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ORIGINAL PAPERS

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ORIGINAL PAPER

Epidemiologic study of urolithiasis in seven countries of South-Eastern Europe: S.E.G.U.R. 1 study

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Summary ***Objective: To investigate some epidemiological aspects of kidney stones in the South-Eastern European area.***
Materials and methods: From September 2015 to December 2015, 538 consecutive patients were treated and evaluated for reno-ureteral stones in eight departments in Bulgaria, Greece, Italy, FYR Macedonia, Romania, Serbia and Turkey.
Results: The age of onset was lower in Turkey and higher in Italy. The rate of recurrent patients was higher in Romania and Serbia, while first renal stone formers were more frequent in Italy. The previous history of kidney stones, the characteristics of the stones and the dietary habits of the patients were different in different countries. In Bulgaria, Greece and Romania larger calculi from recurrent patients were more frequent. In Italy and Turkey smaller calculi from first renal stone formers were more frequent.
Conclusions: The previous history of kidney stones, the characteristics of the stones and the dietary habits of the patients were different in different countries. A common dietary pattern associated with the formation of kidney stones was not observed, but each country showed different risk factors.

KEY WORDS: *Urolithiasis; Epidemiology; Diet.*

Submitted 7 May 2017; Accepted 15 July 2017

INTRODUCTION

The epidemiology of urolithiasis has been frequently correlated with geography, climate and culture (1).
The area of *South Eastern Europe* is relatively homogeneous in topography, climate and eating habits. In some countries of this area the prevalence of urolithiasis was assessed according to population-based studies. In *Italy*, the prevalence was estimated at 6.8% (males) and 4.9% (females) in 1986 and 10.1% (M) and 5.8% (F) in 1998 (2), in *Turkey* it amounted to 14.8% in 1989 (3) and in Greece 15% in 2006 (4). Limited information is available about renal stone prevalence in *Bulgaria*, *FYR Macedonia*, *Romania* and *Serbia* (5). These prevalence rates are higher than those reported in other regions of *Europe* such as *Germany* (4.7%) (6) and the *United Kingdom* (3.5%) (7) and can be explained by the warmer climate. On the contrary, the *South-East European* area is characterized by the consumption of the Mediterranean diet, that has long been associated with lower incidence of cardiovascular disease and cancer (8, 9). Some components of the Mediterranean diet as vegetables, fruits, potatoes, legumes and dairy products may be potentially favorable for the prevention of kidney stones.
Aim of this study was to evaluate several epidemiological features and dietary habits, in patients with renal stones treated in seven countries of the *South-Eastern Europe*.

MATERIALS AND METHODS

From September 2015 to December 2015, 538 consecutive patients were treated for reno-ureteral stones in eight urological departments in *Bulgaria, Greece, Italy, FYR Macedonia, Romania, Serbia* and *Turkey*. The patients were evaluated on the basis of a questionnaire posted on www.segurgroup.eu website. The questionnaire investigated extensively patient characteristics, including age, gender, weight, height, *body mass index* (BMI), working and sporting activity, bowel habits, urinary volume, presence of urological diseases or medical diseases related to stone formation, previous urinary tract infection, renal function, fluid intake and dietary habits, stone history and stone characteristics (size, location, composition, side and treatment modality).
Working activity was scored as light, heavy and very heavy and sporting activity as light, intermediate, high and professional; intake of food categories (pasta/rice/pizza, meat/poultry/fish, cheese, vegetables, fruit) as never or rarely, often, daily; milk/yogurt intake as n° cups/day; bread intake n° of loafs/slices/day. Working activity and

No conflict of interest declared.

dietary assessment was carried out by the Urologist which interviewed the patients by recall method.
The results of the questionnaire were compared according to the country of the evaluated subjects.
Stone analysis was performed on the 360 out of 538 patients (the ESWL patients didn't have stone analysis) and was mainly chemical analysis (82%) whereas the rest by diffractometry.

Statistical analysis

Normality was tested using the *Shapiro-Wilk* test. Normally distributed data were presented as mean (S.D.) as for not normally distributed data median and *interquartile range* (IQR) were used. Comparisons between countries for normally distributed data was conducted using ANOVA. Comparisons for not normally distributed data was performed using *Kruskal-Wallis* test. *Fisher's* exact test was applied for comparisons with categorical data. Dunn's multiple comparisons test was applied after a significant Kruskal-Wallis or *Fishers* exact test. *Sidak* correction was used for multiple comparisons between countries. Analysis was conducted using *StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP*.

Results

A total of 538 patients were enrolled of whom 124 from *Bulgaria*, 17 from *FYR Macedonia*, 50 from *Greece*, 65 from Italy, 122 from *Romania*, 55 from *Serbia* and 106 from Turkey.

Gender and age

In total the male to female ratio (M/F) was 1.07 with a 0.82 in *Bulgaria*, 1.42 in *FYR Macedonia*, 1.77 in *Greece*, 1.5 in Italy, 1.03 in *Romania*, 0.62 in *Serbia* and 1.23 in *Turkey*. Difference of distribution of the disease by gender for different countries was not significant ($p = 0.065$).
Age at stone onset was 39.9+/-16.2 in the total population with significant differences between different countries ($p < 0.001$). In *Turkey* it was significantly lower than in *Greece*, *Italy*, *Romania* and *Serbia* whereas in *Bulgaria* and *FYR Macedonia* it was significantly lower than in *Greece* and *Italy* (Table 1).

Height, weight and BMI

There were no statistically significant differences between patients from different countries for height, weight and BMI (Table 1).
There was a statistically significant difference by gender for weight ($p < 0.001$), height ($p < 0.001$) and BMI ($p < 0.001$). No statistical significant differences of weight (ANOVA F-test = 0.185) and BMI (ANOVA F-test = 0.185) were observed in women by different countries.
Height of women by different countries was significantly different (ANOVA F-test < 0.001) with Serbian female patients taller than female patients of other countries (ANOVA F-test < 0.05) except patients from *FYR Macedonia*.
Statistical differences of height, weight and BMI (ANOVA F-test < 0.001) were observed in men from different countries.
Male Turkish patients were shorter than patients from all other countries but male patients from Italy (ANOVA F-test < 0.05).
Male Bulgarian patients were significantly heavier than male patients from Italy, *Turkey* and *Romania* (ANOVA F-test < 0.05) and showed higher BMI scores than male patients from *Serbia* and *Romania*. Also male patients from *Turkey* had higher BMI scores than patients from *Romania* (ANOVA F-test < 0.05).

Urological and medical diseases

Urological anomalies were observed in 63/538. The more common were urethral stenosis (5.39%), ureteral stenosis (2.6%), ureteropelvic junction (UPJ) stenosis (2.33%) and horseshoe kidney (1.49%).
Medical diseases related to renal stone formation were observed in 118/538. The more frequent were bone disease (6.51%), peptic ulcer (6.13%), gout (3.35%), hyperthyroidism (2.24%), diabetes mellitus (2.23%) hyperparathyroidism (1.35%).
Statistically significant different rates of urological diseases and of medical diseases related to stone formation were observed for patients from different countries (chi-2 test $p < 0.001$ and $p = 0.016$) with the highest rate of urological diseases observed in *Romania* (73.7%) and. *FYR Macedonia* (88.2%) and the highest rate of medical diseases in *Turkey* (40%).

Working and sporting activity

Statistically significant difference was observed for working and sporting activity between patients from different countries ($p = 0.001$ and $p = 0.005$) (Table 1).
Bulgarians patients had heavy working activity (47.6%) with respect to patients from other countries (20-32.8%). Heavy or intermediate sporting activity was more frequent in patients from *Bulgaria* and *Serbia* (51.8% and 50%) with respect to other countries (14%-43.8%).

Dietary habit

Intakes of pasta, meat, cheese, vegetables, fruit, milk and bread were significantly different in different countries (ANOVA F-test < 0.001) (Table 2).
Patients from *Italy* tended to consume more pasta products (pasta/rice/pizza) in comparison with patients from all other countries ($p < 0.05$ in all comparisons) except patients from *FYR Macedonia*. Patients from *Romania* tended to consume less pasta products in comparison with patients from *Greece*, *FYR Macedonia* and *Turkey* ($p < 0.05$ in all comparisons) and patients from *Bulgaria* tended to consume less pasta in comparison with patients from all other countries ($p < 0.05$).
Patients from *Romania* tended to consume less vegetables in comparison with patients from all other countries ($p < 0.05$) and those from *Serbia* more vegetables than those from *Turkey* ($p < 0.05$).
Patients from *Italy* and *FYR Macedonia* tended to consume more fruits in comparison with patients from all other countries ($p < 0.05$).
Patients from *Romania* tended to consume more bread in comparison with patients from all other countries except patients from *FYR Macedonia* ($p < 0.05$) and patients

Table 1.
Demographic and clinical data of patients by different countries.

	Bulgaria (n = 124)	FYR Macedonia (n = 17)	Greece (n = 50)	Italy (n = 65)	Romania (n = 122)	Serbia (n = 55)	Turkey (n = 106)	Overall (n = 538)	P value
Gender†									0.065
Female	54.8%	41.2%	36.0%	40.0%	49.2%	61.8%	44.8%	48.3%	
Male	45.2%	58.8%	64.0%	60.0%	50.8%	38.2%	55.2%	51.7%	
BMI‡	27.4 (5.52)	25.1 (2.65)	26.9 (3.62)	26.0 (4.31)	26.7 (6.07)	26.7 (8.43)	26.5 (4.93)	26.7 (5.57)	0.022
Age‡	52.5 (13.67)	49.9 (15.93)	57.1 (13.70)	50.3 (15.23)	44.7 (15.23)	50.3 (13.35)	43.3(14.88)	48.8(15.10)	0.593
Age onset‡	37.1 (17.43)	36.1 (12.30)	47.3 (17.82)	44.9 (17.86)	42.5 (16.32)	42.4(10.86)	33.8(12.52)	39.9(16.18)	< 0.001
First time former	33.9% (n = 42)	35.3% (n = 6)	34.0% (n = 17)	56.9% (n = 37)	14.7% (n = 104)	1.8% (n = 1)	37.1% (n = 39)	45.7% (n = 246)	-
Recurrence£	0.16 [0.09-0.40]	0.17 [0.10-0.40]	0.37 [0.15-0.60]	0.20 [0.13-0.48]	1.0 [0.25-1.0]	0.71 [0.50-1.0]	0.29 [0.14-0.60]	0.37 [0.14-0.84]	< 0.001
Working activity†									0.001
Light	52.4%	76.5%	72.0%	67.2%	75.2%	80.0%	72.6%	68.7%	
Heavy	47.6%	23.5%	28.0%	32.8%	24.8%	20.0%	27.4%	31.3%	
Sports†									0.005
Light	48.2%	75.0%	86.0%	58.1%	55.7%	50.0%	66.1%	62.1%	
Intermediate	48.2%	25.0%	12.0%	32.3%	39.3%	39.3%	23.7%	31.9%	
Heavy	3.6%	0.0%	2%	9.7%	4.9%	10.7%	10.2%	6.0%	
Bowel†									0.002
Regular	79.0%	52.9%	82.0%	79.0%	69.2%	78.4%	58.0%	72.1%	
Non - regular	21.0%	47.1%	18.0%	21.0%	30.8%	21.6%	42.0%	27.9%	
Renal insufficiency†									< 0.001
< 1.2	79.0%	70.6%	84.0%	76.7%	52.7%	74.6%	89.6%	74.7%	
> = 1.2	21.0%	29.4%	16.0%	23.3%	47.3%	25.4%	10.4%	25.3%	

† Fisher's exact test.
‡ Data presented as Mean (S.D.). One-way ANOVA conducted for comparisons between nations.
£ Data presented as Median [IQR]. Dunn test (median test) conducted for multiple comparisons.
**IQR = Interquartile Range.*

Table 2.
Dietary patterns of patients by different countries.

	Bulgaria	FYR Macedonia	Greece	Italy	Romania	Serbia	Turkey	Overall	P value
Pasta/rice/pizza/etc.†									< 0.001
Never/rarely	81.5%	23.5%	8.0%	8.1%	52.5%	25.4%	30.4%	41.9%	
Often	17.7%	17.7%	68.0%	17.7%	43.4%	58.2%	24.5%	33.8%	
Daily	0.8%	58.8%	24.0%	74.2%	4.1%	16.4%	45.1%	24.3%	
Meat (any type)†									< 0.001
Never/rarely	13.7%	29.4%	6.0%	3.2%	3.3%	0.0%	19.6%	9.6%	
Often	56.5%	23.5%	72.0%	24.2%	82.6%	80.0%	56.9%	61.6%	
Daily	29.8%	47.1%	22.0%	72.6%	14.1%	20.0%	23.5%	28.8%	
Cheese†									< 0.001
Never/rarely	11.3%	11.8%	6.1%	29.0%	4.1%	50.9%	18.6%	16.8%	
Often	55.6%	23.5%	53.1%	35.5%	87.6%	47.3%	34.3%	54.3%	
Daily	33.1%	64.7%	40.8%	35.5%	8.3%	1.8%	47.1%	28.9%	
Vegetables†									< 0.001
Never/rarely	1.6%	0.0%	10.0%	21.0%	0.8%	0.0%	12.0%	6.3%	
Often	44.7%	11.8%	36.0%	19.3%	81.7%	23.6%	32.0%	43.6%	
Daily	53.7%	88.2%	54.0%	59.7%	17.5%	76.4%	56.0%	50.1%	
Fruits†									< 0.001
Never/rarely	19.4%	5.9%	36.0%	19.4%	16.5%	9.1%	29.4%	20.7%	
Often	55.6%	23.5%	30.0%	3.2%	68.6%	81.8%	34.3%	47.7%	
Daily	25.0%	70.6%	34.0%	77.4%	14.9%	9.1%	36.3%	31.6%	
Milk†									< 0.001
Never	9.7%	0.0%	68.0%	41.0%	29.7%	0.0%	19.6%	24.0%	
1-2/day	80.6%	87.5%	30.0%	59.0%	64.4%	63.0%	51.0%	62.3%	
3 or more/day	9.7%	12.5%	2.0%	0.0%	5.9%	37.0%	29.4%	13.7%	
Bread†									< 0.001
Never	4.0%	0.0%	6.0%	16.1%	0.0%	0.0%	6.9%	4.7%	
1-2/day	42.8%	58.8%	50.0%	79.0%	25.4%	63.0%	47.0%	47.1%	
3 or more/day	53.2%	41.2%	44.0%	4.9%	74.6%	37.0%	46.1%	48.2%	

† Fisher's exact test.
Comment: Dunn's test implemented for multiple comparisons of eating habits between patients from different nations.

from Italy less bread in comparison with patients from all other countries ($p < 0.05$).
Patients from *Serbia* tended to consume more milk than patients from all other countries except *FYR Macedonia* and *Turkey* ($p < 0.05$) and patients from *Bulgaria* and *Turkey* tended to consume more milk in comparison with patients from *Greece*, *Italy* and *Romania* ($p < 0.05$).
Patients from *Italy* tended to consume more meat products in comparison with patients from all other countries ($p < 0.05$ in all comparison). Patients from *Serbia* tended to consume more cheese product in comparison with patients from all other countries ($p < 0.05$ in all comparisons) and patients from *FYR Macedonia* to consume more cheese products than those from *Romania* ($p < 0.05$).

Discussion

Several studies have shown that urinary calculi tend to be more frequent in men, although infection stones were often more frequently reported in women (10,11). Our study confirmed that nephrolithiasis is more frequent in men, although in *Bulgaria* and *Serbia* we observed more stones in women.
This can be explained by the higher rate of infection stones in Bulgarian patients with respect to patients from other countries. The rate of infection stones in *FYR Macedonia* was much higher but the number of patients from this country was very low. On the other hand, stones were more frequent in females also in *Serbia*, but information of stone composition from this country was limited.
Age at stone onset was lower in *Turkey* and *Bulgaria* and higher in *Italy*.
Stone onset of hereditary stones, such as cystine, tend to be low whereas uric acid stone formation is typical of older patients. In our series, cystine stones were more frequent in *FYR Macedonia* and, at a lesser extent, in *Turkey* and *Bulgaria* and uric acid stones were less frequent in *FYR Macedonia* and *Turkey* than in other countries.
A higher rate of hereditary stones together with a lower rate of uric acid stones could be an explanation of the lower age at stone onset in *Turkey*. In *Italy* the higher age at stone onset could be related to the prevalence of first renal stone formers that are characterized by a later onset of stone disease (12).
The dietary pattern correlated with renal stone formation is complex, because the risk of renal calcium stone formation may depend on a reduced intake of fluids, an insufficient calcium intake, an increased intake of protein and sodium and a reduced intake of potassium (13). Consequently, the formation of calcium stones can be favored by reduced fluid intake, excessive consumption of meat, a low intake of milk and dairy products and insufficient consumption of vegetables. Not necessarily all of these factors must coexist simultaneously, as it is the sum of the effects of each of them to determine the risk of kidney stones (14).
For this reason, it is not surprising to observe different dietary patterns in patients living in different countries where the diet may be different due to geographical, cultural and socioeconomic factors.
Our study was not specifically designed to evaluate stone prevalence in different countries or the potential role of diet in renal stone formation because of the absence of control subjects, but it interestingly demonstrated that renal stone patients from different countries show different dietary patterns.
In *Italy*, socioeconomic changes of the past 50 years have resulted in a progressive abandonment of the traditional Mediterranean diet.
Today, the daily consumption of pasta and rice remained frequent, but the daily meat consumption increased (1 or more servings per day in 75% of cases), while the consumption of cheese and milk is relatively infrequent (never or rarely in 29 and 41%).
The dietary pattern of stone patients in *Bulgaria*, *Greece* and *Turkey* tends to be similar with a moderate consumption of meat (1 or more servings a day only in 29.8%, 22% and 23.5%) and a decent cheese consumption (never or rarely in 11.3%, 6.1% and 18.6%). However, the consumption of vegetables and fruit in these countries is relatively low (1 or more servings of vegetables and fruit per day of 53.7 + 25%, 54 + 34% and 56 + 36.3%, respectively) and milk consumption in *Greece* is low (never or rarely in the 68%).
In *Romania* and *Serbia*, the consumption of meat and cheese is high (often in 82.6% + 87.6% and 80% + 47.3%), but the consumption of vegetables and fruits is very low in *Romania* (1 or more servings a day in 17.5 and 14.9%) and that of fruit is low in *Serbia* (1 or more servings per day in 9.1%); also the consumption of milk is reduced in *Romania* (never in 29.7%).

Conclusions

In conclusion different dietary patterns can be observed in renal stone formers by different countries: high meat/low dairy in *Italy*, moderate meat & cheese/low fruit & vegetables in *Greece, Bulgaria* and *Turkey*, high meat/low vegetables (or fruit) in *Romania* and *Serbia*.

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ORIGINAL PAPER

Single plus one port robotic radical prostatectomy (SPORP); Initial experience

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Summary ***Objective: This article reports on patients with early stage prostate cancer treated with single plus one port robotic radical prostatectomy (SPORP).***
Materials and methods: Since January 2014, we performed SPORP in 8 patients with localized prostate cancer. Age of patients, clinical stage, operation time, intraoperative and postoperative complications, blood loss, histopathological evaluation, postoperative continence, serum level of PSA were evaluated.
Results: Mean age of the 8 patients was 59.85 years. All operations were completed without conversion to standard robotic procedure or open surgery. No intra operative complications occurred. Mean operating time was 143 minutes; prostate excision 123 minutes and urethrovesical anastomosis 20 minutes. Mean blood loss was 45 ml. Preoperative Gleason scores were (3 + 4) in one patient and (3 + 3) in 7 patients. Postoperative Gleason scores were (3 + 4) in 2 patients, and (3 + 3) in 6 patients. All these 8 cases were in T1c clinical stage. Early postoperative complications were drain leakage (n = 1), atelectasis (n = 1), wound infection (n = 1) and fever (n = 1). There was no positive surgical margin. The serum level of PSA was less than 0.2 ng/ml and no other complications happened during the 4 to 12 months follow-up period. Postoperative continence and cosmetic results were excellent.
Conclusions: It is relatively easy for urologists who are skilled in traditional laparoscopic and robotic surgeries to master SPORP. However long-term outcomes of this surgery need further investigations.

KEY WORDS: *Single plus one port robotic radical prostatectomy (SPORP); Prostate cancer; Initial experience; Radical prostatectomy.*

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INTRODUCTION

In recent years, *laparoendoscopic single-site* surgery (LESS) becomes the latest point of minimal invasive surgery. Reducing the number of ports minimizes the complications. Conventional LESS is not easy to learn and perform. In this point da - Vinci enhances the intracorporeal maneuvering and makes the procedure easier (1-3).
Radical prostatectomy is the first treatment of choice for localized prostate cancer. Robotic radical prostatectomy is improved to reduce the invasiveness and to facilitate the difficulty of open procedure; in this point single port radical prostatectomy is the latest technique (4, 5).
The aim of this procedure is to minimize complications associated with number of ports. The present study was designed to define the *single plus one port robotic radical prostatectomy* (SPORP) technique, and to demonstrate its feasibility and safety.
During the past few years, the detection of prostate cancer and the number of operations are dramatically increased with usage of *prostate specific antigen* (PSA). Open surgery, laparoscopic surgery and robot-assisted laparoscopic surgery have the same results for trifecta at early stage cancer (5-7). However, urologists throughout the world are searching for more minimally invasive technique. We reported 8 robotic radical prostatectomy performed with single-site port (8.5 mm) plus one 8 mm port.

MATERIALS AND METHODS

Patients

Since January 2014 we performed SPORP in 8 patients with prostate cancer. Patients with localized prostate cancer were included in the study, and patients with a very high *body mass index* (BMI) (> 35 kg/m^2) were excluded from the study. All cases were verified as prostate cancer preoperatively by trans-rectal ultrasound guided 10-core biopsy. No pharmacotherapy or radiotherapy was administered preoperatively.

Surgical technique

Under general anesthesia, patients were placed in Trendelenburg position. Access was gained using open Hasson technique with 3 cm umbilical longitudinal incision. Rectus fascia was incised and single-site port was inserted transperitoneally. The pneumo-peritoneum was maintained at 12-14 mmHg pressure. 10 mm assistant port was inserted edge of single- site port without incising the fascia (Figure 1).
Another 8 mm trocar was placed under direct vision at the *McBurney* point to ease intra corporeal suturing and drainage extraction (Figure 2).
The procedures were performed technically same as conventional robotic radical prostatectomy with flexible instruments inserted through single-site port and one standard robotic instrument inserted through extra 8 mm port.
Both deferens vasa were identified and dissected. The sem-

No conflict of interest declared.

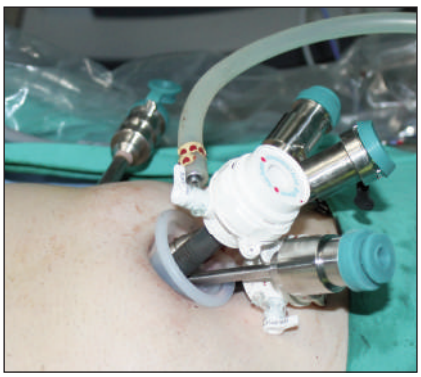

Figure 1. *Port configuration for a SPORP and 10 mm assistant port.*

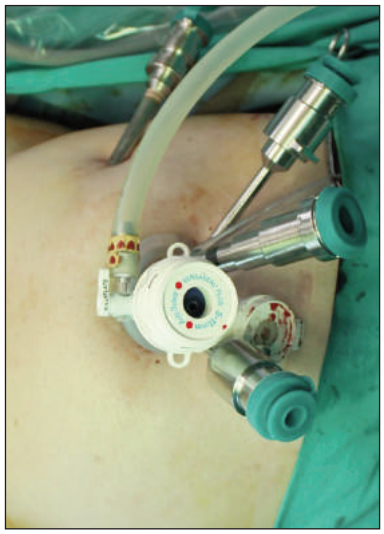

Figure 2. *Demonstrate use of the 8 mm trocar in the McBurney point.*

inal vesicles were dissected inferiorly. The dorsal vein complex was over sewed by using a 2-0-polyglycolic acid absorbable suture. The bladder neck was dissected between the bladder neck and prostate by using monopolar scissors and then the urethra was incised. The posterior aspect of bladder neck was dissected and deferens vasa and seminal vesicles were freed bilaterally. The neurovascular bundle was dissected and freed from prostate base by using Hem-o-lock.

The dorsal vein complex and urethra at the prostate apex were incised. The prostate was released from the Denonvillier fascia. After bleeding control, anastomosis was performed with two fixed 3-0 barbed polyglyconate sutures V-LOC (*Covidien*). Foley catheter was filled with 20 ml sterile water and the watertight anastomosis was verified by filling bladder with 150 ml saline. The prostate specimen was put into organ bag retrieved through the periumbilical incision. A soft drain was placed through the extra 8 mm port (Figure 3). Foley catheter was removed 7 days later.

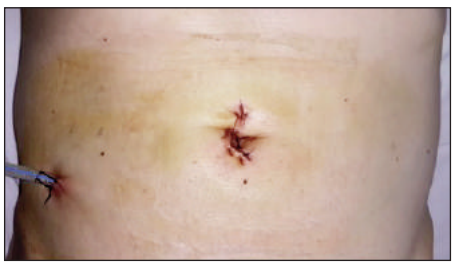

Figure 3. *Drain was placed into the 8 mm trocar.*

Results

Since January 2014 we performed SPORP in 8 patients with localized prostate cancer. The mean age was 59.85 years (range 49-71). The mean level of PSA was 6.91 ng/mL (range 5.78-8.81). Preoperative Gleason scores were (3 + 4) in one patient and (3 + 3) in 7 patients. All operations were completed successfully without conversion to standard robotic procedure or open surgery. No intra operative complications occurred. The mean operating time was 143 minutes (range 100-180 minutes): prostate excision time was 123 minutes (range 86-156 minutes) and urethrovesical anastomosis time was 20 minutes (range 14-24 minutes). The mean blood loss was 45 ml (range 30-55 ml).

All patients were in T1c clinical stage. Postoperative Gleason scores were (3 + 4) in 2 patient and (3 + 3) in 6 patients. There was no positive surgical margin. Early postoperative complications were drain leakage (n = 1), atelectasis (n = 1), wound infection (n = 1) and fever (n = 1). Drain leakage was resolved during follow-up on the postoperative day 3 and the other complications were resolved with medical treatment. Postoperative continence was excellent. The first operated 6 patients were completely dry, whereas the last operated 2 patients, in their follow-up of 3th and 4th months, were using security pad. No other complications happened during the 4 to 12 months follow-up period. The serum level of PSA was less than 0.2 ng/ml. The cosmetic result was excellent (Figure 4).

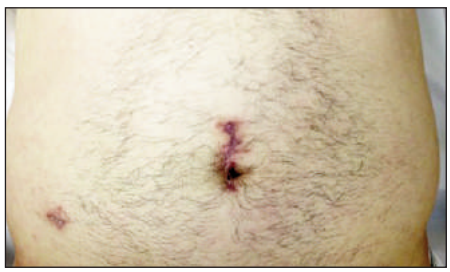

Figure 4. *Semilunar umbilical incision and the cosmetic appearance.*

Discussion

The treatment of localized prostate cancer has evolved over the last few decades from open surgery to laparoscopic, robotic and the newest entity single port robotic radical prostatectomy. An increasing number of centers worldwide have adopted LESS (8). However, it came with surgical limitations such as lack of triangulation, the instrument clashing, and the unfavorable ergonomics. The curved ports allow the instruments to make triangulation on targeted organ. Same-sided hand-eye control of the instruments is maintained by software of the da Vinci. It enables the surgeon control instrument on the right side of the screen with right hand and control instrument on the left side of the screen with left hand (Figure 5).

The use of single-site instrumentation in urology was reported in several studies (9, 10). Increasing number of the series has resulted in experience with robot-assisted LESS radical prostatectomy (11). Currently literatures show that robot assisted laparoscopic prostatectomy is a safe and feasible procedure with favorable oncologic and functional outcomes (2, 7, 12).

Anastomosis is the most challenging part of the SPORP.

Figure 5. *Surgeon control instrument.*

Arms are not conventionally articulated like standard robotic arms.
Their range of motion is limited. In this point we prefer to use an extra 8 mm robotic port, which facilitates the suturing and is also used for drain extraction. Prostate excision and anastomosis time is even less than single port robotic radical prostatectomy (11). In the literature, additional port was used in 14.6% of cases (13). In addition to this, a 10 mm assistant port was inserted edge of single-site port without incising the fascia for the bedside assistant. This facilitates the challenges pointed in the literature related to bedside assisting during LESS (14-16). Conventional robotic procedure is comfortable for surgeon but port scars and complications due to number of ports like hernia or hemorrhage are main handicaps. In one study, mean blood loss during robotic radical prostatectomy was 135 cc, whereas in the present study mean blood loss was found to be 45 cc (17). These handicaps led to identify the technique of SPORP. SPORP is more minimally invasive when compared with conventional multiple ports robotic or laparoscopic surgery (18, 19). Reducing the number of ports concluded with favorable outcomes, such as pain reduction and better cosmesis with robot-assisted LESS radical prostatectomy (20).
In an analysis of 1163 urologic LESS cases, the conversion rate was 4% to conventional laparoscopic/robotic surgery and 1.1% to open surgery (13). In the current study, all operations were completed successfully without conversion to standard robotic procedure or open surgery. Intraoperative complication rate was 3.3%, whereas no intra operative complications occurred in our study (13).
The first operated 6 patients were completely dry, whereas the last operated 2 patients, in their follow-up of 3th and 4th months, were using security pad. Unfortunately with such a small sample the continence outcomes seem to be difficult to evaluate when compared with the literature (11).
As in our experience, minimally invasive techniques have demonstrated less blood loss and shorter convalescence (6). Making small incisions can limit the range of motion and visualization, but flexible robotic instruments have facilitated this difficulty. Choice of appropriate material such as *Hem-o-lok* clips for nerve sparing, barbed suture for anastomosis and long laparoscopic aspirator is also important.
In the current study, patients were relatively young (median age: 59.85 yrs) and in T1c stage, had a low BMI (median: 27.6 kg/m^2), with a median prostate volume of 48 ml and a median PSA of 6.91 ng/ml. Our study population is close to the literature on LESS robotic prostatectomy (12). Surgical margin results seem better than single port laparoscopic radical prostatectomy (11, 21). The most difficult part of the procedure is that it requires robotic and laparoscopic experience.

Conclusions

In conclusion, SPORP does not seem as difficult as presented in the initial reports. It is relatively easy for urologists who are skilled in traditional laparoscopic and robotic surgeries to master SPORP. In addition the procedure would be easier if the arms were articulated. Trifecta is possible with pain reduction and excellent cosmetic results. However, the long-term outcomes of this surgery need further investigations.

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ORIGINAL PAPER

Day case laparoscopic radical prostatectomy

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Summary ***Background: To evaluate the feasibility of performing laparoscopic radical prostatectomy (LRP) as a day case procedure while maintaining patient satisfaction and safety. Herein we report our experience, selection criteria, and discharge criteria for day case LRP.***

Methods: We performed a prospective study with 32 patients undergoing extraperitoneal LRP. These patients were counselled before the procedure that they would go home the same evening of the procedure. Pain scores and quality of life data were recorded day 1 postoperatively via a telephone consultation. The patients underwent routine blood tests on day 2 and an outpatient review on day 7 and regularly thereafter via an assigned key worker. Socio-demographic data, comorbidities, and outcomes were collected for analysis.

Results: All patients were successfully discharged the same day of surgery. Mean patient age was 62 years with a mean body mass index of 25. Mean operative time was 147 minutes, and estimated blood loss was 101 ml. Three patients were treated for post operative urinary tract infections; two patients developed infected lymphoceles which required percutaneous drainage and one patient required re-catheterisation due to a burst catheter balloon. Of these six complications four patients required re-admission. Post-operative pain, nausea and vomiting were low whilst patient satisfaction scores were unanimously high in all patients surveyed.

Conclusions: The early experience with extraperitoneal LRP as a same day surgery is promising although patients who are at high risk of lymphocele should be excluded.

Preoperative patient counselling and selection is paramount. Patient satisfaction is not adversely affected by the shortened stay. Surgeon experience, a well-motivated patient, meticulous attention to detail through an integrated pathway, a multidisciplinary team and adequate postoperative assessment are essential.

KEY WORDS: Day surgery; Laparoscopy; Laparoscopy malignant disease; Prostate cancer.

Submitted 16 May 2017; Accepted 2 July 2017

INTRODUCTION

Since *Schuessler* first described the technique over 20 years ago (1), *laparoscopic radical prostatectomy* (LRP) has been established as an effective minimally invasive surgical treatment option for localised prostate cancer with the advantages of decreased blood loss, decreased analgesic requirements and earlier hospital discharge and convalescence compared with open radical prostatectomy (2-6). Hospital stays have shortened dramatically over the years such that it has become standard practice for patients to spend 1-2 nights in hospital after minimally invasive radical prostatectomy with benefits to both patients and healthcare providers. These incentives for early discharge, however, must always be trumped by the patient's best interest i.e. safety and in particular readmission rates.

In 2012 we reported the evolution of a care pathway for LRP that set out to systematically reduce the impact of surgery to the patient through thorough patient preparation and complete minimization of perioperative symptoms (7). Our aim was to evaluate the feasibility of performing LRP as a day case procedure while maintaining patient satisfaction and safety.

Herein we report our experience and to our knowledge the first in the published literature the selection and discharge criteria and outcomes for day case LRP.

PATIENTS AND METHODS

Patients were considered for same day discharge if they met the following conditions: ASA 1 or 2, BMI < 30, short procedure with minimal blood loss, minimal perioperative opioids, watertight anastomosis, minimal discomfort or malaise, drain not required and responsible adult at home. Demographics, perioperative and follow up data were prospectively collected and recorded on a database.

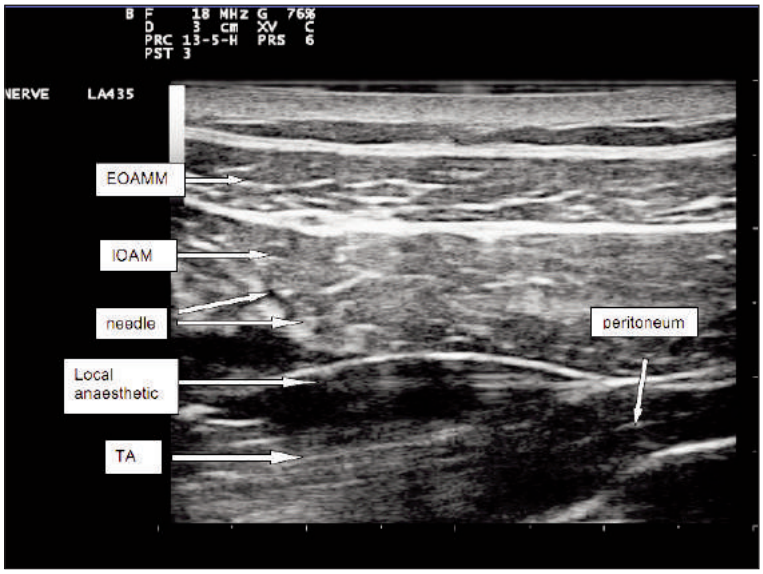
Patients received a standardized general anaesthetic with fentanyl as the opioid of choice intra-operatively and *transversus abdominis plane* (TAP) blocks with *bupivacaine* 0.5% were routinely performed for all patients (Figure 1). Towards the end of surgery they received paracetamol and a non-steroidal anti-inflammatory drug. Invasive monitoring was not utilized. Post-operative pain in the initial recovery period was managed with morphine sulfate as required. Once on the ward, patients received regular paracetamol, diclofenac and oxynorm as required.

All of the patients were scheduled as the first case of the day to allow for clinical assessment by the consultant urologist before discharge in the evening of surgery.

All cases were performed by an experienced surgeon who had performed > 100 LRPs using the technique described by *Stolzenburg* which utilizes extraperitoneal balloon dissection (8). Extra attention was given to careful haemostasis which included the use of intracorporeal haemostatic adjuncts such as *Surgiflo*^{TM} and *Surgicel*^{TM}.

No conflict of interest declared.

Figure 1.
Transverse ultrasound view of classic 'crescent shape' of the fascial layers splitting between IOAM and TAM on injection of local anaesthetic.



Generally the use of drains was avoided. A leak test with 250cc of normal saline was always performed to guarantee a strong and watertight anastomosis and avoid anastomotic leak. No special restrictions were placed on resident or fellow participation, which received modular training as customary in teaching hospitals.

Post operatively patients were allowed to eat and drink as soon as they wished and early mobilization was encouraged. Patients were provided with direct telephone contact details of the surgeon and specialist nurse in case of any early complications not recognized prior to discharge (Appendix A).

Patients were followed up with a telephone consultation and questionnaire on the first day post-operatively to address safety concerns and accurate prospective capturing of complications. Patients were specifically asked to score their level of post-operative pain and nausea and vomiting and satisfaction on a linear scale from 1-5 with 1 being no pain/very satisfied and 5 representing dissatisfaction and worst pain imaginable (Appendix A). Nurse led trial without catheter took place seven days post operatively where the catheter was removed without prior cystogram. Routine catheter urine and midstream urine cultures were obtained to seek out proactively and treat infections at the time of catheter removal and again at first outpatient review. Outpatient review was arranged early at 30 days for the same reason. All complications were classified according to the modified Clavien-Dindo system.

Results

Patient demographics, relevant pre-operative clinical and pathological data are illustrated (Table 1).

Between June 2009 and December 2014, 353 laparoscopic radical prostatectomies were performed. Of these 32 were deemed suitable for same day discharge. In total all 32 patients were discharged on the same day.

The median time spent in hospital was 12 hours (7am to 7pm) and the latest discharge time was 8pm.

Mean total operative time (i.e. from skin to skin) was 147 minutes. The mean estimated blood loss was 101 mL. Seven patients had bilateral pelvic lymph node dissection. There were no significant perioperative complications in this series of patients. In total six patients developed postoperative complications of which 4 required re-admission (Table 2). Three patients were treated for post-operative urinary tract infections; two patients developed infected lymphoceles which required percutaneous drainage and one patient required re-catheterization due to a burst catheter balloon (equipment failure). No events requiring general anaesthetic were observed (*Clavien 3b*).

Sixteen of the 32 patients agreed to participate in the survey portion of the study. The other sixteen patients were not surveyed on day 1 postoperatively, but did not have any immediate issues on review of their medical records.

All patients were discharged from hospital in the evening of their surgery without complication.

Table 1.
Demographic data and salient descriptive statistics of day case prostatectomy patients.

		Day case patients (n = 32)
Age (years)		62
Pre-op PSA (ng/ml)		8.58
Clinical stage (%)	T1c T2 a/b T2c	56 31 13
Pre op Gleason sum (%)	3+3 = 6 3+4 = 7 4+3 = 7 4+5 = 9	41 50 3 6
Operating time (min)		147
Blood loss (ml)		101
Transfusion rate		0
Conversion		0
LOS (days)		0

Table 2.
Clavien-Dindo classification of complications for cohort.

		Day case patients (n = 32)
ASA	Class 1 Class 2	12 20
Clavien	None 1 2 3a 3b 4a 4b 5	0 0 3 3 0 0 0 0

Table 3.
Functional and oncological outcomes.

Continence	Number of patients	Erectile dysfunction	Number of patients
Dry	27	Potent	14
1-2 pads/day	4	Mild ED	9
3 or more pads/day	1	No erections	4
		Not interested in erections	5
Total	32		32

All patients reported post-operative satisfaction scores of 1 (n-14) or 2 (n-2) out of 5. Post-operative pain was deemed minimal in 14 out of 16, with one patient scoring their pain 3 out of 5 and one patient scoring their pain 4 out of 5. Similarly day 1 nausea and vomiting was absent in all patients.
Functional outcomes were assessed at 3 months post LRP (Table 3). Twenty-seven patients were dry, whilst four patients were using 1-2 pads per day, and one patient required 3 or more pads per day. In terms of erectile dysfunction (ED) 14 patients were completely potent, nine patients had partial ED, four patients could not achieve erections and five patients were not interested in sexual activity. At 46 months median follow up 11 of the 32 patients showed evidence of biochemical recurrence, with no prostate cancer related deaths in the series. All eleven patients went on to have salvage radiotherapy.

Discussion

There continues to be growing concern over the cost of national health services in the *United Kingdom*.
Resources are limited and our aging population continues to expand. Several studies have looked at the potential economic effect of laparoscopic versus open versus robotic surgery prostate cancer. Robotic surgery adds significant additional costs to the hospital, with several studies showing cost advantages with laparoscopic over robotic prostate surgery when excluding case volume.
Our aim was to investigate whether the procedure could be performed as a same day surgical procedure, which to our knowledge has not been reported with respect to LRP. One night in hospital amounts to approximately £700 a night thus such a pathway amounts to a substantial saving if implemented safely. Further theoretical cost advantages to the hospital include a greater reimbursement tariff for day case procedures over in-patient stay as well as the cost savings with regards to a hospital bed saving. With regards to the *United Kingdoms National Health Service*, the aim should be to perform more day case prostatectomies in order to negotiate higher tariffs with the clinical commissioning groups so that hospitals could be reimbursed for an '*outpatient prostatectomy*' and ultimately decrease overall costs. The authors recognize that this may not be applicable to other healthcare systems, however the benefits of reduced time in hospital such as early mobility, reduced infection risk and psychological benefits of being at home are transferrable to the wider healthcare community. The incentives for early discharge, however, must always be trumped by the patient's best interest and thus there is a need to maintain a low threshold for admitting a patient following LRP. Consequently careful case selection and a review by the senior operating surgeon prior to discharge should be mandatory.
Utilizing the extra-peritoneal approach minimizes the chances of post-operative ileus and other bowel complications and has the potential to reduce time in hospital. This was also shown with the robotically assisted approach in a small patient cohort (9). Patients with a BMI > 30 are more likely to have surgical complications and pose challenges to the anaesthetist and surgeon alike. Such patients lead to a more technically challenging dissection with narrowing of the operative field within the extraperitoneal space. We therefore opted to admit such patients for observation.
We found that patients could be discharged home the same day of the surgical procedure if they met strict criteria that we set without increased perioperative complications. We also performed follow up satisfaction surveys and found that all patients who completed the survey were satisfied with their experience and that they stayed for the appropriate amount of time.
The observed complications are in line with contemporary series except a high rate of infected lymphoceles in 2 of 7 patients with pelvic lymphadenectomy. This is reflected in a high readmission rate of 12%. We conclude that it is best to insert a post-operative drain for a minimum of 24 hours after extended lymphadenectomy and patients be given the choice of being discharged with the drain in situ or being admitted overnight for observation. We also acknowledge that in order to increase the yield of day case surgery candidates, including selected patients who have a drain left in situ as potential day case candidates would be safe. Discharging patients with drains postoperatively is routine practice in some surgical disciplines and therefore should not preclude LRP patients from similar benefits.
The success of this technique is in the standardized, team approach in the context of a well-motivated medically fit patient. It was realized early that the majority of pain arises from the anterior abdominal wall after extraperitoneal LRP. As such, minimizing post-operative pain through a *transabdominal plane* (TAP) block within the pathway and sparing use of opioids to overcome postoperative nausea and vomiting have proved effective (7). The majority of patients only needed a combination of Paracetamol and NSIADs for post-operative pain. The probability of side effects from opioids for break-through pain was minimized by switching from *Tramadol* (partial agonist and antagonist) to *Oxynorm*, which has an improved side effect profile.
We report the outcomes of a pilot cohort of patients, without a control group to compare to. We aim to conduct studies of suitable patients to further validate the findings reported. The percentage of patients surveyed was also low and thus any further studies should aim to have a higher participation from included patients. Furthermore we utilized an unvalidated questionnaire tool that was constructed in house by the research team. In future validated surveys such as the Patient Judgment

System-24 (PJS-24) questionnaire should be utilized. The PJS-24 gives a global overall satisfaction with care rating and 9 multi-item satisfaction components.
The PJS-24 has been validated for hospital quality assurance and shown to accurately reflect and capture issues of patients undergoing prostatectomy (10, 11). A cost analysis compared to the standard patient pathway would be a welcome addition to the literature and would provide further evidence for the feasibility of such a pathway.

Conclusion

The early experience with extraperitoneal LRP with same day discharge home is promising.
Preoperative patient counselling and selection is paramount. Patient satisfaction is not adversely affected by the shortened stay. Surgeon experience, a well-motivated patient, meticulous attention to detail through an integrated pathway, a multidisciplinary team and adequate postoperative assessment are essential.

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ORIGINAL PAPER

The impact of bladder neck sparing on urinary continence during laparoscopic radical prostatectomy; Results from a high volume centre

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Summary ***Objective: To evaluate the effects of bladder neck reconstruction techniques on early continence after laparoscopic radical prostatectomy (LRP).***
Materials and methods: This non-randomized retrospective study analyzed prospectively collected data concerning LRP. In total, 3107 patients underwent LRP between March 1999 and December 2016. Exclusion criteria were preoperative urinary incontinence, previous history of external beam radiotherapy, co-morbities which may affect urinary continence such as diabetes mellitus and/or neurogenic disorders, irregular follow-up, and follow-up shorter than 24 months. All patients were divided into one of three groups, posterior reconstruction being performed in Group 1 (n = 112), anterior reconstruction in Group 2 (n = 762), and bladder neck sparing (BNS) in Group 3 (n = 987). Demographic and pre-, peri-, and postoperative data were collected. Multivariate analyses were performed to determine factors affecting early continence after LRP.
Results: 1861 patients were enrolled in the study. The mean follow-up period was 48.12 ± 29.8 months, and subjects' mean age was 63.6 ± 6.2 years. There was no significant difference among the groups in terms of demographic or preoperative data. Postoperative data, including oncological outcomes, were similar among the groups. The level of early continence was higher in Group 3 than in the other groups (p < 0.001). Multivariate analyses identified BNS and age as parameters significantly affecting early continence levels after LRP (p < 0.001 and p < 0.001, respectively). Bladder neck reconstruction provided less earlier continence than BNS.

KEY WORDS: *Bladder neck; Laparoscopy; Surgery; Prostate cancer; Radical prostatectomy; Urinary continence.*

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INTRODUCTION

Prostate cancer (PCa) is the most common solid organ cancer among men worldwide (1). Although there are different ways to treat PCa, *radical prostatectomy* (RP) is still the gold standard treatment modality for organ-confined PCa (2, 3). Nearly two-thirds of PCa cases are confined to the prostate and can be treated by RP (3). Recently, minimally invasive surgical techniques, such as *laparoscopic radical prostatectomy* (LRP) and *robotic-assisted laparoscopic radical prostatectomy* (RALP), have been successfully used as contemporary surgical options in organ-confined PCa with similar oncological and fuctional results (4). However, the RALP procedure, including the robotic device,is still expensive. LRP thus still assumes a more important place among surgical treatment options for PCa. Although LRP can provide the well-known advantages of laparoscopy, urinary incontinence is one of the main functional problems that can concern patients after surgery. In addition, incontinence has an adverse impact on quality of life and causes indirect workforce losses (5). Early continence is therefore important for rapid recovery after LRP. The level of continence ranges between 60% and 94% at short-term follow-ups (6, 7). This variation may be also due to different definitions of continence levels and different follow-up strategies. Various surgical modifications, such as *bladder neck sparing* (BNS), have been introduced for early continence (8, 9). However, in addition to surgical modifications for providing early continence, surgeons are also consistently developing new techniques for achieving continence in the light of improvements in endourological technology (10). Nonetheless, the exact factors affecting urinary continence after LRP have not yet been clearly defined. Additionally, to the best of our best knowledge, no comparison of techniques performed on the bladder neck, such as posterior reconstructions, anterior reconstructions and BNS, in LRP have to date been reported in the literature. The purpose of this study was to investigate BNS and bladder neck reconstruction techniques in term of providing early continence after LRP.

MATERIALS AND METHODS

This study represents a non-randomized retrospective view of prospectively collected data. All patients fully understood the treatment and aim of the study and provided written informed consent. All data were recorded prospectively on a *Microsoft Office Excel* spreadsheet. This series is part of an ongoing LRP project in our department.

Patient selection

We identified 3107 patients undergoing LRP due to organ-confined PCa between March 1999 and December 2016.

No conflict of interest declared.

Exclusion criteria were preoperative urinary incontinence, previous history of external beam radiotherapy, comorbidities which may affect urinary continence, such as diabetes mellitus and/or neurogenic disorders, irregular follow-up, and a follow-up duration of less than 24 months. Finally, 1861 patients were enrolled into the study.
All LRP patients were divided into three groups depending on BNS or bladder neck reconstruction techniques in order to evaluating the impact of these on early continence after surgery. Group 1 (n = 112) consisted of patients undergoing posterior reconstruction (dorsal reconstruction), Group 2 (n = 762) of patients undergoing anterior reconstruction (ventral reconstruction), and Group 3 (n = 987) of patients undergoing BNS. Subgroups based on early and late continence status were also established. Factors affecting early continence were investigated.

Data collection

Patient data including age, *body mass index* (BMI), preoperative *prostate specific antigen* (PSA), previous operations, co-morbidities, clinical stage, operation time, surgical methods used for bladder neck reconstruction, nerve sparing surgery, *estimated blood loss* (EBL), prostate volume, length of hospital stay, duration of urethral catheter, histopathological and oncological outcomes and urinary continence rates were recorded. Potency was defined as erection sufficient for intercourse, with or without medication. Patients were administered *International Index of Erectile Functions* (IIEF) *questionnaires*, before and after surgery. Patients with IIEF-5 scores ≤ 11 were regarded as having *erectile dysfunction* (ED).

Surgical techniques

The *Heilbronn* ascending LRP technique has been described previously in the literature (11, 12). Pelvic lymph node dissections were performed in an extended fashion for patients with PSA > 10 ng/mL and/or a Gleason score > 6. Urethro-vesical anastomoses were performed with continuous sutures as described by van Velthoven, including reconstruction of the bladder neck (13).

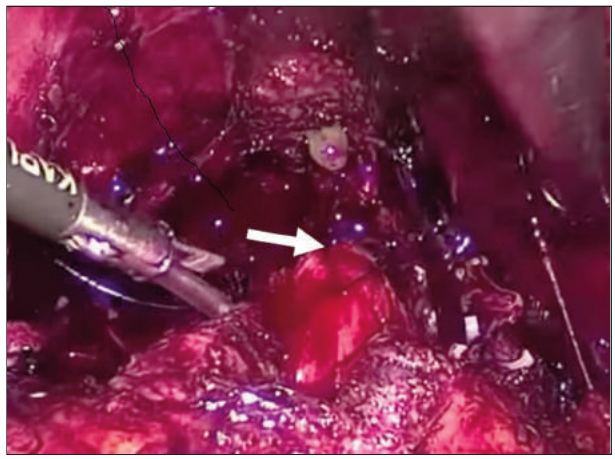
Posterior reconstruction technique

This technique was used in cases with a large prostate, with a large median lobe, with a possible bladder neck invasion and in case of a previous transurethral resection of prostate (Group 1). The bladder neck should be reconstructed in these cases, after the necessary wide resection. Posterior reconstruction began from the distal and close to the trigonal part of bladder neck to the superior part of the bladder neck using a running suture (3/0 Vicryl-V-loc). The bladder neck should resemble a 'reverse tennis racquet' after the reconstruction (Figure 1), as reported by *Sarle et al.* (14) A DJ stenting was necessary in 3 cases. Anastomosis was performed after the bladder neck reconstruction using the *Van Velthoven* technique (10, 11).

Anterior reconstruction technique

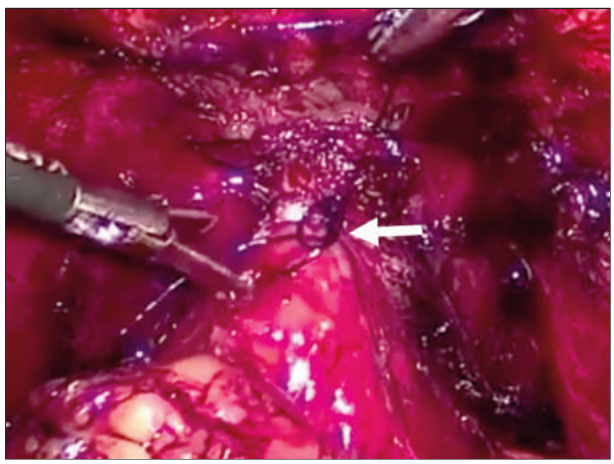
This procedure was performed in the case of bladder neck was larger than urethral lumen (Group 2). Our aim was to reconstruct the bladder neck based on its unique anatomical structures (15). We closed the bladder neck in the form of figure-of-eight stitches, on the ventral side

Figure 1.
Posterior bladder neck reconstruction resembling a "reverse tennis racquet". The arrow shows the tip of the racquet.



(12 o clock) (Figure 2.). The larger bladder neck has been adjusted in this way to the urethra.

Figure 2.
Anterior bladder neck reconstruction with "figure-of-eight" stitches on the ventral side of the bladder neck.



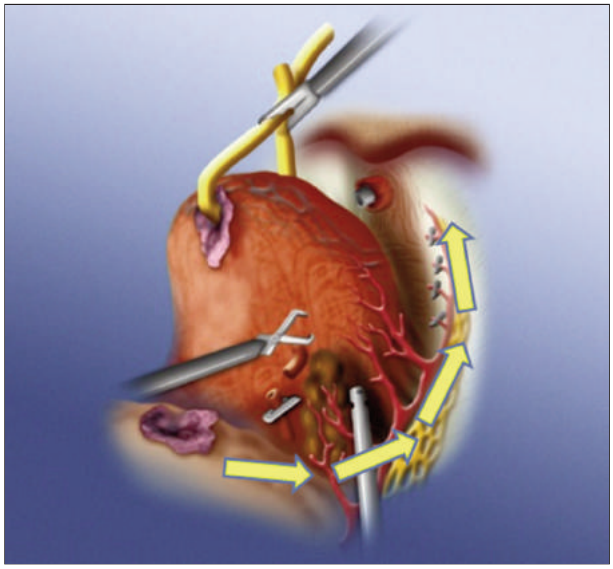
Bladder neck sparing technique

Group 3 consisted of patients undergoing a full bladder neck preservation. Briefly, the base of the prostate was hold to the ventral side by the application of traction to the urethral catheter balloon. The fatty space between the bladder and the anterior leaf of *Denonvilliers'* fascia was observed. Blunt dissections were then performed using a right-angle dissector around the bladder neck. The anterior wall of the bladder neck was incised thereafter horizontally, and careful stepwise dissections were performed around the catheter, thus exposing the muscle fibers of bladder neck (Figure 3.)

Follow-up and continence status

Cystography was performed in all cases, on the 7th day of surgery. If no leak was determined, the urethral catheter was removed. All complications were classified according to the modified *Clavien* classification (16). Indications for

Figure 3.
The bladder neck sparing surgical technique. Anatomical dissections were able to be performed to separate the bladder neck and prostate. The yellow arrows shows the neurovascular bundle.



adjuvant hormone therapy and radiotherapy were determined using the Walz score (17). Self-administered modified *International Continence Society* questionnaires were used to evaluate early continence status. This was also evaluated by physical examination, including the Valsalva or cough stress tests. All patients were advised to perform Kegel's exercises after removal of the urinary catheter. No patients received any surgical treatment for stress urinary incontinence during 24-month follow-up after LRP. Safety pads were applied before the tests. Patients without urine leakage during coughing or sneezing, as well as those who stayed totally dry, were considered urinary continent. Patients who were consistently dry but used a safety pad occasionally during normal daily activity (ie, work, exercise, and walking) were considered continent. Patients who used more than one protective pad per day and/or who experienced urine leak during coughing, sneezing or nocturnally were considered incontinent. Time to continence was classified into two time intervals; early (within 3 months after LRP), and late continence (4-24 months after LRP). Continence status was evaluated at the 1st and 3rd month after LRP by physical examinations including the tests summarized above.
Continence status was then assessed at quarterly intervals within the first year and semi-annually thereafter. The BNS and reconstruction techniques, nerve sparing surgical techniques, clinical stage, BMI, age, prostate volume, duration of urethral catheter use, and oncological results were evaluated using multivariate analyses in order to determine the factors affecting continence.
All postoperative complications were evaluated based on modified Clavien-Dindo classifications (18).

Statistical analysis

Associations in the subgroups were examined using the Chi square, One Way Anova and *Kruskal Wallis* tests. Multivariate logistic regression analyses were performed to evaluate factors affecting early continence. All statistical tests were performed on *Statistical Package for Social Sciences*, version 16.0 (*SPSS, Chicago, IL*) software. Statistical significance was set at $p < 0.05$.

Results

The mean follow-up period was 48.12 ± 29.8 months, and mean age was 63.6 ± 6.2 years. Mean values for demographic data are shown in Table 1. No significant difference was determined among the groups in terms of demographic data. Parameters including mean PSA, clinical stage, and prostate volume were also comparable between the groups. These are summarized in Table 2. Operative and postoperative data are presented in Table 3.
No significant difference was determined between the groups in terms of operative time ($p < 0.001$). Levels of nerve sparing surgical techniques, EBL, hospital stay, and duration of catheterization were similar among the groups (Table 4).

Table 1.
Details of demographic and operative data.

Parameter	Data
Mean age	63.9 ± 6.2
Mean BMI	26.8 ± 1.2
Mean PSA	10 ± 3.7
Mean prostate volume	36.2 ± 16.5

BMI: Body mass index; PSA: Prostate specific antigen.

Table 2.
Perioperative results of groups.

Parameter		Group 1 (n = 112)	Group 2 (n = 762)	Group 3 (n = 987)	P value
Mean age (years)					
One way anova		64.5 ± 5.9	64 ± 5.9	63.7 ± 6.4	0.26
BMI (kg/m^2)					
	< 25 (n,%)	35 (30.7%)	242 (31.7%)	335 (33.6%)	0.76
Chi square	25-30 (n,%)	43 (37.7%)	283 (37%)	377 (37.8%)	
	> 30 (n,%)	36 (31.5%)	238 (31.1%)	284 (28.5%)	
Mean PSA (ng/ml)					
One way anova	10 ± 7	9.8 ± 6.4	10.1 ± 12.4	0.86	
Clinical stage (n, %)					
Chi square	T1	22 (19.2%)	150 (19.6%)	231 (23.1%)	0.42
	T2	57 (50%)	367 (48%)	452 (45.3%)	
	T3	35 (30.7%)	246 (24.6%)	313 (31.4%)	
Prostate volume (cc) (n, %)					
Chi square	≤ 50	93 (81.5%)	637 (83.4%)	844 (84.7%)	0.59
	> 50	21 (18.4%)	126 (16.5%)	152 (15.2%)	
Mean prostat volume					
One way anova)		38.6 ± 18.8	35.6 ± 18	36.4 ± 14.9	0.15

BMI: Body mass index; PSA: Prostate specific antigen.

Table 3.
Details of operative and postoperative data.

Parameter	Data
Mean operation time	212.3 ± 43.4
Mean EBL	828.4 ± 440.6
Mean hospital stay	10.2 ± 4.5
Mean duration of catheter	9.4 ± 4.9
Continence	n = 1753, 94.1%
Biochemical recurrence	n = 337, 18.1%

EBL: Estimated blood loss.

No significant difference were also determined in terms of pathological findings, including pathological stage, Gleason score, positive surgical margins, and biochemical recurrence.
Complication rates were similar in the groups (Table 5). Forty-two (36.8%) patients in Group 1.374 (49%) patients in Group 2 and 601 (60.3%) patients in Group 3 were continent 3 months after LRP.

Table 4.
Peri and postoperative results of groups.

Parameter	Group 1 (n = 112)	Group 2 (n = 763)	Group 3 (n = 996)	P value
Mean operation time (min.)	212 ± 45	217.3 ± 45.8	208.5 ± 41	< 0.001*
Nerve sparing surgery (n,%)	54 (47.3%)	375 (49.1%)	432 (43.3%)	0.052
Mean EBL (ml)	775.4 ± 352.6	824.7 ± 468.4	837.2 ± 427.5	0.34
Mean Hospital stay (day)	9.7 ± 2.8	10.3 ± 3.3	10.3 ± 5.4	0.41
Mean duration of catheter (day)	9.1 ± 4.1	9.4 ± 4.8	9.4 ± 5	0.86

*Abbreviations: EBL: Estimated blood loss *Statistical signifiant p value.*

Table 5.
Oncological and functional results of groups.

Parameter		Group 1 (n = 114)	Group 2 (n = 763)	Group 3 (n = 996)	P value
pT	pT0-2	64 (56.1%)	474 (62.1%)	594 (59.6%)	0.35
	pT3-4	50 (43.8%)	289 (37.8)	402 (40.3%)	
Mean prostate volume (cc)		44.8 ± 20.4	44.4 ± 18.3	43.6 ± 17	0.59
Mean pathological Gleason acore (n, %)	< 7	40 (35%)	340 (44.5%)	425 (42.6%)	0.23
	7	60 (52.6%)	348 (45.6%)	486 (48.7%)	
	> 7	14 (12.2%)	75 (9.8%)	85 (8.5%)	
Pozitive surgical margin		34 (29.8%)	178 (23.3%)	237 (23.7%)	0.31
Early continence (n, %)		42 (36.8%)	374 (49%)	601 (60.3%)	< 0.001*
Biochemical recurrence		21 (18.4%)	160 (20.9%)	196 (19.6%)	0.75

**Statistical significant p value.*

Continence levels were similar between Group 1 (posterior reconstruction) and Group 2 (anterior reconstructions). The level of early continence was higher in Group 3 than in the bladder reconstruction groups ($p < 0.001$). At multivariate analyses, BNS and age were determined as parameters that significantly affected early continence levels after LRP ($p < 0.001$ and $p < 0.001$, respectively) (Table 6).

Discussion

Urinary continence is an essential parameter for early recovery after LRP (19). Surgical modifications have therefore been introduced in order to provide early continence after prostatectomy in patients with PCa. BNS and bladder neck reconstruction techniques can provide early continence after radical prostatectomy (20). All these surgical techniques can be performed during LRP, which includes the well-known benefits of laparoscopy (12). No published data, including comparisons of all surgical techniques with large numbers of patients, after LRP have to date been available. Additionally, the exact factors involved in the provision of early continence had not been identified. To the best of our knowledge, this is the first series with large patient numbers to investigate early continence was investigated after LRP in terms of BNS and bladder neck reconstruction techniques. On the basis of our results, bladder neck reconstruction techniques (Group 1 and Group 2) provided similar continence levels. High levels of early urinary continence were achieved with BNS in younger patients after LRP.

Clinical stage, nerve sparing surgical technique, biochemical recurrence, and pathological stage did not significant affect early continence levels at multivariate analysis.
Stolzenburg et al. reported early continence using BNS after LRP (21). *Chlosta et al.* achieved similar results in their series of 194 LRP patients (22). Our series involved 987 (53%) BNS patients, 601 (60.3%) of whom were continent in the 3rd month of LRP. The BNS technique contributes a sphincter mechanism which includes striated and smooth muscle fibres (23).
Additionally, the striated muscle fibers in the urethra are horseshoe-shaped and these also assist with continence. However, urological stud-

Table 6.
Factors effecting early continence status in multivariate logistic regression analyses.

Parameter	P value
BNS surgical technique	< 0.001*
Anterior reconstruction	0.3
Posterior reconstruction	0.4
Clinical stage	0.47
Age (year)	< 0.001*
BMI	0.15
Prostate volume	0.28
Preoperative PSA	0.95
Operation time	0.2
Nerve sparing surgical technique	0.06
Duration of urethral catheter	0.3
Surgical margin	0.74
Biochemical recurrence	0.55

*BMI: Body mass index; BNS: Bladder neck sparing; PSA: Prostate specific antigen *Statistical significant p value*

ies have shown that these cannot sustain contraction over 60 sec. (24, 25) Smooth muscle fibers of course assist continence. The BNS technique permits the smooth muscle fibers to remain place. We tried to perform as many BNS procedures in LRP cases as possible. During LRP, these fibers can be preserved more than with open surgical techniques through the well-known advantages of laparoscopy. *Rosenblatt et al.* reported that bladder neck reconstruction surgical techniques may be required by 10-15% of LRP patients (26). *Rocco et al.* described a surgical technique for bladder neck reconstruction and reported early continence as one advantage of this (27). In another study, they reported no significant complications associated with the posterior musculofascial plate reconstruction technique, and described reconstruction of the posterior musculofascial plate as encouraging in terms of earlier continence recovery (27). Nevertheless, this subject is still controversial (28). Posterior reconstruction was performed in 114 (4.4%) of our cases. The early continence level was 54% in LRP patients, lower than that achieved with BNS (60.3%). We performed posterior bladder neck reconstruction in 71 (6.1%) cases. *Daouacher* and *Walden* recently described anterior and posterior reconstructions during LRP as safe and effective, without affecting voiding or surgical margins (29). In our recent series, anterior reconstruction was performed in 763 (40.9%) cases. Both posterior and anterior reconstructions may provide early continence. However, the level of early continence was statistically significantly higher in Group 3 (BNS) than in the other groups. *Poon et al.* compared the outcomes of BNS with those of bladder neck repairing techniques as anterior and posterior reconstructions in a series of patients undergoing open radical prostatectomy (30). No significant difference was determined in early and late continence levels during follow-up. Our series differs from that of *Poon et al.* (30). The normal anatomy of the bladder neck was preserved by using laparoscopy in all patients in Group 3. Optic magnification of anatomical structures and the use of precision instruments may have contribute to the good results as well as the advanced laparoscopic techniques employed.

Katz et al. reported that a wide resection of the bladder neck can decrease positive margins on bladder neck (31). But, this may also have an adverse effect on continence after LRP. However, the positive surgical margin levels were similar among the groups in the present study. Additionally, a positive surgical margin did not emerge as a significant factor in early continence at multivariate analyses.

Multivariate analysis identified mean age as a factor affecting early continence. *Kadono et al.* reported age as a predictive factor for incontinence following minimally invasive surgical treatment of PCa (32). *Kumar et al.* investigated 3241 patients and concluded similar results (33). Our data are comparable with those previous studies, and early continence was adversely affected by advanced age. This raises the question of early detection of PCa. Robot-assisted laparoscopic prostatectomy (RALP) can provide more anatomical details for surgeons during surgery (25). BNS can thus be performed more accurately during RALP. *Tunc et al.* reported their early continence results after RALP by presenting a novel technique for BNS. Our results are parallel to those of their study. We think that superior magnification can improve surgeons techniques and learning curves (25). Early continence can thus be established after LRP/RALP, and this will in turn assist early recovery after surgery.

The main limitation of this study is that numbers of patients in the groups were not similar, because our surgical technique did not usually require bladder neck reconstructions (34). The aim of the present series is to compare BNS and bladder neck repairing techniques in LRP among large numbers of patients. To the best of our knowledge, this series is unique in the literature due to the features described.We recommend that surgeons make every effort to perform BNS during LRP.

Conclusions

Bladder neck reconstruction surgical techniques and BNS can provide good continence results after LRP. However, BNS is significantly superior to bladder neck reconstruction techniques in terms of establishing early continence after LRP, notably in younger patients. Additionally, BNS involved more anatomical dissections without altering oncological outcomes.. More standardized and multi-centered studies are now needed to optimize current surgical techniques for providing early continence after LRP.

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ORIGINAL PAPER

A randomized study to assess the efficacy of herbal product to prevent cisplatin-induced nephrotoxicity in a rat model

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Summary ***Objectives: This study aimed to investigate the protective effect and antioxidant activity of an herbal product that made from multiple plants in a rat model of kidney dysfunction induced by intraperitoneal cisplatin.***
Materials and methods: Twenty-four rats were divided into four different groups namely: Group 1 - control healthy animals without any specific medication, Group 2 - Herbal product only 5 mg/kg, Group 3 - cisplatin only and Group 4 - Herbal product 5 mg/kg + cisplatin.
Results: Evaluation of our findings demonstrated a significant (p = 0.017) reduction in Catalase activities and a significant increase (p = 0.001) in renal tissue Malondialdehyde levels in cisplatin- treated rats when compared with the control group. Also, Glutathion and Glutathione peroxidase content revealed significant (p = 0.031) reduction in renal tissues of cisplatin-treated rats compared with the control group. Pre-treatment of rats with the herbal product ameliorated these cisplatin-induced changes of the antioxidant enzymes. No statistically significant changes were demonstrated in Superoxide dismutase activities in the tissue specimens of any group.
Conclusions: This potent antioxidant herbal medicine was found to have potential antioxidant activity, which may in turn to be effective in the protection of kidney tissue resulting from cisplatin application. Therefore, much attention should be given to the possible role of natural dietary antioxidants for protecting the kidney.

KEY WORDS: Animal model; Antioxidants; Cisplatin; Herbal medicine; Nephrotoxicity.

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INTRODUCTION

Despite their well-established curative effects in certain solid organ tumors, chemotherapeutic agents may exhibit dose dependent toxic effects during the course of chemotherapy on certain organ systems, a reality that should inevitably be taken into account by all physicians. *Cisplatin®* (cis-diamminedichloroplatinum II) is one of the most widely used chemotherapeutic drugs for the treatment of various solid tumors, including those of the breast, head, neck, lung, testis, bladder and ovary (1). Of these side effects, nephrotoxicity is the most well-known, established and clinically important toxicity of this drug (2).

Over the last few decades, different studies were made to investigate the pathophysiological basis of cisplatin-induced nephrotoxicity and how to protect kidney from this toxicity. These studies demonstrated number of mechanisms including oxidative stress, DNA adducts, inflammation, mitochondrial dysfunction, and direct cytotoxicity to the tubular epithelial cells (2-4). Also literature revealed that *Cisplatin®* application might cause renal vasoconstriction that reduces blood flow, causing ischemic damage to the kidney and deteriorate the glomerular filtration rate. These alterations eventually trigger ischemia-induced oxidative stress, a well-known phenomenon that ultimately results in renal tubular cell injury and death. *Cisplatin®* administration in a mice model resulted in marked renal failure characterized by a significant increase in serum urea and creatinine levels due to the formation of oxidative stress as indicated by increased lipid peroxidation and decreased levels of glutathione (GSH), glutathione peroxidase (GSHPx), superoxide dismutase (SOD) and catalase in renal tissues (5, 6). Being aware of the well-known side effects of *Cisplatin®* on the functional and morphological integrity of the kidneys, physicians began to look for protective agents to prevent or at least limit the extent of the renal toxic effects of *Cisplatin®* based chemotherapy. Related to this issue, evaluation of literature data demonstrated that AsAG or TMG, lutein, ascorbic acid and alpha tocopherol may reduce cisplatin-induced renal toxicity either by limiting the extent of renal functional deterioration or increasing the antioxidant capacity of the kidneys (3, 4, 7, 8).

On the other hand, in addition to the use of these medical agents, recent data demonstrated that phytotherapy might prevent toxic effects of certain medications causing morphologic as well as functional changes in different organ systems (3, 4, 8-10). In this study, we investigate the potential renoprotective effects of a herbal medication (*Tutukon®*) on cisplatin-induced oxidative stress-related nephrotoxicity in a rat model.

No conflict of interest declared.

Methods

Animals

This study was made with 24 male Wistar white rats, each weighing 250-300 g. Ethical committee approval (No: 94-14/2013) was obtained from the animal laboratory of the *Pendik Animal Research Laboratory* (*Istanbul, Turkey*) and all procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted. All animals were fed standard chow and kept under normal room conditions at a constant temperature (25°C) under a 12 hours light/dark cycle. Rats underwent a complete physical examination, biochemical evaluation including blood and urine analyses and stool examination.

We estimated that total of 24 subjects would be needed to detect difference among groups with α of 0.05 and a (1-β) of 80%. Rats randomly divided into four groups (each with n = 6): Group 1 (control group) received only standard rat chow and distilled drinking water without any specific medication. Group 2 (*Tutukon® group*) received an herbal product (*Tutukon®*) given via a feeding catheter (20 ml/kg). Group 3 (Cisplatin group) received *Cisplatin®* only (7.5 mg/kg once i.p.). Group 4 (*Tutukon®* + *Cisplatin®* group) received a combined medication (20 ml/kg of *Tutukon®* for seven days + 7.5 mg/kg *Cisplatin®* i.p. after seven days for once). Control group animals received only distilled drinking water during all study phases. After two weeks bilateral nephrectomy was performed with bilateral flank incision. All surgery was performed under sodium pentobarbital anesthesia, and all efforts were made to minimize suffering.

Main chemicals and drugs

Cisplatin® was used to induce nephrotoxicity in rats according to the method of *Prabhu et al.* (11). Applied dose was 7.5 mg/kg rat body weight (intraperitoneal).

Plant-based herbal medication (*Tutukon®*) fixed-dose combination. Dosage form: hydrolate, bottles of 600 ml, 45 ml three times/daily. Ingredients: Essential oils, flavonoids-quercetin, polysaccharides, rosemarinic acid, boldin, flavonglicozides. Composition (per 100 ml of solution): *Enguisetumarvensis* 570 mg, *Spergulariarubra* 330 mg, *Peumusboldus* 280 mg, *Opuntiaficusindica* 170 mg, *Sideritisangustifolia* 170 mg, *Rozmarinusofficinales* 170 mg, *Cynodondaktylon* 170 mg, *Melissa officinalis* 170 mg.

Measurement of Malondialdehyde (MDA) and glutathione levels, Superoxide dismutase (SOD) and catalase (CAT) activities in renal homogenate

The homogenization of tissues was carried out in a Teflon-glass homogenizer with a buffer containing 1.15% KCl to obtain 1/10 (w/v) whole homogenate. MDA levels were directly measured in the homogenates. The homogenates were centrifuged for 30 min at 25000 g at +4°C to determine GSH-Px and CAT activities. The obtained supernatants were centrifuged again at 25000 g, +4°C for 30 min to determine SOD activities. The MDA concentrations of tissue homogenates were measured according to a modified method from *Ohkawa et al.* (12) based on the reaction with TBA and the results were expressed as nmol/g protein. The GSH-Px activities were determined according to the method of *Beutler*, (13) which records the disappearance of NADPH at 340 nm, and results were expressed as U/g protein. The CAT activities were determined by measuring the decomposition of hydrogen peroxide at 240 nm, according to the method of *Aebi* (14).

The results were expressed as k/g protein, where k is the first-order rate constant. SOD activities were determined using the method of *Sun et al.* (15) and the results were expressed as U/g protein. Tissue GSH concentrations were measured by an assay using the dithionitrobenzoic acid recycling method described by *Elman* (16) and expressed as nmol/mg protein. Protein concentrations were measured according to *Lowry et al.* (17).

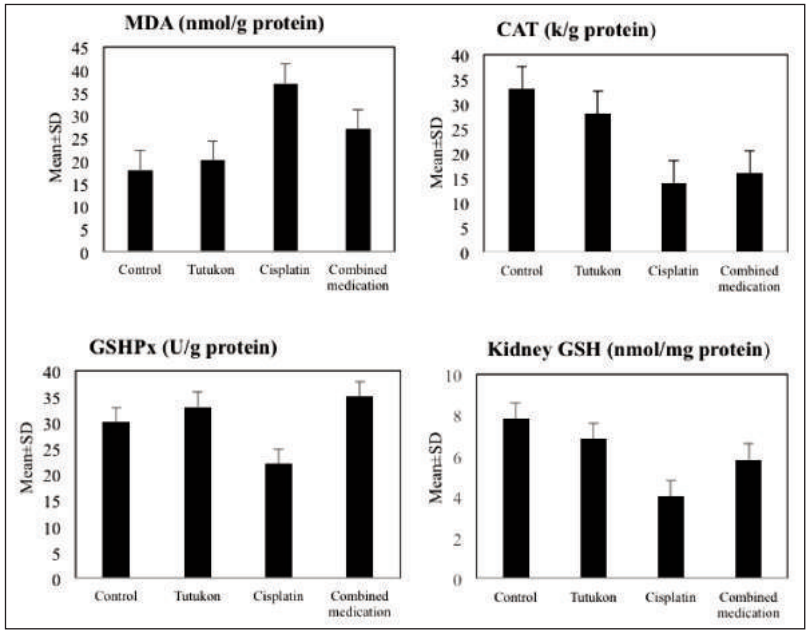
Statistical analysis

For statistical analysis of the obtained data NCSS (*Number Cruncher Statistical System*) 2007&PASS (*Power Analysis and Sample Size*) 2008 Statistical Software (*Utah, USA*) program was used. The data was expressed in mean +/- standard deviation. *Mann-Whitney U* and *Kruskal-Wallis* tests were used to compare the parameters between two or more groups that don't fit to normal distribution. A P value of < 0.05 was considered as significant.

Results

Evaluation of the tissue enzyme levels demonstrated the following findings (Figure 1).

Figure 1.
MDA, CAT, GSH-Px and kidney GSH levels according to the groups.



MDA: There were statistically significant differences among groups regarding levels of MDA ($p < 0.001$) (Table 1). There was a significant increase in renal tissue MDA levels in cisplatin-treated rats (*Cisplatin®* only or *Tutukon®* + *Cisplatin®*) compared with the control and *Tutukon®* groups ($p < 0.05$). There was no statistically significant difference with respect to MDA levels between the *Tutukon®* and control groups. Lastly, although not statistically significant, renal tissue MDA levels of the *Tutukon* + *Cisplatin®* group were found to be comparably lower than the *Cisplatin®* group ($p = 0.055$) (Table 2).

SOD: There were no statistically significant differences among groups regarding SOD activities ($p > 0.05$) (Table 1 and 2).

CAT: CAT activity of the cisplatin-treated rats (*Cisplatin® only or Tutukon®* + *Cisplatin®*) was lower than the other groups (Figure 1). The combined medication group showed significantly lower CAT activity than the control and *Tutukon®* groups ($p = 0.025$, $p = 0.016$, respectively). According to comparative studies, CAT activity of the *Cisplatin®* group was significantly lower than the control group ($p = 0.037$). It was also found to be lower but not statistically significant than the *Tutukon®* group ($p = 0.055$) (Table 2).

GSH-Px: There was statistically significant difference of GSH-Px levels among groups ($p = 0.031$) (Table 1). According to dual-comparison of the groups, GSHPx levels in the *Cisplatin®* group showed significant reduction compared with *Tutukon®* and combined medication groups ($p = 0.037$, $p = 0.016$, respectively) (Table 2).

GSH: There were statistically significant differences among groups for GSH levels ($p = 0.007$) (Table 1). According to dual comparison results, GSH levels of the *Cisplatin®* group were significantly lower than the *Tutukon®* and combined medication groups ($p = 0.010$, $p = 0.037$, respectively) (Table 2).

Discussion

Cisplatin® is a chemotherapeutic agent widely used for the treatment of various solid cancers. However, nephrotoxicity is one of the major side effects of *Cisplatin®* and published data have shown that an estimated 20% of patients receiving high-dose *Cisplatin®* suffer severe renal dysfunction and approximately one third of patients may experience kidney injury following initial treatment (18, 19). Renal tubular injury and cell death are the most prominent pathologic findings originating from reduced blood flow (ischemia) induced oxidative stress in renal tubular cells following the application of this agent.

In literature, several mechanisms were documented to be important in renal tubular injury. *Yonazewa et al.* showed that organic cation transporter 2 (OCT2) mediates the entry of *Cisplatin®* into the renal tubular cells and stimulate the sensitivity of *Cisplatin®* in these cells. *Cisplatin®* reduces the activity of mitochondrial respiratory complexes, resulting in reactive oxygen species (ROS) generation (20). The other mechanism of generation of reactive oxygen species is depletion of endogenous antioxidant, glutathione. *Cisplatin®* may damage the kidney by depletion of critical sulfhydryl centers, including GSH inside the cells, and may provoke damage to the cell by generating a cascade of lipid membrane peroxidation, mitochondrial dysfunction and DNA injury which reduces the internal antioxidant storages (21, 22). Likewise in our study we found that *Cisplatin®* treatment decreased GSH, GSHPx levels, CAT activites and increased MDA levels.

Thus, all these findings clearly have shown that cisplatin-induced generation of ROS, cytokines and chemokines are directly related to its cytotoxicity. ROS produce by the xanthine-xanthine oxidase system, mitochondria, and NADPH oxidase in cells. Following treatment with *Cisplatin®*, ROS that produced throughout these systems, are implicated in the pathogenesis of acute renal injury (22).

Related to this subject, in their original study both *Maliakel and Atasayar et al.* showed that administration of AsAG or TMG markedly reduced the cisplatin-induced higher plasma creatinine and urea levels and counteracted the deleterious effects of formed oxidative stress markers by protecting the renal tissue from the cisplatin-induced lipid peroxidation (3, 7).

In another study, *Sindhu and Kuttan* applied lutein, a non-toxic carotenoid with strong antioxidant activity, to reduce cisplatin-induced renal damage in mice.

As shown by the reduction of serum urea and creatinine levels, nephrotoxicity, origi-

Table 1.
The evaluation of MDA, SOD, CAT, GSH-Px and kidney GSH.

	MDA (nmol/g protein) Mean ± SD	SOD (U/g protein) Mean ± SD	CAT (k/g protein) Mean ± SD	GSH-Px (U/g protein) Mean ± SD	Kidney GSH (nmol/mg protein) Mean ± SD
Control	18.62 ± 2.21	50.87 ± 9.22	30.22 ± 11.3	30.21 ± 8.87	7.76 ± 1.56
Tutukon®	19.89 ± 3.73	48.55 ± 10.56	26.90 ± 4.99	32.02 ± 5.79	6.68 ± 1.49
Cisplatin®	35.47 ± 7.04	38.75 ± 16.62	14.86 ± 10.63	22.14 ± 7.95	4.19 ± 0.82
Tutukon® + Cisplatin®	27.10 ± 4.95	47.19 ± 18.59	16.30 ± 4.85	35.45 ± 6.02	5.85 ± 1.41
[a]**p**	0.001**	0.667	0.017*	0.031*	0.007**

*[a]Kruskal -Wallis Test; **p < 0.01; *p < 0.05.*

Table 2.
Dual comparison of groups.

	MDA	SOD	CAT	GSH-Px	Kidney GSH
Group 1 *vs* **Group 2**[b]	0.749	0.749	0.522	0.631	0.262
Group 1 *vs* **Group 3**[b]	0.004**	0.200	0.037*	0.109	0.006**
Group 1 *vs* **Group 4**[b]	0.006**	0.873	0.025*	0.262	0.055
Group 2 *vs* **Group 3**[b]	0.004**	0.337	0.055	0.037*	0.010*
Group 2 *vs* **Group 4**[b]	0.037*	0.873	0.016*	0.337	0.423
Group 3 *vs* **Group 4**[b]	0.055	0.522	0.109	0.016*	0.037*

*[b]Mann Whitney U Test; **p < 0.01; *p < 0.05.*
Group 1: Control; Group 2: Tutukon®; Group 3: Cisplatin®; Group 4: Tutukon® + Cisplatin® (combined medication).

nating from reduced activity of the antioxidant enzymes in the kidney (SOD, as well as CAT) and increased MDA levels, was reduced by lutein treatment (4). The results of this study showed that lutein might effectively protect the kidneys of mice treated with *Cisplatin®*, which was also supported by the histopathologic evaluation of the kidney tissues of the treated animals. Last but not least, *Ajith et al.* gave 250 mg/kg or 500 mg/kg vitamins (ascorbic acid and alpha tocopherol) to their subjects to protect from the nephrotoxicty induced by *Cisplatin®* and they found that 500 mg/kg vitamins significantly protected the kidneys. However, the protective effect of vitamins from the cisplatin induced decline of activities of renal antioxidant enzymes such as SOD, CAT, GSHPx noted only in 500 mg/kg dosage group. Additionally, Authors have observed that both vitamins at dosages of 250 and 500 mg/kg could increase the concentration of reduced GSH and limit the extent of cisplatin-induced lipid peroxidation (8).

Recent data showed that herbal medicine might prevent some toxic effects of certain medications (3, 4, 8-10). Phytotherapy on this aspect may be applied in a complementary fashion to ameliorate these effects. Majority of these phytotherapeutic agents have diuretic, anti-inflammatory, antioxidant and vasodilating effects. The active ingredients like essential oils, flavonoids, saponins, xanthine derivatives and glycosides were found responsible of these protective effects (23-25).

In a study, administration of plant extract mixtures produced improvements in biochemical, histopathological and cytogenetic parameters (26).

Other similar studies focused on the possible protective effects of plant extracts with certain ingredients demonstrating the protective effects on both the kidney as well as their specific protective effects on other pathologies in different organ systems (27, 28). Antioxidant, diuretic and antidiabetic effects of such agents also might be effective in limiting the toxic effects induced by *Cisplatin®* administration.

Taking into account the established effects of antioxidants as well as anti-inflammatory agents in the prevention of ischemia-induced injury in renal tubular epithelium, we aimed to evaluate the possible limitation of the extent of oxidative stress resulting from cisplatin-induced toxicity by using a potential antioxidant and anti-inflammatory agent (*Tutukon®*) in a rat model.

Tutukon® (*Grand Medical, Spain*) is a medication composed of different herbal ingredients demonstrating certain biological effects in tissues. Among these effects, the antioxidant potential is one of the most important characteristics of this drug due to its active ingredients. Among the eight different ingredients of *Tutukon®*, alkaloids rosmarinic acid, flavonoids, apigenin, luteolin, ekvizetonin saponin, and essential oils are well known for their antioxidant as well as anti-inflammatory effects shown in different studies (23, 25, 29). Regarding the mechanism of action, studies showed that these active ingredients may reduce the permeability of kidney capillaries, dilate kidney blood vessels and ureters, restore the tubular epithelial function, induce an osmotic effect, inhibit synthesis and activation of inflammatory mediators and thus prevent inflammatory alterations (24, 30).

Our current findings clearly showed that pre-treatment with this herbal product also might significant reduction in MDA levels and significant elevation of CAT activities and GSH levels of the renal tissues in cisplatin-treated rats. Evaluation of the antioxidant enzyme (*Catalase and GSHPx*) content revealed significant reduction in renal tissues of cisplatin-treated rats compared with the control group as well as in the groups receiving *Tutukon®*. These findings may provide evidence of the antioxidant effect of *Tutukon®* against cisplatin-induced oxidative stress and lipid peroxidation. Parallel to the data reported in the literature so far, we found that reduction in the activity of antioxidant enzyme (CAT), increased lipid peroxidation (MDA) and depletion of GSH in renal tissues were implicated in the pathogenesis of *Cisplatin®* nephrotoxicity.

Our results also showed that ischemia-induced oxidative stress in renal tubules as well as the inflammatory changes might be the major underlying causes of cisplatin-induced renal functional as well as morphologic deterioration. *Tutukon®* with its potent ingredients may be protective in the limitation of such alterations at least in experimental models.

As a conclusion, *Tutukon®* showed an ameliorative effect against cisplatin-induced oxidative stress and renal damage through its antioxidant, anti-inflammatory and anti-apoptotic properties. Due to the potential antioxidant activity, medicinal plants and natural herbal products like *Tutukon®* may be used as natural dietary antioxidants in protecting the kidney from damage originating from certain chemical agents. However, further studies with larger series of patients under clinical conditions are certainly needed.

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ORIGINAL PAPER

Effect of green tea catechins in patients with high-grade prostatic intraepithelial neoplasia: Results of a short-term double-blind placebo controlled phase II clinical trial

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Summary ***Background and study objective: Several studies suggest a protective role of green tea catechins against prostate cancer (PCa). In order to evaluate the efficacy of green tea catechins for chemoprevention of PCa in patients with high-grade prostate intraepithelial neoplasia (HG-PIN) we performed a phase II clinical trial.***
Methods: Sixty volunteers with HG-PIN were enrolled to carry out a double-blind randomized placebo-controlled phase II clinical trial. Treated group took daily 600 mg of green tea catechins (Categ Plus®) for 1 year. Patients were screened at 6 and 12 months through prostatic biopsy and measurements of prostate-specific antigen (PSA).
Results: Despite the statistically significant reduction of PSA observed in subjects who received green tea catechins for 6 and 12 months, we did not find any statistical difference in PCa incidence between the experimental groups neither after 6 nor after 12 months. However, throughout the one-year follow-up we observed very limited adverse effects induced by green tea catechins and a not significant improvement in lower urinary tract symptoms and quality of life.
Conclusions: Although the small number of patients enrolled in our study and the relatively short duration of intervention, our findings seems to deny the efficacy of green tea catechins. However, results of our clinical study, mainly for its low statistical strength, suggest that the effectiveness of green tea catechins should be evaluated in both a larger cohort of men and longer trial.

KEY WORDS: *Prostate cancer; Green tea catechins; High-grade intra-epithelial neoplasia (HG-PIN); Herbal medicines; PSA; Complementary therapies.*

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INTRODUCTION

Prostate cancer (PCa) is a leading cause of cancer related death among men in Western countries, representing a major public health problem with high economic and social costs. However, it is typically diagnosed in men over 50 years of age and, as clinically significant PCa, usually, requires more than two decades for its development. Thus, it can be considered as an important chance for early prediction or chemoprevention through therapeutic or nutritional interventions, especially in the case of pre-malignant lesions such as high-grade prostate intraepithelial neoplasia (HG-PIN) (1). A chemoprevention approach in patients with high risk of PCa can be proposed in order to reduce the disease progression rate. It is known that natural product can be used to prevent and/or alleviate several health disorders (2-4), including those affecting the urinary tract (5). Moreover, regular dietary habits coupled with a healthy lifestyle may protect against certain types of cancer (6, 7), including PCa. In particular, epidemiological studies have shown that Asiatic populations have lower rates of PCa compared to others races and that Asian men who adopt a lifestyle typical of Western countries because of migration to the United States, have a significantly higher risk of PCa when compared to their native Asian counterparts (8). These findings strengthen the hypothesis that environmental factors may contribute to PCa development and that the use of dietary agents such as green tea may be an important way to prevent or slow down the process of carcinogenesis, hence the growing interest toward both dietary supplements and complementary and alternative medicine. In such context, diet-derived polyphenols have received great attention among nutritionists, food scientists, and consumers for their health-promoting effects, including their use in the chemoprevention of PCa (9), because oxidative stress has been implicated in the aetiopathogenesis of PCa (10). Regardless, unresolved issues still linger.

Tea is the most consumed beverage worldwide, second only to water in terms of popularity. It is prepared by infusion of the *Camelia sinensis L. (Theaceae)* leaves.

On the basis of both the differences in the processing methods and chemical composition, it could be classified in three main types, the green tea (unfermented), the oolong tea (partially fermented) and the black tea (fully fermented). Habitual green tea consumption has long been associated with preventive effects against chronic pathologies including both heart and neurodegenerative disease and cancer. In the latter field, several *in vitro* and

Funding and competing interests: This clinical trial received no specific funding. The authors declare that there is no conflict of interest regarding the publication of this paper. *Sofar S.P.A*, Milan provided free samples of *Categ Plus*® employed in this study, without any role in data collection and analysis, decision to publish, or preparation of the paper.

in vivo studies showed that tea and its bioactive molecules might modify the incidence and the progression of PCa through their antioxidant properties and the ability to interact with specific intracellular targets in cancerous cells (11).
The beneficial effects of green tea are attributed especially to its water soluble polyphenolic flavonoids, known as catechins, including epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG) and the major flavonoid (–)-epigallocatechin-3-gallate (EGCG).
Their content is 30-40% of dry green tea weight, and EGCG may represent up to 50% of the catechins by weight. However, other polyphenols present in green tea are quercetin, myricitrin and kaempferol.
Bettuzzi et al. (12) proposed the green tea catechins as chemopreventive agents against prostate cancer in men with HG-PIN, confirming this suggestion in a long term follow up study (13). However, others studies (14) often report conflicting results, suggesting that habitual green tea consumption may not provide the alleged protection against cancer. Therefore, the aim of the study was to evaluate the efficacy of green tea catechins for chemoprevention of PCa in patients with HG-PIN by a double-blind randomized placebo-controlled phase II clinical trial.

Methods

Study design

Sixty volunteers with HG-PIN were enrolled to carry out a double-blind randomized placebo-controlled phase II clinical trial in order to investigate whether green tea catechins could prevent the occurrence of PCa in men at high-risk.

Ethics approval and consent to participate

This study was approved by the *Modena Ethic Committee (Italy)* on 2007-04-10 (number 23/07) and carried out in the *Modena University Hospital (Italy)* from May 2007 to February 2011. The recommendations of the Declaration of Helsinki and the guidelines of the *International Conference on Harmonization Good Clinical Practice* were observed. All volunteers have been properly informed about the clinical trial and signed a free informed consent form.
Study objectives. The primary objective was to determine the efficacy of green tea catechins for chemoprevention of PCa in patients with HG-PIN. Therefore, the first goal of our study was to point out PCa incidence during the 1-year study in the two arms. Moreover, during the whole study, we recorded possible changes in total serum prostate-specific antigen (PSA) values (secondary objective), together with the toxicity evaluation as well as the patient's *lower urinary tract symptoms* (LUTS) and *quality of life* (QoL) scores assessments by questionnaires. Subjects who were detected PCa during the clinical trial were excluded from the study and subjected to chemotherapy.
Study population. Eligibility criteria for enrolment included: Caucasian men aged between 55 to 65 years old with HG-PIN, as assessed by prostate biopsy. All volunteers were properly advised about the clinical trial and signed a free informed consent form. Exclusion criteria included: men aged > 65 years, previous malignancies, cancer diagnosis, antiandrogenic or chemoprevention therapies, obesity, diabetes or other endocrinologic diseases. The subjects enrolled in the trial were instructed to abstain from green tea and its derivatives, antioxidants or nutritional supplements and herbal therapies.

Study procedures

During the initial visit, volunteers underwent an interview to obtain medical history as well as a brief physical assessment including a digital rectal examination. Moreover, blood samples were collected for complete blood count and serum PSA levels. Finally, baseline assessments of LUTS and QoL, were obtained.
Upon determination of eligibility, a total of 60 patients participating to the clinical trial were randomized (1:1) to receive daily green tea catechins 600 mg (*2 tablets of 300 mg of Categ Plus®, Sofar S.P.A, Milan, Italy*) or placebo for 1 year. The random allocation sequence was obtained by means of "*Easy Random Picker*" software (*TrustFm© 1998-2016*). Both participants and care providers were blinded after assignment to interventions, in order to avoid any bias. Two capsules of *Categ Plus®* or placebo per day were given to all subjects by the clinical trial investigators, according to the double blind method.
Follow up was carried out at 6 and 12 months with toxicity assessment (side effects), LUTS and QoL evaluation, medical examination, rectal inspection, serum PSA levels and prostate biopsy. PSA measurements as well as immunohistochemistry evaluation of prostatic biopsies were performed in the same hospital's central laboratory where was carried out the clinical trial (*Modena University Hospital, Italy*). Possible changes in LUTS, using the International Prostate Symptom Score (IPSS), and QoL were evaluated as described (15, 16).

Statistical analysis

Statistical analyses of results were performed using the Student's t test. P-values < 0.05 were considered statistically significant.

Results

First, we have ensured that the randomization of volunteers in the two arms of the clinical trial had resulted in two homogeneous groups with one another. A *Consort flow diagram* of the study is shown in Figure 1. In particular, at the time of enrollment the age of subject, their weight, the PSA value and the prostate volume were recorded and statistically analyzed. In Table 1 are reported their mean values. None of the variables considered were significantly different in the two arms (age, $p = 0.8$; PSA value, $p = 0.16$; prostate volume, $p = 0.23$). The two groups were statistically analyzed to ensure homogeneity between the two groups by the t test of Student (age, $p = 0.580$; PSA value, $p = 0.790$; prostate volume, $p = 0.738$). Among the 60 patients that entered the study, 44 subjects completed the study (22 cases and 22 controls) with a drop out of 26.7%, whereas minimal side effects were recorded. Indeed, although the majority of patients tolerated the green tea relatively well, 8 patients with-

Figure 1.
Consort flow diagram.

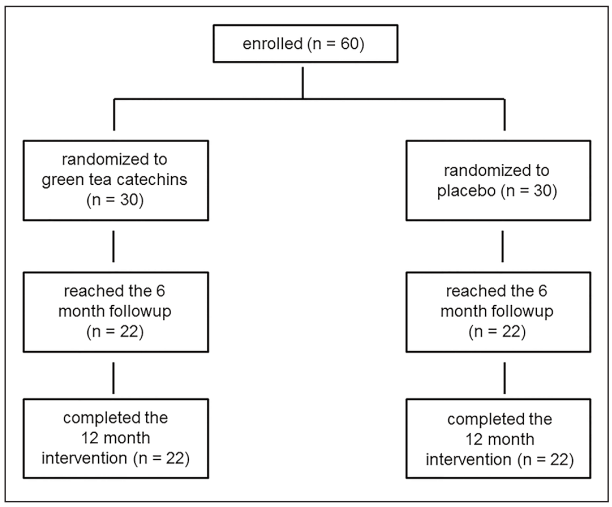

Table 1.
Patient characteristics at the time of enrollment (mean ± SD).

	Mean age	Weight (kg)	Prostate volume (ml)	PSA value
Total population enrolled	64.34 ± 8.4	82.77 ± 6.6	44.74 ± 16	5.31 ± 2.5
Placebo arm	64.4 ± 8.9	80.9 ± 6.4	42.15 ± 15	4.7 ± 2.5
Green tea catechins-treated arm	64.27 ± 8	84.64 ± 6	46.,87 ± 17.8	5.95 ± 2.3

drew from the clinical study because one selves' decision. When toxicity did occur, it was of Grade 1 or 2, including the following symptoms: nausea, emesis, abdominal pain, insomnia, fatigue and diarrhea.

Figure 2A shows that the incidence of new diagnoses of PCa at 6 months was 9% (2/22) in the green tea catechins-treated arm, and 18.1% (4/22) in the placebo group; although these values are the one of the other half, the difference between green tea-treated and placebo groups has not reached the statistical significance ($p = 0.5$). Moreover, at 12 months follow up, two more cases of PCa were diagnosed in the green tea catechins group, reaching a 18% of PCa incidence also in the treated arm (Figure 2B).

In the green tea catechins group we observed a progressive reduction of the PSA value throughout the 1-year study, as well as we found a deceleration of the PSA rise in the green tea catechins group with respect to the placebo ones, however without reaching statistical significance (Table 2). Interestingly, after 12 months of treatment we found a significant reduction of PSA values in the green tea catechins group with respect to the placebo ones (3.85 ± 1.8 ng/dl and 5.83 ± 2.65, respectively; $p < 0.05$; Table 2).

Finally, a certain improvement in LUTS and QoL scores was found by analyzing the patient's questionnaires filled by the subjects belonging to green tea catechins group throughout the 1-year study. However, no significant differences between the treatment and placebo arms were observed from baseline to end of study (data not shown).

Figure 2.
Incidence of new diagnosis of PCa at 6 (A) and 12 (B) months' follow up.

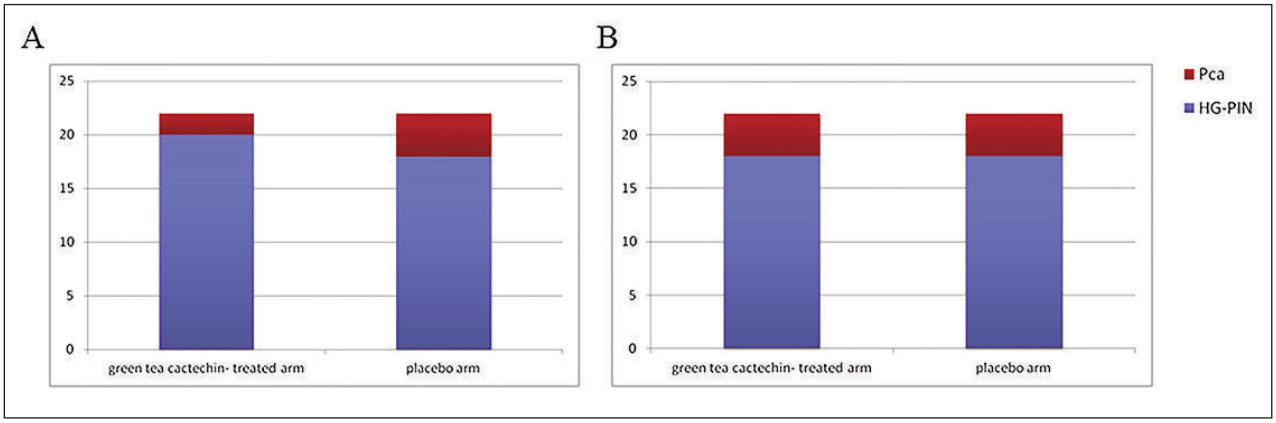

Table 2.
PSA values (ng/ml) throughout the 1-year study (mean ± SD).

	Green tea catechins-treated arm	Placebo group	P value
Time of enrolment	5.9 ± 2.3	4.7 ± 2.5	
6 months	4.9 ± 1.9	5.2 ± 2.1	N.S.
12 months	3.8 ± 1.8	5.8 ± 2.6	< 0.05

Discussion

PCa is considered the most common malignancy and the second leading cause of cancer death among men in *United States and Europe*. During its progression, cell phenotype changes from normal to severe dysplasia (high-grade prostatic intraepithelial neoplasia), to early (superficial) cancers, and finally to metastatic disease. The occurrence of latent PCa is consistently distributed, suggesting that external issues such as diet, physical

activity, and other lifestyle factors may be important in the evolution into aggressive clinical diseases (17).

HG-PIN is a premalignant condition, defined by neoplastic development of epithelial cells among pre-existing benign prostatic acini or ducts, appearing as a sort of intermediate stage between benign epithelium and malignant carcinoma. Histologically, the main difference with the prostate carcinoma is the conservation of the basement membrane, which orients pathologists in indicating an HG-PIN. On the other hand, cellular parameters can be mismatched with a carcinoma, like the prominent and abnormal nuclei, that are also characteristic in HG-PIN (18). The incidence of HG-PIN on prostatic biopsy averages approximately 15%, increasing with patient's age. Moreover, some areas of HG-PIN are frequently found around prostatic cancerous lesions and evolution into carcinoma is estimated in about 30% of cases (19). Recent literature states that 30% of men with HG-PIN would develop prostate cancer within 1 year after repeated biopsy (1). In this contest, the chemoprevention (the administration of agents to prevent the induction or to delay the progression of cancers) play an important role, trying to stop multistage carcinogenesis before its development in malignancy. PCa with its high prevalence and long latency provides a promising approach for evaluating agents for chemoprevention.

It is known that the possible protective action of green tea on PCa is due to the presence of catechins, above all EGCG, since black tea, poor of these compounds, does not play a role in prevention from PCa (20). An important clinical trial investigating the effectiveness of green tea catechins on PCa was carried out by *Bettuzzi et al.* (12), suggesting that green tea polyphenols may be effective for treating premalignant lesions before PCa develops. In this prospective, randomized, double-blind, placebo-controlled clinical trial, 60 volunteers with HG-PIN received orally 600 mg per day of green tea catechins or placebo for one year, and were subjected to medical examinations and prostate biopsies at 6 at 12 months. *Authors* concluded that green tea catechins might provide a 90% of chemoprevention efficacy. Following the same HG-PIN cohort of subject for two years (despite a considerable dropout rate), the reduction of PCa incidence in the green tea catechins arm still remained significant, thus suggesting a long lasting inhibition of cancer development achieved with one-year therapy (13).

In our study, we failed to confirm a clear association between green tea catechins and PCa chemoprevention, suggesting that the lack of effectiveness we described could be due to the somewhat small number of enrolled volunteers as well as to limited length of the study. However, results of our clinical trial are consistent with studies supporting the notion that green tea intake does not protect against prostate cancer. For instance, a prospective cohort study performed using data from a follow-up database of 27.293 of Singapore Chinese men, concluded that there was no association between daily green tea intake and prostate cancer risk, compared with no green tea intake (21). Moreover, results of a prospective cohort study that involved 19.561 Japanese men from Ohsaki to whom was self-administered a questionnaire suggested that green-tea intake did not reduce PCa (22). On the contrary, a case-control study in *China* found that green-tea intake was associated with a lower risk of prostate cancer (23), whereas a case-control study in *Japan* showed a modest reduction in PCa (24).

Borderline results were obtained also in a randomized, double-blind, placebo-controlled trial performed in men with PCa scheduled to undergo radical prostatectomy that received daily either a drug containing 800 mg green tea catechins or placebo for 3 to 6 weeks before surgery. Results of the study indicate that the treatment with green tea catechins resulted in favorable but not statistically significant changes in serum PSA as well as the proportion of subjects who had a decrease in Gleason score between biopsy and surgical specimens (25). A phase II trial aimed to estimate percentage of patients with androgen independent metastatic PCa who sustained a decline in PSA level with green tea, showed its limited capability to breakdown PSA, although no patient manifested a tumor response during the months of treatment (26). Another prospective clinical trial for hormone refractory prostate cancer indicated minimal clinical activity of green tea extract capsules in 15 men (27). Finally, a meta-analysis indicated that consumption of green tea may have a protective effect on PCa in Asian populations, suggesting that further prospective cohort studies are needed to obtain a definitive conclusion in this field, especially with regard to the protective role of green tea on PCa across different regions apart from *Asia* (20).

It is known that inflammation plays an important role in the aetiology of prostate cancer (28). On the other hand, several in vitro and in vivo studies have shown that both green tea and their catechins may inhibit carcinogenesis during the initiation, promotion and progression stages through many mechanisms, including the antioxidant effects (29). Moreover, *Mukherjee et al.* (30) reported that EGCG suppresses inflammation in prostate cancer cells, thus reducing the risk of PCa. Therefore, we speculate that the significant reduction of PSA values throughout the one-year study, as well as the not significant decrease of PCa at the 6 month follow up, we observed in our study, could be linked to the anti-inflammatory property of green tea. This hypothesis was also supported by a recent open label, phase II clinical trial carried out in 113 men diagnosed with prostate cancer randomized who received six cups daily of brewed green tea or brown tea or water for three to eight weeks prior to radical prostatectomy (31). In prostate tissue, *Henning et al.* found that green tea consumption led to a significant decrease in nuclear immunostaining of nuclear factor kappa B (NFκB) compared to water control, which may reduce inflammatory processes that may contribute to prostate cancerogenesis. Moreover, evidences of both systemic antioxidant effect (reduced urinary 8-hydroxydeoxyguanosine) and small but statistically significant decrease in PSA levels were observed. LUTS are a complex of obstructive (intermittency flow issue, incomplete voiding, weak urinary stream) and irritative (pollakiuria nocturia, urgency and burning during urination) symptoms that affect the quality of life and are quite common in men over the age of 60 years and in those with benign prostatic hyperplasia (32). Interestingly, the analysis of

questionnaires administered to subjects participating in the clinical study showed a small but not significant improvement of LUTS or QoL scores in the green tea-treated group respect to the control one. This finding supports the hypothesis that the anti-inflammatory effect of green tea catechins both can determine the reduction in blood levels of PSA and can relieve the symptoms of LUTS, thus enhancing the quality of life.

Conclusions

In recent decades, natural drugs gained particular attention mainly because of their antioxidant and anti-inflammatory activities exploitable in the prevention of certain chronic degenerative pathologies (4, 33-35). However, the increased employment of alternative and complementary medicines requires a lot of attention from the scientific community in order to evaluate the effectiveness and safety of herbal preparations since studies have cast some doubts on whether their use is really producing an alternative to synthetic drugs (5, 36, 37).
Although numerous *in vitro* and *in vivo* studies have suggested a protective effect of green-tea polyphenols against development of prostate cancer, to date this has not been unequivocally demonstrated in humans. Despite the small number of patients we enrolled and the relatively short duration of intervention, results of our clinical trial indicate that green tea catechins do not reduce the chance of a later development of PCa in men with HGPIN. However, the minor incidence of new diagnoses of PCa at 6 months follow-up (albeit not statistically significant) and the significant reduction of PSA levels at both 6 and 12 months follow-up, associated to the quite favourable trend that we observed in our clinical trial (very limited adverse effects and improvement in LUTS and quality of life) suggest that future studies with a larger cohort of men and longer durations of interventions are warranted. Moreover, the results of our trial provide a glimpse of the possibility that the green tea catechins might be useful, alone or in combination with other drugs, for the prevention or treatment of other prostatic pathologies.

Ethics approval and consent to participate

This study was approved by the *Modena Ethic Committee (Italy)* on 2007-04-10 (number 23/07) and carried out in the *Modena University Hospital (Italy)* from May 2007 to February 2011. All volunteers have been properly informed about the clinical trial and signed a free informed consent form.

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ORIGINAL PAPER

Etiological factors and management in priapism patients and attitude of emergency physicians

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Summary *Objective: To present the underlying etiological factors in patients referring with priapism, sharing how they are managed according to etiology and priapism type together with our experiences, creating awareness so that urologists and emergency physicians may play a more active role together in priapism management.*
Materials and methods: Patients referring to emergency service with priapism were examined. Penile Doppler ultrasonography (PDU) and/or corporeal aspiration and blood gas analysis were made in order to determine priapism type after anamnesis and physical examination. The most appropriate treatment option was chosen and applied on the patients considering priapism type, underlying etiological factors and priapism time.
Presence of a statistical difference between etiological factors causing priapism, priapism type and applied treatment methods was calculated using Chi square ($\chi 2$) test.
Results: A total of 51 patients referring to emergency service with priapism attacks for 53 times were included in the evaluation.When compared to other etiological factors, number of priapism cases developing secondary to papaverine after PDU was found statistically significantly high ($p < 0.001$). Ischemic priapism ratio was detected statistically higher compared to other groups ($p < 0.001$). Aspiration and/or irrigation treatment were the most common method used for treatment at a statistically significant level ($p < 0.001$). All patients (100%) were hospitalized in urology service without applying any treatment in emergency service and had treatment and intervention under the control of the urologist.
Conclusions: Application of non-invasive treatments in suitable priapism patients would protect patients from invasive painful interventions. We believe that emergency physicians should be more effective in priapism phase management and at least non-invasive treatment phase.

KEY WORDS: *Priapism; Prolonged erection; Emergency.*

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INTRODUCTION

Priapism takes its name from god *Priapus* who is the symbol of virility and fertility in ancient *Greek culture* and is constantly in the state of erection (1). Priapism is a painful erection condition of penis or clitoris lasting more than four hours without sexual desire. Glans and corpus spongiosum do not participate in this period (2). Although observed rarely, it is one of the urological emergency pathologies. It is an urgency which may result in permanent erectile dysfunction unless treated quickly. Even though the incidence is rare (0.3-1.5/100.000), it is more common in males than females. It is frequent in 20-50 age group of males (3, 4).
Although the possible causes of priapism differ according to priapism types, it is observed that they are mostly related to idiopathic and iatrogenic causes. Alcohol, medicine, drug use (21%), perineal trauma (12%) and sickle cell nephropathy (5%) are other possible etiological causes in order (4). Among iatrogenic priapism causes, penile papaverine application made for penile Doppler ultrasonography (PDU) used most commonly for erectile dysfunction diagnosis and use of phosphodiesterase 5 enzyme (PDE5) inhibitors used for erectile dysfunction treatment are responsible (5, 6). In order to be able to start priapism treatment, it is required to present priapism etiology primarily.
There are three different types of priapism: ischemic (veno-occlusive, low flow), non-ischemic (arterial, high flow) and stuttering (recurrent) priapism.
Pathophysiological causes and treatment methods of every priapism type are different (3).
Although priapism patients routinely refer to emergency service, patient management is frequently made by urologists. It is observed that generally emergency physicians demand urology consultation before intervening these patients.
The aim of this study is to present underlying etiological factors causing pathology in patients referring with priapism and sharing how these patients are managed according to the etiology and priapism type together with our experiences. At the same time, our aim was to create awareness so that emergency physicians may also actively participate in priapism management together with urologists.

MATERIALS AND METHODS

Without any relief through orgasm and ejaculation, erection state lasting longer than 4 hours was defined as priapism. Patients referring to emergency services between October 2006 and November 2016 were examined. A total of 51 patients referring to emergency service in two centers with a total of 53 priapism attacks were included

No conflict of interest declared.

in the evaluation. In the anamnesis of these patients, erection duration, previous priapism story, medicine, drug, alcohol use, phosphodiesterase type 5 inhibitor use (PDE5 inh), penile Doppler ultrasonography (PDU) story, penile papaverine and intracavernosal medicine application during or apart from PDU, presence of sickle cell anemia, trauma history, previous penile surgery, urinary system surgery and vertebra surgery story were questioned. All patients were examined physically after anamnesis. Continuation/discontinuation of erection, accompanying pain, presence of rigid erection, color of the penis, color and tissue changes for considering permanent circulation disorder in penis were evaluated. Penile Doppler ultrasonography and/or corporeal aspiration and blood gas analysis were made in order to determine priapism type. Blood count, prothrombin time and activated partial thromboplastin time were studied in order to evaluate possible hematological parameters in patients. The most appropriate treatment option was chosen and applied on the patients considering priapism type, underlying etiological factors and priapism time.

Table 1.
General information of patients.

		P value*
Number of patients	51	
Number of priapism attacks	53	
Mean age (years)	47.2 (10-69)	
Mean priapism duration (hours)	17.68 (5-104)	
Mean hospitalization duration (hours)		
	19.2 (4-215)	
Etiology (n = 51)	PDU: 31 (60.7%)	< 0.001
	PDE 5 inh.: 9 (17.6%)	
	Idiopathic: 5 (9.8%)	
	Urethral intervention: 2 (3.9%)	
	Pelvic trauma: 2 (3.9%)	
	Pelvic mass: 1 (1.88%)	
	Antipsychotic drugs: 1 (1.88%)	
Priapism type (n = 53)	Ischemic: 46 (86.7%)	
	Non-ischemic: 3 (5.6%)	
	Stutter: 4 (7.5%)	< 0.001

PDU: Penile Doppler ultrasonography;
*PDE5: Phosphodiesterase 5 enzyme inhibitors; *Chi square(χ2) test.*

Statistical analysis

Statistical analysis was performed with SPSS 15.0 for Windows version 15.0 (*SPSS Inc., Chicago, IL, USA*). Presence of a statistical difference between etiological factors causing priapism, priapism type and applied treatment methods was calculated using Chi square test (*X2*). $P < 0.05$ was used as a threshold for statistical significance.

Results

A total of 51 patients referring to emergency service in two centers with a total of 53 priapism attacks between October 2006 and November 2016 were included in the evaluation. Mean age of the patients was measured as 47.2 (10-69). Mean priapism duration was detected as 17.68 (5-104) hours. In relation to etiology, priapism was observed after Doppler ultrasonography (secondary to intracavernosal 60 mg papaverine application) in 31 patients (60.7%), after PDE5 inhibitor use in nine patients (17.6%), secondary to urethral intervention in two patients (3.9%), after pelvic trauma in two patients (3.9%), pelvic mass related in one patient (1.88%), antipsychotic drug use related in one patient (1.88%) and related to unexplainable idiopathic causes since no cause was found in five patients (9.8%). When compared to other etiological factors, number of priapism cases developing secondary to papaverine after PDU was found statistically significantly more frequent ($p < 0.001$).

According to the penile Doppler ultrasonography and/or corporeal aspiration with blood gas analysis and the patient's clinic, four out of 53 priapism attacks (7.5%) were stutter (two attacks each for two patients), three (5.6%) were non-ischemic and 46 were ischemic priapism (86.7%). Ischemic priapism ratio was detected statistically more frequently compared to other groups ($p < 0.001$).

In the etiology of non-ischemic type of patients, two patients had pelvic trauma and one patient had urethral intervention. Among two stutter type of patients, one had overdose PDE5 use and one had idiopathic etiology. General information for priapism patients are available in Table 1.

All patients (100%) had urology consultation, were hospitalized in urology service without applying any treatment in emergency service and had treatment and intervention under the control of the urologist.

During the treatment of 53 priapism attacks, one non-ischemic priapism patient with pelvic trauma etiology was treated with pudendal artery micro-embolization by interventional radiology, two patients with 4 stutter attacks were orally given pseudoephedrine 60 mg+diazepam 5 mg+ketoconazole 200 mg and two non-ischemic priapism patients were orally given pseudoephedrine 60 mg. Four ischemic priapism patients were given pseudoephedrine 60 mg+ diazepam 5 mg medical treatment. But since detumescence was not provided, corporeal aspiration and/or phenylephrine irrigation were applied to a total of 46 patients including these four patients (200 mcg/ml, maximum: 1 mg). For corporeal aspiration and irrigation, a transcavernosal 18 Gauge needle was placed percutaneously into the lateral aspect of the proximal penile shaft. Aspiration and evacuation of blood from the corpora cavernosa were performed with irrigation of normal saline followed by irrigation with phenylephrine (200 ug/mL) in saline and administered intermittently as 1.0 mL, every 3-5 min to a maximum dosage of 1 mg. Detumescence was provided in 39 patients through aspiration and/or irrigation. Spongiocavenous (distal) shunt was applied to seven patients unresponsive to aspiration and irrigation. Winter shunt and T shunt were applied as spongiocavernous shunt. Safenocavernous (proximal) shunt was applied to three patients not benefitting from this approach. Aspiration and/or irrigation treatment were the most common method used for treatment at a statistically significant

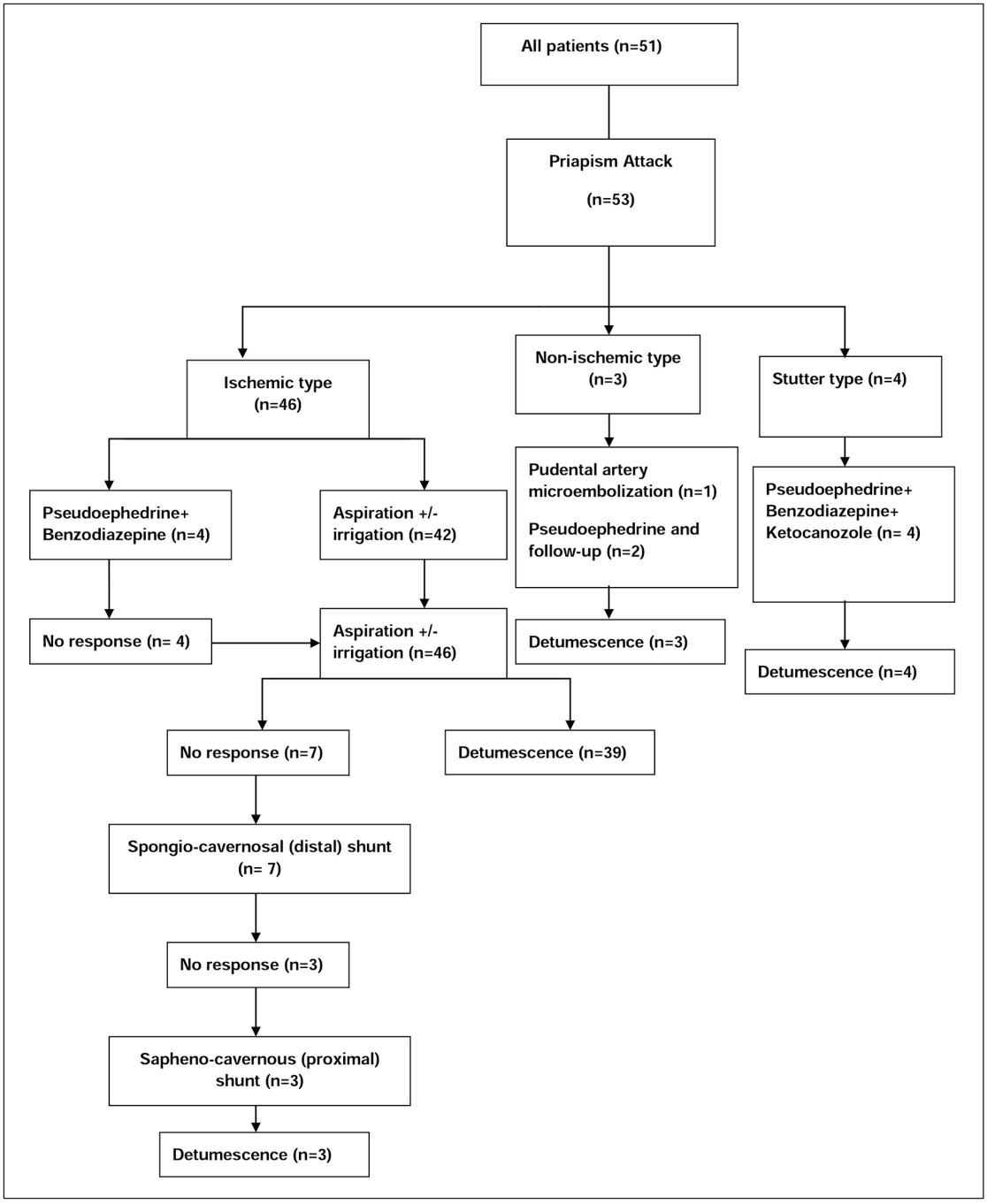

Figure 1. *Number of the patients and the study flow chart in each step.*

level ($p < 0.001$). Mean hospitalization time of the patients was measured as 19.2 hours (4-215). Number of the patients and the study flow chart in each step are demonstrated in Figure 1.

Discussion

Priapism was published in 1845 for the first time in modern medicine literature (7). Recurrent priapism was defined in 1980 together with sickle cell anemia cases (8). After that it became a pathology covering a wide range of the studies in literature.

During the first referral of priapism patient, priapism duration, possible etiological factors, previous priapism story, presence of accompanying pain should be questioned and penile Doppler ultrasonography and/or corporeal aspiration with blood gas analysis should definitely be made in order to determine priapism type (2, 3). There are three different types of priapism: ischemic (veno-occlusive, low flow), non-ischemic (arterial, high flow) and stuttering (recurrent) priapism.

Pathophysiological causes and treatment methods of every priapism type are different. There is no or very low arterial flow in corpus cavernosum in ischemic priapism (IP). In non-ischemic priapism, cavernosal flow can be normal, high or irregular and arteriosinusoidal fistule or pseudoaneurism may be observed. Stuttering priapism has repetitive, spaced erections (1-4). Ischemic priapism

is the most common type among priapism types. Ischemic priapism constitute 95% of all priapism cases. It is characterized by painful erection accompanied by significant permanent hardness in corpus cavernosum due to venous blood exit disorder. Occurrence of hypoxia, hypercapnia and acidosis is similar to penile compartment syndrome and this situation may cause tissue damage. In ischemic priapism, the ultrastructural changes in cavernosal flat muscle are observed 12 hours later, focal necrosis 24 hours later and finally necrosis and transformation of wide necrosis and fibroblast-like cells are observed 48 hours later.

Thus emergency inspection and management are required and delayed treatment may cause total erectile dysfunction (ED) (2-4). In the patient group in this study, ischemic priapism ratio was detected as 86.7%.

There is an increase in priapism cases recently due to the frequent use of phosphodiesterase 5 enzyme (PDE5) inhibitors in ED treatment and to penile Doppler ultrasonography (PDU) generally accompanied by intracavernosal papaverine injection used for erectile dysfunction (ED) diagnosis. Prolonged erections after intracavornosal injection may be seen with a ratio of 5-35% (9). In our priapism patient group, intracavernosal injection related priapism accounted for 60.7% and priapism developing after PDE 5 use for 17.6% of cases. All patients were using papaverine in priapism occurring due to intracavernosal injections. Idiopathic causes with a ratio of 9.8%, urethral intervention and pelvic trauma with 7.5%, antipsychotic drug use with 1.96% and pelvic mass with 1.96% played a role in etiology in this order. One of the most common causes of priapism is sickle cell disease (10). Interestingly, sickle cell disease was not detected as etiology in any of the patients in our group. This may be due to the fact that these patients were generally followed up by hematology department and were referred to their own hematologists or to child emergency service since they had their first attack between the ages 15 and 18 generally.

Suggestions of *European Association of Urology* guidelines and *American Urological Association* guidelines were used for the treatment of all patients (2, 11). Spontaneous resolution ratio is 62% with follow-up in non-ischemic priapism treatment and selective artery embolization can be made on demand (12). We followed up one patient with selective artery embolization and two patients with pseudoephedrine treatment in this group.

A complete response was obtained in all three patients. It is recommended to manage stutter priapism like priapism (13).

Medical agents such as pseudoephedrine, ketoconazole, GnRh agonists and 5-alpha reductase inhibitors were used for priapism attack and for preventing the attack (2, 12, 14).

We applied pseudoephedrine+benzodiazepine+ketoconazole medical treatment for our stutter priapism patients and we were successful in the treatment of four attacks. Time is important in ischemic priapism since serious complications may occur. So aspiration and/or irrigation should be the primary treatment. Primarily distal and then proximal shunt treatments should be used in irresponsive cases. Penile prosthesis may provide an effective treatment to preserve penile length in ischemic priapism patients not responding to conventional treatment (15). Penile prosthesis application was not required in any of the patients in this study.

Non-invasive treatment approaches are recommended for ischemic priapism in current studies. *Habous et al.* provided detumescence in 34% of priapism patients in 60 minutes with salbutamol 4 mg oral treatment which is a β2 adrenergic agonist (9). *Lowe* and *Jarow* compared terbutaline which is a *X*2 adrenergic agonist and pseudoephedrine which is β- and β2-adrenergic agonist in priapism patients and with a respond ratio of 38% with terbutaline and 28% with pseudoephedrine (16). Due to their antiandrogenic effect, gonadotropin-releasing hormone agonists, estrogens, anti- androgens and 5α-reductase inhibitors can also be used as non-invasive medical treatment of priapism (2, 3). We recommend the use of these medicines in early-period priapism and stutter type priapism especially. This is due to the fact that delay in ischemic priapism treatment especially may result in permanent erectile dysfunction in the patient.

Especially in case of the patient being responsive to the application of symptomatic medicines such as terbutaline, salbutamol and pseudoephedrine during the first intervention in emergency service, the patient would be saved from an invasive intervention.

Emergency physicians generally leave priapism intervention to urologists in Turkey. In our study, treatment of all patients were managed by urologists. Since patients primarily refer to emergency service for priapism which is among the important urological emergencies, we believe that emergency physicians should have a good mastery of non-invasive and invasive treatment protocols for priapism and have equipment to provide required intervention on this.

Conclusions

Underlying etiological factors and priapism type should definitely be determined before starting priapism management. Application of non-invasive treatments in suitable patients would protect patients from invasive painful interventions. We believe that emergency physicians be more effective in priapism first phase management and at least in non-invasive treatment. Deficiencies during this phase may be made up through common education programs in urology and emergency medicine clinics.

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ORIGINAL PAPER

Comparison of conventional dressings and vacuum-assisted closure in the wound therapy of Fournier's gangrene

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Summary ***Objective: The purpose of our study was to compare Vacuum-assisted closure (VAC) and conventional dressings in the wound therapy of Fournier's gangrene (FG).***
Materials and methods: The study evaluated 54 patients, retrospectively. Following initial removal of necrotic and devitalized tissue, in Group I patients the wounds were covered with conventional antiseptic dressings and patients continued to be treated with conventional dressings. In Group II patients VAC therapy was initiated. The collected data were compared between groups.
Results: The difference between two groups were statistically significant in terms of number of daily dressing (group I: 2, group II: 0,5), VAS (group I: 8, group II: 5), number of daily analgesics (group I: 4, group II: 2), number of daily narcotic analgesics (group I: 1, group II: 0), duration of mobilization per day (group I: 40, group II: 73 minutes) ($p < 0.05$).
Conclusions: Our study does not determine that a VAC therapy is better than conventional dressings in terms of clinical outcome. However, vacuum dressing appears an effective and successful method, which offers fewer dressing changes, less pain, and greater mobility comparing to conventional dressings in the management of FG patients.

KEY WORDS: *Debridement; Gangrene; Prognosis; Treatment outcome; Wound closure techniques.*

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INTRODUCTION

In 1883, *Jean Alfred Fournier* described a syndrome with necrosis of the perineum in five men; this type of necrotizing fasciitis was subsequently given his name and is known as *Fournier's gangrene* (FG) (1). FG is a potentially life-threatening progressive infection necrotizing fasciitis of the perineal, genital, or perianal regions. It is characterized by thrombosis of the nutrient vessels leading to tissue ischemia and tissue ischemia promotes infectious dissemination leading to skin necrosis. In most cases, FG is a polymicrobial infection, with both aerobic and anaerobic organisms, which originates from a urogenital, colorectal, or cutaneous source (2).
In spite of aggressive management; it is associated with high morbidity and mortality (3-67%) and a delay in diagnosis and treatment is known to increase mortality rates (3). Classical treatment consists of radical excision of all necrotic tissue, broad-spectrum antibiotics and intensive care. Usually repeated debridement is necessary. For this reason wounds of the patients remain open for a long time, and require frequent dressing. Different protocols have been proposed for postoperative open wound care: unprocessed honey, hyperbaric oxygenation, grown hormones, growing agents, and vacuum-dressing technologies (4). Vacuum-assisted closure (VAC) device (*KCI USA, Inc. San Antonio, TX USA*) is a wound care system that works on the basis of negative pressure vacuuming; removes exudate and infectious materials, reduces edema and promotes healing.
The purpose of our study was to compareVAC and conventional dressingsin the wound therapy of FG.

MATERIALS AND METHODS

The study evaluated 54 patients who diagnosed of FG and received treatment between June 2001 and October 2014 at our *Urology Department*. All data and parameters were analyzed retrospectively. FG was diagnosed by evidence of a necrotizing fasciitisin the scrotal or perineal region. Patients with a simple inflammation without involvement of the fascia, necrotizing fasciitis at other locations and patients with incomplete clinical data were excluded from the analysis.
Intravenous replacement of fluid and electrolytes, third-generation cephalosporin and metronidazole antibiotherapy were started at admission. All patients underwent surgical debridement during admission day (Figure 1). Empiric antimicrobial therapy was revised according to the results of bacterial culture and drug-sensitive tests of the removed tissue samples.
Following initial removal of necrotic and devitalized tissue, in Group I patients the wounds were covered with conventional antiseptic dressings and patients continued to be treated with conventional dressings by washing repeatedly with saline until healthy granulation tissue was formed in the wound. Wound dressings were changed twice a day. After surgical debridement, in Group II patients VAC therapy was initiated. Silver nitrate sponge was used for the wounds then drape was placed over the

No conflict of interest declared.

Figure 1.
Patient during surgical debridement with Fournier's gangrene.

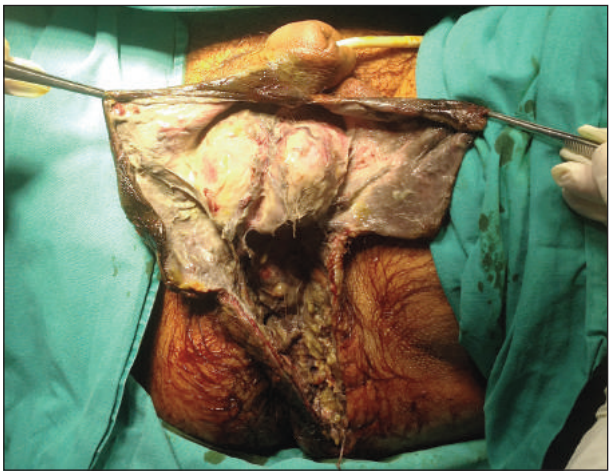
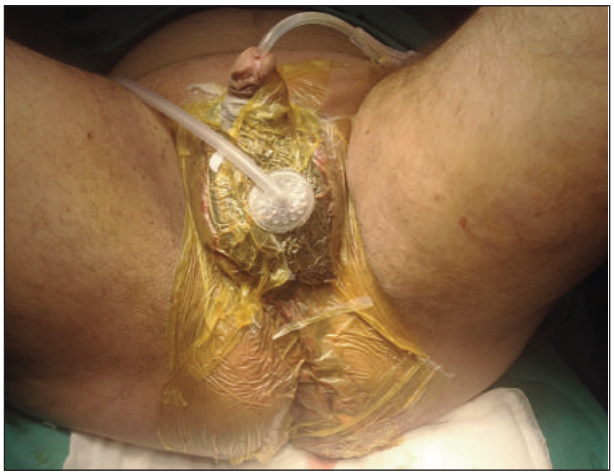


Figure 2.
VAC therapy at negative pressure.

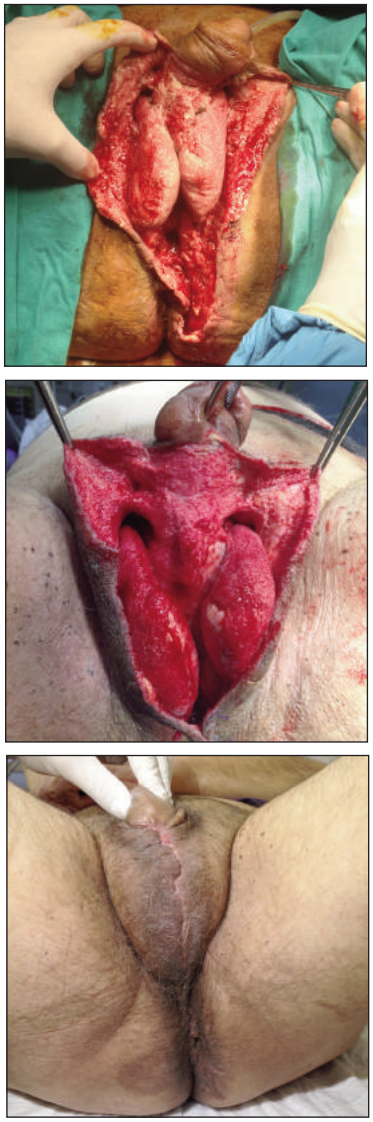


sponge, suction was inserted and continuous negative pressure was applied to the wounds (Figure 2). Initially, the pressure is set to 50 mm Hg and increased to a maximum of 125 mm Hg. VAC dressings were changed every 48-72 hours. Additional changes were performed in both groups if the dressings became wet due to blood or fluid from the wounds. In the case of progressive necrosis, surgical debridement was repeated. After the wounds were clinically healed, in small residual defects tertiary wound closure was performed; otherwise, skin flap or graft surgery was performed (Figure 3).

We collected data on patient age, gender, history of diabetes mellitus, origin, wound diameter, duration of operation, use of VAC, the number of daily dressing, visual analogue scale for pain (VAS), need for analgesics, the duration of mobilization per day, number of surgical debridement, time from initial surgical debridement to wound closure, wound closure technique, length of hospital stay (LOS), number of deaths.

The Independent-Samples t-test, the *Mann-Whitney U* test, chi-square test and Fisher's exact test were used for statistical analysis. Results were considered statistically significant if the P value was less than 0.05.

Figure 3.
Same patient as in Figure 1 and 2.



A: *After the second session of vacuum therapy.*

B: *After the third session of vacuum therapy.*

C: *Three months after wound closure.*

Results

All the 54 patients were male, with a mean age of 55.8 ± 14.9 in conventional dressings group and 61.6 ± 7.6 in VAC group ($p > 0.05$). Group I consisted of thirty-one patients and group II consisted oftwenty-three patients. The two groups were similar in the distribution of history of diabetes mellitus (Group I: 41.9%, Group II: 60.9%), wound diameter (Group I: 17, Group II: 15 cm), duration of operation (Group I: 55, Group II: 48 minutes), number of surgical debridement (Group I: 1, Group II: 2), and length of hospital stay (Group I: 14, Group II: 17 days) ($p > 0.05$). The origin of FG was anorectal diseases in 13 patients in Group I (41.9%) and 10 patients in Group II (43.5%). The other origin was urogenital diseases in 18 patients in Group I (58.1%) and 13 patients in Group II (56,5%), time from initial surgical debridement to wound closure (Group I: 12 (7-25), Group II: 13 (11-21) days) ($p > 0.05$) (Table 1).

However the difference between two groups were statistically significant in terms of number of daily dressing (Group I: 2, Group II: 0.5), VAS (Group I: 8, Group II: 5), number of daily analgesics (Group I: 4, Group II: 2),

Table 1.
Preoperative characteristics of patients.

	Conventional dressings group (n: 31)	VAC group (n: 23)	P
Mean age, years	55.8 ± 14.9	61.6 ± 7.6	> 0.05
DM	13 (41.9%)	14 (60.9%)	> 0.05
Origin (anorectal/urogenital)	13/18	10/13	> 0.05
Median wound diameter, cm	17 (10-45)	15 (9-44)	> 0.05

DM = Diabetes mellitus.

Table 2.
Clinical characteristics of patients.

	Conventional dressings group (n: 31)	VAC group (n: 23)	P
Duration of operation, minutes	55 (30-110)	48 (30-98)	> 0.05
No. of daily dressing	2 (2-3)	0.5 (0.5-1)	< 0.05
VAS	8 (4-10)	5 (4-10)	< 0.05
No. of daily anelgesics	4 (3-5)	2 (2-3)	< 0.05
No. of daily narcotic anelgesics	1 (0-2)	0 (0-1)	< 0.05
Duration of mobilization per day, minutes	40 (0-70)	73 (30-120)	< 0.05
No. of surgical debridement	1 (1-3)	2 (1-3)	> 0.05
Time from initial surgical debridement to wound closure, day	12 (7-25)	13 (11-21)	> 0.05
Wound closure technique (tertiary/flap or graft)	19/10	11/10	>0.05
Length of hospital stay, days	14 (2-32)	17 (4-32)	> 0.05
No. of deaths	2 (6.5%)	2 (8.7%)	> 0.05

VAS = Visual analogue scale for pain.

number of daily narcotic analgesics (Group I: 1, Group II: 0), duration of mobilization per day (Group I: 40, Group II: 73 minutes) ($p < 0.05$).
Wound closure was performed by tertiary closure in 19 and 11 patients among group I and group II, respectively. On the other hand, the wounds of twenty patients (Group I: 10, Group II: 10) were reconstructed with skin flap or graft ($p > 0.05$). The mortality rate was lower in the group I at 6.5% (2/31) compared with the group II, which was 8.7% (2/23). But this difference was not statistically significant ($p > 0.05$) (Table 2).

Discussion

FG is an uncommon but life-threatening condition. Males are reported to be ten times more likely than females to develop the disease.The predisposing factors include diabetes mellitus, alcohol abuse, immunodeficiency, malignant neoplasms, and liver and renal diseases. Multiple predisposing factors represent a poor prognosis and high mortality (5). The most frequent comorbidity in patients with necrotizing fasciitis is diabetes mellitus (10-60%). In the literature the incidence is highest in the sixth decade of life and patient age in our study groups was similar to that reported (6).
FG maybe the result of surgical wounds, skin abscess drainage, and pressure sores. It can also present as a complication of colorectal disease due to anorectal infection, ischiorectal abscesses, and colon perforations. Other causes include a possible urethral stricture and a trauma from an indwelling Foley catheter (7). Previous studies from general surgery departments reporting perianal abscess as the most common etiological factor (8). As a urology department we found that the most common origin of FG was urogenital diseases (57.4%).
The two groups were similar in origin of disease ($p = 1$). Timing and the extent of the first debridement are the most important risk factors in terms of increased mortality rate. The relative risk of death was 7.5 times greater in cases of restricted primary debridement (9). Surgical removal of necrotic tissue caused halting the progress of the infection and eliminating the systemic effects of necrotic material, toxins, and bacteria (10).
After initial surgical debridement, management of the wound is important, along with proper nutrition of the patient. In most cases, wounds are managed with conventional dressings that contain a wide variety of active agents such as saline, povidone iodine, potassium permanganate, *Dakin's* solution, enzymatic agents for wound cleansing, or polyhexanide.
The other proposed protocols are unprocessed honey, hyperbaric oxygenation, grown hormones, growing agents, and vacuum-dressing technologies (4).
VAC is a device used in the general surgery, orthopedic, and gynecology in wound care management. It is also applied in the management of large wounds resulting from FG. VAC therapy has several benefits with wound area reduction and formation of granulation tissue being the most prominent. Other benefits, such as effective wound cleaning and the ability to remove the exudate render VAC a promising adjuvant therapy for wound closure (7).
Since the conventional dressings require painful changes twice a day, this has a large negative impact on the patient's quality of life. Patients in the Group II reported less pain and less need for analgesics, had greater mobility, needed fewer dressing changes than the patients in the Group I. Since patients did not need significant sedation and analgesia every day, oral intake was not limited. Thus VAC therapy can be more comfortable for patients. In a study faster discharge-using VAC device was found however, in another study no difference was reported in wound healing time comparing conventional dressing with VAC (4, 11). In the present study, VAC therapy does not decrease wound healing time when compared with conventional dressing techniques. However, VAC effectively converts an open wound into a temporarily closed and controlled environment an it is possible to obtain much cleaner wounds without exudate by draining stagnant fluid and the debris. These devices stimulate angiogenesis and lead to an improvement of nourishment and tissue formation and create a favorable environment for healing in wound beds (12).
The length of hospitalization can be exacerbated by large tissue defects or sepsis-induced complications. The mean hospital stay was similar between group I (14 days) and in group II (17 days). The mean length of stay for all 54 patients was 16 days, which is shorter to the result reported by *Czymek et al.* (40 days) (13).This is due to our patients have smaller soft-tissue defects.
Death is caused by coagulopathy, acute renal failure, diabetic ketoacidosis, severe sepsis, or multi-organ failur-

erather than local tissue defects.In the present study, there was no significant difference between the groups in mortality rate (p = 1). Fifty of the 54 patients survived and the mortality rate of all patients was 7%. The deaths of these four patients were at 6, 4, 2 and 8 days. This is compatible with mortality from FG increase within the acute sepsis phase (14).

Conclusions

Our study does not determine that a VAC therapy is better than conventional dressings in terms of clinical outcome. However, vacuum dressing appears an effective and successful method, whichoffers fewer dressing changes, less pain, and greater mobility comparing to conventional dressings in the management of FG patients.The present study's outcomes should be supported by further prospective studies with a larger patient volume.

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ORIGINAL PAPER

Effect of superoxide dismutase supplementation on sperm DNA fragmentation

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Summary

Background: antioxidants supplementation improves sperm quality, but few trials have analyzed the effects on sperm DNA fragmentation (SDF). This study compares the effectiveness of SOD-based antioxidant supplementation plus hydroxytyrosol and carnosol in reducing SDF with other antioxidants without SOD, hydroxytyrosol, and carnosol.
Materials and methods: men with high SDF at baseline were selected in our clinical database. The patients taken into account had a 2-month control. SDF was measured by Sperm Chromatin Dispersion test (SCD). Untreated men were used as a control group. The remaining subjects received some oral antioxidant supplements (12 different combinations of both hydrophilic and lipophilic antioxidants), with some of them receiving nutritional support with a SOD-based antioxidant supplementation plus hydroxytyrosol and carnosol.
Results: 118 men were selected for a retrospective study. Mean age 39.3 ± 5.4 years. Fifteen had no treatment, 55 were treated with a SOD-based antioxidant supplementation plus hydroxytyrosol and carnosol, and 48 took some antioxidant supplements for 2 months. Clinically, variations of at least 10% in baseline values of classic semen parameters and sperm DNA fragmentation were taken into consideration. Classic seminal parameters did not vary significantly in the three groups, with the exception of viability (p = 0.001). We assessed which of the active substances (no. 19) in different formulations were associated with variations in SDF. In the multivariable analysis of the 7 active substances that passed the univariable analysis, only the SOD molecule appeared to be linked to an improvement in SDF (< 0.0001). In detail, only one patient in the control group showed a spontaneous improvement in SDF (6%), compared to 16/48 (33%) of those taking various oral antioxidant supplements, and 31/55 (56%) of those taking a SOD-based antioxidant supplementation plus hydroxytyrosol and carnosol.
Conclusions: SOD-based antioxidant supplementation plus hydroxytyrosol and carnosol seems to provide a better chance of improving sperm DNA integrity than other classical antioxidant molecules.

KEY WORDS: *Sperm DNA fragmentation: Male infertility; Superoxide dismutase; Hydroxytyrosol; Carnosol.*

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INTRODUCTION

Sperm DNA fragmentation (SDF) is an important factor in the etiology of male infertility. SDF negatively correlates with pregnancy in natural cycles (1), intrauterine inseminations (2), and *in-vitro* procedures (3). SDF is also associated with recurrent miscarriage (4), both during in-vivo and in-vitro procedures. It is well known that SDF may be present in men with both normal and abnormal semen analysis (5) and that infertile men have higher proportions of sperm with DNA damage compared to fertile men (6). *Cohen-Bacrie et al.* (2009) (7) found elevated levels of sperm DNA damage in over 60% of men attending fertility clinics, with 30% being severe. Because conventional semen analysis is a poor predictor of sperm DNA damage (8), SDF assays have been suggested in selected cases of infertility, e.g. unexplained infertility, recurrent miscarriages, and asthenoteratozoospermia.
Abortive apoptosis, infection, defective spermatogenesis, and oxidative stress (OS) are thought to be causes of SDF (9), with the latter being the most common cause (10). Oxidative stress occurs when reactive oxygen species (ROS) overcome the semen's natural antioxidant defenses. In physiological conditions, oxidative stress is suitably balanced by the action of endogenous enzymatic antioxidants, including superoxide dismutase (SOD), catalase, and glutathione peroxidase/reductase, as well as non-enzymatic antioxidants such as ascorbate, urate, vitamin E, pyruvate, glutathione, albumin, vitamin A, ubiquinol, taurine, and hypotaurine (11). These endogenous antioxidants scavenge both intracellular and extracellular superoxide radicals, preventing the lipid peroxidation of plasma membranes (12). Pathological stressors that generate endogenous ROS include infections, varicocele, aging, cancer, drugs, cigarette smoking, obesity, pharmaceutics, industrial chemicals, radio-frequency electromagnetic radiation and, lastly, abnormal spermatozoa (13, 14). All these stressors decrease sperm motility and viability, while stimulating DNA base adduct formation and, ultimately, DNA fragmentation.
Physiologically, homeostasis between free radicals and antioxidant substances is guaranteed by very complex systems. The most efficient seems to be the system mediated by the Nrf2 (*Nuclear factor [erythroid-derived 2]-like 2 transcription factor*) pathway. The latter regulates a wide variety of antioxidant cytoprotective enzymes through a promotion sequence known as ARE (antioxidant response element) (15).

No conflict of interest declared.

At present, several tests have been developed to evaluate sperm DNA fragmentation. These include the *Sperm Chromatin Dispersion test* (SCD) (16), a simple and inexpensive test for basic diagnosis in clinical practice. When no clear SDF etiological factors exist, antioxidants drugs are empirically prescribed (17, 18). Numerous combinations of hydrophilic and lipophilic antioxidants are available in drugstores and online, e.g. vitamin C, vitamin E, folic acid, DHA, L-acetyl carnitine, L-carnitine, astaxanthin, ethyl cysteine, coenzyme Q10, zinc, and selenium. In view of the fact that recent *in-vitro* and *in-vivo* trials support the theory that Nrf2 activation strategies could effectively combat oxidative stress, the purpose of our retrospective study is to match the effectiveness of SOD-based antioxidant therapy plus hydroxytyrosol and carnosol (*FertiPlus® SOD*) in reducing sperm DNA fragmentation with other antioxidants without SOD, hydroxytyrosol, and carnosol.

Materials and methods

Selection of participants and data collection

Male partners of infertile couples referred to our *Fertility Center* were selected by a query in our clinical database (June 2014 - November 2016). Inclusion criteria were oligo-normozoospermia, according to the 2010 *World Health Organization criteria for the Evaluation of Human Semen (5th Edition)* (19); Sperm DNA fragmentation > 15%; no current seminal infections according to sperm culture and/or seminal leucocyte (< 10^6 x ml); no sperm antibodies (*Sperm Mar IgG; Ferti Pro, N.V., Origio, Florence, Italy*); no varicocele. These patients had i) mildly or severely high levels of DNA fragmentation at baseline examination and ii) SCD control after 2 months.
The medical histories of all patients were taken into consideration and physical examinations plus ultrasonography of reproductive apparatus were conducted by three clinical andrologists (LN, RB and AP). Semen analyses, as well hormone profiles, were evaluated in our hospital. The presence of previous cryptorchidism, long-term medication use (e.g. selective serotonin reuptake inhibitors, tranquilizers, antihypertensives, substances for the prevention of fatty acid metabolism disorders, mesalazine), and idiopathic hypogonadism were not considered exclusion factors as they are representative of everyday real-life clinical practice. Table 1 shows the clinical characteristics of patients.
This retrospective study was approved by our hospital's *Institutional Ethical Committee* and all patients provided written informed consent for the scientific use of their clinical data. The primary endpoint of the study was to analyze the improvement in sperm integrity (SDF reduction) after antioxidant oral supplementation. The secondary endpoints were the effects on classic semen parameters (sperm count, progressive motility, normal forms, viability) and the presence of adverse events. Pregnancy, miscarriage, and live birth rates were not considered due to the short duration of treatment (2 months).

Table 1.
Conventional seminal parameters and clinical characteristics of patients - TPMC means total progressively motile sperm count [(volume x sperm concentration x progressive motility)/10^8].

	At baseline	2 Months control	P
Patients	118	118	
Infertility duration (months)	32.9 ± 24.8		
Male age (yrs.)	39.4 ± 5.4		
Female age (yrs.)	35.1 ± 4.3		
Male BMI	25.7 ± 3.0		
Total orchidometry (ml)	28.7 ± 8.2		
Active smoking	27 (22.88%)		
FSH (mu/ml)	5.43 ± 3.07		
Comorbidities	35 (29.66%)		
Medication use	25 (21.19%)		
Semen volume (ml)	3.52 ± 1.51	3.43 ± 1.55	0.393
Total sperm count (106)	70.4 ± 63.2	80.9 ± 78.4	0.159
TPMC (106)	13.9 ± 15.4	17.2 ± 20.0	0.160
Progressive motility (%)	18.3 ± 10.2	19.3 ± 11.4	0.738
Normal forms (%)	3.49 ± 2.09	3.64 ± 1.86	0.334
Viability (%)	63.6 ± 11.9	66.6 ± 10.4	0.014

Semen processing

Semen samples were obtained in a collection room located in the same facility as the andrology laboratory after 3-5 days of sexual abstinence. After liquefaction at 37°C in sterile cups, seminal volume and pH, sperm concentration, motility, morphology, and viability were evaluated according to *World Health Organization guidelines (2010)* (19). We analyzed the total sperm count instead of the concentration/ml, as it is more representative of actual testicular function.

SCD test

The method used was *Halosperm G2®* (*Halotech, Madrid, Spain*), in keeping with the manufacturer's protocol (*http://www.halotechdna.com/wp-content/uploads/2015/04/IU-halosperm-G2_10det_v2.pdf*). The SCD test is based on the principle that sperm with fragmented DNA fail to produce the characteristic halo of dispersed DNA loops observed in sperm with non-fragmented DNA, following acid denaturation and removal of nuclear proteins. Sperm cells with very small halos or without halos are to be considered as containing fragmented DNA.
The extent of DNA damage for each semen sample is expressed as the sperm DNA fragmentation index (SDF). In humans, a threshold of 30% SDF is suggested as a cut-off to distinguish between a potentially fertile vs infertile semen sample, although a threshold of 18% has been suggested as predictive of a poor fertilization rate. In order to understand whether the patient achieved a clinically useful improvement in SDF, we arbitrarily selected a cut-off of 10% DNA fragmentation percentage change, calculated as:

Statistics

The data were described as number and percentage, or mean and standard deviation, as appropriate. Differences were explored with the Wilcoxon test for paired data when comparing data at baseline and 2 months control, or the Kruskal-Wallis test when comparing improvements in SDF or integrator type. The association between the percentage variation and the commercial product

was explored with an univariable linear regression; all the products with a p less than 0.1 were then subjected to a multivariable linear regression.
All analyses were made with stata13 software (*StataCorp LP, 4905 Lakeway Drive, College Station, TX 77845, USA*). A $p < 0.05$ was considered as significant.

Results

118 male partners of infertile couples treated from June 2014 - November 2016 were selected for a retrospective study. Mean age was 39.3 ± 5.4 years, infertility duration was 32.9 ± 24.8 months. Female age on examination was 35.1 ± 4.3 years. Conventional seminal parameters and clinical characteristics of patients are reported in Table 1. None of the patients reported any adverse events after oral antioxidant supplementation.
Of these men, 15 had received no medical or surgical treatment and were used as a control group.
The remaining 103 had received some oral antioxidant supplementation (12 different combinations of both hydrophilic and lipophilic antioxidants), whose composition is shown in Table 2. Fifty-five were treated with SOD-based antioxidant *FertiPlus® SOD*, whose formulation contains *ORISOD®*, *Extramel®*, α-lipoic acid, glutathione, folic acid, zinc, and vitamins B2, B3, B6, B12. *FertiPlus® SOD* is a balanced combination of enzymatic and non-enzymatic antioxidants (*SOD micro encapsulated [Extramel®]*), alpha lipoic acid, glutathione (low dose), zinc, B vitamins, a micronutrient complex (*ORISOD®*) containing substances of plant origin, hydroxytyrosol, and carnosol, identified as substances able to activate the antioxidant system and detoxify intracellular endogenous NRF-2 (nuclear transcription factor-erythroid 2).
Five patients had a clinical history of juvenile orchidopexy and one had a history of previous unilateral seminoma without chemoradiotherapy; one had testicular microlithiasis, one reported a low birth weight, one had unilateral absence of the vas deferens and ipsilateral renal agenesis, and one had unilateral testicular torsion without antisperm antibodies. Another 25 patients were taking medication for anxiety and depression (n. 1), asthma (n. 6), Behçet's disease (n. 1), gastroesophageal reflux (n. 5), nasal polyposis (n. 1), hypertension (n. 3), hypothyroidism (n. 1), Crohn's disease (n. 1), juvenile diabetes (n. 1), epilepsy (n. 1), mild chronic renal insufficiency (n. 1), hypercholesterolemia (n. 1), and pudendal nerve entrapment (n. 1). One patient was using cannabis.
We then assessed which of the active substances were associated with variations in DNA fragmentation, individually considered and corrected on an individual basis for the statistically significant cases. The results are shown in Table 2. In the multivariable analysis of the seven active substances that passed the univariable analysis, only the SOD molecule appears to be linked to an improvement in SDF.
Clinically, variations of at least 10% in baseline values of classic semen parameters and sperm DNA fragmentation were taken into consideration. Variations between the two limits were not considered clinically relevant. Table 3a shows the clinical and seminal parameters compared to the percentage change in SDF. No seminal parameters were associated with the variation in DNA fragmentation, except for the improvement in sperm viability ($p = 0.001$) and, to a slight extent, the improvement in progressive motility ($p = 0.07$). The distribution of comorbidities and medication use is homogeneous in the three analyzed groups. Furthermore, no differences in age, BMI, active smoking, FSH, and total testicular volume were observed in the three groups. Classic seminal parameters (total sperm count, progressive motility, and morphology) do

Ingredients	Commercial products (n. 12)	No. patients (n. 118)	Absent (mean ± SD)	Present (mean ± SD)	P (univariable)	P (multivariable)
Vit. E	7	28	6.96 ± 27.83	-4.66 ± 28.47	0.1189	
Vit. C	6	33	7.21 ± 26.90	-3.57 ± 30.69	0.0920	0.2505
Zinc	6	82	-7.54 ± 28.93	9.36 ± 26.60	0.0024	0.3565
Arginine	6	23	6.18 ± 28.64	-3.96 ± 25.84	0.1404	
Selenium	5	16	5.87 ± 28.44	-6.43 ± 25.74	0.1141	
L-carnitine	5	17	5.57 ± 28.11	-3.91 ± 28.90	0.2902	
Folic acid	5	71	-7.36 ± 27.23	11.86 ± 26.50	0.0002	0.6156
Coenzyme Q10	3	17	5.3 ± 29.63	-3.70 ± 17.11	0.1341	
Inositol	3	8	5.18 ± 27.90	-9.30 ± 32.36	0.2702	
Vit. B	2	57	-6.54 ± 26.55	15.69 ± 25.65	< 0.0001	0.2226
Astaxanthine	2	8	4.77 ± 28.85	-3.56 ± 18.80	0.2941	
α-lipoic acid	2	57	-6.54 ± 26.55	15.69 ± 25.65	< 0.0001	-*
DHA	2	8	4.33 ± 28.04	2.47 ± 33.80	0.4799	
SOD	1	55	-7.13 ± 26.65	17.18 ± 24.46	< 0.0001	< 0.0001
L-taurine	1	12	4.81 ± 27.78	-1.14 ± 33.47	0.7997	
Aspartic acid	1	10	5.02 ± 28.95	-4.60 ± 18.90	0.2308	
Glutathione	1	60	-7.06 ± 25.45	15.09 ± 26.78	< 0.0001	0.6537
Tryptophan	1	2	4.71 ± 28.11	-25.06 ± 33.09	0.1961	
Maca	1	6	4.22 ± 27.98	3.93 ± 36.88	0.5648	
Any treatment		103	-16.15 ± 22.39	7.17 ± 27.93	0.0028	

** α-lipoic acid omitted from multivariable analysis for collinearity.*

Table 2.
The table lists the substances contained in 12 commercial products.
The second column shows the number of prescriptions in the 103 patients evaluated in the study.
The fourth and fifth columns report the percentage variation in DNA fragmentation for each individual active substance. Data are expressed as mean ± SD.

	SDF variation			
	> 10% deterioration	Unchanged	> 10% improvement	P
N	36	34	48	
Male age (yrs.)	38.6 ± 4.2	39.9 ± 4.8	39.6 ± 6.5	0.640
Female age (yrs.)	35.2 ± 4.3	34.8 ± 4.2	35.1 ± 4.4	0.923
Male BMI	25.5 ± 2.9	26.1 ± 2.8	25.5 ± 3.2	0.364
Total orchidometry (ml)	30.6 ± 7.9	27.8 ± 8.8	27.8 ± 7.9	0.302
Infertility duration (months)	32.8 ± 28.6	33.7 ± 22.7	32.5 ± 23.7	0.587
Active smoking	6 (16.67%)	7 (20.59%)	14 (29.17%)	0.419
FSH (mu/ml)	5.20 ± 2.90	5.87 ± 3.53	5.28 ± 2.87	0.512
Medication use	6 (16.67%)	6 (17.65%)	13 (27.08%)	0.471
Comorbidities	8 (22.22%)	9 (26.47%)	18 (37.50%)	0.296
Antioxidants				< 0.001
None	8 (22.22%)	6 (17.65%)	1 (2.08%)	
Other	21 (58.33%)	11 (32.35%)	16 (33.33%)	
SOD	7 (19.44%)	17 (50.00%)	31 (64.58%)	
Baseline semen volume (ml)	3.47 ± 1.40	3.65 ± 1.68	3.45 ± 1.50	0.918
Δ Semen volume (%)	11.5 ± 28.7	2.5 ± 34.7	-5.6 ± 28.1	0.025
Baseline total sperm count (106)	80.2 ± 79.1	57.1 ± 52.2	72.4 ± 56.3	0.299
Δ Total sperm count (%)	68.4 ± 163.1	18.3 ± 77.5	16.0 ± 68.9	0.307
Baseline TPMC (106)	17.1 ± 19.7	10.3 ± 9.5	14.1 ± 14.8	0.4971
Δ TPMC (%)	98.6 ± 179.1	27.0 ± 124.1	83.9 ± 269.7	0.204
Baseline progressive motility (%)	19.8 ± 11.5	17.0 ± 7.7	18.3 ± 10.8	0.6110
Δ Progressive motility (%)	11.8 ± 55.0	-3.4 ± 43.4	43.3 ± 115.6	0.074
Baseline normal forms (%)	3.36 ± 2.17	3.32 ± 2.40	3.71 ± 1.82	0.2039
Δ Normal forms (%)	10.2 ± 54.0	25.0 ± 70.0	54.6 ± 161.0	0.717
Baseline viability	63.4 ± 11.6	65.5 ± 8.2	62.4 ± 14.2	0.8646
Δ Viability (%)	2.9 ± 21.9	-0.4 ± 12.5	20.0 ± 47.5	0.001

Table 3a.
Clinical and seminal parameters compared to the percentage change in SDF.
The Δ are calculated as (post-pre)/pre and expressed as a percentage.

	No drugs	Other drugs	SOD	P
N	15	48	55	
Male age (yrs.)	38.7 ± 4.4	38.9 ± 5.5	40.0 ± 5.6	0.454
Female age (yrs.)	34.3 ± 5.2	35.1 ± 3.5	35.2 ± 4.6	0.709
Male BMI	24.8 ± 2.1	25.6 ± 2.7	26.0 ± 3.4	0.441
Total orchidometry (ml)	30.7 ± 7.4	29.6 ± 8.9	27.3 ± 7.7	0.421
Infertility duration (months)	34.7 ± 21.5	32.3 ± 24.8	33 ± 26.1	0.754
Active smoking	1 (6.67%)	14 (29.17%)	12 (21.82%)	0.202
FSH (mu/ml)	4.39 ± 1.16	5.72 ± 3.59	5.46 ± 2.91	0.464
Medication use	3 (20.00%)	12 (25.00%)	10 (18.18%)	0.703
Comorbidities	3 (20.00%)	13 (27.08%)	19 (34.55%)	0.521
Baseline SDF	34.9 ± 12.5	37.0 ± 9.5	40.0 ± 12.6	0.3728
Δ SDF (%)	16.1 ± 22.4	4.3 ± 27.5	-17.2 ± 24.5	< 0.001
Baseline semen volume (ml)	3.64 ± 1.26	3.60 ± 1.55	3.40 ± 1.56	0.639
Δ Semen volume (%)	8.7 ± 27.5	2.5 ± 31.4	-0.5 ± 31.5	0.596
Baseline total sperm count (106)	76.4 ± 90.0	62.4 ± 50.8	75.7 ± 64.9	0.825
Δ Total sperm count (%)	52.1 ± 78.2	45.5 ± 145.4	16.1 ± 75.7	0.165
Baseline TPMC (106)	15.1 ± 15.7	11.8 ± 11.7	15.5 ± 17.9	0.857
Δ TPMC (%)	74.6 ± 144.5	63.1 ± 155.4	79.0 ± 263.4	0.644
Baseline progressive motility (%)	22.2 ± 13.4	17.7 ± 8.5	17.9 ± 10.6	0.473
Δ Progressive motility (%)	11.1 ± 57.1	9.2 ± 49.2	32.2 ± 111.7	0.529
Baseline normal forms (%)	2.53 ± 1.41	3.60 ± 2.16	3.65 ± 2.15	0.229
Δ Normal forms (%)	45.5 ± 98.1	15.1 ± 58.9	44.9 ± 150.3	0.483
Baseline viability	68.1 ± 11.0	63.6 ± 10.1	62.4 ± 13.5	0.161
Δ Viability (%)	-5.8 ± 11.4	6.8 ± 17.8	14.6 ± 46.4	0.029

Table 3b.
Clinical and seminal parameters in the three groups. Classic seminal parameters (total sperm count, progressive motility, and morphology) do not vary significantly in the three groups, except for viability and SDF, showing an improvement in the group receiving SOD-
The Δ are calculated as (post-pre)/pre and are expressed as a percentage.

not vary significantly in the three groups, except for SDF, showing an improvement in the group receiving SOD (Table 3b). In particular the post-hoc evalution of SDF variation test power (*by Cohen's d*) is greater than 0.98 confirming the adeguacy of sample size. In greater detail, only one patient in the control group showed a spontaneous improvement in SDF (6%), compared to 16/48 (33%) of those taking various oral antioxidant supple-

ments and 31/55 (56%) of those taking oral antioxidant supplements with SOD. Nevertheless, it should be considered that although fragmentation can also improve spontaneously in patients with risk factors for comorbidities or drug therapy, the positive impact of the integrator administration persists, succeeding in combatting the oxidative damage caused by free radicals and highly reactive oxygen species, which have been identified as the agents responsible for sperm DNA damage.

Discussion

It is believed that about 80 million people worldwide are affected by the inability to have children (20), with male factor subfertility accounting for up to 50% of these cases (21). Some 30-80% of male factor subfertility cases are believed to be due to the damaging effects of oxidative stress (21). Oral supplementation with antioxidants is thought to improve sperm quality by reducing oxidative stress (22) and these products are widely available and inexpensive when compared to other fertility treatments. This suggestion is so widely spread by the media that, currently, a high percentage of couples turning to our *Fertility Center* are already taking antioxidants, prescribed by gynecologists, general practitioners, or even self-prescribed.

At present, several tests have been developed to evaluate sperm DNA fragmentation, e.g. TUNEL (*TdT-mediated dUTP nick-end labeling*) (23), *Comet Assay* (24), *Sperm Chromatin Structure Assay* (SCSA) (25) and *Sperm Chromatin Dispersion test* (SCD) (16). While TUNEL and Comet Assay directly detect DNA damage (the latter also finding single and double strand breaks), SCSA and SCD measure DNA fragmentation after a mild denaturation process. TUNEL and SCSA employ flow cytometry, with little intra-technician variability. However, they are complex, time consuming, and expensive (flow cytometer). *Comet Assay* is not suited for rapid diagnosis and requires highly specialized personnel to analyze the results.

The SCD test is a simple and inexpensive technique, but could have higher intra-individual variation.

There are currently six meta-analyses of antioxidant treatment for male infertility available (22, 26-30) and all report improvements in pregnancy rate and sperm quality after therapy. *Ross et al.* (2010) (29) report improvement in at least one semen variable in 13 out of 17 studies analyzed. In a more recent Cochrane meta-analysis (22), comprising 48 studies, 4.179 men were analyzed; of these, 2.466 received oral antioxidant supplementation and 1.713 received no treatment. The patient population was made up of the male partners of couples who had attended a fertility clinic. Surprisingly, only two trials performed on a total of 100 patients (64 + 36) analyzed the effects of oral antioxidant supplementation on SDF (31, 32) and both observed a reduction in SDF when compared to placebo (mean difference: -13.85, 95% CI -17.28 to -10.41, $P < 0.00001$). One investigator used vitamin C + vitamin E, while the other used docosahexaenoic acid (DHA). *Menezo et al.* (2007) (33) (not included in the meta-analysis) treated 58 men with an SDF > 15% with oral antioxidant therapy (vitamins C and E, beta carotene, zinc and selenium) for 13 weeks and reported a significant improvement in DNA fragmentation (-19.1%, $p < 0.0004$).

Our data are not all consistent with those reported in literature, not providing a significant improvement in classic seminal parameters (total sperm count, progressive motility, and morphology). Basic semen parameters do not vary significantly in the three groups (antioxidants, *FertiPlus® SOD*, no medication), except as regards viability. The reasons may be related to the older age of our population (39.4 ± 5.4 yrs.), which reflects the later age at which couples are deciding to have children. Secondly, the selection of patients was as close as possible to everyday real-life clinical practice. Indeed, we only excluded patients with varicocele and seminal infections, as diseases associated with SDF, but susceptible to effective specific treatment (antibiotics and surgery). Patients with antisperm antibodies were excluded as in other studies, although the two available cases did not have a high degree of DNA fragmentation (data not shown). Most of the studies published to date did not enroll men with a considerable number of risk factors, such as smoking, recreational drug use, systemic diseases, long-term medication use, alcohol, oligozoospermia, high serum gonadotropins, previous orchidopexy, and anatomic abnormalities of the genital tract. While this approach permits a better appreciation of the effect of medical treatment, it also drastically reduces the number of candidates for oral antioxidant treatment. At our *Fertility Center*, perfectly healthy, young patients without any bad habits are really very few.

Our selection criteria could, therefore, justify unsatisfactory results in terms of classic sperm parameters. Antioxidants not containing SOD led to an improvement of at least 10% in TPMC in 43.8% patients vs 45.5% in men treated with *FertiPlus® SOD* (n.s.). In the same two groups sperm morphology increased by at least 10% to 31.3% and 36.4%, n.s.), respectively, while oral antioxidant supplementation proved effective in reducing sperm DNA fragmentation. As mentioned in the Results section, only one patient in the control group showed a spontaneous improvement in SDF (6%), compared to 16/48 (33%) of those taking various oral antioxidant supplements and 31/55 (56%) of those taking oral antioxidant supplements with SOD ($p < 0.0001$).

From a clinical viewpoint, the possibility to reduce sperm DNA fragmentation in 56% of otherwise untreatable infertile patients is certainly an ethically and economically sound approach. We must therefore consider that almost one quarter of our patients had untreatable diseases, requiring long-term treatment; 13 had high FSH (7.6-21.1 mu/ml), 17 had a testicular volume of less than 12 ml, 10 had class 1 obesity, and 27 were active smokers. Nevertheless, we were surprised to observe that the presence of co-morbidities, signs of testicular impairment and bad habits did not affect the chances of improving DNA fragmentation.

While oral SOD supplementation seems to work better than any other antioxidant molecules analyzed, it remains unclear why the benefit is observed in just over half of the cases treated. One could assume that 2 months intake are insufficient to fully express the therapeutic effect. Another possible explanation may be that antioxidant therapy could be ineffective if given to males whose subfertility is not caused by oxidative stress (34) and, in this respect, no

patients underwent an objective test indicating that oxidative stress was the key factor behind their condition. Our study has a number of limitations. Firstly, it is retrospective, meaning that neither a causality hypothesis nor mechanistic models can be drawn up due to the nature of our study. Secondly, the data derive from patients entering an IVF-ICSI program, who could have different characteristics from the general male population. In addition, another limitation is the low number of subjects examined. Lastly, the seminal OS levels were not assessed. Although to be confirmed in a randomised trial this result is a new and relevant data in patient's counselling.

Conclusions

Oral SOD supplementation appears to produce a better reduction in sperm DNA fragmentation in the infertile population than other commonly used antioxidant formulations. When used in unselected infertile patients, representative of daily clinical practice, *FertiPlus® SOD* reduces DNA fragmentation in 56% of cases compared to 33% of cases using other antioxidant formulations. Therefore, given the absolute tolerability of the product and the affordable cost, this approach is to be considered clinically and ethically acceptable.

Author contributions

NL provided the study design concept, drafted the article and interpreted the data.
NL, RB and AP recruited the subjects, compiled the medical records, performed physical examinations and the color-Doppler ultrasound evaluations.
EM performed the SCD test and semen analyses
EM performed the statistical analyses
PELS made a substantial contribution to critically revising the article.

Ethics approval and consent to participate

We declare that our study has been conducted according to the Helsinki Declaration on clinical research and to the Ethical Code on animal research set forth by WHO (*WHO Chronicle 1985; 39:51*) and that has been approved by *IRCCS Istituto Clinico Humanitas INDEPENDENT ETHICS COMMITTEE*, reference number 1/17, on January 17, 2017. A written informed consent was obtained from each participant before study.

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ORIGINAL PAPER

Investigation of the effect of body mass index (BMI) on semen parameters and male reproductive system hormones

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Summary

Aim: *To evaluate the effects of body mass index (BMI) ratio on semen parameters and serum reproductive hormones.*

Materials and methods: *The data of 454 patients who prsented to male infertility clinics in our hospital between 2014 and 2015 were analyzed retrospectively. Weight, height, serum hormone levels and semen analysis results of the patients were obtained. BMI values were calculated by using the weight and height values of the patients and they were classified as group 1 for BMI values ≤ 25 kg/m^2, as group 2 for BMI values 25-30 kg/m^2 and as group 3 for BMI values ≥ 30 kg/m^2.*

Results: *The mean values of BMI, semen volume, concentration, total motility, progressive motility, total progressive motile sperm count (TPMSC), normal morphology according to Kruger, head abnormality, neck abnormality, tail abnormality, FSH, LH, prolactin, T/E2, total testosterone and estradiol parameters of the patients were considered.*

Patients were divided according to BMI values in Group 1 (n = 165), Group 2 (n = 222) and Group 3 (n = 56).

There was no statistically significant difference in terms of all variables between the groups.

Conclusions: *We analyzed the relationship between BMI level and semen parameters and reproductive hormones, demonstrating no relationship between BMI and semen parameters. In our study, BMI does not affect semen parameters although it shows negative correlation with prolactin and testosterone levels.*

KEY WORDS: *Infertility; BMI; Semen parameters; Reproductive hormones.*

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INTRODUCTION

Being overweight and obesity are among the most significant health problems in our era. *World Health Organization* (WHO) described as overweight a patient with *body mass index* (BMI) ≥ 25 kg/m^2 and as obese a patient with BMI ≥ 30 kg/m. According to WHO data, 35% of the young patients, who are in their twenties, are overweight and 11% of them are obese (1). It was reported that the overweight and obesity incidence dramatically increased in developed countries in last 30 years (2).

Infertility is another health problem affecting 15% of the couples in developed countries (3). A significant decrease in the sperm quality was shown by studies conducted in last 25 years (4, 5). The reason of this decrease aroused interest and it became a subject for research. Especially, its relation with the obesity was analyzed in a number of studies and in some studies this decrease was found as associated to the increase in obesity prevalence (2). But, there is not a consensus in the literature and contradictory results were published. In this study, we analyzed the effect of BMI on semen parameters and the relationship with reproductive hormone levels.

MATERIALS AND METHODS

The data of 454 patients who presented to male infertility clinics in our hospital between 2014 and 2015 were analyzed retrospectively. Weight, height, serum hormone levels and semen analysis results of the patients were considered. BMI values were calculated by using the weight and height values of the patients and they were classified as Group 1 for BMI values ≤ 25 kg/m^2, as Group 2 for BMI values 25-30 kg/m^2 and as Group 3 for BMI values ≥ 30 kg/m^2.

Semen analysis was performed after a 3-5 days of sexual abstinence. Semen analysis was performed according to WHO 2010 criteria (semen volume ≥ 1.5 ml; sperm concentration ≥ 15 × 106/ml; total motility ≥ 40%, progressive motility ≥ 32% and morphology ≥ 4%). After 5-30 minutes of sample collection, the analysis was performed after the sample was liquefied. For the microscopic examination in semen analysis, phase contrast light microscope was used and the examination was performed with 10 x 20 magnification. For sperm concentration, *Makler* counting chamber was used and the sperm count (concentration) was found in million/ml with the sperm count in 10 squares in a 100 square area. Motility was evaluated in 3 Groups as linear progressive motility, non-progressive motility and immotility. For the morphological examination, semen sample which was dropped on slides, washed with 70% alcohol previously, according to sperm concentration were dried with 45 degrees angle. Then, it was stained with Diff-Quick kit and at least 200 sperm were analyzed under immersion oil with 100X objective and the percentage of the sperm having normal morphology was determined.

For the hormone levels, blood sample was collected in the morning before 10.00 a.m. Hormone analysis was performed with *Roche Hitachi Cobase 601 equipment* and by using microparticle enzyme immunoassay method. FSH, LH, prolactin, total testosterone and estradiol levels were analyzed. The statistical analysis was performed with IBM *Statistical Package for Social Sciences* (SPSS) Version 22.0

No conflict of interest declared.

Parameter	BMI < 25.0 kg/m²	25.0-30.0 kg/m²	> 30.0 kg/m²	p value
BMI (kg/m²)				
Minimum	18.78	25.01	30.04	
Maximum	24.98	29.98	43.55	
Mean	22.65	27.06	33.09	
Std. Dev.	1.69	1.35	3.44	
Volume (mL)				0.330
Minimum	0	0	0	
Maximum	11	8	8	
Mean	2.88	2.69	2.58	
Std. Dev.	1.71	1.67	1.65	
Concentration (10^6/mL)				0.576
Minimum	0	0	0	
Maximum	168	170	140	
Mean	33.28	35.56	33.74	
Std. Dev.	36.91	36.29	35.59	
Total motility (%)				0.754
Minimum	0	0	0	
Maximum	85	85	90	
Mean	46.34	49.76	47.63	
Std. Dev.	25.29	22.22	27.26	
Progressive motility (%)				0.694
Minimum	0	0	0	
Maximum	80	94	80	
Mean	30.15	31.94	30.66	
Std. Dev.	21.89	21.55	22.91	
TPMSC (Million)				0.790
Minimum	0	0	0	
Maximum	352.8	361.08	220	
Mean	40.66	44.40	41.97	
Std. Dev.	59.97	62.83	56.67	
Normal morphology (Kruger) (%)				0.554
Minimum	0	0	0	
Maximum	10	9	7	
Mean	2.43	2.60	2.26	
Std. Dev.	2.23	2.12	2.00	
Head abnormality (%)				1.000
Minimum	0	0	0	
Maximum	100	91	86	
Mean	50.16	51.75	48.20	
Std. Dev.	39.93	38.41	40.82	
Neck abnormality (%)				0.937
Minimum	0	0	0	
Maximum	14	14	14	
Mean	5.72	6.15	6	
Std. Dev.	5.12	4.89	5.29	
Tail abnormality (%)				0.561
Minimum	0	0	0	
Maximum	11	13	14	
Mean	4.16	4.66	3.80	
Std. Dev.	3.86	3.94	4.02	
FSH (mIU/mL)				0.299
Minimum	1.56	1.57	1.68	
Maximum	31	44.72	17.15	
Mean	3.42	2.76	2.18	
Std. Dev.	5.58	2.18	3.74	
LH (mIU/mL)				0.452
Minimum	2	1.63	2.02	
Maximum	14.63	19.57	16.87	
Mean	5.61	5.29	6.04	
Std. Dev.	2.74	5.72	3.22	
Prolactin (ng/mL)				0.018
Minimum	3.35	2.98	5.83	
Maximum	27.85	49.29	27.04	
Mean	11.44	9.87	10.88	
Std. Dev.	5.51	5.84	4.37	
T/E ratio (%)				0.815
Minimum	6.98	2.05	8.31	
Maximum	22.16	39.13	14.87	
Mean	11.82	15.49	11.59	
Std. Dev.	8.26	9.77	4.63	
Testosterone (ng/dL)				0.001
Minimum	9.1	4.31	147.10	
Maximum	851.7	856	676.20	
Mean	488.32	398.20	377.61	
Std. Dev.	175.13	139.71	113.36	
Estradiol (pg/mL)				0.270
Minimum	16.32	7.21	32.76	
Maximum	44.24	160.30	57.29	
Mean	29.88	34.93	45.02	
Std. Dev.	9.87	37.12	17.34	

Table 1.
Mean volues of data and p values according to BMI groups.

programme. A value of $p < 0.05$ was accepted as statistically significant.

Results

The mean values of BMI, semen volume, concentration, total motility, progressive motility, *total progressive motile sperm count* (TPMSC), normal morphology according to *Kruger*, head abnormality, neck abnormality, tail abnormality, FSH, LH, prolactin, T/E2, total testosterone and estradiol parameters of the patients are shown in Table 1. Patients were divided according to BMI values in Group 1 (n = 165), Group 2 (n = 222) and Group 3 (n = 56). There was no statistically significant difference in semen parameters between the groups. BMI ratio do not affect semen parameters but it shows negative correlation with prolactin and total testosterone.

Discussion

The effect of obesity on semen parameters is multifactorial and it was tried to be explained with different pathophysiological mechanisms (6, 7).

The fact that testosterone is aromatized to estradiol (E2) in fat tissue (8), the decrease in *sex hormone binding globulin* (SHBG) levels (9), the suppression of *luteinizing hormone* (LH) secretion with the increase of endorphin levels (10), hyperinsulinemia and hyperlipidemia (11) were found as responsible for this relationship, although there are contradictory results in the literature.

In a meta-analysis conducted by *MacDonald et al.*, no relationship between semen parameters and BMI was detected (12). Moreover, in other similar original studies, this relationship was not found (13, 14). On the contrary, in a meta-analysis conducted by *Sermondade et al.*, a negative relationship between BMI and semen parameters was detected (7). There are also original studies reporting similar results (15-17). While a statistically significant negative relationship was detected between BMI and semen volume, concentration and motility in a comprehensive cohort study including 10665 patients conducted by *Belloc*

et al., no relationship with morphology was detected (18). In another study with 42 patients conducted by *Leisegang et al.*, it was reported that BMI level and sperm concentration are negatively correlated and no correlation was detected with motility and morphology (19). In a cohort study, which *Stewart et al.* conducted with 225 fertile male patients, it was reported that BMI and sperm count are negatively correlated (20). In our study, no statistically significant relationship was found between BMI level and semen parameters. In a recent study, on the other hand, the relationship between BMI and semen parameters and reproductive hormone levels was analyzed and a statistically significant negative relationship between BMI and semen volume, SHBG and total Testosterone (T) level was detected (21). In the study conducted by *Relwani et al.*, it was reported that BMI level does not affect semen parameters but it statistically significantly decreases T, SHBG and free T level (22). In the literature, there is a general consideration that obesity especially decreases total testosterone and SHBG levels but it is partially correlated to free testosterone levels (16, 23). In our study, we observed that when BMI level is high, prolactin and total testosterone levels are significantly lower.

Conclusions

In our study, when we analyzed the relationship between BMI level and semen parameters and reproductive hormones, no relationship was detected between BMI and semen parameters. On the contrary BMI level shows a negative correlation with prolactin and testosterone levels. However, to reveal the relationship between BMI and male infertility, large, randomized and prospective studies are needed.

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ORIGINAL PAPER

Evaluation of per-operative cough stress test during transobturator mid-urethral sling surgery

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This study has been presented in EAU 2015 Meeting in Madrid.

Summary ***Purpose: Currently, it is unclear how the mesh tension should be adjusted on the transobturator tape surgery (TOT) for improving continence. The aim of this study was to evaluate the effects of per-operative cough stress test on TOT.***
Materials and methods: Between March 2007 and December 2011, 206 women with SUI were enrolled in this study. Patients were randomly categorized to treatment with TOT (96) or TOT with cough stress test (110). The IIQ-7 and the UDI-6 were used to identify satisfaction level. At the end of 1st year, two groups were compared patient characteristics, operation time, duration of hospital stay, cure and complication rates.
Results: The cure rate was 84.37% 81/96) versus 83.63% (92/110) in TOT and TOT with cough test groups, respectively. Postoperatively ten patient (10/110, 9.09%) suffered voiding difficulties (> 250 ml residual urine) in TOT with cough stress test group. Five patients were discharged with transurethral catheter, whereas, in traditional TOT group, two patients (2/96, 2.1%) had transient postoperative voiding difficulty and two patients were treated with repeated catheterization for 1 week ($p < 0.05$). Postoperative groin pain was present in 7/96 (8%) versus 24/110 (22%) in TOT and TOT with cough test groups, respectively ($p < 0.05$). TOT with cough stress test group had an higher rate of complications like, retention of urine, necessitating to cut the tape, mesh erosion and pain in groin or leg. No patient had resistant voiding difficulty or prolonged urinary retention (> 1 week) in traditional TOT group.
Conclusions: We believe that per-operative cough stress test leads to overtreatment of stress urinary incontinence when the complication rates were considered.

KEY WORDS: *Cough stress test; Transobturator tape; Stress urinary incontinence (SUI).*

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INTRODUCTION

Stress urinary incontinence (SUI) is a condition of involuntary urine leakage due to increased abdominal pressure without detrusor muscle contraction and affect nearly 25% women population all around the world (1-2). Further, 4% of women will undergo SUI surgery in their lifespan (3). Since introduction of urology practise by Delorme, *transobturator tape* (TOT), has became a most preffered method for the treatment of SUI (4-5). In addition to short learning curve, decreased operative time and hospitalisation time, TOT has a high success rate up to 90% with lower complication rate (6-7). Although TOT is a safe and favorable for surgery for SUI, success of procedure is related with age, *body mass index* (BMI), diabetes mellitus, intrinsic sphincter deficiency and concomitant prolapsus surgery (8-9). Also urodynamic parameters including Q_{max}, maximum urethral closure pressure and *Valsalva* leak point pressure have effects on operation success (10). Additionally, achieve adequate mesh tension is the one of most important point to prevent urinary incontinence. For assessment of the mesh tension, *cough stress test* (CST) is used intreoperatively while TOT procedure (11). As less tension is associated with leaving the patient incontinent, more tension may cause voiding disorders (12).
In this study, we evaluated affect of CST on TOT procedure success rate and patients quality of life with using the *Incontinence Impact Questionnaire* and *Urinary Distress Inventory Questionnaire*. Also we assessed the effect of the adjustment of mesh tension with using CST on postoperative voiding disorders.

MATERIALS AND METHODS

From March 2007 to December 2011, 206 patients diagnosed with either pure SUI or mixed incontinence with predominance SUI symptoms in two urogynecologic centers were enrolled into the study. Patients were randomly categorized to two groups as TOT procedure without using CST (Group 1) and TOT procedure with using CST (Group 2).
Full medical histories and bladder diary were requested from all patients. Demographic characteristics of patients, including age, BMI, number of pregnacies and comorbidities were recorded. Physical examination including stress test and Q-tip test were performed. Urine analysis, urine culture and urinary ultrasonography for measurement of post voiding residue were completed. In the urodynamic assessment, filling cystometry, uroflowmetry and abdominal leak point pressure were evaluated before the TOT procedure. Intrinsic sphincter deficiency (ISD) was defined as maximal urethral closure pressure of 20 cm H20 or less and urethral mobility is defined as Q-tip test results of 300. The 1 h pad

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weighing test was used to define SUI as a loss of 1 gr of urine in 1 h, as explained by the EAU guidelines on urinary incontinence. Severety and impact of incontinence on quality of life were analysed by using *Incontinence Impact Questinnaire* (IIQ-7) and the *Urinary Distress Inventory* (UDI-6). Patients with overactive bladder, neurogenic bladder, immobile urethra, gynecologic malignancies and concomitant prolapsus surgeries were excluded from the study. All procedure were performed by two exprienced surgeon under spinal or epidural anesthesia. After placing mesh, mesh tension was adjusted by using a right angle clamp or long scissor. Mesh tension was assessed by CST in group 2 and if necesssary mesh tension was reduced or increased. Duration of operation, hospitalisation day, intraoperative and post operative complications were registered as well. The first day after operation, the *Foley* catheter was removed. Uroflowmetry and post voiding residue were evaluated before discharged. If patient inability of voiding or post voiding residue was > 250 cc, *Foley* catheter was indwelled again for a week. Voiding disorders were defined as postoperative voiding difficulties and pain while voiding, high post voiding residue (> 250 ml) and retention of urine needed catheterization or mesh cutting. Follow up visits were scheduled on 7th day, 1st month and 1st year. At the end of 1st year, the two groups were compared in relation to patients characteristics, operation time, cure and complication rates.

Statistical analysis

Data analysis was performed using the software SPSS® version 13.0 for Windows (*SPSS Inc., Chicago, IL, USA*). Data are presented as number, mean, and standard deviation, and comparisons were performed using the Chi-square test and Mann Whitney U test.

Results

In 96 patients TOT procedure was performed without CST (Group 1) and in other 110 patients CST was done (Group 2). The mean age and BMI of 206 patients was 52.3 ± 9.2 years and 27.8 ± 3.6 kg/m^2, respectively.

Most common comorbidities were smoking (in 52/206,25.2%) and diabetes mellitus (DM)(in 27/206, 13.1%).

Preoperative characteristics of patients and physical examination findings were summarized in Table 1.

The mean operation time was 26.4 ± 8.4 minutes. None of patients required blood transfusion. Duration of hospital stay was similar between two groups. Any lethal intraoperative or postoperative complication occured. The most common postoperative complaints were voiding difficulties and pain. Postoperatively, ten patients (9.09%) suffered voiding difficulties in group 2, five patients were discharged with transurethral catheter, whereas, in group 1, two patients (2.1%) had transient voiding difficulty and two patients were treated with repeated catheterization for 1 week ($p < 0.05$).

Postoperative groin pain was present in 7 patients (8%) versus 24 patients (22%) in group 1 and in group 2, respectively ($p < 0.05$). No patient had resistant voiding difficulty or prolonged urinary retention (> 1 week) in group 1. Mesh excision was performed in 2 patients in group 2. The mean follow up period was 16.4 (12.2-21.3) months with no significant difference between groups. The cure rate was 84.37% (81/96) versus 83.63% (92/110) in group 1 and group 2, respectively (at the end of 1st year). All women completed the IIQ-7 and UDI-6 questionnaire at the first year follow up.

The symptoms scores were significantly better at follow up, when compared to preoperative assesment (Table 2).

Table 1.
Demographic characteristics of patients.

Parameters	Mean ± standard deviation
Age (years)	52.3 ± 9.2
BMI (kg/m^2)	27.8 ± 3.6
DM	27/206 (13.1%)
Smoking	52/ 206 (25.2%)
HT	22/206 (10.67%)

Table 2.
Postoperative parameters in Group 1 and Group 2.

	Group 1	Group 2
Number of patients	96	110
Cure rate	84.37% (81/96)	83.63% (92/110)
Voiding difficulty (≥ 250 ml post voiding residue)	(2/96, 2.1%)	(10/110, 9.09%)
Postoperative pain	(7/96, 8%)	(24/110, 22%)
Mesh excision	-	2
Mesh erosion	-	1
IIQ-7		
Preoperative	22.8 ± 2.7	23.2 ± 1.9
After first week	3.8 ± 1.8	3.4 ± 1.4
After first year	2.7 ± 1.5	2.5 ± 1.2
P value	**0.001**	**0.001**
UDI-6		
Preoperative	13.7 ± 1.9	14.1 ± 1.7
After first week	1.7 ± 0.8	1.9 ± 0.9
After first year	1.9 ± 0.4	2.0 ± 0.6
P value	**0.001**	**0.001**

Discussion

According to *DeLancey* and *Asthon-Miller*, damage of pelvic floor muscle and endopelvic fascia, the supportive layer under urethra, is related with delayed closure of urethral lumen (13, 14). If abdominal pressure increase as in cough, urethra is displaced in a dorsocaudal line and the anterior edge of urethra move longer interval than posterior edge of urethra, so SUI would be occur (15). To prevent the movement of urethra and support urethra against increased abdominal pressure, polyprolen mesh is placed in the obturator foramen in TOT procedure with a route of the trocar that avoid potential complications as bladder, bowel and vessels injuries (16). *Stav et al.* demonstrated a 86% success rate after TOT surgery in their series of 1225 patients (17). Some surgeon reported up to 91% cure rate after one year follow up (18). In this study, we achive 84 % cure rate after one year follow up period.

To assess mesh tension intraoperatively, some maneu-

vers were developed. Some authors apply manual suprapubic pressure or the *Credè* maneuver on full bladder to create conditions simulating increased intra-abdominal pressure (19). However, standardization of this methods is difficult and affected by surgeon experience and patients BMI. To date, CST is the most preferred method to adjust mesh tension intraoperatively in mid urethral sling surgeries until patient does not leak urine (20). There only few reports about the effect of CST on TOT success but technique and results of CST on TVT are well described and there is no reason to believe CST will have different characteristic between TVT and TOT. *Murphy* has demonstrated significant improvement in SUI after TVT procedure with CST (21). In contrast, Lavy et al. compared women who undergone TVT with CST and without CST and reported no diffrence in success rate (22). In this study we found 84.37% (81/96) versus 83.63% (92/110) success rate of TOT without and with CST, respectively. Our results demostrated that CST does not affect on TOT success.

Voiding dysfunction is one of the most common complication of mid urethral sling surgeries that requires surgical intervention (23). However, there is no standard definition of voiding dysfunction after TOT making difficult to compare the results of different studies. In literature, postoperative retention rates in TOT were between 2.0% and 10% (1, 10, 19). According to *Ulmsten*, minimal tissue dissection, appropriate positioning of the sling and proper mesh tension were the essential for prevention of urinary retention (24). *Schreiner et al.* reported that performing *Valsalva* maneuver during preoperative assessment increased voiding dysfunction nearly seven fold (25). Similarly, we believe that intraoperative CST leads to more mesh tension with associated postoperative voiding disorders.

Preoperative urodynamic parameters are considered important to estimate TOT success and voiding disorders. *Kawashima et al.* reported that preoperative detrusor contractility failure is significantly related with postoperative voiding difficulty (26). *Dawson* found that preoperative flow urine flow and low peak urinary flow were associated with postoperative voiding disorders (27). On the other side, *Mostafa* and *Lemack* showed that there were no urodinamic parameter to predict postoperative voiding disorders (28, 29). In our study urodynamic assessment were evaluated before the TOT procedure.

Most voiding dysfunction after TOT are transient and improved with intermittent catheterization, behavioral or drug therapy (30). If these treatments fail, tape incision is the best way to solve voiding problem. However, SUI recurs in almost 60% of patients (31). In our study, among patients which had TOT performed without CST, two patients (2.1%) had transient voiding difficulties and two patient were treated with repeated catheterization for 1 week. Postoperatively ten patient (9.09%) suffered voiding difficulties in TOT with CST group and five patients were discharged with transurethral catheter. Mesh excision was performed in two patients and these patients suffered from SUI again.

Incontinence-related quality of life is measured with UDI-6 and IIQ-7, as they can be validated in the Turkish population (32). Heinonen et al. used them to assess the outcome of TOT, and confirmed a significant improvement in quality of life (33). Another large study evaluated quality of life in women who underwent TOT, with a 1-year follow-up. Postoperatively, UDI-6 and IIQ-7 were shown to be improved, so the authors concluded that the TOT procedure significantly improved health-related symptoms during daily life (34). In this study, there were benefits in postoperative scores with each assessment tool. We also concluded that TOT surgery improved quality of life at the first year follow-up.

This study had some limitations. First we did not assess preoperative incontinence grade and included it in statical analysis. Further we did not have postoperative urodinamic parameters such as detrusor pressure, flow rate and urethral resistance to compare with preoperative assessment. Small number of patients and short-term follow-up are other limitations of the study.

Our study showed that TOT is a safe and effective treatment modality for SUI. Additionally, we believe that perioperative CST leads to overtreatment of stress urinary incontinence when the complication rates were considered.

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ORIGINAL PAPER

Renal access in PNL under sonographic guidance: Do we really need to insert an open end ureteral catheter in dilated renal systems? A prospective randomized study

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Summary ***Purpose: To evaluate the true necessity of open end ureteral catheter insertion in patients with moderate to severe pelvicalyceal system dilation treated with percutaneous nephrolithotomy (PNL) under sonographic guidance.***
Patients and methods: 50 cases treated with PNL under sonographic guidance in prone position for solitary obstructing renal stones were evaluated. Patients were randomly divided into two groups; Group 1: Patients in whom a open end ureteral catheter was inserted prior to the procedure; Group 2: Patients receiving no catheter before PNL. In addition to the duration of the procedure as a whole and also all relevant stages as well, radiation exposure time, hospitalization period, mean nephrostomy tube duration, mean drop in Hb levels and all intra and postoperative complications have been evaluated. Results: Mean size of the stones was 308.5 ± 133.2 mm^2. Mean total duration of the PNL procedure in cases with open end ureteral catheter was significantly longer than the other cases ($p < 0.001$). Evaluation of the outcomes of the PNL procedures revealed no statistically significant difference between two groups regarding the stone-free rates (86% vs 84%). Additionally, there was no significant difference with respect to the duration of nephrostomy tube, hospitalization period and secondary procedures needed, complication rates as well as the post-operative Hb drop levels in both groups ($p = 0.6830$). Conclusions: Our results indicate that the placement of an open end ureteral catheter prior to a PNL procedure performed under sonographic access may not be indicated in selected cases presenting with solitary obstructing renal pelvic and/or calyceal stones.

KEY WORDS: *Percutaneous nephrolithotomy; Ureteral catheter; Renal stone; Ultrasonographic access.*

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INTRODUCTION

Following its first application in 1976, percutaneous nephrolithotomy (PNL) technique has evolved substantially over the last three decades and became the preferred choice in the management of larger stones (> 2 cm) both in adults and children (1-3). Although the procedure is safe and successful with stone-free rates of > 90 %, certain complications may develop during all stages as well as early and late follow-up period of this procedure (4-9).
Related to this subject, an appropriate initial puncture of the most desirable calyx of the kidney is of paramount importance and access can be established either under fluoroscopic and/or ultrasonographic guidance. Although fluoroscopic guidance has been used as the most common method for a long period of time, increasing experience in sonographic applications has enabled endourologists to use this method more commonly than ever to get an access to the renal collecting system. Use of sonography will allow the surgeon to identify the pelvicalyceal system as well as the surrounding organs in a safe manner (particularly in relatively dilated systems) to reduce the radiation exposure in a meaningful manner (10, 11). On the other hand, an open end ureteral catheter has been commonly used during percutaneous stone removal procedures to visualise the renal collecting system, avoiding the passage of small stone fragments into the ureteric lumen and lastly but most importantly to dilate the renal collecting system to ease the puncture when needed. Despite all these well-established advantages however, insertion of an "*open end ureteral catheter*" may certainly be associated with some possible problems. First of all, a certain injury to the urethra particularly in male cases as well as to the mucosa of the relevant ureter could be caused. Additionally, loss of time due to the insertion of the catheter first in supine position and turning of the case into prone position will further prolong the duration of the procedure (the duration of the anesthesia as well). Thus, in the light of the safe and practical renal puncture in a quick manner in dilated kidneys as well as the problems related to the placement of a catheter use of an open end ureteral catheter in all cases becomes really questionable.
In this present study we aimed to evaluate the true necessity of open end ureteral catheter insertion prior to PNL for a succesful procedure as well as the safety of renal puncture performed under sonographic guidance in patients with pelvicalyceal system dilation (Grade 2 or higher) by comparing two group of cases treated with and without insertion of an open end ureteral catheter before PNL.

PATIENTS AND METHODS

Study population

Between January 2015 and January 2017, of all the 236 cases undergoing PNL, procedure in our department, 72 patients meeting the inclusion criteria were included into study program and randomized. Upon randomization

No conflict of interest declared.

while 27 cases in Group 1 and 28 cases in Group 2 were operated with PNL technique, cases who were not operated due to some certain reasons were excluded from the study program. Moreover, 2 cases in Group 1 and 3 cases in Group 2 were lost to follow-up for several reasons and finally 50 cases (31 males, 19 females) were analyzed. Patients' enrollment algorithm has been illustrated in Figure 1.

In an attempt to assess the sample size, power analysis was made by using *G*Power (v3.1.7)* program.

Depending on the index of effect size of *Cohen*; supposing that the evaluations between two independent groups will have the highest effect size (d = 0.85), our calculations did show that at least 23 cases should be included into each group. Additionally, taking the possibility of patient drop-out risk during the study program, final number of the cases in each group has been proposed to be 25.

While cases presenting with pelvicalyceal system dilation (Grade 2 or higher) due to moderate sized solitary renal pelvic and/or calyceal stones were included into the study program, all other cases with a detectable pathology with respect to the integrity of the ureter prior to the PNL were excluded from the study program.

Patients with renal anomalies, non-dilated renal collecting systems and younger than 18 years of age were also excluded from the study program.

Study design

This study is a prospective single center, randomized clinical trial with balanced randomization [1:1] which was performed in the referral hospital *Dr. Lutfi Kirdar Kartal Training and Research Hospital*. For randomization procedure a simple randomization method by generating a random digit (0-60 in each group) has been used. Even numbers have been used for cases in whom an open end ureteral catheter was inserted and odd numbers have been used for cases whom operated without an open end ureteral catheter.

Study protocol was approved by the *Ethics Committee* of the relevant hospital (September 08, 2016-2016/514/91/3). All steps of the study were planned and applied carefully according to *Helsinki Declaration*.

All PNL procedures were performed in prone position by experienced urologists and access to the renal collecting system was performed under sonographic guidance. Depending on the placement of an open end ureteral catheter, the patients were divided into two different groups namely; Group 1: Patients in whom a 5 French (F) open end ureteral catheter was inserted prior to the procedure; Group 2: Patients not receiving an open end ureteral catheter insertion before PNL.

Following a complete biochemical and radiological evaluation; patients with urinary tract infections were treated with appropriate culture test based antibiotics.

Regarding the radiological evaluation, *ultrasonography* (USG), *kidney-ureter-bladder* (KUB) film and low-dose *computed tomography* (CT) have been performed to assess the renal anatomy, degree of hydronephrosis, position of the relevant kidney with neighboring organs and location, burden of the stone(s) to be treated. Stone area has been calculated by using the two dimensions of the stone(s) from CT images.

While the primary outcome of our study was to evaluate and compare the ultimate stone free rates after both approaches, secondary end points were the evaluation of operational duration, complication rates, mean fluoroscopy time and hospital stay period in both groups in a comparative manner.

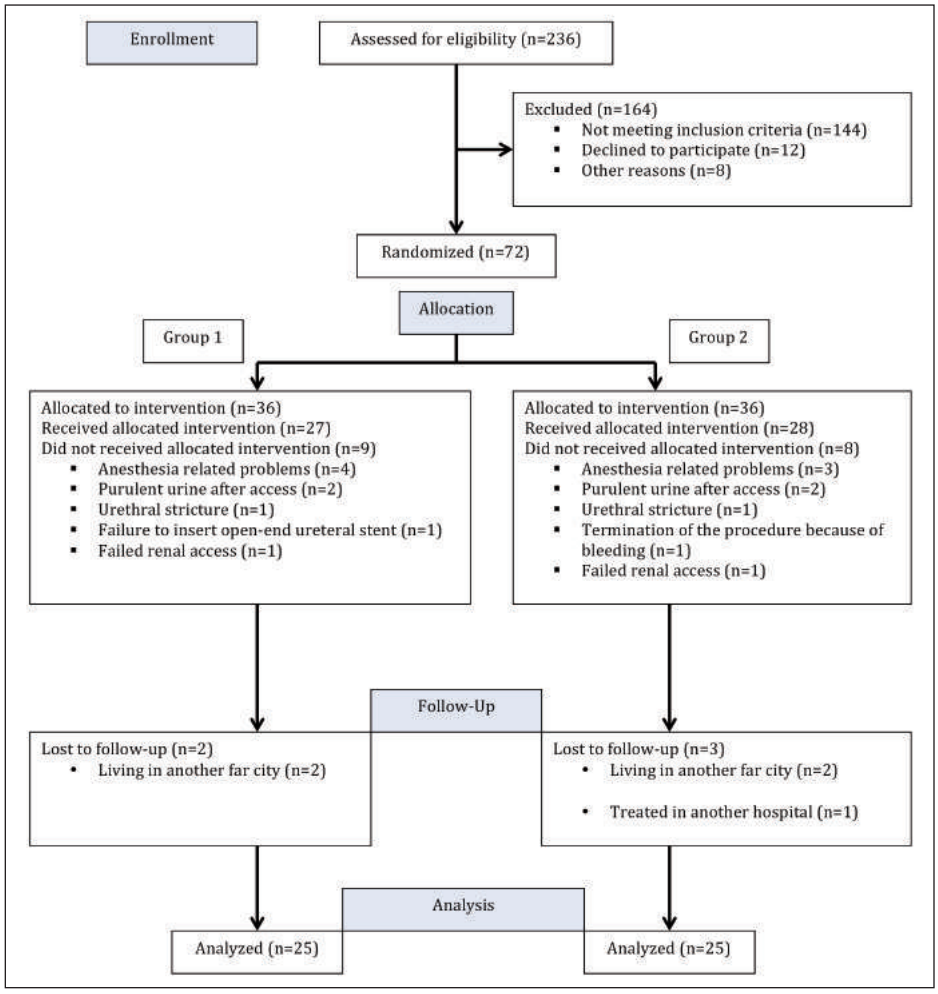

Figure 1.
CONSORT Flow Diagram of study.

Surgical technique of PNL procedure

Following general anesthesia, while performing cystoscopy, a 5 F open end ureteral catheter was placed into the relevant ureter till ureteropelvic junction area in Group 1 cases in the lithotomy position, no open end ureteral catheter was inserted in Group 2 cases and a prone position has been given directly in these cases.

An appropriate calyceal puncture under full sonographic guidance was done with a 18 gauge percutaneous entrance needle (*Boston Scientific, Natick, MA, USA*).

Following puncture of the kidney, a 0.038 inch guide wire was inserted into the collecting system (into the ureter when possible) and *Amplatz* mechanical dilatators were used for percutaneous tract dilatation (*Amplatz sheath, Boston Scientific, Natick, MA, USA*) until 28-30 F. Following the placement of an appropriate access sheath a standard 26 F nephroscope (*Karl Storz, Tuttlingen, Germany*) was placed directly into the kidney through the tract and the stone disintegrated using an ultrasonic lithotripsy probe (*Swiss Lithoclast®, EMS Electro Medical System, Nyon, Switzerland*). Fragments were removed by suction, tipless basket, or grasping forceps. At the end of the procedures, a re-entry nephrostomy catheter (14 F) was placed, and an antegrade pyelography was performed to check for possible complications in all cases. The open end ureteral catheter was removed at the end of the operation in Group 1 cases. The nephrostomy tube was removed postoperatively on the first or second day as soon as the urine became clear.

Outcome assessment

All patients were re-evaluated by a plain abdominal film and/or sonography after 24 hours and by a non-contrast abdominal tomography at the end of a 4 weeks period. The operation was considered successful if there were no fragments at all or if the size of the residual fragments were smaller than 4 mm.

In addition to the duration of the procedure as a whole and also all relevant stages as well, the duration of radiation exposure, hospitalization period along with the mean duration of nephrostomy tube, mean drop in *hemoglobin* (Hb) levels, all intraoperative, and postoperative complications have been evaluated and recorded.

Statistical analysis

The Prism 5.0 (*GraphPad Software, San Diego, CA*) was used for the statistical analysis. Data are presented as mean standard deviation of mean. *Mann Whitney U* test was used for both comparison of descriptive statistical methods and evaluation of quantitative data and *Fisher* exact test were used to compare the qualitative data between two groups, a two-sided $p < 0.05$ was considered statistically significant.

Results

A total of 50 cases (31 males/19 females M/F: 1.63) were treated with standard PNL for moderate sized solitary calyceal or pelvic stones and sonographic guidance was used for renal puncture. While the age of the cases ranged from 22-72 years (mean 44.90 +/- 12.32 years, 95% CI: 41.00-48.40), the mean size of the treated stones was 308.5 +/-133.2 mm^2, (95% CI: 270.7-346.4). Demographic as well as radiologic characteristics of the cases are given in Table 1. The stones were located in the calyceal system in 28 cases (6 cases upper, 9 cases middle, 13 cases lower calyx) and in the renal pelvis in 22 cases. There was no significant difference regarding the size of the stones in both groups.

Evaluation of our findings in both groups revealed following data.

Regarding the duration of the treatment as a whole or in certain parts of the procedure, our results show clearly that the mean total duration of the PNL procedure in cases with open end ureteral catheter was significantly longer than the other cases (85.80 +/- 16.18 *vs* 60.84 +/- 13.21 minute respectively, $p < 0.001$). The mean duration for an open end ureteral catheter insertion in Group 1 was 27.96 +/- 5.86, (95% CI: 25.54-30.38) min. and this time period was the main cause for prolonged total operative time in these cases. On the other hand however, there was no statistically significant difference with respect to the mean duration of other isolated stages of PNL procedure (renal puncture, access sheath placement, stone disintegration and removal) as shown in Table 2.

As an important parameter again, although the mean fluoroscopic exposure time was relatively longer in cases treated with an open end ureteral catheter, this difference was not statistically significant ($p = 0.3595$). Evaluation of the outcomes of the PNL procedures in terms of success rates as well as early post-operative follow-up data revealed no statistically significant difference between the two groups regarding the stone-free rates (84 % vs 88 %) and also the percentage of the cases with residual fragments sizing > 4 mm ($p = 1.00$) (Table 3). Additionally, when we evaluated the cases with respect to the duration of nephrostomy tube, hospitalization period and secondary procedures needed Double J stent placement and *ureteroscopy* (URS) again we were not able to show any significant difference in these

Table 1.

Evaluation of patient and stone characteristics in both groups.

Variables[a]	Overall n = 50	Group 1 Ureteral catheter (+) n = 25	Group 2 Ureteral catheter (-) n = 25	P value
Age, year; mean ± SD (range)	44.90 12.32 (22-72)	47.00 11.05 (26-60)	42.80 13.36 (22-72)	0.2175
BMI, kg/m^2; mean ± SD (range)	27.18 4.14 (18.2-38.0)	28.52 4.20 (22.3-38.0)	25.84 3.69 (18.2-34.5)	0.0380
Stone burden, mm^2; mean ± SD (range)	308.5 133.2 (195-570)	297.8 106.5 (195-570)	319.2 157.0 (200-530)	0.7784
HU, Hounsfield unit; mean ± SD (range)	812 198.3 (450-1500)	766.3 164.5 (450-1480)	857.5 202.4 (470-1500)	0.1276
Degree of hydronephrosis, Grade; mean ± SD (range)	2.22 0.50 (2-4)	2.16 0.47 (2-4)	2.28 0.54 (2-4)	0.3024

BMI: Body mass index; HU: Hounsfield unit.

[a] Continuous variables were compared by Mann Whitney U test.

Table 2.
Evaluation of the procedure related parameters with an emphasis on the duration of the interventional steps in both groups.

Variables[a]	Overall n = 50	Group 1 Ureteral catheter (+) n = 25	Group 2 Ureteral catheter (-) n = 25	P value
Mean duration of the procedure (min)	73.12 18.90	85.80 16.18	60.84 13.21	< 0.0001
Mean duration of open end catheter insertion (min)	-	27.96 5.86	-	-
Mean duration of access to the collecting system (min)	5.42 2.32	5.28 2.08	5.76 2.45	0.4909
Mean duration of dilation and access sheath placement (min)	10.34 3.96	10.08 3.22	10.67 4.02	0.5118
Mean duration of fragmentation and stone removal (min)	27.38 12.53	25.96 11.80	28.80 12.86	0.3896
Mean fluoroscopy time (sec.)	18.20 9.60	19.60 11.08	17.36 7.63	0.3595

[a] *Continuous variables were compared by Mann Whitney U test.*

values. Last but not least as another important parameter to be evaluated, there was also no notable difference regarding the post-operative drop in Hb levels in both groups (p = 0.6830).

Finally, evaluation of the complications in the light of modified *Clavien* grading system demonstrated no statistically significant difference between the two groups particularly concerning bleeding after PNL (Table 4). As summarized in this table, while one case in each group required double J stent insertion due to the prolonged urine leakage after nephrostomy tube removal, a stone passing into the ureter despite open end ureteral catheter placement was removed with URS in one case of Group 1. Relocation of the disintegrated stone fragments down into the ureteric lumen could be a significant drawback of this approach however, as we tend to remove all relatively larger fragments during the procedure with great care, there will be very limited chance for fragment relocation in these cases with moderate sized calculi. Moreover, it is clear that passage of the fragments down into the ureteric lumen might occur despite given care and open end ureteral catheter insertion (like the case in Group 1 of our study) in a certain percentage of the cases.

Discussion

Percutaneous nephrolithotomy has been performed as a minimally invasive method of removing kidney stones since 1976. As a result of the improvements in operative technique and miniaturization of the available equipment, this approach is now commonly performed as a safe and successful management option in larger stones. However, despite the high stone free rates obtained in a single session; PNL could be associated with certain types of complications like bleeding, organ perforation and sepsis (12). Such complications could be encountered during all steps of PNL among which the access to the renal collecting system seems to be the most important one (13).

Related to this subject, an appropriate initial puncture of the most desirable calyx of the kidney is extremely important for a successful and safe procedure by limiting the chance of both bleeding as well as injury to the surrounding organs (e.g. colon, spleen, liver, pleura, lung). Access to the renal collecting system from the most suitable calyx can be established either under fluoroscopic and/or sonographic guidance. Main aim of these two different guiding procedures should be a direct path which will be identified and used from the skin through the papilla of the desired calyx (14). Accumulated experience so far has clearly demonstrated that each of these methods could be associated with certain advantages as well as disadvantages. Related to this subject, during fluoroscopic guidance renal puncture is usually done after the placement of an open end ureteral catheter through cystoscopy. Use of this catheter will in turn allow the

Table 3.
Evaluation of the outcomes of the procedures in terms of success rates as well as early post-operative follow-up data.

Variables[a, b]	Overall n = 50	Group 1 Ureteral catheter (+) n = 25	Group 2 Ureteral catheter (-) n = 25	P value
[b] Stone free rate; n, (%)	43 (86.0)	21 (84.0)	22 (88.0)	1.0000
[b] Residual stone > 4 mm n, (%)	7 (14.0)	4 (16.0)	3 (12.0)	1.0000
[a] Mean drop in hb levels (g/dL)	1.52 0.68	1.60 0.69	1.45 0.57	0.6830
[a] Mean duration of nephrostomy (day)	1.86 0.88	1.83 0.79	1.92 0.92	0.7246
[a] Mean hospital stay (day)	2.88 0.96	2.84 0.96	2.92 1.03	0.9010
[b] Secondary intervention; n, (%)	3 (6.0)	2 (8.0)	1 (4.0)	1.0000

[a] *Continuous variables were compared by Mann Whitney U test.*
[b] *Continuous variables were compared by Fisher exact test.*

Table 4.
Evaluation of the type and grade of complications according to modified Clavien classification in both groups.

Grade	Complication	Overall n = 50	Group 1 Ureteral catheter (+) n = 25	Group 2 Ureteral catheter (-) n = 25	[b] P value
1	Fever > 38 0C; n, (%)	5 (10.0)	3 (12.0)	2 (8.0)	1.0000
	Hemorrhage not requiring blood transfusion; n, (%)	4 (8.0)	2 (8.0)	2 (8.0)	
2	Hemorrhage requiring blood transfusion; n, (%)	2 (4.0)	1 (4.0)	1 (4.0)	1.0000
3a	Double J stent placement for urine leakage > 24 h; n, (%)	2 (4.0)	1 (4.0)	1 (4.0)	1.0000
3b	Endoscopic treatment for ureteral stone; n, (%)	1 (2.0)	1 (4.0)	-	1.0000

[a] *Continuous variables were compared by Mann Whitney U test.*
[b] *Continuous variables were compared by Fisher exact test.*

surgeon to dilate the collecting system with saline injection for an easy puncture particularly in cases with minimal or no dilation and also to visualize the pelvicalyceal system with contrast medium. To accomplish this task however, patients are initially placed into a lithotomy position for the placement of the ureteral catheter and then brought into the prone position to perform the kidney puncture and access to the renal collecting system. It is clear that these procedures and maneuvers will certainly lengthen the total operational time for these cases being operated under general anesthesia. Additionally and more importantly a certain injury to the urethra particularly in male cases as well as to the mucosa of the relevant ureter could be caused.

On the other hand again, the administration of contrast agent may cause severe, contrast-related complications and the contrast agent may affect the opacity of the stone, causing challenges for the endourologist during stone manipulation. Moreover, the fear of injuring structures during a '*blind*' approach under fluoroscopic guidance up to the renal capsule constitutes another major concern. Last but not least, using fluoroscopy during percutaneous access to the kidney is accompanied by the exposure of the operators, patients as well as the other working staff to radiation. Long-term ionizing radiation may lead to considerable hazardous effects on certain organs (15). Taking the above mentioned problems related to fluoroscopic access into account, endourologists began to use sonographic guidance more commonly then ever in an attempt to avoid such certain problems with some certain advantages. First of all, this approach is totally free of ionizing radiation with shorter operating duration (16). Additionally, this form of guidance allows the endourologist to identify the neighboring organs in an accurate manner to minimize the risk of injury (17). Lastly, the *European Association of Urology* recommends the initial puncture under sonographic guidance because it reduces radiation hazards (18).

As stated above use of sonographic guidance in gaining access to the renal collecting system gained more importance than ever in the last decade. Related with this issue, in a prospective and randomized study *Zu W et al.*, aimed to compare the safety and efficacy of *fluoroscopic* (FG), total *ultrasonographic* (USG) and combined (CG) guidance for percutaneous renal access during *mini-percutaneous nephrolithotomy* (mini-PCNL) in a total of 450 consecutive patients with renal stones larger than 2 cm. While the overall complication rates using the Clavien grading system as well as stone free rates were similar between the three groups; multiple-tracts PNL were used more frequently in the FG and CG group than USG group and the mean access time was longer in CG than for FG and USG group patients. Mean total radiation exposure time however was significantly greater for FG than for CG (19). In another study again, 45 children with unilateral stones underwent PNL procedures under totally sonographic guidance with a mean time to establish access as 2.9 (range 2.1-5) min. Blood loss requiring transfusion, sepsis, adjacent organ injury and kidney loss were not observed in any case and the authors concluded that the ultrasound-guided mini-PCNL is feasible and safe in patients aged < 3 years, without major complications or radiation exposure (20). Last but not least, in their well organized systematic literature review including 18 studies with 2919 patients, *Liu Q et al.* stated in the final analysis that when compared with fluoroscopic guidance, use of ultrasonography provided shorter puncture time, higher success rate of fist puncture, less blood loss, and less complications as the main advantages of this approach (21).

On the other hand again, sonographic access to the kidney will be more practical and safe in relatively dilated renoureteral units in experienced hands. Easy and quick identification of the renal structures but most important the desired calyx in such dilated kidneys will allow the endourologist to establish the puncture in a safe manner which will diminish the importance of open end ureteral catheter insertion to a certain extent. Thus, taking the advantages of renal puncture in a safe and quick manner under sonographic guidance in dilated kidneys as well as the problems related to open end ureteral catheter placement into account use of an open end ureteral catheter in all cases becomes really questionable. Regarding the performance of percutaneous nephrolithotomy without open end ureteral catheter insertion, there is highly limited data reported so far in the literature. Only one study conducted by *Tabibi et al.* compared the outcomes of renal calyceal system puncture with and without retrograde pyelography in 55 patients with opaque renal calculi. They were able to show no differences in outcome, infection, operative time, duration of hospital stay, and radiation exposure, indicating that ureteral catheter placement may be precluded (22). We believe that our current study is a comprehensive one focusing on this critical issue in a detailed manner.

In this present study we aimed to evaluate the true necessity of open end ureteral catheter insertion in terms of the success as well as safety of renal puncture in patients with diated pelvicalyceal system (Grade 2 or higher) performed under sonographic guidance by comparing them with the cases in whom the catheter was inserted. Our results demonstrate clearly that the mean total duration of the PNL procedure in cases with open end ureteral catheter was significantly longer than the other cases. However, use of open end ureteral catheter did not shorten the renal access time in both groups of cases indicating that the presence of a dilated system doesn't require a catheter placement particularly in the light of the disadvantages mentioned above.

Evaluation of the outcomes of the PNL procedures in terms of success rates as well as early post-operative follow-up data revealed no statistically significant difference between the two groups regarding the stone-free rates (84% *vs* 88%). Additionally, when we evaluated our cases in both groups with respect to nephrostomy tube duration, hospitalization period and percentage of secondary procedures, no statistically significant difference again could be demonstrated from these aspects. Last but not least, as an important parameter again, although the mean fluoroscopic exposure time was relatively longer in cases treated with open end ureteral catheter, this difference was not statistically significant.

Our results demonstrate clearly that despite its well-known advantages during PNL procedure performed under fluoroscopic guidance; placement of an open end ureteral catheter may not really be necessary particularly in selected cases with a dilated renal collecting system

operated under sonographic guidance. Renal puncture under sonographic guidance can be done in a safe and practical manner in experienced hands in such cases without any need for such a catheter placement. Furthermore visualisation of the entire collecting system could be done via antegrade way in all these cases whenever needed. It should be kept in mind that; open end ureteral catheter insertion is a time consuming procedure which will in turn definitely prolong the total duration of a certain procedure during which the patient receives anesthesia in an unusual position. Additionally, when we add the time period needed for the change of the position from lithotomy to prone in the majority of the cases again the total duration of the intervention (as well as the anesthesia) will further increase in these cases. Additionally, it is very clear that urethra as well as ureter are both exposed to a certain degree of trauma during stent placement particularly in male cases. Taking all these facts into account, we believe that an open end ureteral catheter may not be inserted in selected cases treated with PNL under sonographic access for solitary renal pelvic and/or calyceal stones causing dilatation in the upper urinary tract.

Our study may have one limitation: The number of cases included and evaluated may be small. But taking the lack of publications regarding this issue and comprehensive evaluation of the necessity for an open end ureteral catheter performing PNL in dilated renal systems under sonographic guidance, we believe that our current findings will certainly be contributive enough to the existing literature on this critical subject.

Conclusions

In the light of the findings obtained in our current study and the above mentioned well known associated problems, we believe that placement of an open end ureteral catheter prior to a PNL procedure performed under sonographic access may not be indicated in selected cases presenting with solitary renal pelvic and/or calyceal stones causing dilatation in the upper urinary tract.

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ORIGINAL PAPER

Narrow band imaging (NBI) cystoscopy and assisted bipolar TURBT: A preliminary experience in a single centre

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Summary *Objective: The aim of this study was to compare, in order to increase our ability to detect bladder cancer, the predictive power of narrow band imaging (NBI) versus white light cystoscopy (WL).*
The secondary objective was to evaluate how the preoperative use of NBI cystoscopy can increase the ability to detect bladder lesions in terms of status, multi-focality and dimensions.
Materials and methods: Between June 2010 and April 2012, 797 consecutive patients, 423 male and 374 female, affected by suspected bladder cancer lesions, underwent to WL plus NBI cystoscopy and subsequently to WL Bipolar Gyrus PK (Olympus, Tokyo, Japan) transurethral resection of bladder tumour (WL-TURBT). The average follow-up was 24 (16-38) months. Mean age was 67.7 yrs. (range 46-88).
All the patients underwent by same surgeon to WL resection (WL-TURBT) of the previously identified lesions by same surgeon. All the removed tissue was sent separately for histological evaluation after mapping the areas of resection on a topographic sheet.
Results: In our study we considered 797 patients that matched our inclusion criteria. Through the use of WL cystoscopy, we identified 603 patients (75.53%) with suspicious lesions, instead, with the use of light NBI, we found 786 patients with suspicious lesions (98.49%).The use of NBI cystoscopy increases by approximately 30% the specific ability to detect lesions not otherwise visible with WL cystoscopy (OR 21.9 and RR 1.30), in particular for patients with lesions size < 3 cm (OR 24.00; RR 1.40), unifocal (OR: 22.28; RR 1.47) and recurrent (OR 58.4; RR 1.34). Pathology demonstrated the presence of cancer in 512 (64.2%) patients, of whom 412 (51.8%) were visible both with WL cystoscopy and NBI cystoscopy.
In our experience, only 11 (1.38%) lesions were only positive at WL cystoscopy (negative at NBI cystoscopy) thus 501 (62.8%, OR 10.13; RR 1.21) patients showed bladder oncological lesions positive at NBI cystoscopy. In these patients, the use the NBI Cystoscopy has better highlighted a recurrence (p < 0.005; OR 22.8, RR 1.23; 95% CI-1.13 to 0.24) or a lesion < 3 cm (p < 0.05; OR 11.4 , RR 1.30; 95% CI-0.18 to 0.29) or a unifocal lesion (p < 0.005; OR 10.38, RR 1.34, CI 0.18 to 0.30).
Conclusions: The use of NBI cystoscopy, significantly increases by approximately 30% our predictive power to identify neoplastic lesions, especially unifocal or < 3 cm or recurrent lesions. Following WLTURBT, stage, dimension and focaliity are statistically significant determinants (p < 0.001) of the bladder oncological lesions detected by NBI cystoscopy rather than by WL cystoscopy.

KEY WORDS: *Bladder cancer; Narrow band imaging (NBI); Cystoscopy; Bipolar TURBT.*

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INTRODUCTION

Bladder cancer is a very common malignant genitourinary tumour and transitional cell carcinoma accounts for almost 90% of all primary bladder tumours. The standard method used to diagnose bladder cancer and monitor patients in the follow-up is *white light* (WL) cystoscopy. Unfortunately, this method may not be able to detect small papillary lesions and *carcinoma in situ* (CIS) lesions (1). Tumours not detected in the course of TURBT will appear later as a relapse, and some of them may become invasive. This calls for the development of better endoscopic methods, namely fluorescence (2-4), and *narrow banding imaging* (NBI) cystoscopy (5). NBI is a technique for improving optical images. It is designed for endoscopy and its purpose is to increase the contrast between mucosal surfaces and microvascular structures without resorting to dyes. This technique is based on a phenomenon by which the depth of light penetration into the mucosa increases as the wavelength increases. In NBI, the tissue surface is illuminated with narrow band light, with wavelengths in the blue and green light spectra (415 nm and 540 nm respectively) (6). The primary objective of this study was to assess the ability of NBI to increase the detection rate of lesions not visible with WL cystoscopy. The secondary objective was to evaluate how the preoperative use of NBI cystoscopy can increase the ability to detect bladder lesions in terms of status, focality and dimensions after TURBT, as opposed to WL cystoscopy.

MATERIALS AND METHODS

From June 2010 to April 2012, 797 consecutive patients (pts.), 423 male and 374 female, affected by primary (461 pts, 57.8%), recurrent (336 pts, 42.1%), unifocal (491 pts., 61.6%), multifocals (306 pts., 38.3%), < 3 cm (570 pts., 71.5%) and > 3 cm (227 pts., 28.4%) suspicious non-muscle invasive bladder tumours, underwent WL plus NBI cystoscopy and WL plus NBI Bipolar TURBT with a Bipolar Gyrus PK Scalpel in saline (TURis). The mean follow-up was 24 (16-38) month.
Indication of suitability for TURBt was provided on the basis of the *EAU Guideline* 2010. All patients provided written informed consent prior to the study.
All procedures were carried out initially by performing a cystoscopy with white light. The characterization of the sites, including the number, size and appearance of the neoplasms, were recorded on a topographic bladder map.

No conflict of interest declared.

Subsequently a cystoscopy with NBI was carried out to confirm what had been seen by white light examination, and to report other suspicious areas at NBI light. These, too, were recorded on the topographic bladder map. All endoscopic resections were performed with an Gyrus PK scalpel, bipolar generator (*Olympus, Tokyo, Japan*), in saline, with optics at 30 degrees. Resection of each lesion was carried out with white light by the same surgeon who had performed cystoscopy and all histopathological evaluations were performed by the a single pathologist on the basis of 2004 WHO classification.

In order to evaluate the efficacy of NBI vs WL cystoscopy, we conducted a hypothesis test to determine whether the difference between the two proportions of positive results obtained by WL and by NBI (p_wl and p_nbi) was significant. The two-proportion z-test was administered on the overall sample and, after TURBT, on the hystologically positive set of patients. The appropriate test assumes a model for matched pairs (7).

The analysis was carried out in relation to status (primitive and recurring), focality and dimension of detected lesions. All Z-scores (before and after TURBT) were largely below the selected significance level ($\alpha = 0.05$). The related confidence intervals were also calculated.

In addition we estimated *odds ratio* (OR) and *relative risk* (RR) to quantify how strong is the difference between NBI and WL results. Logistic regression was applied to predict which lesions were in fact malignant after NBI cystoscopy. Multiple linear regression analyses tested the association between different prognostic variables and their impact on the ability to identify bladder lesions following NBI cystoscopy.

Results

In our study we considered 797 patients that matched our inclusion criteria. WL cystoscopy was used to identify 603 patients (75.5%) with suspicious lesions, while the use of NBI following WL allowed identifying a total of 786 patients (98.49%).

A total of 1.571 suspicious lesions were identified in 797 patients, some of whom had multifocal lesions. Of these lesions, 496 (50.6%) were single lesions and 1.075 (49.3%) multiple lesions. Of these 1,571 lesions, 1.337 (85.11%) were identified by WL cystoscopy alone. The subsequent use of NBI light allowed finding 234 lesions (14.89%), not visible otherwise with WL, reaching a total of 1.571 suspicious lesions.

The use of NBI cystoscopy increases by approximately 30% the ability to detect lesions not otherwise visible with WL cystoscopy alone (OR 21.9 and RR 1.30), particularly in patients with lesion size < 3 cm (OR 24.00; RR 1.40), unifocal (OR: 22.28; RR 1.47) and recurrent lesions (OR 58.4; RR 1.34) (Table 1).

All 797 patients were subjected to bipolar TURBT with Gyrus PK (*Olympus, Tokyo, Japan*). The final histology results demonstrated the presence of cancer in 512 (64.2%) patients (Table 2), of whom 412 (51.8%) were visible both with WL cystoscopy and NBI cystoscopy.

In our experience, 501 (62.8%) patients showed bladder oncological lesions positive in NBI cystoscopy thus only 11 (1.38%) lesions were only positive at WL cystoscopy. Totally, 1,571 cancer lesions were identified as suspicious, 1,051 lesions (66.85%) were positive for malignancy and 520 (33.14%) negative for malignancy.

The histology after WLTURBT showed the ability of NBI cystoscopy to identify, in more than 20%, a lesion oncologically significant than was not evident at WL cystoscopy (Table 2).

Table 1.
WL and NBI cystoscopy results (before TURBT).

All cases	Yes	No	Total	Odds	Odds ratio	Absolute risk	Relative risk
NBI positive	786	11	797	66.14		0.985	
WL positive	603	194	797	3.087	21.9	0.755	1.304
Primitive							
NBI positive	452	9	461	45.10		0.978	
WL positive	354	107	461	3.26	13.79	0.785	1.27
Recurrent							
NBI positive	334	2	336	167.0		0.994	
WL positive	249	87	336	2.86	55.34	0.741	1.341
Unifocal							
NBI positive	481	10	491	43.6		0.978	
WL positive	325	166	491	1.95	22.28	0.662	1.47
Multifocal							
NBI positive	305	1	306	305.0		0.997	
WL positive	277	29	306	9.55	31.93	0.905	
< 3 cm							
NBI positive	560	10	570	56.0		0.982	
WL positive	399	171	570	2.33	24.00	0.700	1.404
> 3 cm							
NBI positive	226	1	227	22.6		0.991	
WL positive	203	24	227	8.45	13.3	0.894	1.108

Table 2.
WL and NBI cystoscopy results (hystologically positive after TURBT).

All cases	Yes	No	Total	Odds	Odds ratio	Absolute risk	Relative risk
NBI positive	501	11	512	41.6		0.977	
WL positive	412	100	512	4.12	10.1	0.805	1.21
Primitive							
NBI positive	317	9	326	31.6		0.969	
WL positive	263	63	326	4.17	7.57	0.807	1.20
Recurrent							
NBI positive	184	2	186	92.0		0.989	
WL positive	149	37	186	4.02	22.84	0.801	1.235
Unifocal							
NBI positive	290	10	300	26.2		0.963	
WL positive	215	85	300	2.5	10.38	0.717	1.344
Multifocal							
NBI positive	211	1	212	211.0		0.995	
WL positive	197	15	212	13.3	16.06	0.929	1.071
< 3 cm							
NBI positive	309	10	319	30.9		0.989	
WL positive	223	85	319	2.70	11.40	0.730	1.326

Thanks to use of the NBI light we identified 500 patients with lesions NBI positive oncologically significant (62.7%; OR 10.13; RR 1.21). In particular, NBI cystoscopy improved bladder neoplasms detection rate of WL cystoscopy in recurrent (OR 22.8 *vs* 7.5; RR 1.23 *vs* 1.20), < 3 cm (OR 11.4 vs 7.4; RR 1.30 vs 1.06) and unifocal tumours (OR 10.38 *vs* 16.06; RR 1.34 *vs* 1.07). The difference in detection rate is not so high as in recurrences in primitive lesions (RR 1.23 *vs* 1.20). In 512 patients with tumors detected after WL TURBT, the use the NBI cystoscopy has more frequently demonstrated a recurrent injury ($p < 0.005$; 95% CI-1.13 to 0.24) or a lesion < 3 cm ($p > 0.05$; 95% CI-0.18 to 0.29) or an unifocal lesion ($p < 0.005$; CI 0.18 to 0.30). It is clear that with the NBI cystoscopy, compared to WL cystoscopy alone, we could identify a statistically significantly greater number of neoplastic lesions, in relation to pathological stage and grade ($p < 0.005$, IC-95% 0.13- 0.21 and $p < 0.005$; 95% CI-0.14 to 0.24, respectively). In particular, we highlighted an higher number of CIS lesions ($p < 0.005$, IC-95% from 0.48 to 0.92) and HG lesions ($p < 0.005$; CI-95%. In our experience we identified in the group of 512 patients with bladder cancer confirmed after WLTURBT, 88 patients who had bladder neoplastic lesions detected only through the use of NBI cystoscopy (WL cystoscopy negative) with an adjunctive detection rate (ADR) of 11.4%.

The overall false positive detection rate was 33.14% (521 lesions) and after NBI cystoscopy this rate was 39.44%.

Using the logistic model, we observed that the use of NBI cystoscopy significantly increases our predictive power to identify lesions not visible with WL cystoscopy: primitive lesions (95% CI 2.97-1.095; $p < 0.02$), multifocal (95% CI 0.06-012; $p < 0.0001$), and < 3 cm (95% CI 0.05-0.13; $p < 0.001$). It is interesting to note that HG (high-grade) neoplasms (95% CI 0.14-0.24; $p < 0.001$) tend to reach a value very close to significance compared to papillary urothelial neoplasms of low malignant potential (PUNMP) (95% CI 0.004-0.04; $p < 0.005$) and low grade neoplasms (low-grade) (95% CI 0.10-0.21; $p < 0.001$).

Using NBI cystoscopy, the likelihood of identifying patients with a primitive tumour, compared to patients with a relapse, reached approximately 80% (point estimate 1.790, 95% CI 1095-2927). In a patient with a unifocal tumour, the likelihood of having a bladder tumour detected by NBI cystoscopy increases by about seven times compared with those a multifocal tumour (point estimate 0.153, 95% CI 0.060-0.390).

NBI cystoscopy has also proved to be very useful in CIS. By comparing the sensitivity, specificity, positive predictive value and negative predictive value (NPV) of NBI versus WL cystoscopy for CIS lesions, we noticed that sensitivity and NPV were the statistically significant values (100%, 95% CI, $p < 005$, and 80.62%, 95% CI, 100%, 95% CI, $p < 005$, and 78.35%, respectively). NBI cystoscopy increases the likelihood of detecting a CIS lesion by about one and a half times compared to a patient with a pTa lesion ($p < 0.001$).

Discussion

Bladder cancer is considered the most expensive tumour both in terms of costs for patients per year and in terms of operating costs per patient. Up to 70% of patients with NMIBC will develop a recurrence after TURBT (8).

Photodynamic diagnosis with Hexaminolevulinate blue light cystoscopy has made significant advances in terms of rates (9) of diagnostic accuracy and recurrence for the detection of CIS lesions (10), as well as pTa and pT1 tumours (11).

However, some questions have been raised as regards the cost-effectiveness of this approach.

Numerous studies have demonstrated the ability to display improved images of the surface layers of the various apparatuses using NBI (10, 12-18). NBI is a diagnostic imaging technique that improves the contrast between mucosal surfaces and microvascular structures, based on the wavelength-dependent increase in the depth of light penetration into the mucosa, without additional costs to conventional cystoscopy and without lengthening the operating time.

In our experience, using WL and NBI cystoscopy together, we have identified 234 lesions (14.1%) that WL cystoscopy alone would not have otherwise been able to identify. However, the essential result is not so much the number of lesions that can be identified using NBI as opposed to the number of those visible with WL alone, but rather how many of these are neoplasms. Of these 234 lesions identified with NBI alone, as many as 127 were bladder tumours (12.17%) in 88 patients (11,4%).

Comparing our experience with the data available in the literature, we were able to find some interesting data.

The experience of *Bryan et al.* (5) showed a greater capacity to identify lesions (Δ = -7.15%) compared to our results, while our technique showed an improvement (Δ = +3.81%) compared to the results of *Herr et al.* (19)

In fact, we detected 12.17% of lesions not otherwise detectable, by WL cystoscopy, thus placing our experience between the two aforementioned studies.

To better understand the diagnostic efficacy of the NBI compared to WL cystoscopy an analysis of the odds ratio was performed (positive results against the negatives for each type of investigation). The two methods of cystoscopy did not change the state of the patient on which they were performed. Therefore 797 cases can be considered as a sample to which two different but non-interacting methods were administered.

The odds ratio, measuring the frequency of success of a technique respect to another, in our case highlights the success of NBI. In fact a value greater than 1 indicates greater effectiveness of NBI in the detection of lesions against the non-detection. If we consider all the cases, the calculated value of OR = 21.90 (Table 1) shows a strong prevalence of NBI identification of lesions. A more intuitive interpretation of the results is made up of the relative risk. In fact, this index relates the absolute risk (ratio of successes and the total number of cases) of the two methods. In this way it is possible to assess with greater immediacy the effectiveness of the method NBI compared to WL.

The use of NBI cystoscopy has therefore allowed improving our ability to overall detect lesions not otherwise visible with WL cystoscopy alone (ADR= +30%) in terms of focality (unifocals: OR 22.28; RR 1.47) as well as dimensions < 3 cm, OR 24.00; RR 1.40) and status (recurrences: OR 58.4; RR 1.34).

Following WL TURBT, we observed 500 pts with NBI bladder oncological lesions, with a ADR of 20%. The use of NBI cystoscopy, significantly increases our predictive power to identify lesions not visible with WL cystoscopy, especially for unifocal lesions ($p < 0.005$, IC-95%0.18-0.30), those < 3 cm ($p < 0.005$, IC-95% 0.18-0.29) and recurrent lesions ($p < 0.005$, IC-95% 0.13-0.24).
Similarly, through the use of NBI light, we observed that, as regards pathologic stage and grade, we registered an overall increase in bladder lesion detection rate ($p < 0.005$, IC-95% 0.13-0.21 and $p < 0.005$; IC-95% 0.14-0.24, respectively).
In our experience, the use of NBI cystoscopy significantly increased the ability to detect both CIS lesions ($p < 0.0001$) and HG ($p < 0.005$) (Table C: d-e) compared to WL cystoscopy. The relative risk (RR) to identify a bladder tumour with NBI TURBT is 3 times greater in the case of a pTa LG lesion and about 8 times greater if the lesion is a CIS. In our experience, as well as in *Herr's* experience (19), the use of NBI cystoscopy in comparison to WL cystoscopy was particularly useful in the identification of CIS lesions, showing a sensitivity and NPV of 100% *vs.* 80.62% and 100% *vs.* 78.35% ($p < 0.05$) respectively.
By contrast, we recorded a non-significant specificity and PPV. In our experience, the overall false positive detection rate was 33.14% (521 lesions) and after NBI cystoscopy this rate amounted to 39.44%. These data overlap with other international experiences.

Conclusions

This is the first study in the literature in which the ability of NBI cystoscopy to increase the ability to detect suspicious bladder lesions was compared with the use of WL cystoscopy alone in the same patient. The use of NBI cystoscopy, significantly increases our predictive power to identify lesions not visible with WL cystoscopy, especially for unifocal lesions, those < 3 cm and recurrent lesions. Following WL TURBT, status, dimension and focality are statistically significant determinants in order to detect bladder oncological lesions by NBI cystoscopy rather than WL cystoscopy.
In conclusion, NBI is an effective method for the identification of bladder lesions and can be useful in supporting WL cystoscopy.

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CASE REPORT

A case of seminoma presented with clinical manifestations of testicular torsion

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Summary ***Testicular tumors rarely manifest themselves with clinical picture of testicular torsion. In this presentation of ours, we reported a 30-year-old patient whose post-orchiectomy histopathology report revealed the presence of seminoma. The patient consulted us with acute scrotum whose physical examination and Doppler ultrasonographic findings showed testicular torsion. Though rarely seen patients, in cases who consulted with acute scrotum, the possibility of testicular tumor should not be discarded. For the establishment of differential diagnosis detailed anamnesis and physical examination findings should be supported with laboratory tests and imaging modalities.***

KEY WORDS: Testicular torsion; Seminoma; Orchiectomy.

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INTRODUCTION

Testicular torsion is a scrotal emergency case occurs as a result of rotation of spermatic cord around its axis leading to impairment of testicular perfusion and testicular ischemia. Scrotal pain spreading into the lower abdominal quadrant can cause concomitant symptoms of nausea and vomiting. The incidence rate of testicular torsion is around 3.5/100000. It is mostly idiopathic and 20% of the cases are related to trauma (1). Torsion is a scrotal phenomenon, which can be observed in adolescents.
1-2% of all malignant tumors seen in men are testicular cancers and incidence rate of testicular cancers increases among young men aged between 15-40 years old. 80% of testicular tumors are seminomas, and most of them present themselves as clinical stage I disease. These two scrotal diseases can complicate each other, torsion due to testicular tumor may occur, however the possibility of simultaneous occurrence of these two diseases in the same testis is very low. Scrotal *color-Doppler ultrasound* (CDUS) has a major role for differential diagnosis, however despite higher rates of diagnosis, in case of uncertainty, taking a decision to perform surgical exploration and orchiectomy without delay is essential. In this presentation of ours, we reported a 30-years-old patient whose post-orchiectomy histopathology report shows the presence of seminoma. The patient consulted to us due to acute scrotum. His physical examination and Doppler ultrasonographic findings were consistent with testicular torsion.

CASE REPORT

A 30 years-old male patient, has two children, applied to the emergency service due to left testicular pain lasted for a day. The patient stated that his pain started suddenly without any history of trauma. Also there was not any similar attack before. Besides the patient doesn't have any known systemic comorbidity. On physical examination left testis seen oedematous and scrotal skin overlying the left testis was hyperaemic. Left hemiscrotum was extremely tender on palpation and comparing with its counterpart, the left testis was seem to be elevated because of the inflammation. His urinalysis was unremarkable. Leukocytosis (16.000/ml, normal range 4600-10200/ml), extremely high levels of serum *lactic acid dehydrogenase* (LDH) (650 U/L, normal range 125-220U/L), and C-reactive protein (9 mg/dl, normal range 0-0,5 mg/dl) were detected. Serum beta- HCG, and alfa-fetoprotein (AFP) values were within normal limits.
Left testis demonstrated a heterogeneous structure on scrotal CDUS obtained in the emergency service and blood flow was not detected. CDUS images suggested testicular torsion. The spermatic cord manually detorsed prior to his surgical procedure but his clinical signs didn't change. We talked about possible orchiectomy with the patient and his family. There was no suspicion of testicular tumor prior to orchiectomy. Our main surgical intervention purpose was treatment of testicular torsion, so we performed scrotal exploration under general anesthesia immediately. Testicular blood flow was not observed and no/any rotation wasn't observed at cord. Testis and spermatic cord were wrapped with warm compress for 15 minutes. Then testicular parenchyma was controlled and any evidence of blood flowing was not detected. Tunica vaginalis was incised with a surgical blade to detect if there is any bleeding. Testicular bleeding on the exploration is important, because it shows that there is still circulation to the testis. But, just purulent and necrotic fluid was drained (Figure 1). For microbiological analysis specimens were taken and then scrotal orchiectomy was performed. The patient was discharged on postoperative 1. day, there was not any complication depending on the surgery. Histopathology results were reported as granulomatous inflammation and seminoma (Figure 2). CT obtained at postoperative 2 weeks, metastatic lesion in the lungs was not detected. Serum LDH levels regressed to 121 U/L. Adjuvant chemotherapy was planned

No conflict of interest declared.

for the patient with the diagnosis of pT1N0M0 seminoma and medical oncological treatment was initiated. Now the patient is still monitored by the oncologist.

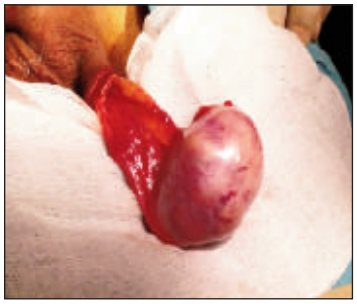

Figure 1.
During surgical exploration nontorsioned cord, heterogenous testicular structure, and necrotic, and purulent discharge observed when vaginal tunica was incised with a scalpel.

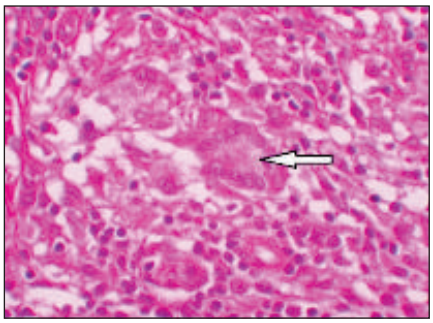

Figure 2.
Microscopic examination reveals patchy areas of diffuse groups of tumoral cells associated with small lymphocytes in a fibrous stroma. Tumoral cells consist of atypical germ cells with clear or eosinophilic cytoplasm, generally uniform large round nuclei with thin chromatin, marked nucleoli, and mitotic figures. Granulomatous reaction partly associated with tumor is seen.

Discussion

Testicular torsion is a scrotal emergency disease, which occurs before the age of 20 and characterized by sudden onset of testicular pain. The ratio of testicular torsion among men aged over 20 years in the literature reported cases varies between percent 10 and 56 of all cases (2). Our case was 30 years old who can be considered as over aged by comparing the average age mentioned in the literature of testicular torsion. Acute testicular pain is considered as testicular torsion unless proved otherwise. Testicular parenchyma damage starts to take effect within the first 4 hours of occlusion of testicular veins/arteries after the torsion of the spermatic cord. Therefore in case of testicular torsion suspect, one should not hesitate to perform testicular exploration. On physical examination even some findings suggest testicular torsion, concomitant testicular swelling or hydrocele may mask testicular torsion. In testicular torsion the involved testis is solid, tender and tense and it can be elevated because of the shortening of the spermatic cord of the affected testis when compared with its counterpart. If testicular pain is relieved with testicular elevation then probability of epididymo-orchitis is present. In spermatic cord torsion cases, testicular pain is not relieved after manual elevation of the testis. Cremaster reflex is not seen in testicular torsion, however cremaster reflex can be seen in the torsion of appendix testis, and it can show symptoms similar to those seen in cases with torsion of the spermatic cord. In our case the involved testis was tender to touch and elevated relative to other testis and there was no cremaster reflex. Urinalysis is generally unremarkable and 50% leukocytosis can be seen. In our case leukocytosis was present, while results of urinalysis were within normal limits.

Since most of the scrotal diseases show similar symptoms, clinical diagnosis of testicular torsion is a challenging issue. CDUS is a reliable method in the accurate diagnosis of scrotal pathologies. In addition to scrotal pathologies, CDUS can also comparatively evaluate normal scrotal anatomy. *Becker et al.* reported higher diagnostic sensitivity (90.5%), and specificity (98.3%) of scrotal CDUS for testicular torsion (3). Despite all physical examination findings and test results, if clinical suspicion still persists, then surgical exploration should not be declined. As is the case with other organ tumors, organ-preserving surgeries are revived for testicular tumors, however in cases with normal contralateral testis, this approach is not recommended. Besides, biopsy is not a suitable option because of causing a possible shift in the lymphatic pathway and a risk of false positivity testicular. In patients for whom orchiectomy is decided, testicular tumor should be suspected, and spermatic cord should be clamped at the level of internal ring of the inguinal canal, and high-level orchiectomy should be performed. Indeed CDUS images of our patient did not demonstrate apparent characteristics of a testicular tumor, and any evidence of testicular blood flow was not detected. So we performed scrotal exploration to treatment of torsion. The patient underwent orchiectomy with the indication of torsion, and histopathology report of the specimen indicated pT1 seminoma.

Conclusion

For the establishment of differential diagnosis detailed anamnesis, and physical examination findings should be reinforced with laboratory tests, and imaging modalities. Even if all preoperative examinations and tests indicate testicular torsion, clinical common sense should never rule out the possibility of testicular cancer.

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CASE REPORT

Distant subcutaneous spreading of Fournier's gangrene: An unusual clinical identification by preoperative ultrasound study

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Summary ***We present here the first case of successful management via preoperative ultrasonographic (US) study to detect a distant spreading of Fournier's gangrene (FG), which was happened in a 75-year-old man. US study showed the necrotizing infection in the periumbilical region distant 22 cm from the genital tract. A target incision of this periumbilical area and debridement of necrotic tissues was made. Computed tomography (CT) is superior to ultrasonography to confirm the diagnosis of FG and support in surgical management, but a CT evaluation in patients with FG may be limited by the frequent presence of concurrent acute renal failure or patient hemodynamic instability. Ultrasonography is an ideal technique for evaluating patients in bedside settings and can be routinely used in an emergency.***

KEY WORDS: *Fournier's gangrene; Ultrasonography; Computed tomography.*

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INTRODUCTION

Fournier's gangrene (FG) is an acute, rapidly progressive necrotizing soft-tissue infection of the external genitalia and perineum (1). If not recognized and treated early, it is associated with high morbidity and mortality (2).
In addition to the physical exam, there are several diagnostic procedures that can be used to evaluate this necrotizing infection. *Ultrasonographic* (US) study allows to evaluate a scrotal pathology or soft tissue collection, and has been shown to identify subcutaneous gas, even prior to the overt development of crepitus on physical exam (3). We here report the first case of successful management via preoperative US study to detect a distant spreading of FG and allow proper surgical debridement.

CASE REPORT

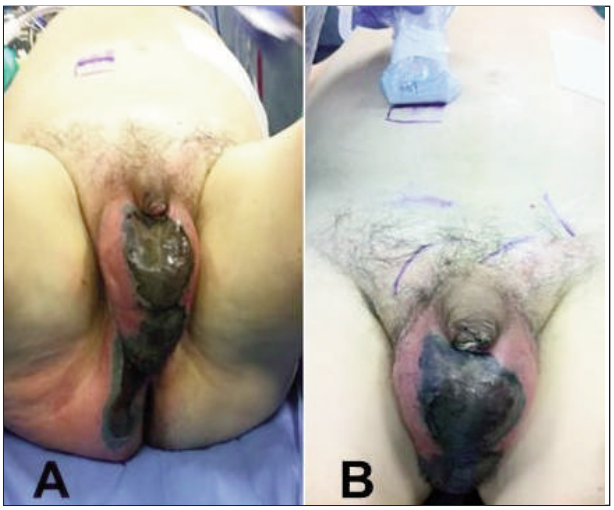
A 75-years-old male patient presented to our *Emergency Department* for generalized malaise, fever, appearance of edema, scrotal erythema, and pain symptoms in the perianal region not responsive to the most common anti-inflammatory drugs. The patient's medical history was remarkable for a history of hypertension and diabetes mellitus, diagnosed twenty years ago. On admission, his vital signs were as follows: blood pressure 135/80 mmHg; heart rate 98 bpm and body temperature 38°C. His blood count showed: haemoglobin level, 11.3 g/dL, white blood cell count, 17.000/mm^3, and platelet count, 185.000/mm^3.
C-reactive protein level was 13 mg/dL, glucose 280 mg/ dL and creatinine level was 1.4 mg/dL. Physical examination showed genital and perineal swelling, with erythema, edema and necrotic tissue over his scrotum with extension to the perineum (Figure 1A); subcutaneous crepitation was also present. As part of the initial assessment, the patient received an US study that demonstrated marked thickening of the scrotal fascia with edema and high-amplitude echoes, as well as an area of subcutaneous gas in the periumbilical region was discovered distant 22 cm from the genital tract (Figure 1B). However, a contrast-enhanced *computed tomography* (CT) was performed to differentiate areas of subcutaneous gas in the periumbilical and genital regions (Figure 2). These findings were compatible with Fournier gangrene. Immediate broad spectrum antibiotic administration were initiated. Although the initial vital signs were normal, he rapidly developed septic shock and was emergently taken to the operating room for aggressive surgical therapy including target incision on the periumbilical localization of infection and debridement of necrotic tissues until to be able to contain the progression of the gangrene. The patient was discharged after a flap reconstruction over the scrotum and 28 days of hospitalization. The clinical follow-up was 6 months and showed no signs of infectious or ischaemic complications.

DISCUSSION

FG was first described by *Jean Alfred Fournier*, a French venereologist, in 1883. At that time, it was described as abrupt in onset with rapid progression to gangrene, but without a clear aetiology. The disease was noted to occur most commonly in young males (4). Today, FG is most commonly found in middle-aged men (50-60 years) and, to a much lesser extent, in women (2). FG shows vast heterogeneity in clinical presentation, from insidious onset and slow progression to rapid onset and fulminant course. The characteristic of this necrotizing infection is gas production by the bacterial organisms, which can sometimes (but not always) be assessed on physical exam. However,

No conflict of interest declared.

Figure 1.
Genital and perineal swelling, with edema and necrotic tissue over the scrotum and perineum secondary to Fournier's gangrene (A). Ultrasonographic probe reported an area of subcutaneous gas in the periumbilical region (distant 22 cm from the genital tract, B).



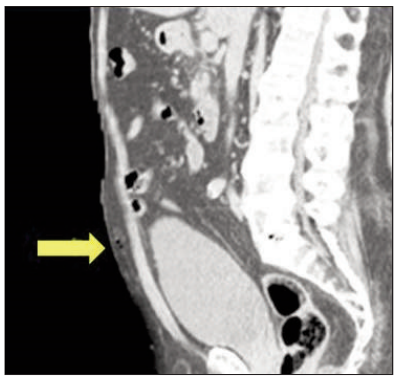


Figure 2.
Longitudinal scan of contrast-enhanced computed tomography shows a distant subcutaneous spreading of Fournier's gangrene (yellow arrow).

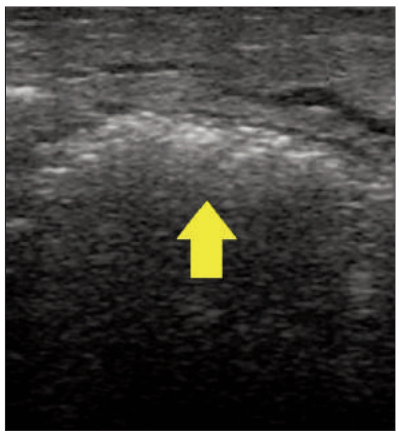


Figure 3.
The characteristic ultrasonographic features of necrotizing infection comprise subcutaneous multiple echoic spots that show reverberation artefacts, causing "dirty" shadowing that represents gas (yellow arrow).

an early diagnosis is important because immediate surgical debridement and aggressive antibiotic treatment are indicated (1, 3). Thorough physical examination and clinical assessment are favourable for a correct diagnosis of FG, but laboratory studies and imaging can be useful for risk stratification and to identify a potential source, respectively. Radiological exams, including radiography, ultrasonography, and CT, can be of value to assess the extent of disease. Radiography is the least costly option and can, in some cases, show hyperlucency representing soft-tissue gas before the accompanying clinical crepitations (3). Traditionally, owing to its low cost, ready availability, US study has been the primary modality for imaging of the scrotum and can be utilized to examine the scrotal contents, and determine testicular involvement. Overall, CT is superior to both ultrasonography and radiography to confirm the diagnosis of FG and support in surgical management. *McGillicuddy et al.* in a review of CT findings on adult patients undergoing imaging for the evaluation of a soft-tissue infection reported a sensitivity of 86.3% and a specificity of 91.5%, with a negative predictive value of 85.5% (5). However, imaging evaluation in patients with FG may be limited by the frequent presence of concurrent acute renal failure (thus precluding the use of intravenous contrast material) or patient hemodynamic instability making transport to the *Radiology Department* unsafe. US study can be readily performed in bedside settings, which is of particular benefit to patients who are hemodynamically unstable but whose physical examination findings are equivocal (6). The characteristic US features of necrotizing infections comprise subcutaneous multiple hyperechoic foci that show reverberation artefacts, causing "*dirty*" shadowing that represents gas (Figure 3) (1, 6).
In conclusion we believe that US study constitutes an excellent minimally invasive alternative in such situations, reduces the extension of surgical field allowing a quick recovery and the risk of under treatment, can value alternate pathologies, such as epididymitis and torsion, does not expose patients to radiation, and does not require contrast-enhanced. Based on our experience, a preoperative US study may identify easy and precisely distant foci of infection spreading avoiding wide surgical field and provide earlier control of disease.

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CASE REPORT

Bladder carcinosarcoma: A case report with review of the literature

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Summary ***Carcinosarcoma of the urinary bladder is a rare neoplasm that is histologically composed of malignant epithelial and mesenchymal components. The etiology of sarcomatoid tumors is unclear, but smoking and history of previous radiotherapy or chemotherapy may lead to bladder disorders and to the formation of sarcomatoid carcinoma. These neoplasms behave as highly aggressive tumors and optimal treatment is uncertain. Herein, we report a case of sarcomatoid carcinoma of urinary bladder presenting as a giant intravesical mass in a 61-year-old man complaining of macroscopic hematuria.***

KEY WORDS: Bladder carcinosarcoma; Urothelial carcinoma; Prognosis.

Submitted 11 June 2017; Accepted 19 July 2017

INTRODUCTION

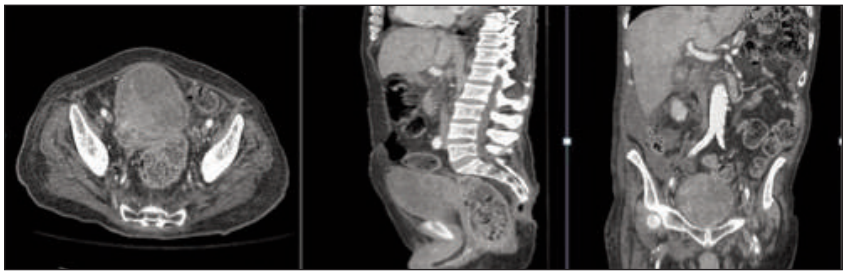
The majority of bladder cancers (95 to 98%) originate from the urothelium (1). Carcinosarcomas or sarcomatoid carcinomas are extremely rare malignancies, which have a biphasic character involving epithelial and mesenchymal components (2). Loss of heterozygosity in stem cells is considered as the main factor in the underlying development of sarcomatoid carcinomas (2, 3). In addition, cyclophosphamide chemotherapy, smoking, and radiotherapy are considered to play a role in the etiology (4, 5). In most cases, epithelial component includes high grade-urothelial carcinoma, whereas mesenchymal component includes a chondrosarcoma, malignant fibrous histiocytoma, osteosarcoma, leiomyosarcoma, and rhabdomyosarcoma (5-7). Herein, we present a paraplegic case who was diagnosed with a bladder carcinosarcoma in the light of literature data.

CASE REPORT

A 61-year old, paraplegic male patient was admitted to our clinic with painless, gross hematuria with clots for three days. He had a history of coronary artery bypass grafting 12 years ago, spinal anesthesia-related paraplegia which developed two years before, and congestive heart failure (ejection fraction: 35%). He was a smoker. On examination, the paraplegic patient had a catheter without any other remarkable finding. Laboratory test results were normal. Whole abdominal ultrasonography (USG) showed a 9 x 8 cm mass which filled the bladder. Abdominopelvic *computerized tomography* (CT) showed a 9 x 7 cm mass lesion, originating from the right lateral wall of the bladder and occupying the entire bladder (Figure 1). A written informed consent was obtained from the patient and cystoscopic examination was performed under general anesthesia. The mass, which originated from the bladder neck and filled the bladder, was incompletely resected. Pathological examination showed a biphasic pattern, and the result was reported as a sarcomatoid carcinoma. The epithelial component included an adenocarcinoma and squamous-cell carcinoma, whereas the sarcomatous component included a spindle-cell and chondrosarcoma. As the all resection specimen consisted of tumor tissues, we were unable to evaluate the depth of invasion.

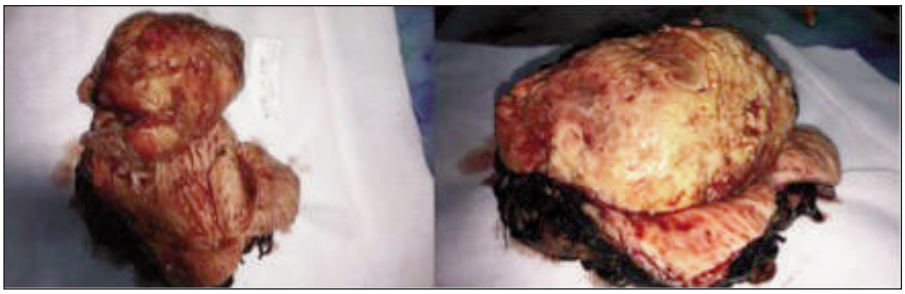
Computed tomography showed no sign of lymph node or organ metastasis. Four weeks after transurethral resection (TUR-BT), radical cystoprostatectomy, lymph node dissection, and ileal conduit surgery were performed. Cystoprostatectomy specimen had a 10 x 8.5 cm tumor in-diameter (Figure 2). After histological examination, tumor was reported as a high-grade sarcomatoid carcinoma, pT2a, pN0, pMx. The histological pattern consisted of 70% sarcomatous component (spindle-cell and chondrosarcoma), and 30% epithelial component (adenocarcinoma and squamous-cell carcinoma). All surgical margin samples and lymph nodes were reported as normal. Four days after the surgery, the patient died due to myocardial infarction.

Figure 1.
A computed tomography image of a 9 x 7 cm heterogeneous mass within the bladder.



No conflict of interest declared.

Figure 2.
A gross view of a solid tumor invading the bladder completely.



Discussion

Bladder carcinomas are extremely rare tumors, which show polypoid character, and can reach large sizes, as assessed in gross examination. Similar to other types of bladder cancer, these tumors are more common in males, and the incidence increases with age (8).

Tumors usually originate from the lateral walls, dome, trigon, and anterior wall (8). Smoking, cyclophosphamide, and radiotherapy are considered to play a role in the etiology of carcinosarcomas due to their undesired effects on the cell proliferation (2, 4).

Similar to all other bladder cancers, these patients are admitted with painless gross hematuria. Dysuria, increased need to urinate, and obstructive symptoms can be also seen (9).

In our case, the patient was admitted with painless gross hematuria and a 10 cm mass originated from the right lateral wall of the bladder.

In most cases, the epithelial component is reported as a high-grade papillary urothelial carcinoma (5, 6).

Sarcomatous component, on the other hand, usually include one or more of the followings: chondrosarcoma, leiomyosarcoma, and malignant fibrous histiocytoma (5-7). In our case, pathological examination showed that the sarcomatous component consisted of a spindle-cell and chondrosarcoma, whereas the epithelial component consisted of an adenocarcinoma and squamous-cell carcinoma. Furthermore, sarcomatoid tumors may affect several organs; however, clinical progression may vary according to the site (10).

The best prognosis is seen, when the tumors involve the respiratory and gastrointestinal system, whereas tumors located in kidneys, bladder, prostate, and stomach have a poor prognosis (10). Bladder carcinosarcomas are considerably aggressive, and there is no consensus on the standard treatment of these malignancies. However, TUR-BT, radical cystectomy, radical cystectomy + radiotherapy, partial cystectomy + neoadjuvant radiotherapy followed by radical cystectomy are used for the treatment. Although the efficacy of these methods is controversial, the main treatment methods are radical cystectomy and lymph node dissection (8, 11).

Aggressive surgery during early period is the only curative treatment option (5).

In addition, radical cystectomy can be performed effectively in patients who have superficial or deep invasion, whereas transurethral resection and partial cystectomy are usually not preferred due to the increased risk of incomplete resection (8). Recently, the combination of radical cystoprostatectomy and lymphadenoctomy with neoadjuvant or adjuvant chemotherapy and/or radiotherapy has been recommended (11).

On the other hand, cancer-specific survival of carcinosarcomas is extremely poor, and tumor grade and subtype of epithelial component are the most important factors affecting survival (11, 12).

While the majority of patients die within the first year, some patients live longer than 10 years (10). According to a recent study, one-, five-, and 10 years survival rates for bladder carcinosarcomas are 53.9%, 28.4%, and 25.8%, respectively (10).

Unfortunately, our case died due to myocardial infarction four days after radical cystoprostatectomy.

Conclusions

Due to aggressive and fatal nature of carcinosarcomas, a radical treatment approach should be implemented immediately as possible after the diagnosis.

Considering available data on carcinosarcomas in case reports, further large-scale studies should be carried out to gain a better understanding of the biological basis of this disease and to develop targeted therapies.

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CASE REPORT

Giant primary scrotal lipoma: A case report

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Summary ***Lipomas are benign mesenchymal tumours that are rarely seen in the scrotum. Few cases of primary scrotal lipomas originating from the scrotal wall have been reported in the literature. We describe the case of a giant primary intrascrotal lipoma presenting as scrotal swelling and discomfort. Findings from scrotal magnetic resonance imaging were highly suspicious for lipoma. The mass was completely excised and histological examination confirmed the diagnosis of lipoma.***

KEY WORDS: Magnetic resonance imaging; Scrotal lipoma.

Submitted 22 June 2017; Accepted 19 July 2017

INTRODUCTION

Lipomas are common benign mesenchymal tumours that may occur in any part of the body. These neoplasms, however, are rarely seen in the scrotum (1). In most cases, scrotal lipomas originate from the adipose tissue of the spermatic cord evolving towards the scrotum or develop in the spermatic cord itself. Lipomas that originate from the isolated adipose lobules of the scrotal subcutaneous tissue are uncommon and are called "*primary scrotal lipomas*" (2-5). We describe the case of a giant primary intrascrotal lipoma presenting as swelling of the scrotum causing discomfort.

CASE REPORT

A 54-year-old man was referred to our Institution for swelling of the scrotum causing discomfort. His past medical history was unrelevant. On physical examination, an irreducible, elastic, regularly shaped mass was evident on the midline of the scrotum. Both testes and spermatic cords were found to be localized in the scrotum and were of normal consistency and size. Serum α-feto protein, beta-human chorionic gonadotropin, and lactate dehydrogenase levels were within the normal ranges. Ultrasound evaluation showed an heterogeneous, hyperechoic solid mass, not infiltrating the testes. *Magnetic resonance imaging* (MRI) was required and revealed an 8 x 10 x 12 cm mass with homogeneous high signal intensity in T1-weighted images. No enhancement was seen after administration of gadolinium contrast material. These findings were highly suspicious for lipoma. Surgery was planned. A longitudinal midline scrotal incision was performed. The testicles, epididymis and cord structures were intact. A well encapsulated, ovoid yellow-orange mass was found located within the scrotal wall and was easily removed (Figure 1). The incision was closed with no drainage and the postoperative course was uneventful. The specimen weighed 600 g. Microscopic examination of the tissue revealed the presence of mature adipocytes and the absence of cellular atypia. Finally, the diagnosis of primary scrotal lipoma was made. Surgery provided a rapid resolution of symptoms.

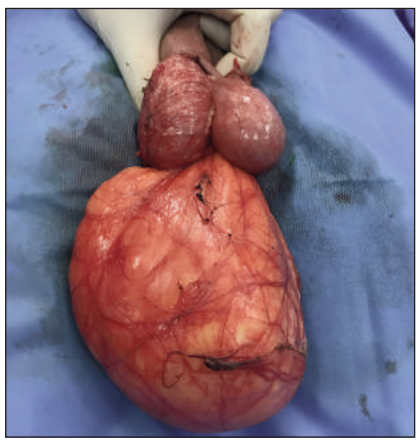

Figure 1. *Intra-operative photograph showing a lobulated yellow-orange mass.*

DISCUSSION

Intrascrotal lesions provide a diagnostic challenge for the urologyst due to the multiple anatomic structures found in this confined space (3, 4). While most testicular lesions are malignant, the majority of tumours arising from extratesticular structures are benign (3). Despite rare, however, malignant neoplasms may also originate from extratesticular structures and include liposarcoma, leiomyosarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma, mesothelioma, and lymphoma. Lipomas are the most frequent benign neoplasm of the scrotum. However, they are rarely seen in everyday clinical practice (5). These tumors may develop from the spermatic cord, from herniation of properitoneal fat or may originate from isolated fat cells of the subcutaneous tissues of the scrotal wall. In many cases, the specific site of origin cannot be easily identified. To our knowledge, there are very few cases of primary scrotal lipomas (i.e. lipomas

No conflict of interest declared.

originating from the scrotal wall) published in the scientific literature. Symptoms vary with mass size and pressure caused with growing. According to literature data, the size may vary considerably and weight can reach 9 kg (2). Ultrasonography and MRI play a pivotal role in the evaluation of scrotal masses. Ultrasonography is the the first-line imaging modality as it allows to determine whether a lesion is cystic or solid and its localization. Lipomas commonly appear as uniformly hyperechoic lesions, without internal flow at color Doppler imaging. However, ultrasound findings may be variable and are often nonspecific. MRI has the potential to narrow the diagnosic range and can be very helpful in the evaluation of lipomas as it can easily recognize fatty components. Indeed, high T1 signal intensity is characteristic of fat-containing tumors. Moreover, lipomas can be differentiated from liposarcomas on MRI by the lack of any enhancing soft tissue. However, lesions in this location may have overlapping imaging findings (5). Sometimes, well-differentiated liposarcomas may simulate benign lipomas and the differential diagnosis is complicated (2). The present case presented with typical MRI findings thus emphasizing the diagnostic role of MRI. Surgical excision, through scrotal or combined scrotal and inguinal incision, represents the treatment of choice for symptomatic lesions or when a definitive diagnosis cannot be made at imaging (5).

Surgical excision was requird in the present case in order to manage symptoms. The surgial procedure we described was easy to peform, efficacious and safe.

Conclusions

Primary scrotal lipomas are rare, benign tumors that should be take into account in the differential diagnosis of paratesticular scrotal masses.
Surgical excision provides histopathologic diagnosis and resolution of symptoms.

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LETTER TO THE EDITORS ABOUT:

A retrospective comparison between transrectal and transperineal prostate biopsy in the detection of prostate cancer

Arch Ital Urol Androl 2017; 89:55-9.

The eternal enigma in prostatic biopsy access route

KEY WORDS: *Prostate Biopsy; Transperineal; Transrectal; Detection rate.*

Dear Editors,
We read with interest the article by *Di Franco et al.* (1). The introduction of prostatic magnetic resonance and the relative fusion-biopsy have not yet allowed the expected improvements in prostate biopsy. To our knowledge, there are no works that demonstrate the superiority of fusion techniques on the remaining ultrasound guided prostate biopsies that are still the widely used in the diagnosis of prostate cancer. Furthemore, these technologies are expensive exams and they are not yet available in all centers, especially in those minors. We work at a "*minor*" center and we always keep in mind that the goal of prostatic biopsy is the diagnosis and the staging of prostatic neoplasms.. However, it remains uncertain which of the two techniques, *transperineal* (TP) or *transrectal* (TR), is superior in terms of detection rate during first biopsy setting. Several studies have compared the prostate cancer detection rate but TR and TP access route in prostatic gland sampling seems to be equivalent in terms of efficiency and complications, as reported by *Shen PF et al.* (2), despite several methodological limitations recognized in their work. The results reported by *Di Franco CA et al.* represent the real life experience of most urologists that perform the PB based on their own training experience and available technical devices. From an historical viewpoint, the TP route has been the first one to be used to reach the prostate, both for diagnostic and therapeutic purposes. To date, because it seems to be more invasive and difficult, the TP route is less used worldwide than the TR one (2). Theoretically, the TP approach should detect more prostate cancer than the TR way because the cores of the TP approach are directed longitudinally to the peripheral zone and the anterior part of the prostate (4). The results reported by *Di Franco et al.* seems to confirm these considerations. However, our real life experience differ from the conclusions reached in their work. We recently conducted a prospective evaluation of 352 patients who underwent their first prostate biopsy because of a suspicious of prostate cancer (elevated prostate specific antigen (PSA) and/or abnormal digital rectal examination and/or abnormal findings on transrectal prostatic ultrasound). Patients was randomized as following. A total of 187 patients (Group A) underwent a prostatic biopsy with a transperineal approach in a lithotomic position, using a biplane probe (*8818 BK Medical, Denmark*) and a fan technique with a single perineal median access (5). The remnants 165 patients (Group B) underwent a transrectal ultrasound guided prostate biopsy in a left lateral position, using a end fire probe configuration (*8818 BK Medical, Denmark*) and a sagittal technique. The bioptic prostatic mapping was performed with a 12-core scheme sec. *Gore* (3) by a single experienced operator and the histopathologic evaluation was performed by a single dedicated uro-pathologist. Statistical evaluations were made with a T Student test ($p < 0.005$). Group A and Group B was similar in term of mean patient age (67.9 years and 67 years respectively), mean total PSA (12.1 ng/ml *vs* 12 ng/ml) and digital rectal examination positivity (22% *vs* 29%). The global cancer detection rate was 33,69% (63/187) in the transperineal prostate biopsy group and 48,48 % (80/165) in the transrectal approach ($p = 0.0047$). No significant statistical differences were found in the complications rates between the two groups. Statistical evaluation of site of tumor localization reveal only a trend to statistical significance in apical site tumors diagnosed with the TR approach versus the TP technique. The TR approach had a better diagnostic accuracy than TP technique in case of PSA < 4 ng/ml, intermediate prostate volume (30 and 50 ml), normal digital rectal examination without any relationship with the patient age. In our experience, two aspect may explain the difference between the two group in term of global detection rate. First, we usually perform transrectal biopsy with a sagittal technique that simulates the transperineal way of needle incidence with the prostatic gland. The lateral and anterior gland portions may be sampled more accurately. Second, our transperineal approach consists in a single perineal median access that can make more difficult the gland sampling between the two lobes. However, there was no significant difference in core positivity rate at the peripheral zone, medium gland, apex or any other site such as reported in many randomized clinical trials (2). Unlike the conclusions reported by *Di Franco et al.*, in our experience we found a statistically significant difference between the TR and TP approach, at the first biopsy setting, in term of global cancer detection rate. No differences were found in terms of complications. Moreover, our data suggest that TR approach had a better diagnostic accuracy than TP technique in case of PSA < 4 ng/ml, prostate volume 30-50 ml, normal digital rectal examination without any relationship with the patient age. The further step of the statistical evaluation of our data will be the definition of the possibility that the TR biopsy determine a better staging of prostate cancer than TP approach as first procedure.

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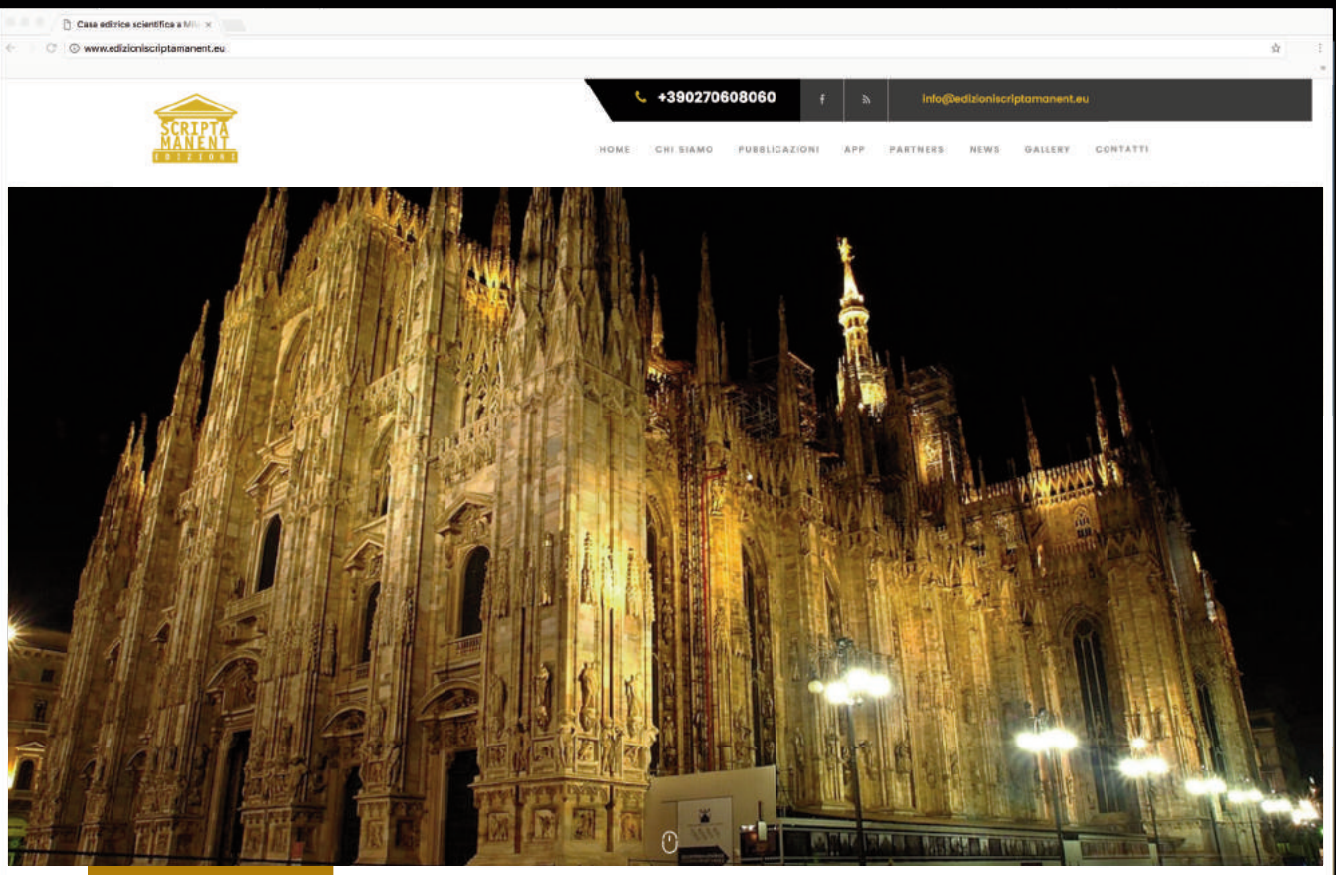

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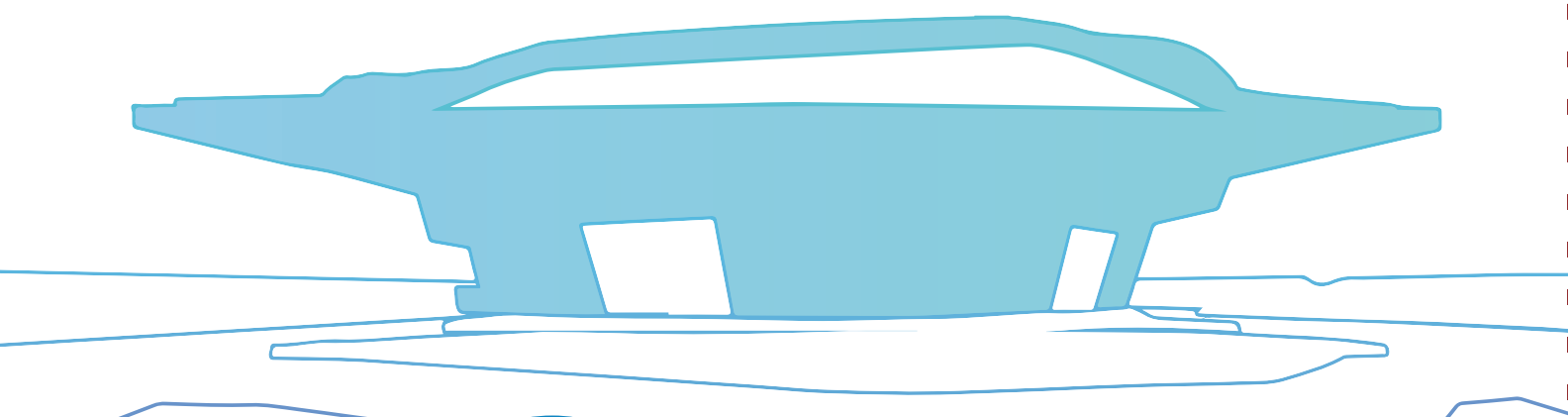

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