway is the prevailing pathway for the 'fast' spontaneously developing detrusor muscle contractions.

Overactivity is seen when in vitro detrusor muscle strips are cut. To some extent they become more overactive when they are cut smaller but in the majority of the cases they become overactive at all (5). In order to induce overactivity we designed an in vitro model for the development of researchers on the field of new treatment modalities for the overactive detrusor, using oxidative stress.

MATERIALS AND METHODS

Experiments were performed on pig urinary bladders obtained from the slaughterhouse approximately 30 minutes after slaughter. Strips of 2 x 2cm were cut from the dorsal side of the bladder dome and transported to the laboratory in oxygenated Krebs solution. The mucosa and the submucosal fat layer were removed using a binocular microscope, and strips of 0.3mm diameter and length between 1 and 2mm were excised. To facilitate diffusion the thin layer covering the muscle fiber was opened and for the greater part removed. Each strip was positioned horizontally in our custom made organ bath (IDEE University Maastricht) between two tweezers of which one was attached to the KG4 force transducer connected to the BAM4C amplifier (Scientific instruments, Heidelberg, Germany). The other tweezer was connected to a translation stage which was regulated by a controller (translation stage M111,1DG; Mercury Controller C860, Physic Instrumente). An electrical field was generated between two platinum electrodes connected to the HM8130 Function Generator from Hameg Instruments. Flow in the organ bath (volume 0.23mL) was regulated with separate in and outflow syringe pumps (Vickers Medical, IP_4). Temperature was kept at 37° C using infrared radiation from a halogen lamp (Philips, Eindhoven, Netherlands 12V, 20W, 6°) and controlled using a 200µm diameter thermocouple (Omega ChAl/005).

The strips were incubated in modified Krebs solution: NaCl, 118mM; KCl, 4.7mM; $NaHCO_3$, 25mM; KH_2PO_4, 1.2mM; CaCl, 1.8mM; $MgSO_4$, 1.2mM; glucose 11mM; pH 7.4; aereted with 95% O_2 / 5% CO_2. All agents were manufactured by Calbiochem. For pharmacological stimulation a 10µM acetylcholine solution (Sigma, St-Louis, MO, USA) was used.

Measurement protocol

The muscle strips were placed in the organ bath and incubated in Krebs. We determined L_0 the length at which maximum isometric force was developed at 37° C. After that, the strips were stimulated at this length. Before incubation with HOCl the strips were stimulated in a random order twice electrically and once with acetylcholine. EFS was applied (10s, 15V amplitude,50ms,100Hz). When a muscle strip developed less than 100µN force it was excluded from further measurements. Between each stimulation, an interval of 10 minutes was introduced. After these initial stimuli 50 strips were incubated with the HOCl solution in order to see whether they became overactive. Control group with 10 muscle strips underwent the same stimulation protocol without treating them with HOCl. Overactivity in this study was defined as a development of more than 5 phasic detrusor contractions per minute without any other provocation in the 30 minutes following addition of HOCl to the solution. After washing out HOCl for twenty minutes a last EF and pharmacological stimulation with acetylcholine was applied.

At the end of the experiment the strips were analysed in order to quantity the isoprostane 8-epi PGF2 alpha amount.

Data analysis

All isometric contractions were sampled at a rate of 100 Hz with a PCI-DAS 1000 card from Computer Boards® in a Pentium® 4 computer. Phase plots, which represent the first derivative of force as a function of the force itself, were calculated. Normally these phase plots of mono

exponential isometric smooth muscle contractions can be characterized by a straight line where F is the measured force, F_{iso} is the maximum extrapolated isometric force, t is time, and C (Eq.1) is the time constant for isometric force development. The time constant is an indicator of the rate limiting process in the excitation-contraction coupling and indicates in which period of time 66% of the saturation level of maximum force development is reached. The smaller the value of C, the faster the rate of force development.

$$F = F_{iso} [1 - e^{-(t/C)}] \quad Eq.1$$

The value of EF-stimulation at L_0 was seen as the optimal stimulation and therefore as the baseline value of F_{iso} and time constant. This is maximum force development without treatment with the HOCl solution. When the strips became overactive, F_{iso} and C of the spontaneously developed contractions were calculated. After washing out the HOCl solution the percentage of reduction of force development was compared to the initial force development. These normalized percentages were averaged for all 49 muscle strips. The time constants were not normalized.

Oxidative Products

EIA of the oxidatively modified product isoprostane 8-epi PGF2alpha was performed. Briefly, HOCl-treated and control bladder tissues were equilibrated for 2 hours in culture medium at 37º C. The medium was exchanged with fresh medium every hour. After the last hour of incubation the levels of isoprostane 8-iso PGF2alpha in supernatant were assayed in triplicate with commercially available EIA kits (Cayman Chemical, Brazil). Microtiter assay plates were scanned with a SpectraMax Plus 384 computer controlled microplate reader. The quantity of isoprostane 8-epi PGF2alpha was standardized as pg/100mg wet weight of tissue per hour.

Statistical analysis

A paired t-test was used for statistical analysis. Changes in provoked electric and pharmacological stimulation with acetylcholine were calculated. Fiso and rate of force development of the overactive contractions were also calculated. All calculations were processed in Matlab® 6.1. For statistical analysis SPSS® version 10 was used.

RESULTS

Percentage of overactivity after HOCl treatment

After treatment with HOCl, 72% (36 out 50) of the muscle strips became overactive, 20% (10 out 50) of the muscle strips did not show overactivity, defined as a development of more than 5 phasic detrusor contractions per minute without any other provocation in the 30 minutes following addition of HOCl. 8% (4 out 50) of the muscle strips became overactive spontaneously within a few seconds before the HOCl solution was added.

Time the strips became overactive

Most of the muscle strips (76%) showed overactivity within 5 minutes. In 19% they became overactive between 5-15 minutes and in 5% it took 15-30 minutes. In 5 muscle strips the recording was continued for 60 minutes and after that time, none of them showed overactivity.

In Figure-1 the bars represent the rate of force development (C). It shows no significant difference between Electrical Field Stimulation (2.45 seconds) and pharmacological stimulation with acetylcholine (2.55 seconds). Using a paired t-test the provoked overactive contractions have a faster rate of force development (1.20 seconds) ($P = 0.001$) compared to the Electrical Field Stimulation and acetylcholine stimulated contractions.

Marker of Oxidative Stress

Isoprostane 8-epi PGF2alpha levels significantly increased in HOCl-treated bladders compared to control group (Figure-2).

DISCUSSION

An important research topic in functional urology has become the search for a way to inhibit the spontaneously developed involuntary contractions and leave the voluntary or evoked contractions unchanged. The development of involuntary contractions can be caused by both a dysfunction

Figure 1 - Time constants for EFS, ACh and non provoked (NP) overactive contractions.

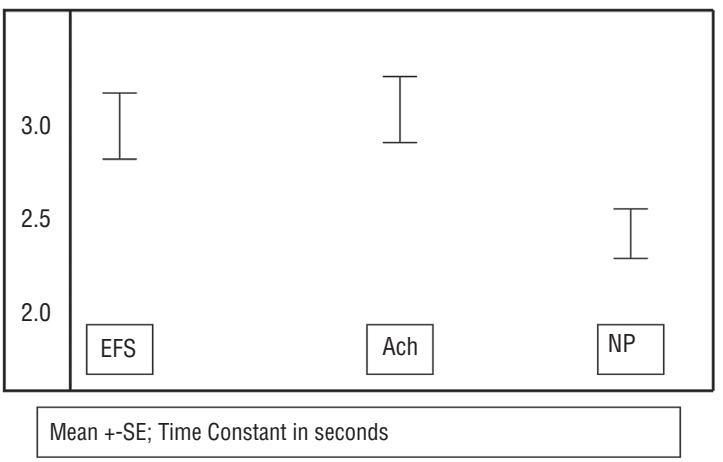
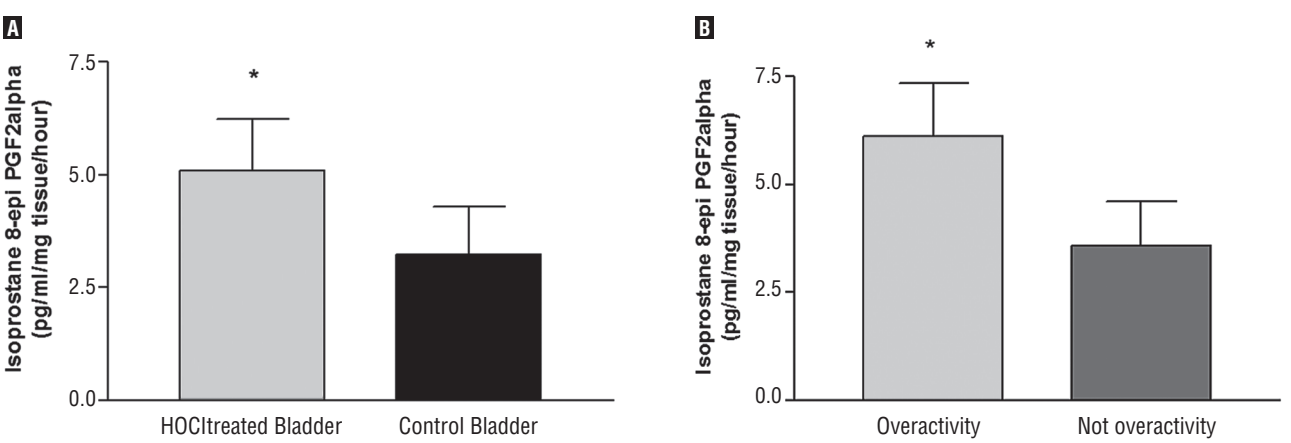


Figure 2 – A) Levels of oxidatively modified product isoprostane 8-epi PGF2alpha after HOCl to be added to organ bath vs control bladder. B) It represents the levels of isoprostane 8-epi PGF2alpha in strips that became overactive vs not overative strips.



* $p < 0.05$

of the efferent nerve supply of the bladder or by an intrinsic overactivity of the detrusor muscle itself (1). Previous research also indicated that a denervation of the bladder leads to an increase in the development of overactive bladder contractions (5). It appears that an adequate innervation reduces the overactive detrusor contractions. Our own experimental in vitro observations showed the same results: to some extent the muscle strips became more overactive, the smaller they were cut.

This study showed that a small number (4%) of the muscle strips became overactive spontaneously while more than half (53%) the strips became overactive after incubation with HOCl. This validates the results seen in previous studies where the role of several reactive oxidative stressors like hydrogen peroxide and hypochlorous acid led to overactivity of smooth muscle (6-8).

This model makes it possible to study overactivity of smooth muscle in more detail. The

Table 1 - Three month follow-up of patients with the first episode of spontaneous AUR.

Patients with successful TWOC	Combination therapy	Monotherapy	P value
During 24 hours after catheter removal	(41/50) 82%	(37/51) 72.5%	0.039
7th day after catheter removal	(35/50) 70%	(32/51) 62.7%	0.3
One month following first episode of AUR	(32/50) 64%	(28/51) 55%	0.07
Three months following first episode of AUR	(26/50) 52%	(24/51) 47%	0.45

contractions caused by HOCl have the same rate and amplitude as the spontaneously developing contractions. Therefore, the induction of overactivity-resembling (overactivity-like) contractions with HOCl makes it possible to study which intracellular pathway is more or less responsible for the development of overactivity in smooth muscle and in particular smooth muscle of the urinary bladder. Changes in amplitude and rate of force development can be observed by using different intracellular pathway inhibiting agents.

During incubation with the oxidative stressor (HOCL 10µM) and after washing out, EFS and acetylcholine were still able to provoke a similar contraction. Therefore it can be assumed that exposure to a 10µM concentration of HOCl causes overactivity but minimal damage.

In our model incubation longer than 15 minutes has no benefit. HOCl is capable of modulating the intracellular calcium pathways or at least cause changes to the contractile units.

Experimental studies that have examined the association between oxidative stress and bladder dysfunction have supported the hypothesis that the generation of free radicals might be linked to bladder dysfunction (9-11). Possibly, the detrusor dysfunction is caused by activation of specific hydrolytic enzymes including calpain and phospholipase A_2 with subsequent damage to intracellular organelles such as the mitochondria and sarcoplasmic reticulum and via generation of reactive oxygen species and subsequent membrane lipid peroxidation (12,13).

A common effect of the activation of these pathways is a change in pattern of gene expression mediated largely through modulation of the activities of transcription factors. Accordingly, a large number of oxidative stress-responsive transcription factors and genes have been identified (14) and some of theses have been implicated in influencing aging processes as well as overactive bladder.

CONCLUSIONS

In conclusion, it can be concluded that the HOCl can induce in vitro smooth muscle overactivity. Thus, it can be very helpful for the investigation of the different pathways responsible for overactivity of the detrusor, mainly in cases where oxidative stress can associated to the disease.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Improved model for the establishment and evaluation of detrusor overactivity in female Wistar rats

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ABSTRACT

Objective: To improve the model for establishment and evaluation of detrusor overactivity in female Wistar rats.
Materials and Methods: We ligated the perineal urethra of female Wistar rats and then performed filling cystometry. The probability of detrusor overactivity, bladder capacity, peak voiding pressure and histological changes were investigated.
Results: Detrusor overactivity ratio of the obstruction group was 32.4%. Bladder capacity increased from 0.273 ± 0.036mL in control group to 0.89 ± 0.19mL in detrusor overactivity group (P < 0.001), and peak voiding pressure increased from 45.9 ± 4.1 cm.H_2O to 63.5 ± 17.4cm.H_2O (P = 0.007). For obstruction group, compared to no detrusor overactivity rats, detrusor overactivity rats had higher bladder capacity (0.89 ± 0.19mL versus 0.43 ± 0.09mL, P < 0.001) and higher peak voiding pressure (63.5 ± 17.4cm.H_2O versus 44.8 ± 6.2cm.H_2O, P = 0.005). Detrusor overactivity rats were classified according to peak voiding pressure (49.2 ± 4.2cm.H_2O versus 80.8 ± 7.1cm.H_2O, P < 0.001). Moreover, bladder weight increased significantly in detrusor overactivity rats (P = 0.003, P = 0.028) and detrusor histological hypertrophy was observed.
Conclusions: Ligating perineal urethra and filling cystometry with intra-urethral cannula approach is a simple and easily reproducible method to establish and evaluate the model of detrusor overactivity in rats.

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INTRODUCTION

Detrusor overactivity (DO) is an urodynamic observation characterized by involuntary detrusor contractions during the filling phase (non-voiding contractions). These contractions, which may be spontaneous or provoked, produce a wave form on the cystometrogram, of variable duration and amplitude. The contractions may be phasic or terminal (1,2). DO may occur in patients with bladder outlet obstruction (BOO), which can be caused by urethral strictures, congenital malformations such as posterior urethral valves, and more commonly, benign prostatic hyperplasia. BOO leads to several structural and functional changes in the detrusor muscle, and the adaptive growth does not fully restitute bladder function as BOO is frequently accompanied by the non-voiding contractions which can lead to clinical symptoms such as urinary frequency, urgency, and nocturia (3,4). Recently, it has been reported that BOO is partially responsible for DO because the prevalence of DO is associated with the degree of obstruction, and the treatment of BOO is potentially able to reverse the bladder wall changes and DO (5,6).

The most common method to create a model of DO rats involved reduction of the urethral diameter by placing a suture around the urethra (7), and significant increases were demonstrated in voiding frequency, voiding pressure and bladder capacity. Moreover, DO rats showed a pronounced "non-voiding contractions" during cystometry, and the categorization of different types of DO in conscious rats has been described (3). However, many disadvantages presented in the model of DO rats established in the previous studies. For example, DO rats were established by partial obstruction with a method of transabdominal pathway, and the abdomen was opened through a midline incision (7). The architecture of cavitas pelvis was dissected, and the trauma might induce impairment of nerves and deformity of bladder which might influence the function of bladder. Therefore, in the study, we improved the method of establishment and evaluation of DO model in female Wistar rats.

MATERIALS AND METHODS

Animals

A total of 50 female Wistar rats (Laboratory Animal Center of Shandong University, China) with an initial weight of 192-204g were used in our study. The rats were housed individually on a 12h light/12h dark cycle at 22-24°C in mesh-bottom cages with free access to food and water ad libitum. The rats were acclimatized to the facilities for 7 days, and all experimental protocols were approved by the Animal Research Ethics Committee of Shandong University.

Before the study, initial cystometric investigation of the 50 rats was performed according to the method of section 2.4-cystometric investigation below, and no DO rat was found (Figure-1a). Then, forty rats were used in an obstruction group (underwent obstruction surgical procedures) and 10 rats were used in a control group (without obstruction surgical procedures), randomly.

Surgical procedures

In the study, the 40 rats of the obstruction group were anaesthetized with chloral hydrate (350mg/kg i.p.). The urethra was exposed and the urinary bladder was catheterized with a human epidural catheter (F3, 1.0mm outer diameter) via the urethral orifice (Figures-2a and b). Care was taken to identify the urethra and vagina, and a needle with 4/0 silk suture was pierced around the perineal urethra (Figure-2c). A constant degree of partial obstruction was created by tying the silk ligature loosely around the urethra in the presence of the intraluminal indwelling catheter (Figure--2d), and then the epidural catheter was removed (Figure-2e). The rats were observed overnight in the recovery room, and then returned to normal conditions with food and water ad libitum. Six weeks later, the ligature around urethra was removed in the obstruction rats.

All of the obstruction rats were performed by one investigator. No prophylactic antibiotic was used after the surgical procedures. Moreover, in our preliminary experiment, we dissected an obstruction rat after surgical procedures for the demonstration to identify the location of ligature (Figure-2a,b and c).

Ligature removal

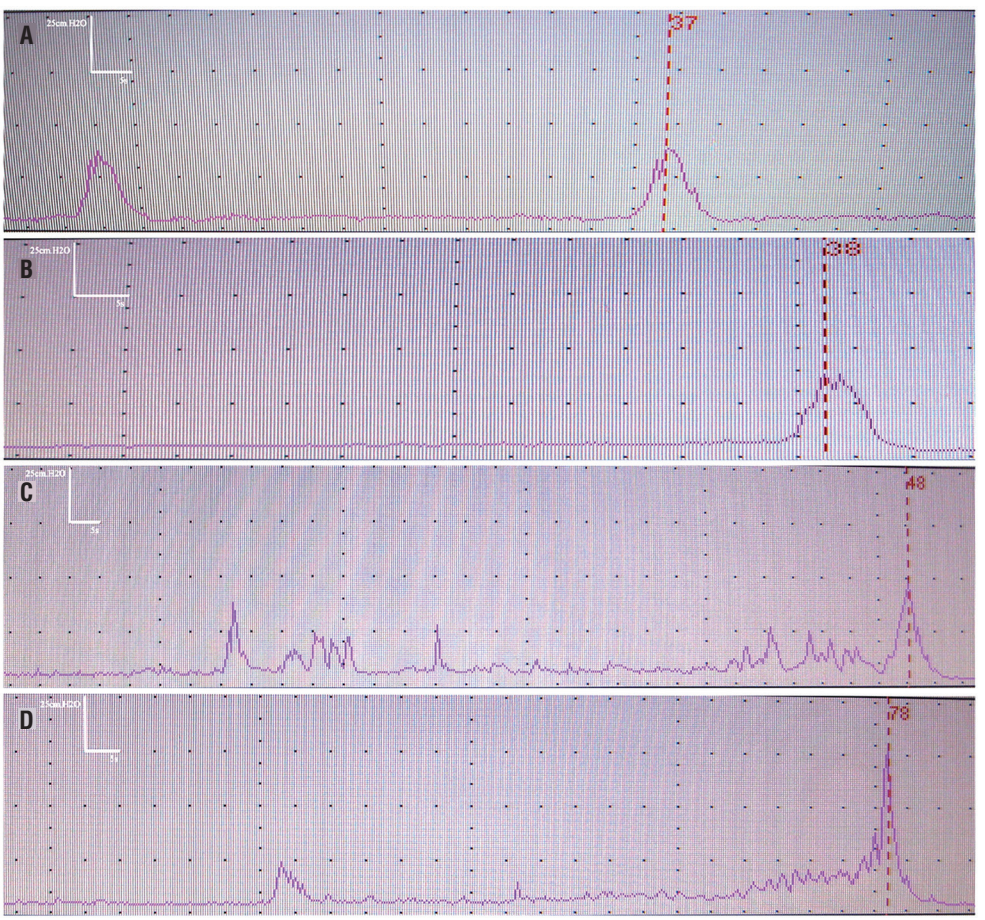
Two rats died within one week after the surgical procedures in the obstruction group, and acute retention was probably the cause of death. Moreover, the rats tried to remove the ligature, and the ligature ablated in 4 rats, which were excluded from the study. Therefore, the ligature was removed in only 34 rats after 6 weeks of obstruction.

The rats were anesthetized with chloral hydrate (350mg/kg i.p.). The ligature around urethra (Figure-3a) was cut and carefully removed to make the stenosis disappeared and enable the transurethral cystometric investigation (Figure--2b). After the ligature around urethra was removed, the rats were allowed to recover for two days. Then, cystometric investigation was performed in the 34 obstruction rats and the 10 control rats, and the probability of DO was analyzed.

Cystometric investigation

In the cystometric investigation, the conscious 44 rats were held under partial restraint in a restraining device we designed (Figure-4) which enabled the measurement of cystometry. The bladder was catheterized through urethra by a

Figure 1 - a) the initial cystometric investigation of the 50 rats before our study (two voiding contractions were observed and the number indicated peak voiding pressure). b) the cystometric investigation of the 10 control rats 6 weeks later (one voiding contraction was observed and the number indicated peak voiding pressure). c) the cystometric investigation of the 6 detrusor overactivity rats 6 weeks later (one voiding contraction was observed and the number indicated peak voiding pressure, the low peak voiding pressure group). d) the cystometric investigation of the 5 detrusor overactivity rats 6 weeks later (one voiding contraction was observed and the number indicated peak voiding pressure, the high peak voiding pressure group).



human epidural catheter (F2, 0.7mm outer diameter, 0.4mm internal diameter), which was connected via a T-tube to urodynamic testing machine (Laborie medical technologies, Corp) and infusion pump (LION WZ-50C6 microinfusion pump, Zhejiang University, China).

The rat was placed supine and the urethral orifice could be observed clearly. Data were collected and analyzed after the animals were seen to be resting quietly in the restraining device (Figure-4). The cystometric investigation was performed by infusing warm saline (37-38°C) at a rate of 9mL/h, and the infusion was stopped when voiding contraction was observed according to the voiding pressure and the leakage of urine around the urethral orifice. Bladder emptying was ascertained by opening the catheter and gently pressing the lower abdomen after the cystometry. At least three voiding cycles per animal were recorded to insure reproducibility of the bladder responses. Bladder function was evaluated using the following criteria: the presence, frequency and amplitude of non-voiding contractions, bladder capacity (volume of infused saline at micturition) and peak voiding pressure (peak bladder pressure during micturition).

Figure 2 - a, b, c, d and e: the surgical procedures for obstruction rats. A, B and C: the dissection of an obstruction rat to identify the location of ligature.

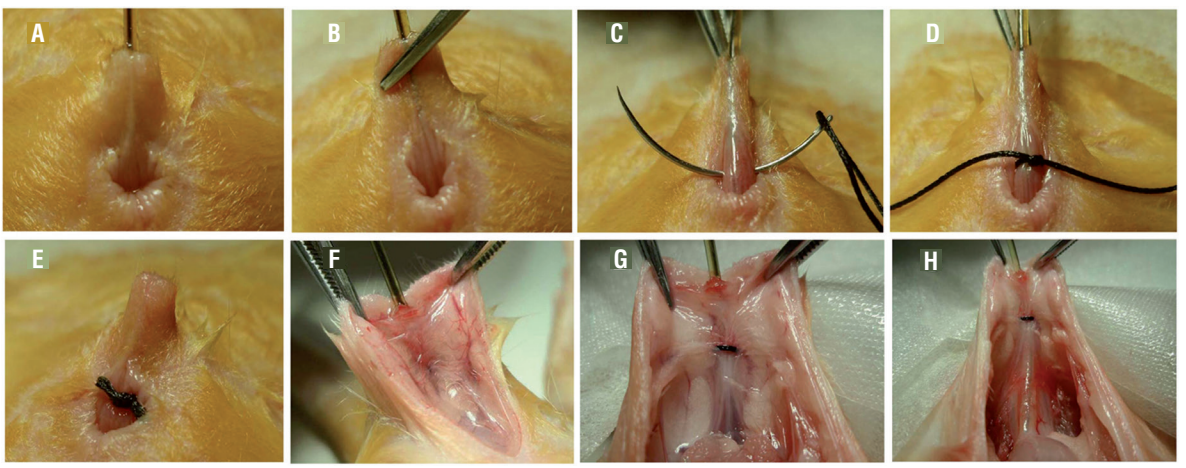


Figure 3 - a) the ligature of obstruction rats 6 weeks later. b) the intra-urethral cannula introduction was performed after the ligature removal.

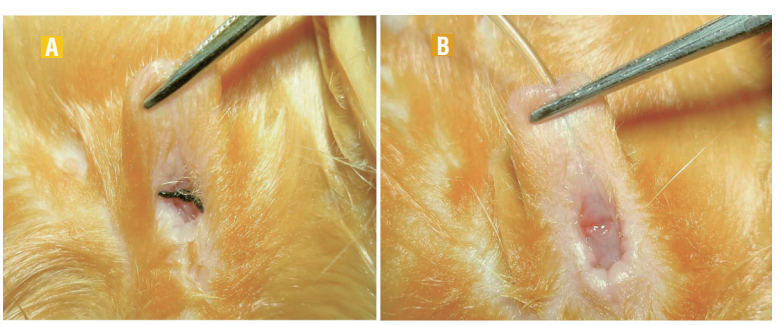
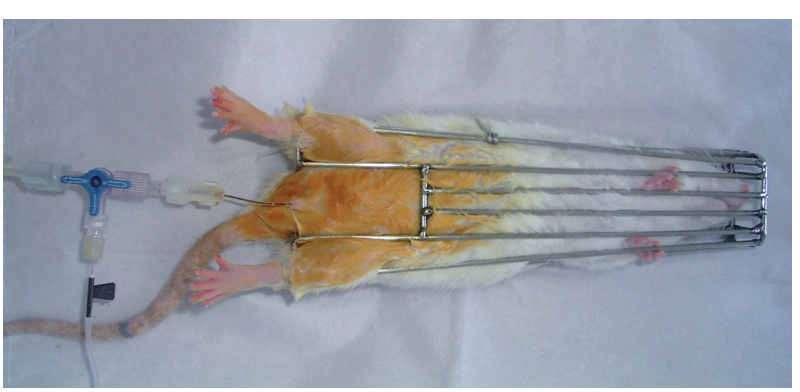


Figure 4 - The restraining device we designed which enabled cystometric investigation.



During the filling phase, some of the obstruction rats had obvious non-voiding contractions before the onset of voiding contraction and thus were defined as having DO and classified as the DO group (8-10).

Data analysis

The Statistical Package for Social Sciences was used to handle the database. To determine the relationship between a categorical variable with two levels and normally or non-normally distributed quantitative variables, Student's t-test or Mann-Whitney U tests were applied. The two-sided $P < 0.05$ was considered to indicate statistically significant differences.

RESULTS

Cystometric investigation was performed in the 34 obstruction rats and 10 control rats. DO ratio of the obstruction rats was 32.4% (11 out of 34) (Figure-1c and d), and the control rats had no DO (0 out of 10) (Figure-1b). Compared to the control rats, the bladder capacity and peak voiding pressure increased significantly in the DO rats.

The bladder capacity increased from 0.273 ± 0.036mL in the control rats to 0.89 ± 0.19mL in the DO rats ($P < 0.001$; Table-1). The peak voiding pressure increased from 45.9 ± 4.1 $cm.H_2O$ in the control rats to 63.5 ± 17.4 $cm.H_2O$ in the DO rats ($P = 0.007$; Table-1). For the obstruction group, compared to the non-DO rats, the DO rats had higher bladder capacity (0.89 ± 0.19mL versus 0.43 ± 0.09mL, $P < 0.001$; Table-1) and higher peak voiding pressure (63.5 ± 17.4$cm.H_2O$ versus 44.8 ± 6.2$cm.H_2O$, $P = 0.005$; Table-1). Moreover, the DO rats were classified into the low peak voiding pressure group (Figure-1c) and the high peak voiding pressure group (Figure-1d) (49.2 ± 4.2$cm.H_2O$ in group 1 versus 80.8 ± 7.1$cm.H_2O$ in group 2, $P < 0.001$; Table-1).

Furthermore, we studied the body mass and bladder weight in the 10 control and 34 obstruction rats 6 weeks later. The bladder weight was the highest in the DO rats, with significant differences between the DO rats and the control rats and non-DO rats ($P = 0.003$, $P = 0.028$; Table-2). We harvested bladder of the control rats and the DO rats for subsequent histological assessment. Histologically, compared to the control rats, the DO rats presented an increased detrusor muscle cell mass due to hypertrophy (Figures-5 a and b). On the other hand, compared to the control rats, the DO rats detrusor muscle cell gap widened with abundant collagen fiber (Figure-6 a and b).

Table 1 - Comparison of cystometric investigation in the control and obstruction rats (Mean ± SD).

Groups	n (%)	BC (mL)	P	VP ($cm.H_2O$)	P
ICI	50	0.18 ± 0.04		38.8 ± 3.2	
CI	44				
Control	10	0.273 ± 0.036	< 0.001[a]	45.9 ± 4.1	0.007[a]
Obstruction	34		< 0.001[b]		0.005[b]
Non-DO	23 (67.6)	0.43 ± 0.09		44.8 ± 6.2	
DO	11 (32.4)	0.89 ± 0.19	0.716[c]	63.5 ± 17.4	< 0.001[c]
group 1	6 (54.5)	0.91 ± 0.21		49.2 ± 4.2	
group 2	5 (45.5)	0.87 ± 0.19		80.8 ± 7.1	

[a]: DO versus control; [b]: DO versus Non-DO; [c]: group 1 versus group 2

BC = Bladder capacity; **VP =** Peak voiding pressure; **ICI =** Initial cystometric investigation of the 50 female Wistar rats before the study; **CI =** Cystometric investigation 6 weeks later; **DO =** Detrusor overactivity

Table 2 - Comparison of body mass and bladder weight in the control and obstruction rats 6 weeks later (Mean ± SD).

Groups	n (%)	BM(g)	P	BW(g)	P
Control	10	311 ± 8	0.244[a]	0.127 ± 0.015	0.003[a]
Obstruction	34		0.500[b]		0.028[b]
Non-DO	23 (67.6)	307 ± 13		0.159 ± 0.041	
DO	11 (32.4)	302 ± 24	0.572[c]	0.226 ± 0.085	0.111[c]
group 1	6 (54.5)	306 ± 23		0.189 ± 0.068	
group 2	5 (45.5)	297 ± 27		0.271 ± 0.087	

[a]: DO versus control; [b]: DO versus Non-DO; [c]: group 1 versus group 2

BM = Body mass; **BW =** Bladder weight; **DO =** Detrusor overactivity

Figure 5 - The frozen section of detrusor muscle cell (H&E staining, x200). a) control group; b) detrusor overactivity group.

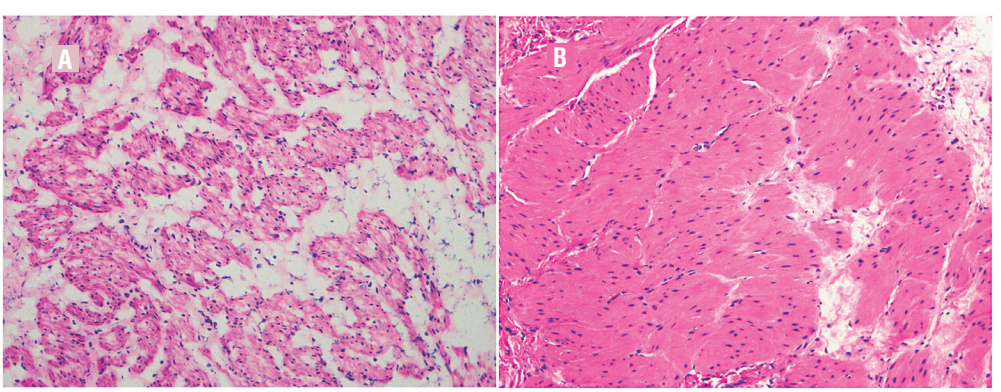
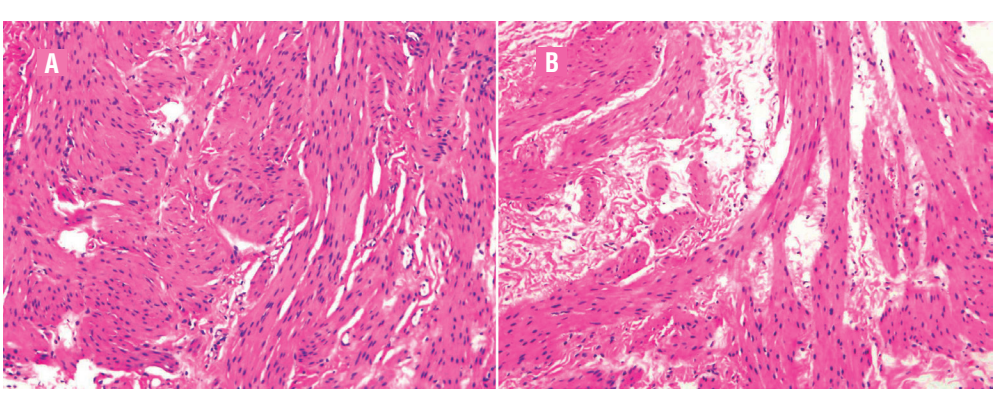


Figure 6 - The frozen section of collagen fiber (H&E staining, x200). a) control group; b) detrusor overactivity group.



DISCUSSION

We established an improved model of DO in female Wistar rats. Our results confirmed that the obstruction-related DO rats presented altered voiding patterns. Non-voiding contractions occurring prior to voiding were observed in the DO rats. Following voiding, no involuntary detrusor contraction was recorded but the involuntary detrusor contractions developed slowly with increasing amplitude until the next voiding occurred.

In the previous study (3), four types of voiding pattern were described in the DO rats with trans-abdominal approach, and the incidence rate was 54% (type I, non-voiding contractions occurring before and after micturition), 26% (type II, non-voiding contractions occurring prior to micturition), 13% (type III, similar to that of control) and 7% (type IV, non-voiding contractions associated with dribbling and no micturition occur), respectively. However, only one type of DO pattern was observed in our study and the bladder capacity was low. The differences between our study and the previous study may be due to the different method in establishing and evaluating DO rats.

Interestingly, the DO pattern observed in our study was consistent with one of the patterns (type II) described in the previous study (3) with approximate incidence rate (32.4% versus 26%) and was characterized by an increased involuntary detrusor contractions during the filling phase, which was in agreement with findings in men showing DO associated with an increase in voiding pressure or men with prostatic obstruction (11). It was conjectured that the other three types of pattern (type I, type III and type IV) may be induced by the impairment of anatomic structure in the previous study (3). Therefore, the DO model established with our method was more consistent with the natural history of obstruction-related DO.

We summarized the characteristics of the improved DO model as follows:

1. The method was simple and convenient. We used a needle with silk suture and tied perineal urethra to establish obstruction-related DO model. Moreover, the survival rate after surgical procedures was satisfactory (38/40, 95.0%).
2. The method did not need a low abdominal incision. The impairment of bladder and its innervation and peri-urethral blood vessel was avoided. Therefore, compared to the previous studies (3,7), the influence of injury on bladder, which might be the etiology of DO, was excluded.
3. Cystometric investigation was performed without anesthesia after ligature removal in obstruction rats, and bladder was catheterized through urethra. No other operation was performed. The wound and cicatricle was reduced, and the equality and stabilization of obstruction was improved. Moreover, compared to the bladder catheter implantation (3,7), cystometric investigation was performed through urethra in the improved model, which was consistent with the clinical examination for patients. In the study, although cystometric investigation was performed through urethra by catheter, no obstruction was observed during voiding.
4. The improved model had no impairment of anatomic structure and had satisfactory adaptive capacity to environment. Therefore, the model can be fed and transported easily, and bulk production is feasible.
5. It was an easily reproducible method for producing obstruction-related DO model in female Wistar rats, which could provide a continuum of tissue and urodynamic data that could be used to further study the pathophysiologic changes underlying DO. Moreover, the improved model was potentially suitable for further evaluation of mechanisms involved in the development of DO and the responses to pharmacological treatment.

However, our study had several weaknesses. Although the improved DO model characterized by an increased contractile activity in detrusor muscle during the filling phase appeared to have common features with human, the incidence rate

of DO shown in the study was lower than the previous study (3). Moreover, the movement of rats interfered with cystometric investigation when they showed the sign of discomfort or distress, though the interference was not frequent.

In conclusion, we studied an improved model for the establishment and evaluation of DO in female Wistar rats. Ligating perineal urethra and filling cystometry with intra-urethral cannula approach is a simple and easily reproducible method to establish and evaluate the model of DO rats, which can provide a continuum of tissue and urodynamic data that can accurately reproduce the urodynamic changes observed in patients with overactive bladder and may be used to study the pathophysiologic changes underlying DO.

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

I am particularly happy to see a manuscript that attempts to create an experimental model for the study of overactive bladder. We know that this disease still lacks adequate animal models and previously published models have potential risk of injury to the bladder nerves of experimental animals adopting a transabdominal approach.

As the authors mentioned, the movement of rats interfered with cystometric investigation when they showed the sign of discomfort or distress, and that can hence loss results reliability. Another fact of concer is the low incidence rate of DO shown in the study.

I believe, however, that even seeming a simple model, only time will tell if this method is easily reproducible in other research centers.

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SURGICAL TECHNIQUE

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Fournier's gangrene – delayed pedicle flap based upon the anterior abdominal wall

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ABSTRACT

Introduction: Fournier's gangrene is a poly-microbial necrotizing fasciitis that involves the perineum and/or external genitalia. Urgent surgical debridement is well recognized as essential acute treatment yet unique challenges arise for plastic surgical reconstruction to obtain a complete functional recovery. This case describes a successful delayed pedicle flap repair based upon the anterior abdominal wall.

Case description: A 24 year old man was admitted to ICU ten days after elective circumcision with Fournier's gangrene. He underwent a number of surgical debridements, and was referred for plastic surgical management. He had penile reconstruction using a random pattern abdominal flap, which was performed as a three stage procedure including flap vascular delay technique.

Discussion: Perineal and penile skin loss can be significant and is difficult to repair. Various techniques have been used to reconstruct lost tissue: skin grafts, transposition of the testes and spermatic cords to the thigh, flaps, and other types of pediculated myocutaneous flaps. Muscle flap reconstruction provides an environment that allows for complete regeneration of the urethral epithelium but is bulky and unsightly. Skin grafts contract and may produce painful and dysfunctional reconstructions. This novel technique produces a functional, and aesthetic reconstruction.

Conclusion: Penile skin recovery following Fournier's gangrene recovery is problematic. This case demonstrates the functionality of a delayed flap repair using the anterior abdominal wall.

ARTICLE INFO

Key words:
Fournier Gangrene; Surgical Flaps; Abdominal Wall

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INTRODUCTION

Fournier's gangrene is a poly-microbial necrotizing fasciitis that involves the perineum and/or external genitalia. Management involves urgent surgical debridement, which will usually need to be repeated, and may extend to total scrotectomy, and less commonly penectomy and colostomy. This case describes a successful delayed pedicle flap repair based upon the anterior abdominal wall.

Case presentation

A 24 year old man underwent a circumcision for "prophylactic hygiene reasons". Several days after surgery he developed pain and swelling, then became unwell and was admitted with sepsis at ICU with a fulminating infection and suppurative tissue necrosis. He underwent a series of emergency debridement. Three weeks after his acute infection he was referred for plastic surgical intervention.

Under general anaesthesia the penile skin and scrotum were further debrided (Figure-1). The

flap was patterned on an imprint of the penile defect, and the template marked on the abdomen with surgical ink (Figures 2 and 3). The penile shaft was exposed, and then it was buried under a large random pattern flap centred over the midline raphe of the abdomen (Figure-4). Once half the flap had been raised and inset onto the penis using 5/0 vicryl rapide sutures, the operation was terminated.

One week later the patient was taken back to theatre and the second half of the flap was delayed. A well established and well described plastic surgical procedure, the flap is raised and inset back into its own donor site without transposition or thinning; this is achieved by making an incision around the surgical ink marked lines and leaving the flap in situ, having been islanded.

Over the ensuing 7 to 10 days, neovascularisation occurs which renders the flap more robust and it can then be formally raised and inset around the penile (Figure-5) shaft and the reconstruction dressed with a soft silicone primary wound dressing (Mepitel®, Molnlycke, Gothenburg, Sweden) and gauze. The scrotal skin was able to be advanced over the exposed testicles, closing this defect primarily. IV antibiotics were administered and the patient was kept in hospital for a further 4 days.

He was then discharged home for follow-up as an out-patient. Wound healing was largely uneventful, but a hydrocolloid dressing was required to facilitate healing of 5mm of the junction of the wrap around the dorsum of the penile shaft. This did not compromise the reconstruction.

Figure 1 - Defect after debridement.

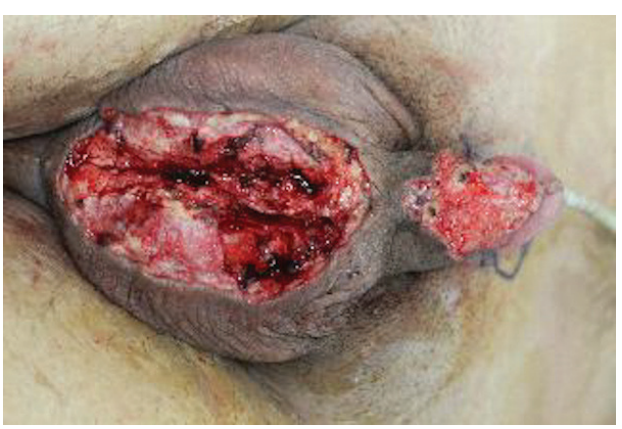


Figure 2 - Outlining the area of anterior abdominal wall for flap repair.

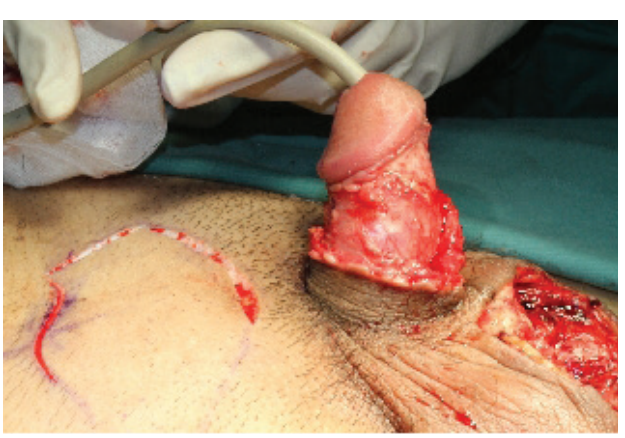


Figure 3 - Ensuring that site and area of flap are appropriate.

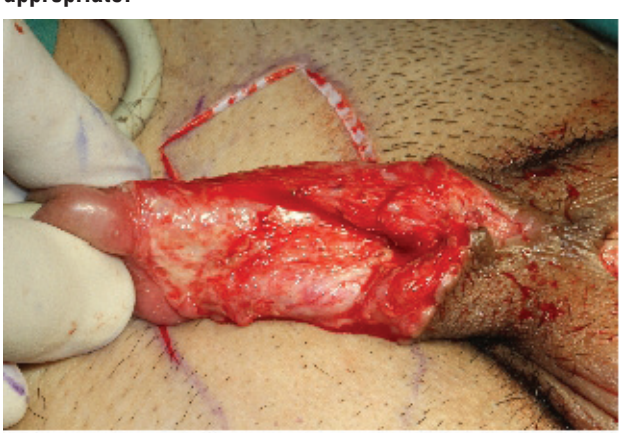


Figure 4 - Exposed penile shaft buried under a large random pattern flap over the midline raphe of the abdomen.

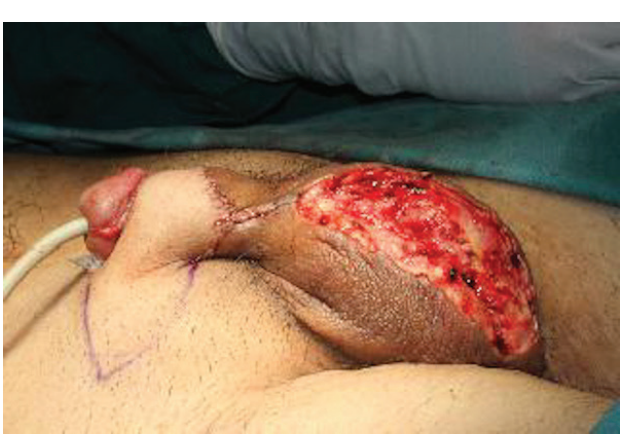
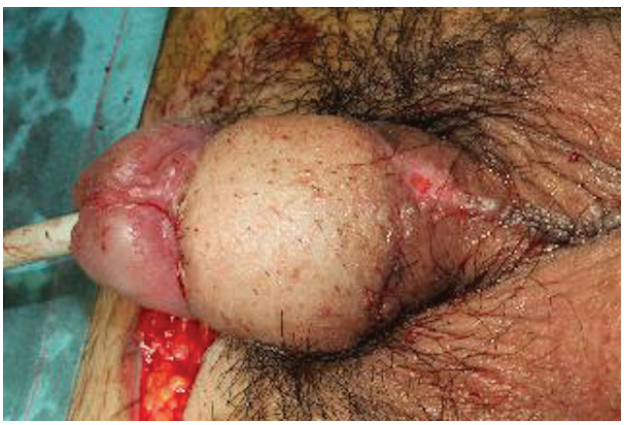


Figure 5 - Flap raised and inset around penile shaft.

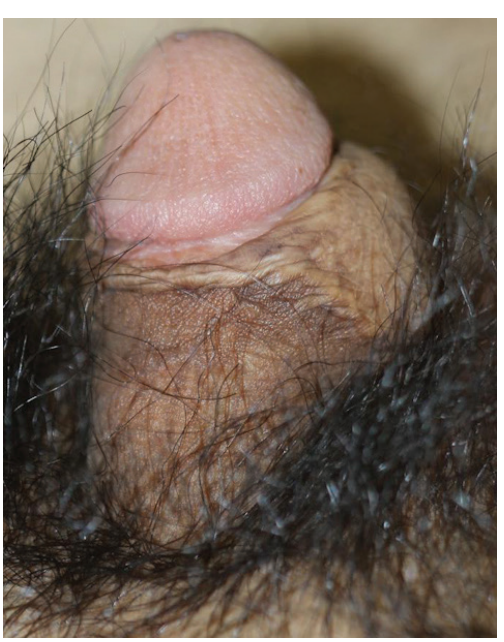


Three months after the final surgery he was able to be sexually active with no pain and minimal deformity, with a very satisfactory aesthetic as well as functional result. This final photo demonstrates his recovery at one year post-op with the penis in the flaccid state. Full erection with no deformity was possible at this time (Figure-6).

DISCUSSION

Fournier's gangrene is an urological emergency with current mortality rates reported as 4-43% (1-6). It is a poly-microbial necrotizing fasciitis that involves the perineum and/or external genitalia.

Figure 6 - One year post operatively



It was initially described by Fournier as an idiopathic condition, but the majority have aetiology involving urogenital or ano-rectal infection and/or trauma (5). Men are ten times more likely to develop this condition; other risk factors include age, diabetes mellitus, immunodeficiency and alcoholism (2,5).

Most presentations include perianal/scrotal pain and swelling, as well as purulent discharge, crepitus and fever. Although considered to be rapidly progressive, reported interval from onset to presentation is 2-8 days (2,6).

Management involves urgent surgical debridement, which will usually need to be repeated, and often extended to total scrotectomy, and less commonly penectomy and colostomy (1,2). The testes are rarely if ever compromised and may even be left exposed to allow tissue to granulate over. Fluid resuscitation, which may include blood transfusion, is often required, especially in those with signs of sepsis. Swabs should be taken promptly before empiric broad-spectrum antibiotics are commenced.

Perineal and penile skin loss can be significant and in general is difficult to repair. Various techniques have been used to reconstruct the debrided tissue: skin grafts, transposition of the testicles and spermatic cords to a subcutaneous pocket in the upper thigh, fasciocutaneous flaps, scrotal musculocutaneous flaps, and other types of pediculated myocutaneous flaps (2). Muscle flap reconstruction provides an environment that allows for complete regeneration of the urethral epithelium (7).

Unfortunately most reconstructions will not enable the patient to regain adequate penetrative sexual function. Thigh flaps utilized may be bulky causing penile shaft distortion and are often reserved for much larger defects (8,9). In the present case the scrotal skin was able to be closed directly which offered a much more aesthetically pleasing outcome. Furthermore, in the case of grafts, marked contractures often result producing painful erections. This is the first report of a delayed wrap-around skin flap which has the

benefit of providing excellent soft tissue cover to the penile shaft, neither too bulky nor prone to scar contractures. It is a stable, supple, flexible but durable reconstruction that allows full return of function. It is also aesthetically satisfactory.

The concept of such a graft is not novel with the delay phenomenon first described in 1975 by Myers (10). This concept results in tissue engineering with neovascularization of the flap, with increased survival of the flap and surgical success. The vascular physiology of delay flaps has been explored thoroughly (11-15). This technique has been used effectively in various areas of plastic and reconstructive surgery (16,17).

Because the flap contains hair bearing skin, the reconstruction has to be manipulated to render the shaft skin hairless. This is performed simply by initially depilating the area (rendering the hair follicles superficial) and later by laser hair removal. This was successfully performed in this case.

CONCLUSIONS

Fournier's gangrene recovery is problematic, especially the plastic surgical management of penile and scrotal skin loss. This case demonstrates the functionality of a delayed flap repair using the anterior abdominal wall.

CONFLICT OF INTEREST

None declared.

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Retrograde exchange of a double J stent via a cystostomy tract

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INTRODUCTION

Ureteral stents have been used for maintaining luminal patency in ureteral obstruction, including cases of malignant ureteral obstruction due to pelvic malignancy, since the late 1970s (1). Due to migration, encrustation, obstruction, and infection, these ureteral stents have to be removed or exchanged within 4-6 months of the initial placement (2-4). Recently, new optional stents such as metallic stents or resonance metallic stents have been introduced to maintain prolonged patency of ureters compromised by encasing neoplasm (4,5). However, conventional stents which need exchange within 4-6 months are commonly used.

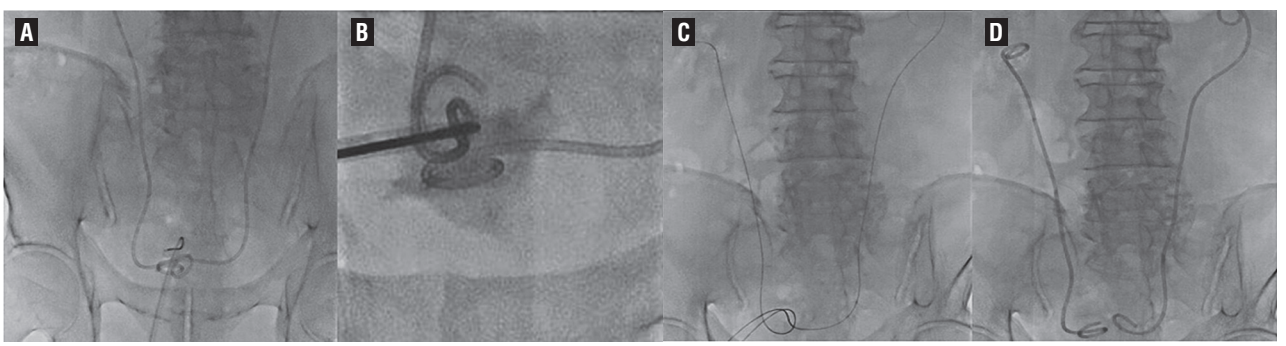
Cystoscopic retrograde removal or exchange of these stents has been considered the standard method (2). However, because of the rigidity and larger diameter of cystoscopes, some patients need deep sedation or general anesthesia for pain management during the procedure (2). In addition, the cystoscopic retrograde approach is impossible in patients with distorted anatomy secondary to urinary diversion, large prostate, or urethral stricture (3).

An antegrade percutaneous approach could be an alternative option for such cases, but a percutaneous nephrostomy itself could yield serious complications, especially in kidneys without hydronephrosis (3). We report a unique case in which retrograde ureteral stent exchange was successfully performed under local anesthesia and fluoroscopic guidance using a cystostomy tract in a patient with distorted lower urinary tract anatomy. A 10-F vascular sheath (Check-Flo Performer Introducer, Cook) was introduced into the bladder under fluoroscopic guidance, which enabled the introduction of grasping forceps (Figure-1). To improve technical manipulation during the procedure, the bladder was slightly distended by injection of 100mL of diluted contrast medium in order to prevent mucosal folds from injury by the grasping forceps. Under fluoroscopic guidance, the tip of the ureteral stent was manipulated using grasping forceps, and the stent was gently withdrawn to just beyond the orifice of the cystostomy site. A 0.035-inch guide wire (Radifocus, Terumo,Tokyo, Japan) was inserted through the ureteral stent up into the renal pelvis. A new ureteral stent with the same size and diameter was advanced in a retrograde direction with a pusher.

Several retrograde methods without conventional cystoscopy have been developed (2,3,6). Successful outcomes have been reported using retrograde ureteral stent exchange under fluoroscopic guidance, but most patients in these studies were female, and only one study included male patients (6).

More studies should be undertaken to investigate the possibility of retrograde ureteral stent change via cystostomy tract in patients who do not have a previous cystostomy tract. Cystostomy is an invasive procedure, but is less invasive than percutaneous nephrostomy.

Figure 1 - Fluroscopic images of retrograde ureteral stent exchange via a cystostomy tract. A 10-F vascular sheath was introduced into the bladder (a). The bladder was distended by injection with 100mL of diluted contrast medium to prevent injury to the mucosal folds by the grasping forceps. The grasping forceps were introduced through the vascular shreath, and the tip of ureteral stent was manipulated with grasping forceps (b). The stent was gently withdrawn to just beyond the orifice of cystostomy site. A 0.035-inch guide wire (Radifocus, Terumo,Tokyo, Japan) was inserted through the ureteral stent up to the renal pelvis (c). A new ureteral stent was advanced in the retrograde direction with a pusher. Finally, the new ureteral stents were both placed (d).



Retrograde ureteral stent exchange via cystostomy site is a simple and feasible technique. This method should be considered in patients who have a distorted lower urinary tract and who have a cystostomy tract.

ACKNOWLDEGEMENT

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CONFLICT OF INTEREST

None declared.

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Postoperative renal cortical necrosis in a patient with contralateral remnant kidney

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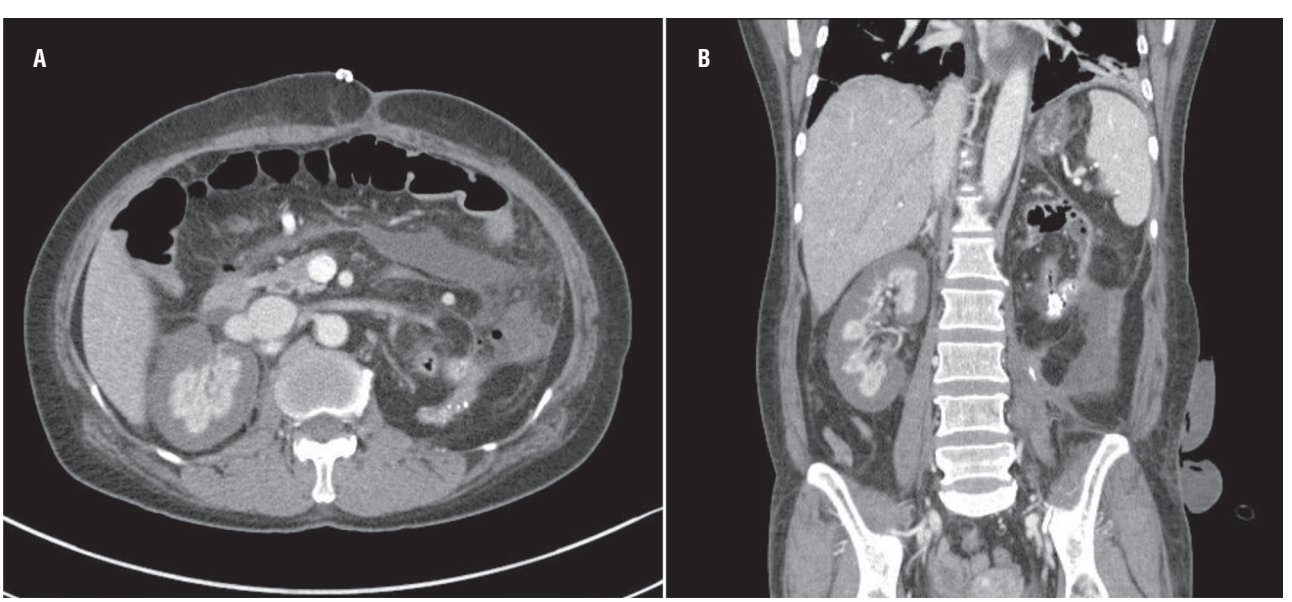
A 58-year-old woman was referred to nephrology department because acute kidney injury had developed after left hemicolectomy and partial ureterectomy due to left ureterocolic fistula with ureteral stone. She had a history of left partial nephrectomy because of traumatic renal injury thirty seven years ago. Her baseline serum creatinine level was 0.9mg/dL. Two days after the operation, serum creatinine level had increased to 2.1mg/dL with oliguria. Contrast-enhanced abdominal computed tomography (CT) showed decreased perfusion in right renal cortex sparing medulla, which is the characteristic finding of renal cortical necrosis (Figure-1). Her renal function did not recover although emergency hemodialysis with conservative management was performed. She has undergone maintenance hemodialysis.

Renal cortical necrosis is a rare cause of acute kidney injury, which is caused by decreased renal arterial perfusion. Obstetric complications remain the leading cause of renal cortical necrosis (1). Non-obstetric causes such as sepsis, hemolytic uremic syndrome and operative procedures are also important causes (2). Contrast-enhanced CT is the useful diagnostic tool although definitive diagnosis is made by renal biopsy (3). It has been suggested that characteristic CT finding is attributed to the selective involvement of interlobular and afferent arterioles (4). Untreated patients have high mortality, and early dialysis is important to improving clinical outcomes (5).

Figure 1 - Axial (A) and coronal scan (B) of contrast-enhanced abdominal computed tomography showed non-enhancement of cortex but enhancement of medulla in right kidney, which is the characteristic finding of renal cortical necrosis.



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VIDEO SECTION

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Laparoscopic resection of tumor recurrence after radical nephrectomy for localized renal cell carcinoma

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ABSTRACT

Introduction: Local recurrence of Renal Cell Carcinoma (RCC) after radical nephrectomy is a rare event. Some known risk factors are: clinical/pathological stage, locorregional disease and lyimph node positivity. Since up to 30-40% of patients can achieve a disease-free status, we show a case (video) in which we performed a laparoscopic excision of a local RCC, taking advantage of all the well-known benefits of laparoscopy.
Case report: A 56 years old female with a history of open radical nephrectomy two years before was diagnosed with a mass at the time of surveillance CT imaging during follow-up. The suspected local recurrence was 12cm, and vascularized predominantly by tributaries originating from the iliac vessels. There was no other site of disease (i.e. brain, lung, liver, bones) and laboratory tests were normal. Laparoscopic approach was approached, by inserting 4 trocars (2 of 10 and 2 of 5mm) with the patient in the lateral position.
Result: The procedure lasted 130 minutes, with 220mL of estimated bleeding; the larger vessels were ligated with polymer clips (Hem-o-lok) and the smaller handled by ultrasonic clamp. The specimen was removed by a small incision below the umbilicus in an appropriate bag. The patient was feed in the first postoperative day and discharged on the third day. Histopathology revealed sarcoma, with a high degree of mitosis, and negative surgical margins. She was referred to medical oncology for adjuvant therapy consideration.
Conclusion: The laparoscopic resection of recurrent tumor should be encouraged in highly selected cases. The minimally invasive method, with its known advantages, especially for more debilitated patients, can be advantageous when applied to suitable cases.

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EDITORIAL COMMENT

The present video by Curcio et al. nicely depicts that the surgical management of locally recurrent renal cell carcinoma (RCC) which was traditionally considered solely suitable for open surgery can now be performed using a laparoscopic approach when applied to highly select cases. The benefits of minimally invasive surgery (MIS) can in consequence be provided to patients in this highly challenging realm of re-operative surgery. It must be highlighted as was mentioned by the authors that such MIS procedures should be offered to only select patients with locally recurrent RCC where no major adjacent organ resection including but not solely encompassing vascular structures anticipated. A fundamental surgical principle applies in that the surgical modality (i.e. pure laparoscopic, robotic, open) should be tailored to the anticipated difficulty of this locally recurrent tumor resection. Lastly, such challenging salvage surgery should only be performed by experienced and highly-skilled laparoendoscopists, who have meticulously reviewed the pre-operative imaging as a roadmap of what this surgical endeavor will likely entail, with the threshold for open surgical conversion being quite low to at no point compromise the therapeutic potential imparted to this procedure.

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VIDEO SECTION

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Athermal bladder neck dissection during robot-assisted radical prostatectomy

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ABSTRACT

Introduction: With improved understanding of the precise anatomy, surgical techniques during robot-assisted radical prostatectomy (RARP) have been refined, with the aim of improving functional outcomes without compromising oncological adequacy and results. Nevertheless, postoperative urinary incontinence remains a frustrating side-effect. Anatomically, bladder neck (BN) serves as an internal sphincter. The longitudinal fibres of BN may be identified and isolated with a meticulous dissection at the prostato-vesical junction, contributing to earlier return of urinary continence. The purpose of this video is to show an anatomical athermal dissection of BN during RARP.

Materials and Methods: After incision of endopelvic fascia and anterior defatting, the morphology of prostate not only laterally, but also at the level of bladder-prostatic junction is well visualized.

With an athermal dissection of the plane between prostate and bladder we can minimize the traumatic effects on the longitudinal fibres of BN. A cold section of the preserved BN permits the complete preservation of integrity of this sphincteric structure.

Results: With this technique we preserve the longitudinal fibres of BN, allowing the sparing of the sphincteric mechanism of BN. The finding of a difficult athermal dissection of these plans may make you suspect the presence of an infiltration, suggesting to sacrifice BN in order to avoid a positive surgical margin. In our series no increase of PSM has been recorded using this technique.

Conclusions: This surgical technique preserving the natural BN mechanism appears to improve urinary continence, allowing at the same time an easy identification of a neoplastic infiltration.

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EDITORIAL COMMENT

In this very elegant video depiction by Del Moro et al., robotic assisted laparoscopic prostatectomy offers great benefits in improving the surgical visualization and manual dexterity to performing key steps of this surgical procedure. The surgeon(s) of the present video beautifully depict how an anatomically meticulous bladder neck preserving approach can be conducted whereby optimizing early and long-term urinary continence. Although such an approach can be technically conducted for most surgically managed prostate cancer cases, it is pivotal to adapt the surgical technique to the specific location of the tumor burden i.e. if significant high volume and phenotypically aggressive (Gleason grade 7 (4+3) or more) is situated at the base of prostate based on pre-operative TRUS biopsy results with or without correlative endorectal MRI of the prostate findings, I would caution surgeons to perform such an extensive bladder neck sparing approach and if so, diligent use of intra-operative frozen section and/or adoption of this surgical technique based on intra-operative findings would be prudent. In summary, like many facets of surgical oncology, an operative procedure must be personalized to the anatomical and tumor characteristics of the individual patient.

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VIDEO SECTION

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Laparoscopic Treatment of Vesicovaginal Fistula

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ABSTRACT

Introduction: Vesicovaginal fistula is a rare disease with great impact for the patients. Laparoscopic repair can be an interesting option in selected cases with goods results but few experience is reported.
Objectives: Detailed demonstration of our laparoscopic vesicovaginal fistula repair technique. Initial results for ten patients are provided Methods: We treated all cases by the same technique. The surgical steps were: Patient positioning in Lloyd-Davis; Cystoscopy and implant of guide wire on fistula and ureteral catheters (that was removed after procedure); Transperitoneal access and 4 or 5 ports in V or W shape; Opening the bladder wall; Dissection between bladder and vagina for tension free repair; Fistula resection; Vagina repair with Vicryl 3-0; Bladder repair with Vicryl 3-0; Peritoneum/omentum interposition; Positioning 20 Fr urethral catheter.
Results: Mean age was 50 years. Mean number of fistulas was 1,2. The most common etiology was gynecologic surgery (7). Mean operative time was 2,5 (1,8-3,2) hours. Mean blood loss was 150 (100-200)mL. Complication rate was 10% (one case of urinary infection treated conservatively). Mean hospital stay was 1,2 (1-2) days. Mean return to normal and activities was 20 (15-30) days. For nine patients mean sexual intercourse time was 3 (1-6) months. Success rate after 1 year was 90% (one case of recurrence in patient with previous radiotherapy). Mean follow-up was 36 (12-60) months.
Conclusions: Laparoscopic repair is feasible, reproducible and present all advantages of minimally invasive surgical procedure. Long term results are similar to conventional open approaches.

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EDITORIAL COMMENT

Vesicovaginal fistula is a potentially devastating complication. Repair of vesicovaginal fistula can prove challenging especially if the patient has received radiotherapy or the fistula is recurrent and/or large. Many vesicovaginal fistulae can be treated using a transvaginal technique (1,2). The video by Tobias et al nicely depicts a laparoscopic technique that utilizes all the components of the open O'Conor technique. Specifically, a transperitoneal approach to open the bladder, followed by excision of the fistula tract, dissection of the bladder off of the vagina with separate closures and omental interposition are used (3). This approach does require advanced laparoscopic skills. In their series with intermediate follow-up they are able to achieve excellent success rates. Their patients seemed to benefit from the laparoscopic approach as they were able to go home within 1-2 days.

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Books:
▪ Sabiston DC: Textbook of Surgery. Philadelphia, WB Saunders. 1986; vol. 1, p. 25.

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