Original Article

Improvement of Health-Related Quality of Life in Patients with Overactive Bladder Syndrome: A Subanalysis of the Prospective, Noninterventional Study BELIEVE in the Greek Population

Abstract

Objective: The BELIEVE study is a prospective, noninterventional study which was conducted in a real-world setting in Europe and assessed quality of life, treatment satisfaction, healthcare resource utilization, and persistence with treatment in patients with overactive bladder (OAB) syndrome prescribed mirabegron as part of routine clinical practice. We present the results of a subanalysis of the BELIEVE study in the Greek population. **Materials and Methods:** The primary endpoint was change from baseline in quality of life (QoL) based on the OAB-questionnaire (OAB-q), consisting of the Symptom Bother Scale and health-related QoL (HRQoL). Change from baseline in QoL based on the EQ-5D-5 L health survey, treatment patterns and persistence with treatment, as well as adverse events during the study were also assessed. The duration of the observation period was 12 months. **Results:** A total of 97 OAB patients from 10 sites in Greece participated in the substudy; 89 completed the OAB-q at baseline and at least at one follow-up visit (Full Analysis Set, mean age 62.7 ± 10.9 years, 86.5% female). At baseline, 73% of patients were "new," 14.6% were "lapsed," 9% switched treatment, and 3.4% were on combination treatment. The scores in the Symptom Bother Scale and HRQoL Scale improved significantly from baseline at 10–12 months (−32.4 ± 2.54 and 30.2 ± 2.49, respectively). The EQ-5D subscales confirmed that mirabegron led to an improvement in the HRQoL of patients. At 10–12 months, 72% of patients were continuing on mirabegron treatment for OAB, either as single treatment (60%) or as combination treatment (12%). Mirabegron was well-tolerated, as no serious drug-related adverse events (AEs) were observed, whereas only a small percentage (6.2%) of drug-related AEs resulted in treatment discontinuation. **Conclusions:** The Greek population subanalysis confirmed the European results of the BELIEVE study. Patients who received mirabegron in a real-world setting showed clinically meaningful improvements in HRQoL. Mirabegron demonstrated a high persistence rate (72% at 12 months), and good tolerability. The overall improvement in HRQoL, particularly in the population continuing to receive mirabegron at 10–12 months, and the low incidence of AEs may have contributed to the high persistence rate.

Keywords: *Mirabegron, overactive bladder, persistence with treatment, quality of life*

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Introduction

Overactive bladder syndrome (OAB) is characterized by urinary urgency, with or without urgency incontinence, usually accompanied by frequency and nocturia, in the absence of urinary tract infection or other detectable pathology.[1] According to the EPIC study, the largest to date population-based survey conducted in five European countries, the overall prevalence of OAB symptoms is approximately 12% with similar rates between men and women and seeming to increase with age. Notably, this study further confirmed that most patients with OAB appear to most commonly have a combination of symptoms in both sexes.[2]

Although not life-threatening, OAB syndrome has a negative impact on patient's daily activities, mental health, sexual and family life, and overall quality of life (QoL). The diagnosis and treatment of OAB are largely driven by patient's reporting of symptoms in combination with the physician's assessment. Patient's perception of treatment outcome should be regarded as an important measure of efficacy since the patient himself is the final recipient of the overall treatment benefit (improvement of symptoms, AEs, and effect on daily life).[3-5] Within the

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context of assessing the effect of the syndrome on the QoL, several valid and reliable questionnaires have been developed,[6] such as the OAB Symptom Score[7] and the OAB -questionnaire (OAB-q).[8]

Currently, several treatment options are available for OAB (bladder training, behavioral, pharmacological, and surgical treatment),[9] with antimuscarinic agents representing the mainstay of pharmacological treatment.[10] Mirabegron is a b3-adrenoceptor agonist approved for the treatment of OAB, with a mechanism of action different from that of antimuscarinic agents.[10-12] It is well-tolerated and effective in the treatment of OAB symptoms, such as urinary incontinence and frequency.[13] It demonstrates similar efficacy to most antimuscarinics, but a lower incidence of dry mouth, the most common AEs of antimuscarinics and one of the main reasons for their discontinuation.[12,14]

Clinical trials with mirabegron have demonstrated improvements in secondary efficacy variables related to QoL using patient self-administered questionnaires (e.g., OAB-q, Patient Perception of Bladder Condition [PPBC], Treatment Satisfaction–Visual Analogue Scale [TS-VAS]).[15,16] The BELIEVE study is a prospective, noninterventional study, which was conducted in a real-world setting of routine clinical practice in Europe and assessed the QoL, treatment satisfaction, healthcare resource utilization and persistence with treatment in OAB patients prescribed mirabegron as part of routine clinical practice.[17] In this article, we present the results of a subanalysis of the BELIEVE study in the Greek population.

Objective

The primary objective of this subanalysis is to assess the effect of mirabegron on patients' QoL in the Greek population, as recorded by the OAB-q. Secondary objectives include patients' persistence with treatment, prescription status, healthcare resource utilization, as well as safety of treatment.

Materials and Methods

The design and methods of the prospective, noninterventional BELIEVE study have already been published.[17] Overall, 862 OAB patients from eight European countries participated in the study, 97 of whom were from Greece. The BELIEVE study received official approval from the Ethics Committee, as well as other regulatory bodies in all participating countries, in accordance with the country-specific requirements. Patients provided their written consent before their study enrollment.

This sub-analysis was conducted in patients with OAB (males and females aged ≥18 years) from 10 sites in Greece, prescribed mirabegron as part of routine clinical practice. Patients were enrolled in the study before the initiation of mirabegron treatment and were kept under medical observation for 12 months. Patients with mixed urinary incontinence where stress urinary incontinence (SUI) was the predominant symptom, patients at risk of acute urinary retention (at the investigator's opinion), and finally, patients undergoing catheterization were excluded from participation in the study.

Patients were categorized as follows:

- New: Patient who is treatment-naïve or has not received any pharmacological OAB treatment for ≥2 years
- Lapsed: Patient who has previously received a prescription for pharmacological OAB treatment, but did not return for a prescription refill >3 months to <2 years from the expected date of refill to the date of enrollment
- Switched: Patient who has returned to the clinic within 3 months of the due date to refill his prescription and a decision has been independently made by the physician to change his treatment to mirabegron as part of the routine clinical practice
- Combination treatment: Patient receiving an oral antimuscarinic treatment for OAB at baseline, but the clinician has decided to add mirabegron for additional improvement of OAB symptoms.

The primary endpoint was change from baseline in QoL, as assessed based on the OAB-q. The OAB-q is a valid psychometric questionnaire which has been extensively used in QoL-related research in individuals with OAB. It can be self-administered and consists of 33 items, 8 of which are referring to symptom bother (Symptom Bother Scale) and 25 referring to health-related QoL (HRQoL), sub-divided in the sub-scales Coping, Concern, Sleep, and Social Interaction.[8] The OAB-q was assessed at baseline visit as well as at each visit during the 12-month observation period.

The secondary endpoints were the following:

- Change from baseline in QoL based on the EQ-5D-5 L. The EQ-5D-5 L is an international standardized, generic instrument for the description and assessment of QoL. It consists of 5 main subscales (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with 5 response levels characterized from no problems to inability to perform the activity. In addition, it contains a VAS, which is used by the patient to self-rate his/her health status
- Utilization of healthcare resources related to OAB management (type of visit, any medical intervention, inpatient hospitalization, or rehabilitation to manage complications associated with OAB-any selective surgery that had been scheduled before patient-initiated mirabegron was not counted under this case)
- Treatment patterns and persistence with treatment, and in particular:
  - Treatment patients were switched to and reasons associated with switching

  - Treatment discontinuation and reasons associated with it.
  - Number of treatment days on current treatment.
  - Time from treatment initiation to discontinuation or switching to another treatment.
  - Time from treatment initiation to prescription of additional oral OAB treatment and reasons for combination treatment.
- Change from baseline in incontinence status. OAB "wet" patients were defined as those having at least one urgency incontinence episode in the 3 days before the visit. SUI and postmicturition dribble were not included in this assessment. OAB "dry" patients were defined as those having no urgency incontinence episodes in the 3 days before the visit
- AEs reported during the study.

All variables were assessed at baseline visit as well as at each visit during the 12-month observation period.

For the statistical analysis, descriptive statistics were used to summarize all collected information of patients participating in the study. For continuous variables, descriptive statistics included the number of individuals (n), mean (for observed values and absolute changes from baseline), standard deviation (SD), median, minimum, and maximum. Moreover, with regard to the questionnaires' analysis, the standard error and 95% confidence intervals are given for the mean change from baseline. For categorical variables, the number and percentage of individuals by each category were recorded by visit. The number of missing observations was specified for each variable.

The full analysis set (FAS) included all enrolled patients who signed the informed consent form and completed the OAB-q at baseline and at least one follow-up visit. The FAS was regarded as the main analysis set for primary and secondary endpoints, baseline characteristics, disposition, and medical history of patients.

The per-protocol set (PPS) included all patients who received mirabegron for 10–12 months and completed the OAB-q at baseline and at 10–12 months. The safety analysis set (SAF) consisted of all patients who received at least one dose of mirabegron during the study.

Results

Overall, 97 patients from 10 sites in Greece participated in the study, with a mean (± SD) age of 63.4 (±10.8) years and the majority of them being females (n = 83, 85.6%). All 97 patients received at least 1 dose of mirabegron during the study (SAF). Of all patients, 70 (72.2%) were "new," 10 (10.3%) were "lapsed," 14 (14.4%) were "switched" and 3 (3.1%) were on combination treatment. The severity of OAB symptoms was evaluated as moderate or as severe by 47 patients (48.5%), respectively.

Fifty-four patients received mirabegron for 10–12 months and completed the OAB-q at baseline and at 10–12 months (PPS). Concomitant medication use (for a disease other than OAB) was reported by 56 patients (57.7%). Ten patients (10.3%) discontinued early from the study (4 were lost to follow-up, 2 due to lack of efficacy, 3 due to AEs, and 1 for "other" reason which was not reported).

Eighty-nine patients with a mean (± SD) age of 62.7 (±10.9) years (77 females, 86.5%) completed the OAB-q at baseline and at least at one follow-up visit (FAS). In the FAS, the severity of OAB symptoms was evaluated as moderate by 44 patients (49.4%) and as severe by 43 patients (48.3%). Sixty-five patients (73%) were "new," 8 (9%) were "lapsed," 13 (14.6%) were "switched," and 3 (3.4%) were on combination treatment.

The most commonly reported medical conditions at baseline were hypertension (FAS 18%, SAF 18.5%), hyperlipidemia (FAS 12.4%, SAF 13.4%), diabetes mellitus (FAS 10.1%, SAF 9.3%), hypothyroidism (FAS 6.7%, SAF 6.2%), osteoporosis (FAS 6.7%, SAF 5.2%), urinary incontinence (FAS 5.6%, SAF 5.2%), pollakiuria (FAS 5.6%, SAF 5.2%), benign prostatic hyperplasia (FAS 4.5%, SAF 3.1%), and nocturia (FAS 3.4%, SAF 3.1%).

The total score in Symptom Bother Scale and HRQoL Scale [Charts 1-5] appears to improve from baseline at 10–12 months both in FAS and PPS, and so does the score in OAB-q subscales regarding Coping, Concern, Sleep and Social Interaction [Table 1]. This improvement, defined as a decrease from baseline of at least 10% in Symptom Bother Scale score or an increase from baseline of at least 10% in the other subscales (Minimal Important Difference, MID), was reported in a higher percentage of patients at 10–12 months for both FAS and PPS and was consistently higher for PPS compared to FAS.

Health status, as described by the EQ-5D-5 L [Chart 6] and the EQ-5D VAS [Chart 7], improved from baseline visit at 10–12 months in the FAS [Table 2], except for the

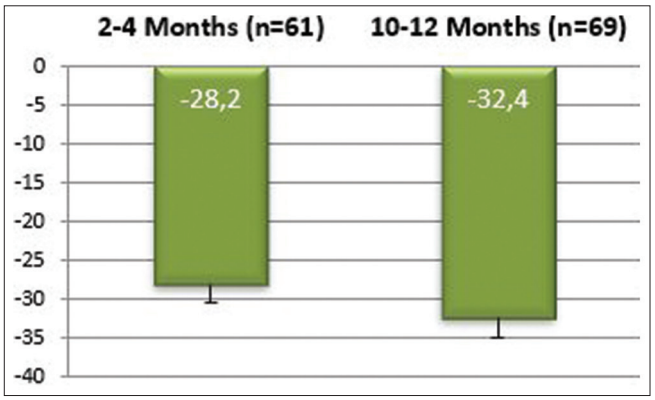

Chart 1: Change from baseline of symptom bother score for full analysis set population

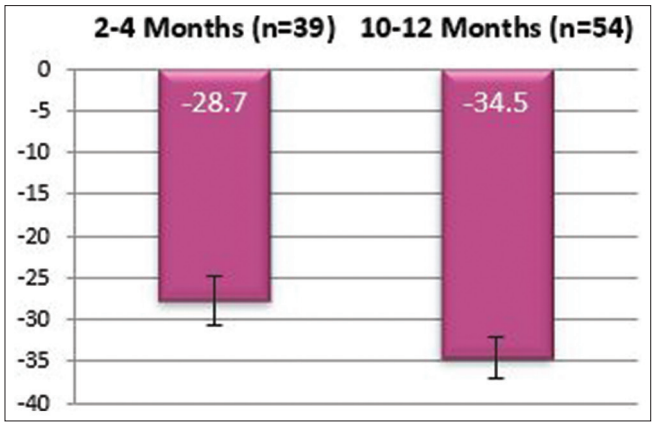

Chart 2: Change from baseline of symptom bother score for per protocol set population

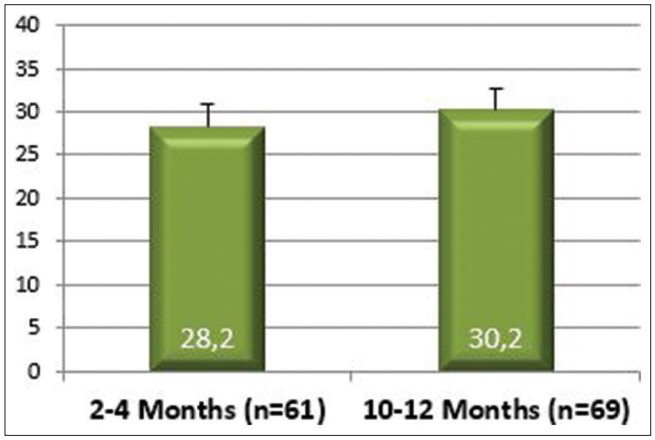

Chart 3: Change from baseline of health-related quality of life total score for full analysis set population

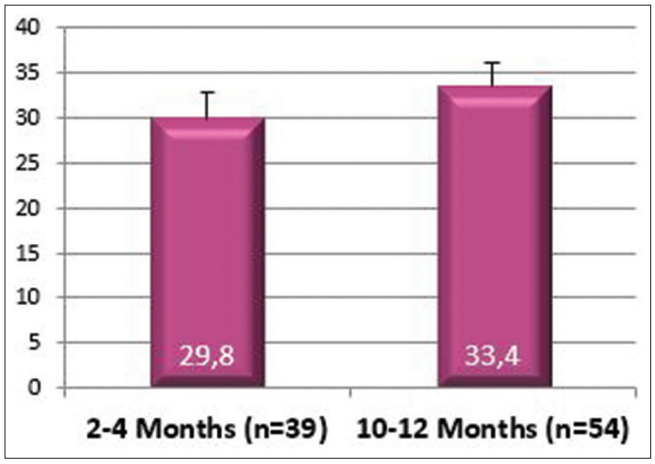

Chart 4: Change from baseline of health-related quality of life total score for per protocol set population

"Self-care" dimension that already had a low symptom score (1.1 ± 0.05) at baseline visit and showed no change at both time-points.

In total, a very small number of patients visited a healthcare professional due to OAB (9 [10.1%], FAS). Urologists were the most frequently visited healthcare professionals. The overall healthcare resource utilization was minimal, based on examinations performed (such as bladder ultrasound), medical interventions, and hospital visits/admissions, as presented in Table 3.

Prescription status reveals persistence with treatment, as well as treatment discontinuation and switching patterns. At 10–12 months, 56 patients (72%) in total were continuing on mirabegron treatment for OAB, either as single treatment (47 patients, 60%) or as combination treatment (nine patients, 12%) (FAS). The rest either switched from mirabegron to another OAB treatment (seven patients, 9%) or discontinued OAB treatment completely (15 patients, 19%) [Table 4 and Chart 8]. The most common reasons for switching or discontinuing mirabegron treatment were resolution/successful treatment of the symptom and medication cost.

Mirabegron was well-tolerated. No serious AEs related to mirabegron were observed. Overall, 23 patients (23.7%) experienced at least 1 AE (31 AEs in total). Eight out of 31 AEs, in six patients (6.2%), were considered as (possibly or probably) related to mirabegron, were of mild or moderate intensity (urinary tract disorders were the most common AEs), and led to permanent drug discontinuation [Tables 5 and 6].

Discussion

HRQoL has been assessed in large (>400 patients on mirabegron), multicenter, randomized, double-blind studies of[12,13,18,19] or 52-week[20] duration, and in large real-world studies (>1000 patients on mirabegron).[21-23] In the context of these studies, treatment with mirabegron (50 mg) for 12 weeks in OAB patients resulted in statistically significant improvements in the objective efficacy variables and secondarily, in patient-assessed outcomes compared to placebo.[13,18,19] Two-thirds (2/3) of patients who received mirabegron experienced a change greater than the MID (10 points) in the Symptom Bother Scale of the OAB-q, which is indicative of the therapeutic benefit as experienced by patients.[24] The efficacy of mirabegron (50 mg) (as recorded by the OAB-q, PPBC, and TS-VAS questionnaires) appears to be maintained throughout a 12-month period.[20,25]

In the present subanalysis, an improvement in HRQoL based on OAB-q scores was recorded. These improvements were observed from baseline to 2–4 months, and were subsequently maintained and further increased at 10–12 months of mirabegron treatment (symptom bother scale score −32.4 ± 2.54 and HRQoL scale total score 30.2 ± 2.49) [Table 1 and Charts 1,3]; confirming the positive results of the 52-week randomized trial (−13.1 ± 0.65 and 10.7 ± 0.58, respectively).[20] In addition, a quite high percentage of patients exceeded the MID (70.8% and 64% in the FAS for the total score in the Symptom Bother and HRQoL scales, respectively), demonstrating clinically meaningful improvements.

Table 1: Improvement (minimal important difference)* from baseline in overactive bladder-q subscales at 2-4 months and 10-12 months (full analysis set and per-protocol set)

OAB-q subscale	2-4 months				10-12 months		
	FAS						
	Baseline (*n*=89) (mean value±SE)	Endpoint (*n*=61) (mean value±SE)	Change from baseline (mean value±SE)	Improvement* *n* (% with MID)	Endpoint (*n*=69) (mean value±SE)	Change from baseline (mean value±SE)	Improvement*, *n* (% with MID)
Symptom bother score	51.3±1.73	23.6±1.95	−28.2±2.38	53 (59.6)	17.9±2.37	-32.4±2.54	63 (70.8)
Coping	46.2±2.75	79.4±2.76	33.9±3.67	48 (53.9)	82.5±2.65	36.6±3.28	57 (64.0)
Concern	51.9±2.20	82.1±2.30	30.3±2.94	47 (52.8)	83.7±2.50	32.6±2.70	57 (64.0)
Sleep	59.6±2.35	81.6±2.10	25.2±2.65	45 (50.6)	87.8±2.01	27.6±3.03	51 (57.3)
Social interaction	70.1±2.28	90.5±1.52	19.1±2.44	41 (46.1)	89.3±2.15	19.1±2.21	48 (53.9)
HRQoL total score	55.2±2.03	82.8±2.12	28.2±2.67	52 (58.4)	85.3±2.26	30.2±2.49	57 (64.0)
OAB-q subscale	**PPS**						
	Baseline (*n*=54) (mean value±SE)	Endpoint (*n*=39) (mean value±SE)	Change from baseline (mean value±SE)	Improvement* *n* (% with MID)	Endpoint (*n*=54) (mean value±SE)	Change from baseline (mean value±SE)	Improvement*, *n* (% with MID)
Symptom bother score	51.1±2.41	22.6±2.59	−28.7±2.87	34 (63.0)	16.6±2.20	-34.5±2.49	52 (96.3)
Coping	42.5±3.43	79.3±3.56	37.3±4.12	34 (63.0)	83.5±2.57	41.0±3.44	48 (88.9)
Concern	49.7±2.87	81.9±3.22	32.1±3.60	31 (57.4)	85.1±2.37	35.3±2.67	47 (87.0)
Sleep	55.8±3.00	80.5±2.95	26.8±2.93	31 (57.4)	87.9±2.11	32.1±3.46	43 (79.6)
Social interaction	71.6±2.56	90.3±1.86	17.4±2.79	24 (44.4)	91.3±1.78	19.6±2.41	40 (74.1)
HRQoL total score	53.0±2.63	82.5±2.85	29.8±3.11	35 (64.8)	86.4±2.15	33.4±2.68	46 (85.2)

*Improvement, i.e., (MID), is defined as a decrease from baseline of at least 10% in the score of the Symptom Bother Scale, or an increase from baseline of at least 10% in the HRQoL score. SE: Standard error, HRQoL: Health-related quality of life, FAS: Full analysis set, PPS: Per protocol set, MID: Minimal important difference

Table 2: Health status based on the EQ-5D-5L health survey and the EQ-5D visual analog scale from baseline to 2-4 months and 10-12 months (full analysis set)

EQ-5D-5L Symptom and EQ-5D VAS Scale	2-4 months, mean value±SE			10-12 months, mean value±SE	
	Baseline (*n*=89)	Endpoint (*n*=61)	Change from baseline	Endpoint (*n*=71)	Change from baseline
Mobility	1.6±0.11	1.3±0.09	−0.1±0.04	1.3±0.09	−0.3±0.09
Self-care	1.1±0.05	1.1±0.05	0.0±0.00	1.2±0.06	0.0±0.04
Usual activities	1.5±0.09	1.3±0.08	−0.3±0.10	1.3±0.08	−0.4±0.12
Pain/discomfort	1.7±0.10	1.4±0.10	−0.2±0.09	1.3±0.07	−0.5±0.09
Anxiety/depression	2.7±0.13	2.2±0.13	−0.6±0.18	1.9±0.11	−0.8±0.14
Health status	66.6±2.04	77.1±1.58	9.6±1.94	77.6±1.53	10.1±2.19

Baseline, 2-4 months and 10-12 months: Contain all patients with data for this time period, regardless of treatment. The EQ-5D-5L questionnaire describes health status. The 5 subscales comprise the following response levels: no, slight, moderate, severe problems, or inability to perform the activity. EQ-5D-5L also contains a visual analog scale, with the following endpoints: Best health status, 100, to worst health status, 0. SE: Standard error, VAS: Visual Analog Scale

At this point, it is worth mentioning that the overall European results of the BELIEVE study[17] demonstrated clinically meaningful improvements, but with lower changes at all the subscales of the OAB-q compared to the Greek sub-analysis (e.g., change from baseline at 10–12 months in the Symptom Bother Scale score was −20.7 and MID responders were 52.5%, whereas in the HRQoL Scale were 17.4% and 45.5%, respectively). The baseline characteristics of the participants may have contributed to the differences observed in the results of the Greek analysis in relation to the results of the European analysis. For instance, with regard to the medical history of patients, differences are evident between the two analyses, especially in terms of prescription status and OAB symptoms at baseline. In the Greek sub-analysis, 73% of all patients were "new" and 14.6% were "switched," while in the European analysis the corresponding percentages were 42.2% and 41.3%, respectively. Moreover, the majority of Greek participants experienced only urgency incontinence (60.7%) and fewer patients experienced urinary frequency/urgency without

Table 3: Utilization of healthcare resources related to the management of overactive bladder in Greece

Healthcare resource utilization	FAS (*n*=89)	
	2-4 months (*n*=57), *n* (%)	10-12 months (*n*=77), *n* (%)
Patients who visited a healthcare professional for OAB since previous visit	0	9 (10.1) (most frequently: Urologist)
Examinations associated with OAB		
Urodynamics	1 (1.1)	0
Urine flow rate	0	0
Bladder ultrasound	0	3 (3.4)
Healthcare resource utilization	**FAS (*n*=89)**	
	2-4 months (*n*=52), *n* (%)	**10-12 months (*n*=77), *n* (%)**
Interventions (due to acute urinary retention) for the management of side-effects or complications due to inadequate management of OAB	0	1 (1.1)
Inpatient hospitalization/rehabilitation facility admission	0	0
Total number of incontinence pads used by the patient in the last 7 days	28 (31.5)	36 (40.4)

FAS: Full analysis set, OAB: Overactive bladder

Table 4: Summary of prescription status and time on treatment in Greece full analysis set

Prescription status	2-4 months (*n*=60)	10-12 months (*n*=78)
Mirabegron as single treatment	53	47
Combination treatment	1	9
Switched from mirabegron to other OAB treatment	5	7
Discontinuation	1	15
Days from baseline on current mirabegron treatment, mean value±SD (*n*)		
Including combination treatment	82.6±17.0 (54)	341.4±38.3 (56)
As single treatment	82.5±17.1 (53)	342.3±41.5 (47)
To first reported discontinuation or switching to another OAB treatment	92.2±4.1 (6)	344.8±21.3 (13)
To first reported prescription of additional oral OAB treatment	92.0 (1)	331.3±4.2 (3)
Reasons for switching mirabegron (*n*)		
Insufficient relief of OAB symptoms	2	1
Cost/amount of co-pay	0	1
Resolution/successful treatment of symptoms	2	0
Other	1	0
Reasons for discontinuation of mirabegron (*n)*		
Insufficient relief of OAB symptoms	0	1
Poor tolerability due to AEs	0	1
Cost/amount of co-pay	0	2
Successful treatment of symptoms	0	5
Other	1	1
Missing data	0	1

AEs: Adverse events, OAB: Overactive bladder, SD: Standard deviation

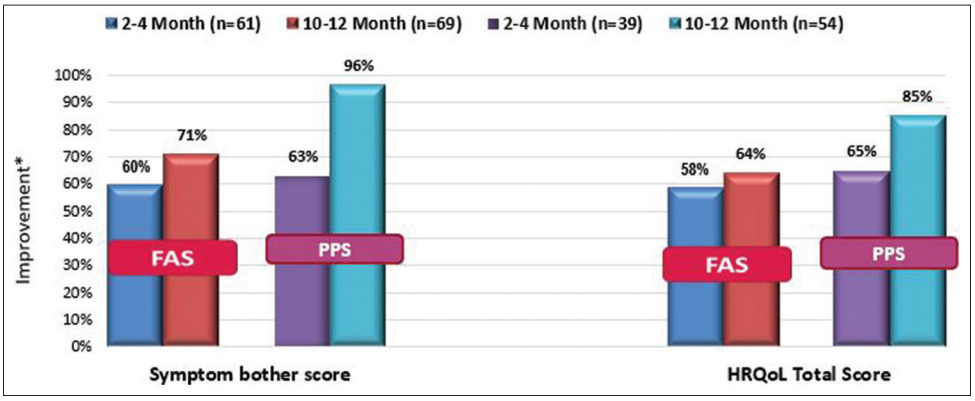

Chart 5: Change from baseline of symptom bother score and health-related quality of life total score

Table 5: Overview of adverse events

	Patients (*n*=97), *n* (%)	Number of events
Patients with at least 1 AE	23 (23.7)	31
Mirabegron-related AEs (25/50 mg)	6 (6.2)	8
Mirabegron-related SAEs (25/50 mg)	0	0
Deaths	0	0
AEs leading to permanent treatment discontinuation	8 (8.2)	10
Mirabegron-related AEs (25/50 mg) leading to permanent treatment discontinuation	6 (6.2)	8

AEs: Adverse events, SAEs: serious adverse events

Table 6: Adverse events leading to treatment discontinuation

Preferred terms (MedDRA version 16.0)	Events	Relation to mirabegron (25/50 mg)
Urinary incontinence (mild)	2	Possible
Discomfort (mild)	1	Possible
Urinary hesitation (mild)	1	Possible
Fatigue (moderate)	1	Possible
Dysuria (mild)	1	Possible
Nocturia (mild)	1	Possible
Pollakiuria (mild)	1	Possible
Urinary retention (mild)	1	Not related
Drug hypersensitivity (mild)	1	Not related

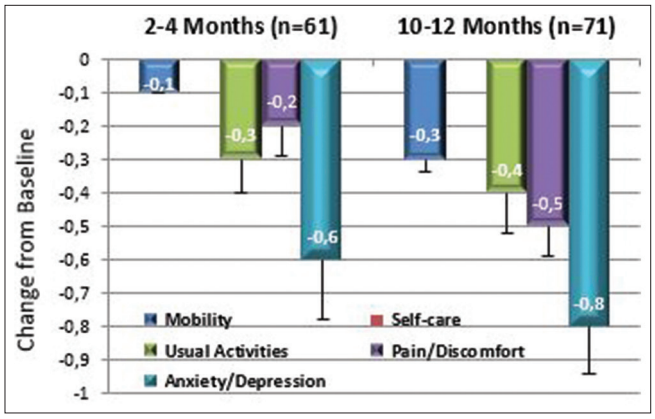

Chart 6: Improvements in the EQ-5D-5 L scale (full analysis set)

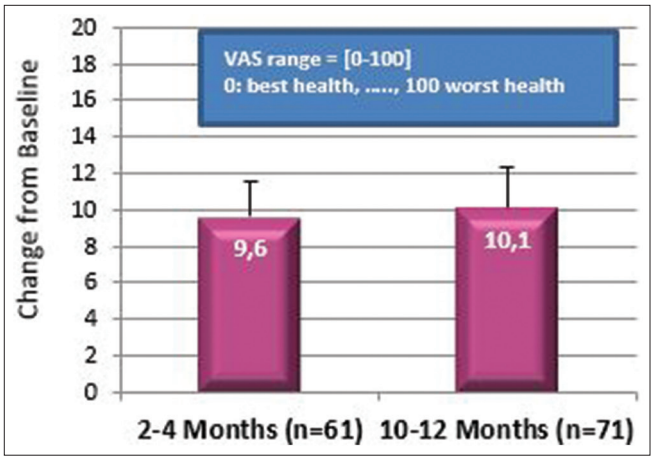

Chart 7: Improvements in the EQ-5D Visual Analog Scale (full analysis set)

incontinence (28.1%), nocturia (21.4%), and mixed stress/urgency incontinence (11.2%) [Table 7]. In the European analysis, these percentages were considerably different (44.5%, 30.4%, 47.5%, and 30.5%, respectively). In addition, another difference between the European and Greek participants was observed in the non-OAB medical history. In particular, the majority of all participants in the BELIEVE study (82% in FAS, 81.7% in SAF) had medical conditions (other than OAB) at baseline, whereas this percentage was quite lower in the Greek sub-analysis (49.4% in the FAS, 49.5% in the SAF). Similar differences between the two populations are also observed in the reported conditions.[17]

All improvements in the OAB-q scores of this sub-analysis at 10–12 months were greater for the PPS than for the FAS. As far as "Social Interaction" subscale is concerned, changes from baseline to endpoint were lower than those in all other measured subscales, at both the European and Greek results. Similar results have also been reported in a phase III trial, which showed statistically significant improvements with mirabegron compared to placebo in the OAB-q subscales (i.e., "Coping" 16.9 ± 1.1 and "Concern" 18.0 ± 1.0), with the exception of "Social Interaction" (7.4 ± 0.8).[19] These results are not surprising, given that "Social Interaction" generally shows less improvement in relation to the other subscales.[26,27]

The EQ-5D Health Survey subscales (individual EQ-5D subscales and health status) confirmed that mirabegron led to an improvement of patients' HRQoL. The EQ-5D VAS has also been used as a secondary outcome in 3 phase III trials, where mirabegron resulted in a quicker and superior improvement in HRQoL compared to tolterodine (an antimuscarinic drug).[28]

Table 7: Baseline characteristics of patients in the full analysis set and safety analysis set

Baseline Characteristics	FAS (*n*=89), *n* (%)	SAF (*n*=97), *n* (%)
Gender		
Male	12 (13.5)	14 (14.4)
Female	77 (86.5)	83 (85.6)
Age (years), mean value±SD	62.7±10.9	63.4±10.8
BMI (kg/m^2), mean value±SD	27.8±5.1 (n=85)	28.0±5.3 (n=91)
Concomitant non-OAB medication	52 (58.4)	56 (57.7)
Medical history, other than OAB	44 (49.4)	48 (49.5)
Hypertension	16 (18.0)	18 (18.5)
Hyperlipidaemia	11 (12.4)	13 (13.4)
Diabetes mellitus	9 (10.1)	9 (9.3)
Hypothyroidism	6 (6.7)	6 (6.2)
Osteoporosis	6 (6.7)	5 (5.2)
Urinary incontinence	5 (5.6)	5 (5.2)
Pollakiuria	5 (5.6)	5 (5.2)
Benign prostatic hyperplasia	4 (4.5)	3 (3.1)
Nocturia	3 (3.4)	3 (3.1)
OAB symptom severity[a]		
Mild	2 (2.2)	3 (3.1)
Moderate	44 (49.4)	47 (48.5)
Severe	43 (48.3)	47 (48.5)
OAB[b]		
Wet	54 (60.7)	59 (60.8)
Dry	35 (39.3)	38 (39.2)
Prescription status		
New	65 (73.0)	70 (72.2)
Lapsed	8 (9.0)	10 (10.3)
Switched	13 (14.6)	14 (14.4)
Combination treatment	3 (3.4)	3 (3.1)
Number of OAB treatments previously exposed		
0	66 (74.2)	71 (73.2)
1	16 (18.0)	19 (19.6)
2	7 (7.9)	7 (7.2)

[a]The categorization of OAB symptoms to mild, moderate, and severe was based on Homma *et al*. (2006), [b]Incontinence status. FAS: Full analysis set, SAF: Safety analysis set, SD: Standard deviation, OAB: Overactive bladder

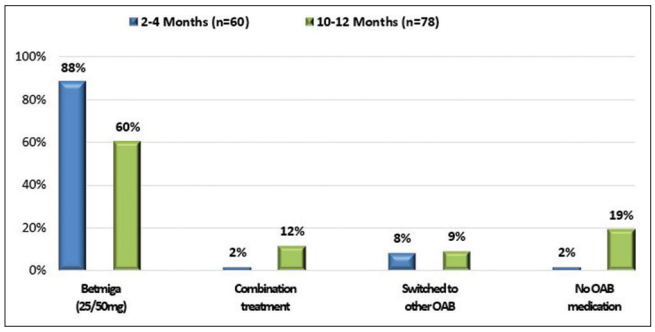

Chart 8: Prescription status (full analysis set)

In addition, a small number of visits to healthcare professionals and interventions associated with OAB management were recorded, demonstrating minimal healthcare resource utilization by Greek participants. These results are consistent with health economic models in the US,[29,30] Canada,[31] and UK,[32,33] which indicate that mirabegron is a cost-effective treatment strategy compared to antimuscarinic drugs. Hakimi *et al*. also observed an improved persistence with mirabegron treatment in routine clinical practice, which is associated with the benefits of reduced healthcare resource utilization compared to antimuscarinic drugs.[34]

Medication persistence and adherence are affected by inadequate efficacy and bothersome side-effects, while their improvement may contribute to successful OAB treatment. In general, reduced persistence and adherence with antimuscarinic treatment for OAB has been observed. In contrast, mirabegron appears to be associated with higher levels of persistence with treatment for OAB in relation to antimuscarinic drugs.[35] In our subanalysis, prescription status showed that 72% of patients (FAS) were continuing on mirabegron treatment (either as single or as combination treatment) at 10–12 months, a fact indicating high persistence, higher than that of the European analysis (53.8%). In addition, our results are in

agreement with those from large retrospective real-world studies in Spain[36] and the United Kingdom.[21,23] In Spain, OAB patients receiving mirabegron experienced longer persistence with treatment than those receiving antimuscarinic drugs (90 vs. 56 days).[36] In a large UK population sample, the mean time to treatment discontinuation was significantly longer for mirabegron compared to antimuscarinic drugs, for example, 169 versus 30–78 days[21] and 101 versus 27–56 days, respectively.[23] Similarly, in a retrospective analysis performed in the US, the mean time to treatment failure for mirabegron was 143 days versus 69 days for antimuscarinic drugs, although the observed adherence and persistence with treatment were similar.[22]

Mirabegron was generally well-tolerated for time periods of up to 52 weeks in adults with OAB in the pivotal clinical trials, with a tolerability profile consistent with that observed at 12 weeks.[13,18-20] Mirabegron had a similar tolerability profile to placebo, with treatment-related AEs recorded in <20% of patients, being rarely serious (≤1% of patients), and leading to treatment discontinuation in <3% of patients.[37] The AEs in this sub-analysis was less than the AEs in the European analysis (23.7% vs. 42.8%), and so were mirabegron-related AEs (6.2% vs. 21%) and mirabegron-related AEs leading to permanent drug discontinuation (6.2% vs. 14%),[17] which were though similar to those of the 52-week randomized trial.[17,20]

According to a meta-analysis, mirabegron appears to be better tolerated than antimuscarinic agents with regard to adverse reactions, such as dry mouth, constipation, and urinary retention.[38] In particular, dry mouth, the most frequently observed adverse reaction and the main AE leading to discontinuation of treatment with antimuscarinics,[39] did not occur at all in our sub-analysis, while it occurred in a very small percentage (0.6%) of the European participants overall.[17]

The limitations identified in the BELIEVE study[17] also apply for this sub-analysis. These include the absence of randomization, as well as the absence of a comparator arm to compare mirabegron with other oral pharmacological treatments, both representing bias points. In addition, the study results may have been influenced by differences in patient's interpretation and understanding of the questionnaires used, depending on the educational background. Nevertheless, it is presumed that we have obtained meaningful information regarding symptom bother and QoL, given that patients were followed up regardless of the treatment they were on throughout the 12-month observation period, and at the same time, patient-reported outcomes in routine clinical practice have been evaluated.

Conclusions

The subanalysis in the Greek population confirmed the European results of the BELIEVE study. Patients receiving mirabegron in a real-world setting experienced clinically meaningful improvements in HRQoL. Mirabegron demonstrated a high persistence rate (72%) at 12 months (FAS population) and good tolerability, as no unexpected safety issues were observed and only a small percentage (6.2%) of drug-related AEs led to treatment discontinuation. In conclusion, the overall improvement in HRQoL, particularly in the population continuing to receive mirabegron at 10–12 months, as well as the low incidence of adverse events, may have contributed to the high persistence rate.

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Conflict of interest

There are no conflicts of interest.

References

1. Drake MJ. Do we need a new definition of the overactive bladder syndrome? ICI-RS 2013. Neurourol Urodyn 2014;33:622-4.
2. Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, *et al.* Population-based survey of urinary incontinence, overactive bladder, and other lower urinary tract symptoms in five countries: Results of the EPIC study. Eur Urol 2006;50:1306-14.
3. Abrams P, Artibani W, Gajewski JB, Hussain I. Assessment of treatment outcomes in patients with overactive bladder: Importance of objective and subjective measures. Urology 2006;68:17-28.
4. Gormley EA, Lightner DJ, Faraday M, Vasavada SP; American Urological Association, Society of Urodynamics, Female Pelvic Medicine. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline amendment. J Urol 2015;193:1572-80.
5. Corcos J, Przydacz M, Campeau L, Gray G, Hickling D, Honeine C, *et al.* CUA guideline on adult overactive bladder. Can Urol Assoc J 2017;11:E142-73.
6. Bartoli S, Aguzzi G, Tarricone R. Impact on quality of life of urinary incontinence and overactive bladder: A systematic literature review. Urology 2010;75:491-500.
7. Homma Y, Yoshida M, Seki N, Yokoyama O, Kakizaki H, Gotoh M, *et al.* Symptom assessment tool for overactive bladder syndrome – Overactive bladder symptom score. Urology 2006;68:318-23.
8. Coyne K, Revicki D, Hunt T, Corey R, Stewart W, Bentkover J, *et al.* Psychometric validation of an overactive bladder symptom and health-related quality of life questionnaire: The OAB-q. Qual Life Res 2002;11:563-74.
9. Wein AJ, Rackley RR. Overactive bladder: A better understanding of pathophysiology, diagnosis and management. J Urol 2006;175:S5-10.
10. Andersson KE. Pharmacotherapy of the overactive bladder.

Discov Med 2009;8:118-24.
11. Chapple CR, Cardozo L, Nitti VW, Siddiqui E, Michel MC. Mirabegron in overactive bladder: A review of efficacy, safety, and tolerability. Neurourol Urodyn 2014;33:17-30.
12. Maman K, Aballea S, Nazir J, Desroziers K, Neine ME, Siddiqui E, *et al.* Comparative efficacy and safety of medical treatments for the management of overactive bladder: A systematic literature review and mixed treatment comparison. Eur Urol 2014;65:755-65.
13. Khullar V, Amarenco G, Angulo JC, Cambronero J, Høye K, Milsom I, *et al.* Efficacy and tolerability of mirabegron, a β(3)-adrenoceptor agonist, in patients with overactive bladder: Results from a randomised European-Australian phase 3 trial. Eur Urol 2013;63:283-95.
14. Benner JS, Nichol MB, Rovner ES, Jumadilova Z, Alvir J, Hussein M, *et al.* Patient-reported reasons for discontinuing overactive bladder medication. BJU Int 2010;105:1276-82.
15. Nitti V. Clinical testing for overactive bladder. Can Urol Assoc J 2011;5:S137-8.
16. Khullar V. Patient-reported outcomes and different approaches to urinary parameters in overactive bladder: What should we measure? Int Urogynecol J 2012;23:179-92.
17. Freeman R, Foley S, Rosa Arias J, Vicente E, Grill R, Kachlirova Z, *et al.* Mirabegron improves quality-of-life, treatment satisfaction, and persistence in patients with overactive bladder: A multi-center, non-interventional, real-world, 12-month study. Curr Med Res Opin 2018;34:785-93.
18. Herschorn S, Barkin J, Castro-Diaz D, Frankel JM, Espuna-Pons M, Gousse AE, *et al*. A phase III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the β3 adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder. Urology 2013;82:313-20.
19. Nitti VW, Auerbach S, Martin N, Calhoun A, Lee M, Herschorn S. Results of a randomized phase III trial of mirabegron in patients with overactive bladder. J Urol 2013;189:1388-95.
20. Chapple CR, Kaplan SA, Mitcheson D, Klecka J, Cummings J, Drogendijk T, *et al*. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a β(3)-adrenoceptor agonist, in overactive bladder. Eur Urol 2013;63:296-305.
21. Chapple CR, Nazir J, Hakimi Z, Bowditch S, Fatoye F, Guelfucci F, *et al.* Persistence and adherence with mirabegron versus antimuscarinic agents in patients with overactive bladder: A retrospective observational study in UK clinical practice. Eur Urol 2017;72:389-99.
22. Sussman D, Yehoshua A, Kowalski J, Lee W, Kish J, Chaudhari S, *et al.* Adherence and persistence of mirabegron and anticholinergic therapies in patients with overactive bladder: A real-world claims data analysis. Int J Clin Pract 2017;71:12824.
23. Wagg AS, Foley S, Peters J, Nazir J, Kool-Houweling L, Scrine L. Persistence and adherence with mirabegron vs antimuscarinics in overactive bladder: Retrospective analysis of a UK General Practice prescription database. Int J Clin Pract 2017;71:12996.
24. Castro-Diaz D, Chapple CR, Hakimi Z, Blauwet MB, Delgado-Herrera L, Lau W, *et al.* The effect of mirabegron on patient-related outcomes in patients with overactive bladder: The results of *post hoc* correlation and responder analyses using pooled data from three randomized Phase III trials. Qual Life Res 2015;24:1719-27.
25. Chapple CR, Kaplan SA, Mitcheson D, Blauwet MB, Huang M, Siddiqui E, *et al.* Mirabegron 50 mg once-daily for the treatment of symptoms of overactive bladder: An overview of efficacy and tolerability over 12 weeks and 1 year. Int J Urol 2014;21:960-7.
26. Coyne KS, Matza LS, Thompson CL. The responsiveness of the Overactive Bladder Questionnaire (OAB-q). Qual Life Res 2005;14:849-55.
27. Coyne KS, Matza LS, Thompson C, Jumadilova Z, Bavendam T. The responsiveness of the OAB-q among OAB patient subgroups. Neurourol Urodyn 2007;26:196-203.
28. Pavesi M, Devlin N, Hakimi Z, Nazir J, Herdman M, Hoyle C, *et al.* Understanding the effects on HR-QoL of treatment for overactive bladder: A detailed analysis of EQ-5D clinical trial data for mirabegron. J Med Econ 2013;16:866-76.
29. Perk S, Wielage RC, Campbell NL, Klein TM, Perkins A, Posta LM, *et al.* Estimated budget impact of increased use of mirabegron, a novel treatment for overactive bladder. J Manag Care Spec Pharm 2016;22:1072-84.
30. Wielage RC, Perk S, Campbell NL, Klein TM, Posta LM, Yuran T, *et al.* Mirabegron for the treatment of overactive bladder: Cost-effectiveness from US commercial health-plan and Medicare Advantage perspectives. J Med Econ 2016;19:1135-43.
31. Herschorn S, Nazir J, Ramos B, Hakimi Z. Cost-effectiveness of mirabegron compared to tolterodine ER 4 mg for overactive bladder in Canada. Can Urol Assoc J 2017;11:123-30.
32. Aballéa S, Maman K, Thokagevistk K, Nazir J, Odeyemi IA, Hakimi Z, *et al.* Cost effectiveness of mirabegron compared with tolterodine extended release for the treatment of adults with overactive bladder in the United Kingdom. Clin Drug Investig 2015;35:83-93.
33. Nazir J, Maman K, Neine ME, Briquet B, Odeyemi IA, Hakimi Z, *et al.* Cost-effectiveness of mirabegron compared with antimuscarinic agents for the treatment of adults with overactive bladder in the United Kingdom. Value Health 2015;18:783-90.
34. Hakimi Z, Nazir J, McCrea C, Berling M, Fatoye F, Ramos B, *et al.* Clinical and economic impact of mirabegron compared with antimuscarinics for the treatment of overactive bladder in Canada. J Med Econ 2017;20:614-22.
35. Kim TH, Lee KS. Persistence and compliance with medication management in the treatment of overactive bladder. Investig Clin Urol 2016;57:84-93.
36. Nazir J, Hakimi Z, Guelfucci F, Khemiri A, Fatoye F, Blázquez AMM, *et al*. A retrospective study of treatment persistence and adherence to mirabegron versus antimuscarinics, for the treatment of overactive bladder in Spain. BMC Urol 2018;18:76.
37. Nitti VW, Chapple CR, Walters C, Blauwet MB, Herschorn S, Milsom I, *et al.* Safety and tolerability of the β3-adrenoceptor agonist mirabegron, for the treatment of overactive bladder: Results of a prospective pooled analysis of three 12-week randomised phase III trials and of a 1-year randomised phase III trial. Int J Clin Pract 2014;68:972-85.
38. Kelleher C, Hakimi Z, Zur R, Siddiqui E, Maman K, Aballéa S, *et al.* Efficacy and tolerability of mirabegron compared with antimuscarinic monotherapy or combination therapies for overactive bladder: A systematic review and network meta-analysis. Eur Urol 2018;74:324-33.
39. Michel MC, Gravas S. Safety and tolerability of β3-adrenoceptor agonists in the treatment of overactive bladder syndrome – Insight from transcriptosome and experimental studies. Exp Opin Drug Saf 2016;15:647-57.

Original Article

Idiopathic Urethritis in Childhood: Presentation of Five Cases

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Abstract

Introduction: Idiopathic urethritis (IU) in childhood is a rare disease with very few cases reported so far. **Methods:** During the past 3 years, the medical records of young boys diagnosed with and treated for IU in our department were retrieved and analyzed. Herein, their clinical course is presented, and a brief review of the literature is performed. **Results:** Five young male patients (mean age: 8.2 years) presented to the pediatric office with blood spotting of the underwear or urethral discharge, with or without dysuria. All the patients were treated in an outpatient basis and the corresponding clinical courses after a mean follow-up was 15.8 months were favorable. **Conclusions:** IU is a rare disease with a generally benign clinical course. Treatment must be tailored to symptomatic relief with avoidance of antibiotics. An aggressive diagnostic workup should be reserved to those with persistent symptoms or frequent recurrences.

Keywords: *Blood, children, idiopathic, spot, urethritis*

Introduction

Idiopathic urethritis (IU) in childhood is a rare disease considering that very few papers on this topic have been published so far.[1-7] Anecdotally, several pediatricians and urologists have treated young patients for intermittent urethral discharge or blood spotting of the underwear. Although it is recognized as a benign condition, some uncertainty exists about the diagnostic workup, optimal treatment, and long-term consequences in the urinary tract.[1-3] Herein, we present our experience after the diagnosis and treatment of 5 children with IU.

Methods

The medical records of the patients diagnosed with IU were retrieved retrospectively, and the clinical course is presented in Table 1. The past medical history focused on urinary and bowel symptoms, arthritis, and ophthalmic symptoms. A meticulous physical examination was performed. In case of uncertainty, urologic, and/or ophthalmologic consultation was requested. Urethral smears along with urine samples were collected from all five patients, and the specimens were microscopically examined. The techniques used for the detection of common bacteria, Neisseria gonorrhea, Chlamydia trachomatis, Mycoplasma hominis/genitalium and Ureaplasma urealyticum are presented in Table 2. Ultrasonographic (u/s) examination of the urinary tract was routinely performed in all patients. Voiding cystourethrogram, urethroscopy, and urodynamics were considered on an "as needed" basis to patients with refractory symptoms or frequent recurrences. The follow-up data were also re-evaluated. In case of inadequate posttreatment information, a telephone communication was attempted.

Results

During the last 3 years (September 2016 till August 2019), five young male patients (mean age: 8.2, range: 3–14 years) presented to the pediatric office with blood spotting of the underwear or urethral discharge, with or without dysuria. Noteworthy, in three patients, urethritis was associated with chronic constipation and stool impaction. On macroscopic examination, three children had a pale colored, low-viscous, purulent-like urethral discharge. Their prepuce and glans were of normal appearance. Arthritis and conjunctivitis were not confirmed in any of the children. The urinalysis revealed hematuria in two patients, but it was negative for pyuria. Investigation for the

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Table 1: Patients characteristics

Age (years)	Urinary symptoms	Other symptoms	Urinalysis	Bacteria detection	Duration (weeks)	Therapy	Recurrence/duration of recurrence (weeks)	Follow up (months)
3	UD, D, BS	Bowel		Sterile	6	BR, UR, NSAID	At 32/3	26
6	UD, BS			Sterile	3	UR	No	20
14	D, BS	Bowel	RBC+	Sterile	9	BR, UR, NSAID	No	15
7	D, UD	Bowel		Sterile	2	BR, UR	at 49/4	14
11	BS		RBC+	Sterile	7	UR, NSAID	No	7

UD: Urethral discharge, D: Dysuria, BS: Blood spotting, RBC: Red blood count, BR: Bowel regimen, UR: Urinary regimen, NSAID: Nonsteroidal anti-inflammatory drug

Table 2: Techniques used to identify bacteria in urethra specimens and urine samples

Type of bacteria	Culture	Other detection techniques
Common	Mac Concey II, blood, chocolate agar	
Naisseria gonorrhoae	Chocolate agar	Microscopy
Chlamydiae	Not performed	Immunocromatography, PCR
Mycoplasma hominis/genitalium	PPLO broth/agar	PCR
Ureaplasma urealyticum	PPLO and urea containing broth/agar	PCR

PPLO: Pleuropneumonia like organism, PCR: Polymerase chain reaction

presence of bacteria in the urethral and urine specimens was negative.

All the patients were treated in an outpatient basis, and the corresponding clinical courses after a mean follow-up was 15.8 months (range: 7–26) were favorable. The mean duration of symptoms (including time of recurrence) was 21.4 weeks (range: 3–53 weeks). Antibiotics were not prescribed. To those with severe urinary symptoms, instructions for timed voiding and pelvic floor relaxation were provided accompanied by non steroid anti-inflammatory regimens for several days. In cases of constipation, laxatives were administered. At the first follow-up visit (within a month), two patients were symptoms free and at 3-month follow-up visit, all of them were in a good condition.

Two patients recurred at 8 and 12 months, respectively. The investigation and management were similar to that of the first presentation. In both cases, symptoms rapidly improved when a stricter adherence to the treatment instruction was reported. The ultrasonic imaging results were normal, making any association of IU with urinary tract abnormalities unlikely. Thus far, the need for more invasive urinary studies is not justified to any of the patients.

Discussion

IU is a rare disease with fewer than 170 patients presented in the international literature.[1-7] It is characterized by urethrorrhagia, urethral discharge, and intermittent hematuria with or without dysuria. It affects primarily the male population of ages between 5 and 15 years.[1-4] The etiology is unknown. Latent bacterial or viral infections or allergic reaction are implicated in the pathogenesis of IU.[4] It has also been associated with urethra metaplasia, hormonal disorders, or abnormal immune response.[1,5]

When urethritis is diagnosed, bacterial infection (BI) should be excluded.[2,4,6] The differential diagnosis also includes the Reiter's syndrome,[4,8] lithiasis of the urinary tract, and urinary tract neoplasia.[2,5] Others have associated the disease with dysfunctional elimination syndrome which is a constellation of symptoms originating from both the urinary tract and the bowel.[1]

Antibiotics are not considered effective for the treatment of this condition[1,2,5] when compared with other regimens such as laxatives, biofeedback or a-blockers, the antibacterial treatment yielded lower response rates and longer time for complete response. Thus, conservative treatment focused on the intestinal and urinary symptoms may be an adequate and effective management. In addition, a-blockers have been reported to be well tolerant by pediatric patients and may lead to a rapid resolution of symptoms.[1]

Despite the lack of specific therapy, the clinical course seems to be benign. In the majority of patients, the symptoms resolve within 1 year, and the mean duration of symptoms is approximately 10 months.[2] Nevertheless, duration of up to 8 years has been reported.[7] In cases with prolonged symptomatology or frequent recurrences, a more detailed investigation of the urinary tract should be considered and voiding cystourethrogram, urethrocystoscopy and urodynamic studies may be used. Early endoscopy is not generally justified, not only because of the need for general anesthesia, but also because of the risk of postendoscopy urethral trauma and development of urethral strictures.[2,5,7] In contrary to previous reports,[3,4,6] we believe that the use of early endoscopy plays a minimal role in the diagnosis, in decision making and in prognosis.

Some IU patients (10%–15%) may develop urethral strictures[3-5] located primarily in the bulbar urethra.[9] The children and their parents should be informed about

this complication which, if ensues, can be treated with urethrotomy (1) or, alternatively, with meticulous dilatation of the urethra (2). Therefore, a prolonged monitoring of the lower urinary tract function could be advised.

Conclusions

IU is a rare disease with a generally benign clinical course. Should BI, lithiasis, tumor and Reiter's syndrome have been excluded, the treatment must be tailored to symptomatic relief with avoidance of antibiotics. An aggressive diagnostic workup should be reserved to those with persistent symptoms or frequent recurrences in which the probability of diagnosing a urethral lesion (e.g., metaplasia and stricture) is higher. Administration of a-blockers in children with IU may offer relief of symptoms but should be further investigated for safety and effectiveness.

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Conflicts of interest

There are no conflicts of interest.

References

1. Herz D, Weiser A, Collette T, Reda E, Levitt S, Franco I. Dysfunctional elimination syndrome as an etiology of idiopathic urethritis in childhood. J Urol 2005;173:2132-7.
2. Walker BR, Ellison ED, Snow BW, Cartwright PC. The natural history of idiopathic urethrorrhagia in boys. J Urol 2001;166:231-2.
3. Dewan PA, Wilson TM. Idiopathic urethritis in the adolescent male. Eur Urol 1996;4:494-7.
4. Williams ID, Mikhael RB. Urethritis in male children. Proc Roy Soc Med 1971;64:133-4.
5. Docimo SG, Silver RI, Gonzalez R, Muller SC, Jeffs RD. Idiopathic anterior urethritis in prepubertal and pubertal boys: Pathology and clues to etiology. Urology 1998;51:99-102.
6. Harrison SC, Whitaker RH. Idiopathic urethritis in male children. Br J Urol 1987;59:258-60.
7. Kaplan GW, Brock WA. Idiopathic urethrorrhagia in boys. J Urol 1982;128:1001-3.
8. Wu IB, Schwartz RA. Reiter's syndrome: The classic triad and more. J Am Acad Dermatol 2008;59:113-21.
9. Husmann D. Use of sympathetic alpha antagonists in the management of pediatric urologic disorders. Curr Opin Urol 2006;16:277-82.

Original Article

Upper-Pole Infra-Costal Access for Supine Percutaneous Nephrolithotomy: Advantage or Risk?

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Abstract

Objective: There are still disagreements in choosing a better approach to establish a percutaneous tract for percutaneous nephrolithotomy (PCNL), between supine and prone positions. The aim of this study is to investigate the safety, efficacy, and practicability of treating upper-pole renal stones, using an infra-costal puncture in both prone and supine positions. **Materials and Methods:** Fifteen patients underwent infra-costal puncture for the percutaneous treatment of upper-pole stones at our institution over a 3-year period. Seven patients underwent a prone procedure and six had a supine PCNL. All punctures were undertaken by two consultant urologists. Stone clearance was assessed with a plain X-ray kidney-ureter-bladder on postoperative day 1. We retrospectively analyzed our prospectively maintained database to assess stone clearance, complications, and length of stay of these patients. **Results:** The overall stone-free rate was 93.3% (all but one patient). One hundred percentage of the prone group were stone free following the procedure. Nearly 87.5% of the supine group had a complete clearance. Complications and length of stay were comparable for both groups. Almost 25% of the supine group and 14% of the prone group required transfusion. The postoperative pyrexia rates were similar for both groups. The overall complication rate was 26.7% (n = 4) – one case of sepsis and three patients required blood transfusion. There were no thoracic complications. **Conclusions:** Upper-pole renal stones can be safely and effectively treated percutaneously using direct upper-pole puncture via an infra-costal approach in supine position, as well as in prone position.

Keywords: *Infra-costal puncture, percutaneous nephrolithotomy*

Introduction

Upper-pole calyceal stones are best accessed for fragmentation with a direct upper-pole puncture. The indications for upper-pole stone access for percutaneous nephrolithotomy (PCNL) are staghorn calculi, large upper-calyceal calculi, calculi associated with ureteropelvic junction pathology, calculi in anomalous kidneys, and calculi in special anatomy such as that seen in morbidly obese patients.[1] The advantage of upper-pole access for nephrolithotomy is direct access to most of the intrarenal collecting system and upper ureter. Upper-pole access can be achieved either supracostally or infracostally. Traditionally, PCNL has been performed in the prone position,[2] which allows a wide field for kidney puncture, avoids abdominal visceral injuries, and makes the puncture pathway short and straight. Multiple routes of access and the intraoperative use of C-arm fluoroscopy X-ray machines may contribute to the vertical positioning of the puncture.[3,4] This position provides posterior access to the collecting system, which theoretically enables the surgeon to puncture a posterior calyx through Brodel's avascular renal plane without significant parenchymal bleeding and peritoneal perforation. However, the prone position also has some disadvantages. For example, the abdominal pressure decreases end-expiratory lung volume and lung capacity, reducing the ability of patients to tolerate prolonged surgery, contraindicating the prone position in morbidly obese patients and individuals with respiratory diseases.[5] An alternative position for PCNL consists of the modified supine position, in which patients are placed in a supine position with a water bag or a specially designed cushion under the flank.[6] The modified supine position has several advantages.[7-9] Due to greater comfort, the position has a low impact on a patient's blood circulation and respiratory system. This position makes it easier for the anesthetist to monitor the patient, and it may decrease the use of anesthetics.[10-12]

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For high-risk patients, the modified supine position can be changed to facilitate endotracheal intubation anesthesia whenever needed. Moreover, the smaller angle between the horizon and the operating channel improves the removal of crushed stones.[13-15] This position also facilitates simultaneous ureteroscope access when necessary, allowing for the combination of PCNL and the ureteroscope in the management of complex stone diseases. The major disadvantage of the modified supine position is that the kidney is more easily pushed forward by the puncture needle and the fascial dilators, leading to the establishment of a deeper channel.[9,16-18] PCNL has been traditionally performed in the prone position, with this still being the most commonly used position. In the past decade, however, several variations in patient positioning for PCNL have been proposed.

Advantages of the supine position include less patient handling, better drainage of the Amplatz sheath, a combination of antegrade and retrograde approaches, the ability of the surgeon to sit, easier change from spinal or regional to general anesthesia, and higher tolerance, especially in patients with pulmonary or cardiovascular disease. The learning curve for the practicing endourologist is minimal.

Furthermore, there were no significant (prone vs. supine) differences in mean blood loss, need for blood transfusion, and mean hospital stay between groups, similar to previous results,[19] suggesting that operations performed in both positions are effective and safe. There were no significant differences in the complication rate and requirements for blood transfusions. However, another randomized study found that the transfusion rate was higher in the supine (27.5%) than in the prone (7.5%) group.[20] Differences between studies may be due to different transfusion thresholds between different centers. Apparently, PCNL in the prone position was thought to exert a longer time because patients are required to be placed in the prone position after ureteral catheterization and to roll back to the supine position after surgery. Supporting evidence has been provided. For example, randomized trials have reported that operation times were significantly shorter in the supine than that in the prone group.[21]

We compared the efficacy and safety of the supra-costal and infra-costal approaches. We present our experience of accessing the upper pole with an infra-costal puncture in both prone and supine positions for the treatment of renal stones and discuss the efficacy and safety thereof.

Materials and Methods

We undertook a retrospective audit of all patients at a single institution who underwent PCNL for upper-pole stones with an infra-costal puncture over a 3-year period, between 2011 and 2014. All punctures were undertaken by two urology consultants under fluoroscopic guidance, one practicing prone PCNL and the other supine, according to surgeon's preference. A retrospective study was carried out for the 15 patients with renal or upper ureteral stones. The inclusion standards were as follows: complete or incomplete staghorn renal stones with sizes ≥2.0 cm; renal calyceal stones with co-existing calyceal obstruction and clinical symptoms; ureteral stones above L4 and >1 cm in size; stone has stayed in the ureter for >2 months complicated by ureteral ectasia above the stone; or patients who have previously failed shock wave lithotripsy or ureteroscopic lithotripsy. The stone burden (cm^2) was calculated by multiplying the maximal length and maximal width of the stone in plain film of kidney-ureter-bladder (KUB).

Under general anesthesia (GA), the patients were placed in the supine position with a gel cushion [Figure 1] beneath the ipsilateral flank to elevate and expose the loin for percutaneous access and to reduce the possibility of pleural damage. Legs were supported on stirrups to have access to the urethra for retrograde rigid/flexible ureteroscopy [Figure 2]. All patients received intravenous antibiotics at induction. Flexible ureteroscopy was performed initially to identify the position of the stone and retrograde study was performed. Under fluoroscopy guidance, puncture was performed with an 18G coaxial needle, which was inserted into the desired calyx. Tract dilatation was performed using NephroMax™ balloon dilator. A nephrostomy balloon dilation catheter was inserted and a 30 Fr Amplatz sheath was placed in the proper position, allowing the introduction of a nephroscope. A LithoClast® Master (LithoClast ultrasonic system) was used to fragment and remove the stone. At the end of the procedure, all patients had ureteric stent insertion that removed about 3-4 weeks later in the outpatient clinic. The targeted point was one of the rear group calyces in the upper pole [Figures 3 and 4]. For both access approaches, we always minimized the angle between the long axis of our percutaneous tract and the long axis of the collecting system when we were dealing with renal staghorn stones. The point we preferred to target was the calyx with the stone inside that was closest to our puncturing point. When we were dealing with ureteral stones, we always minimized the angle between the long axis of our percutaneous tract and the axis between the proximal and the distal segments of the ureter. The puncture point was in the 11th intercostal space or the 12th subcostal margin.

Stone clearance was assessed with a plain X-ray KUB on postoperative day 1 and in the majority of cases, the stent was removed on postoperative day 2 before discharge.

Results

Fifteen patients in total were identified – seven of which underwent a prone PCNL procedure and eight had a supine PCNL. Two patients had complete staghorn calculi – one of whom was treated in the supine position and the other prone. Six had multiple renal stones and

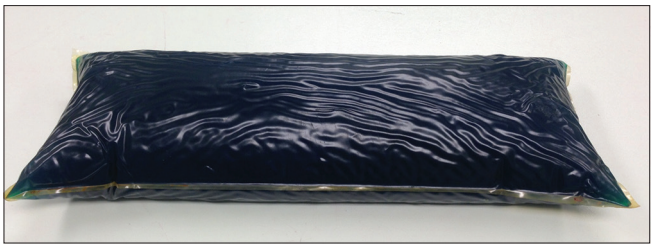

Figure 1: Gel cushion

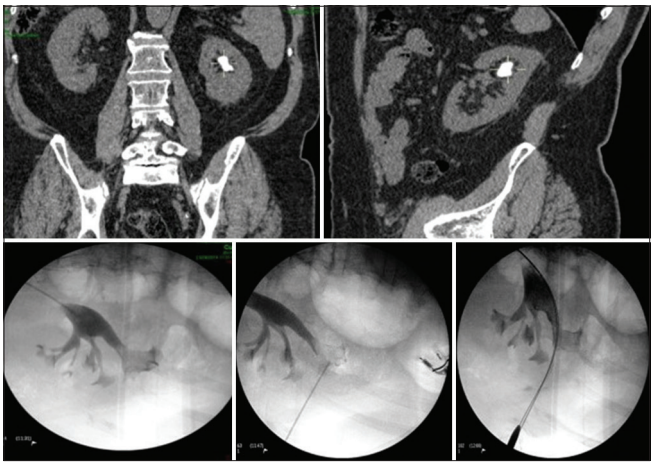

Figure 3: 2.2-cm left upper-pole stone – percutaneous nephrolithotomy – complete clearance with infra-costal access

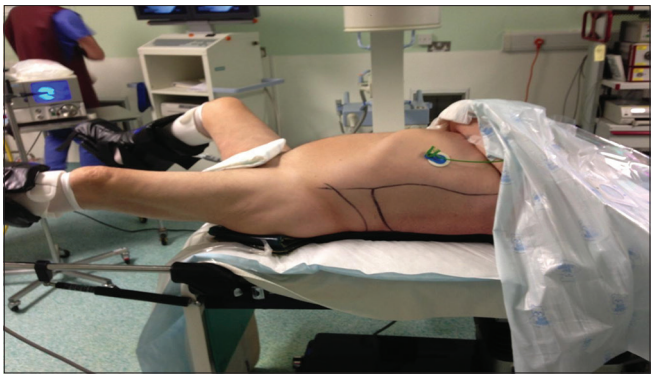

Figure 2: Patient in the supine position – left – percutaneous nephrolithotomy iliac crest, rib cage, and posterior axillary lines marked

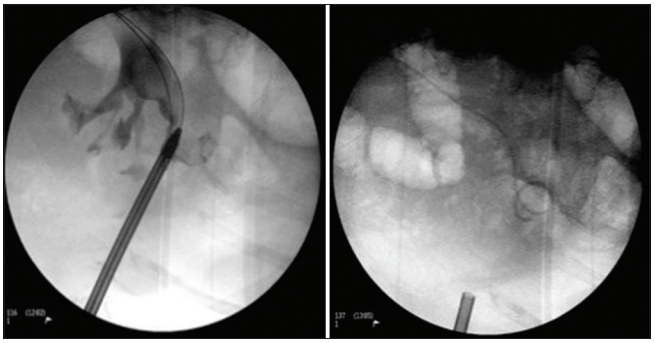

Figure 4: Another case of left upper-pole stone percutaneous nephrolithotomy – infra-costal access

seven patients had a single upper-pole stone requiring treatment. The mean stone size was 24.4 mm (range: 19–41 mm). The mean stone density was 937.1 HU (517 HU–1390 HU).

Fourteen/15 patients (93.3%) were left with a ureteric stent postoperatively, and the other one patient who had an incomplete clearance was left with a nephrostomy.

All but one patient had complete clearance, with a stone-free rate (SFR) of 93.3% (n = 14). Four patients developed a postoperative pyrexia, and was treated for sepsis. There were no bowel or pleural injuries. The length of stay ranged from 1 to 8 days (mean = 3.6 days), which was comparable for both groups (3.4 prone, 3.75 supine). Three patients (20%) required a blood transfusion. Complication rates were similar for the two groups. The stone clearance rates were 100% in the prone group and 87.5% in the supine group although the small numbers and heterogeneity of stone burden make a comparison difficult. Nearly 25% of the supine group and 14% of the prone group required transfusion. The postoperative pyrexia rates were similar for both groups. The overall complication rate was 26.7% (n = 4) – one case of sepsis and three patients required blood transfusion. There were no thoracic complications.

Discussion

Large upper-pole renal stones are best accessed for fragmentation with a direct upper-pole calyceal puncture. This is more commonly undertaken via a supra-costal approach above the 12th or 11th rib. Upper-pole calyceal puncture can also be achieved with an infra-costal puncture. The reported thoracic complication rates with supra-costal puncture range from 5% to 29%.[3,21,22]

We demonstrate that upper-pole calyces can be safely accessed via an infra-costal puncture in both prone and supine positions. SFRs for infra-costal upper-pole access tend to compare less favorably with supra-costal puncture SFR.

Lang *et al*. found that higher SFRs with lower complication rates were achieved when using a prone intercostal approach when compared with that of supine infra-costal puncture. The SFR in their series for infra-costal puncture was just 74% compared with 88% for the supra-costal approach.[3] A further series of 464 patients by Lojanapiwat *et al*. also found higher SFRs in their supra-costal puncture group of 82.2% compared with 77.1% of those treated via an infra-costal puncture. This series did report a significantly higher thoracic complication rate of 15.3% in the supra-costal group however.[5]

Radecka *et al*. also found a higher complication rate for prone supra-costal puncture when compared with that of supine infra-costal approach.[23]

El-Karamany achieved 78% SFRs in their series of supine supra-costal PCNL for staghorn calculi but reported a 10% hydrothorax rate.[24]

More recently, Ozgor *et al*. found comparable SFR and complication rate with supra- versus infra-costal punctures using mini-PCNL in their series of 98 patients.[4]

Falahaktar *et al*. reported an 85% SFR for infra-costal puncture in the supine position in their series with no thoracic complications.[10]

Our series demonstrates that upper-pole stones can be accessed safely and effectively using an infra-costal puncture in both prone and supine positions. Good SFRs which compare favorably with those in the literature were achieved. Our complication rates compare favorably with that of reported series with no major complications.

This is a safe method for treating larger upper-pole stones in select patients and can be used either prone or supine. The main advantage of an infra-costal puncture over a supra-costal puncture is the reduced risk of pleural injury.

PCNL has been traditionally performed in the prone position, with this still being the most commonly used position. In the past decade, however, several variations in patient positioning for PCNL have been proposed. The total cost of performing a supine-combined PCNL is much higher because two endourologists are needed and the costs of using access sheaths and flexible ureteroscope have to be bear in mind, but it is not higher than the cost of a second or third operation to clear all the reaming fragments.[21]

Advantages of the supine position include less patient handling, better drainage of the Amplatz sheath, a combination of antegrade and retrograde approaches, the ability of the surgeon to sit, easier change from spinal or regional to GA, and higher tolerance, especially in patients with pulmonary or cardiovascular disease. The learning curve for the practicing endourologist is minimal.

None of the patients in our study experienced major complications. Complications may occur during or after PCNL and may include extravasation, blood transfusion, and adjacent organ injuries. In other studies, the rates of major complications, however, including septicemia, colonic or pleural injury, and serious bleeding, have been found to vary from 0% to 4.7%.[25] Furthermore, there were no significant (prone vs. supine) differences in the mean blood loss, need for blood transfusion, and mean hospital stay between the groups, similar to that of previous results,[26] suggesting that operations performed in both positions are effective and safe. There were no significant differences in the complication rate and requirements for blood transfusions. However, another randomized study found that the transfusion rate was higher in the supine (27.5%) than in the prone (7.5%) group. Differences between studies may be due to different transfusion thresholds between different centers.[27] Apparently, PCNL in the prone position was thought to exert a longer time because patients are required to be placed in prone position after ureteral catheterization and to roll back to the supine position after surgery. Supporting evidence has been provided. For example, randomized trials have reported that operation times were significantly shorter in the supine than that in the prone group.

Conclusions

The study showed that PCNL in the supine position is an effective and safe method for treating urinary stones. There are numerous advantages for PCNL, including decreasing operating time, evacuation of stone fragment, a more tolerable position for high-risk patients, and sitting position for the surgeon. We hope that this paper could encourage the stone teams to perform PCNL in the supine position. However, we do recognize that our sample size was not large. Larger, prospective studies at multiple clinical centers are warranted to further compare the supra-costal and infra-costal access approaches in treating upper urinary stones using PCNL.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Radecka E, Brehmer M, Holmgren K, Magnusson A. Complications associated with percutaneous nephrolithotripsy: Supra- versus subcostal access. A retrospective study. Acta Radiol 2003;44:447-51.
2. Ray AA, Chung DG, Honey RJ. Percutaneous nephrolithotomy in the prone and prone-flexed positions: Anatomic considerations. J Endourol 2009;23:1607.
3. Sukumar S, Nair B, Ginil KP, Sanjeevan KV, Sanjay BH. Supracostal access for percutaneous nephrolithotomy: Less morbid, more effective. Int Urol Nephrol 2008;40:263-7.
4. Ozgor F, Tepeler A, Basibuyuk I, Kucuktopcu O, Kayali Y, Yanaral F, *et al*. Supracostal access for miniaturized percutaneous nephrolithotomy: Comparison of supracostal and infracostal approaches. Urolithiasis 2018;46:279-83.
5. Lojanapiwat B, Prasopsuk S. Upper-pole access for percutaneous nephrolithotomy: Comparison of supracostal and infracostal approaches. J Endourol 2006;20:491-4.
6. Hopper KD, Yakes WF. The posterior intercostal approach for percutaneous renal procedures: Risk of puncturing the lung, spleen, and liver as determined by CT. AJR Am J Roentgenol 1990;154:115-7.
7. Raza A, Moussa S, Smith G, Tolley DA. Upper-pole puncture in percutaneous nephrolithotomy: A retrospective review of treatment safety and efficacy. BJU Int 2008;101:599-602.
8. Kim SC, Kuo RL, Lingeman JE. Percutaneous nephrolithotomy: An update. Curr Opin Urol 2003;13:235-41.
9. Falahatkar S, Enshaei A, Afsharimoghaddam A, Emadi SA, Allahkhah AA. Complete supine percutaneous nephrolithotomy with lung inflation avoids the need for a supracostal puncture. J Endourol 2010;24:213-8.
10. Valdivia Uría JG, Valle Gerhold J, López López JA, Villarroya Rodriguez S, Ambroj Navarro C, Ramirez Fabián M, *et al*.

Technique and complications of percutaneous nephroscopy: Experience with 557 patients in the supine position. J Urol 1998;160:1975-8.
11. Kumar P, Bach C, Kachrilas S, Papatsoris AG, Buchholz N, Masood J. Supine percutaneous nephrolithotomy (PCNL): 'in vogue' but in which position? BJU Int. 2012;110:E1018-21. doi: 10.1111/j.1464-410X.2012.11188.x. Epub 2012 May 7. PMID: 22564784 Review.
12. Michel MS, Trojan L, Rassweiler JJ. Complications in percutaneous nephrolithotomy. Eur Urol 2007;51:899-906.
13. Lee WJ, Smith AD, Cubelli V, Badlani GH, Lewin B, Vernace F, *et al*. Complications of percutaneous nephrolithotomy. AJR Am J Roentgenol 1987;148:177-80.
14. Aron M, Yadav R, Goel R, Kolla SB, Gautam G, Hemal AK. Multi-tract percutaneous nephrolithotomy for large complete staghorn calculi. Urol Int 2005;75:327-32.
15. Patel RD, Newland C, Rees Y. Major complications after percutaneous nephrostomy–lessons from a department audit. Clin Radiol 2004;59:766.
16. De la Rosette JJ, Zuazu JR, Tsakiris P, Elsakka AM, Zudaire JJ, Laguna MP, *et al*. Prognostic factors and percutaneous nephrolithotomy morbidity: A multivariate analysis of a contemporary series using the Clavien classification. J Urol 2008;180:2489-93.
17. El-Nahas AR, Shokeir AA, El-Assmy AM, Shoma AM, Eraky I, El-Kenawy MR. *et al*. Colonic perforation during percutaneous nephrolithotomy: Study of risk factors. Urology 2006;67:937-41.
18. Vallancien G, Capdeville R, Veillon B, Brissetm JM. Colonic perforation during percutaneous nephrolithotomy. J Urol 1985;134:1185-97.
19. Soucy F, Ko R, Duvdevani M, Nott L, Denstedt JD, Razvi H. Percutaneous nephrolithotomy for staghorn calculi: A single center's experience over 15 years. J Endourol 2009;23:1669-73.
20. Dogan HS, Sahin A, Cetinkaya Y, Akdoğan B, Ozden E, Kendi S. Antibiotic prophylaxis in percutaneous nephrolithotomy: Prospective study in 81 patients. J Endourol 2002;16:649-53.
21. Clavien PA, Sanabria JR, Strasberg SM. Proposed classification of complications of surgery with examples of utility in cholecystectomy. Surgery 1992;111:518-26.
22. Gupta R, Kumar A, Kapoor R, Srivastava A, Mandhani A. Prospective evaluation of safety and efficacy of the supracostal approach for percutaneous nephrolithotomy. BJU Int. 2002;90(9):809-13
23. Lang E, Thomas R, Davis R, Colon I, Allaf M, Hanano A, *et al*. Risks, advantages, and complications of intercostal vs subcostal approach for percutaneous nephrolithotripsy. Urology 2009;74:751-5.
24. El-Karamany T. A supracostal approach for percutaneous nephrolithotomy of staghorn calculi: A prospective study and review of previous reports. Arab J Urol 2012;10:358-66.
25. Tomaszewski JJ, Smaldone MC, Schuster T, Jackman SV, Averch TD.. Factors affecting blood loss during percutaneous nephrolithotomy PRONE-FLEXED PERCUTANEOUS NEPHROLITHOTOMY 953 using balloon dilation in a large contemporary series. J Endourol 2010;24:207-11.
26. Kaufmann OG, Sountoulides P, Kaplan A, Louie M, McDougall E, Clayman R. Skin treatment and tract closure for tubeless percutaneous nephrolithotomy: University of California, Irvine, technique. J Endourol 2009;23:1739-41.
27. Shah HN, Hegde SS, Shah JN, Bansal MB. Safety and efficacy of supracostal access in tubeless percutaneous nephrolithotomy. J Endourol 2006;20:1016-21.

Review Article

Prostate Cancer Therapies and Fertility: What Do We Really Know?

Abstract

We reviewed the literature for articles in English in the Medline database from 1970 until today. The keywords used were "prostate cancer," "fertility," "radical prostatectomy," "external beam radiotherapy," "androgen deprivation therapy," and "chemotherapy." Only the studies with full paper were included in our review. The knowledge for this important issue is minimal and more minimal tends to be the consent of the patients. Prostate cancer does not seem to directly influence fertility, but all its therapies directly or indirectly seem to do so. In many of them, the impact may be reversible, but the mechanisms of this impact are still under consideration. Prostate cancer treatments, predominantly radiation, can cause long-term azoospermia; however, the data in the literature are sparse, mainly derived from small series, and based on these, no safe conclusions can be drawn.

Keywords: *Androgen deprivation therapy, chemotherapy, infertility, prostate cancer, radical prostatectomy, radiotherapy*

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Introduction

According to the American Cancer Society, prostate cancer is the most popular cancer with rates up to 19% (except for skin cancer).[1] The rates of the first diagnosis of prostate cancer in the age group of 35–44 and 45–54 are 0.5% and 9.2%, respectively.[2] The above-mentioned statistic data in conjunction with the mean age of man childbirth (33 years) along with the fact that men tend to start thinking of having children even after 55 years (13.3%), transform the decision for prostate cancer management, in a significant one.[3] In this study, we are reviewing literature about the impact of prostate cancer and its therapy in men fertility, in an effort to increase the 8.7% of informed consent of the patients, according to a very recent study,[4] for fertility issues after prostate cancer therapy.

Prostate Cancer and Infertility

The most important parameter when informing the patient is whether prostate cancer itself can affect spermatogenesis and, as a result, lead to infertility before starting any treatment. In contrast to testicular cancer, which is extensively reported in the literature, the data on prostate cancer are few and not well documented. A recent analysis of 409 men cryopreserving 717 sperm samples showed that just 6% of them suffered from prostate cancer. These patients with an average sperm count of 83.5 × 106 and an average combined motion rate of 50.2% did not have any sperm disorder in their majority.[5] The same results are reported in other relevant studies.[6,7] Cancer can produce catastrophic physiological changes in the body, systematic disorders from mediated factors such as interleukins,[8] tumor necrosis factors, and other factors, as well as organic stress produced by the secretion of various hormonal factors. All the above results in decreased sperm quality ending to infertility.[9] However, it is important to emphasize that none of the above data have been specifically studied for prostate cancer. The above leads us to the conclusion that prostate cancer itself does not cause significant changes in sperm quality fact that must be included in the patient consent form before treatment.

Radical Prostatectomy

The first and obvious mechanism, influencing the fertility of the patient undergoing radical prostatectomy, is anatomical. During radical prostatectomy, ligation of the seminal ducts, removal of the prostate and the seminal vesicles takes place, and erectile dysfunction occurs as a

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direct complication, which causes loss of ejaculation and inability to fertilize. However, the above does not directly affect spermatogenesis and the patient theoretically remains fertile and capable of fertilization by other means like *in vitro* fertilization. However, questions are raised by researchers on the possible effect of prostate removal on the patient's hormonal profile and on whether this effect can negatively affect spermatogenesis. Miller *et al*. studying 63 men who underwent open radical prostatectomy, concluded that postsurgery showed an increase in serum total and free testosterone, oestradiol, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) while showing a decrease in dihydrotestosterone (DHT) ($P < 0.0001$).[10] The researchers conclude that the prostate probably participates in a negative biofeedback mechanism with the hypothalamic–pituitary axis through substances that remain to be demonstrated. Similarly, a more recent study has shown that a statistically significant reduction of LH by 53% and DHT by 13% was observed in a 55-man sample, while FSH increased by 21% and inhibin B was also changed.[11] The above studies, combined with even bigger,[12] suggest a correlation of the hypothalamic–pituitary axis with the prostate as the main mechanism of disorder of the hormone profile of patients after radical prostatectomy. In this case, considering the fact that the values of inhibin B and FSH are directly related to spermatogenesis,[13,14] we conclude that radical prostatectomy itself may play a direct role in the infertility of patients.

Radiation Therapy and Brachytherapy

Testicles are extremely sensitive to radiation, especially the cells of the genital cord. Doses above 4 Gy can cause permanent damage to these cells. Instead, hypogonadism due to Leydig cell damage requires higher doses of radiation (20 Gy). However, radiation therapy for prostate cancer causes a rather negligible destruction of the testicular tissue,[15] despite the fact that the latter receives a 3%–8% of the radiation dose.[16-18] Surprisingly, there are many reports in the literature on clinically significant hypogonadism that persists for at least 2 years after radiotherapy for prostate cancer,[19-21] while histological examination of testis samples taken for recurrent prostate cancer has revealed significant testicular atrophy.[22]

Apart from the dose of radiation, there are other factors that affect the quality of the sperm. These include direct or indirect radiation, number and duration of dosages, and personalized factors such as the response of the patient's tissue to radiation and age. Doses between 0.35 and 0.5 Gy result in reversible azoospermia which is reversed after 10–18 months. However, if the dose rises above 1.2 Gy, then the risk of nonreturn to normal levels is greater.[23-25] Clearly newer imaging and radiotherapy techniques can further reduce testicular radiation in an effort to maintain a patient's fertility.[26] Finally, it is important not to neglect, the potential effects of brachytherapy for prostate cancer on the fertility of patients. Very few data are available in the literature; however, they support that after this therapy, the dose that testicles absorb is clearly negligible (<0.2Gy). A mild and mainly transient oligoasthenospermia may be observed in patients, however the authors suggest waiting from 4 to 12 months for a childbearing attempt.[27,28]

Androgen Deprivation Therapy

Hormonal manipulations succeed in controlling prostate cancer by suppressing testicular testosterone, but it leads to both oligoasthenospermia, loss of libido, and erectile function of patients, leading to infertility. However, most authors are focusing on the study of the potential return of testosterone and spermatogenesis after discontinuation of hormonal manipulation. The quality of the data available in the literature is low because most of them are small case series. In one of these, authors, following 14 patients under androgen blockade, studied the hormonal profile of patients after discontinuation of hormonal manipulation. The conclusion of this study is that although the return of the hypothalamic–pituitary–testicular axis was different among patients, the trend was for prolonged maintenance of low testosterone levels even for more than 1 year after hormone disruption.[29] This low testosterone, following long-term administration of the Luteinizing hormone-releasing hormone (LHRH) agonist, may not stem from permanent suppression of the axis but from an irreversible destruction of Leydig cells.[30] In contrast, a study of animal models revealed a potential reversal of fertility after discontinuation of a short-term hormone therapy.[31]

Chemotherapy

The incidence of chemotherapeutic agents in fertility has been extensively studied for the most widely used agents and for the treatment of the most common neoplasms. In this context, it has been found that alkylating agents such as cyclophosphamide and iphosphamide are at high risk for prolonged azoospermia, while agents such as vincristine and methotrexate are rather low-risk therapies for infertility.[32] However, there are no direct data on the potential for infertility after chemotherapy for prostate cancer, and this may be due to the fact that these patients may not be interested in becoming parents, so organize such a study would be difficult if not impossible. However, there is evidence from indirect studies using the chemotherapeutic agents that are also used in prostate cancer such the recent study by Chatzidarellis *et al*. who found a statistically significant reduction of inhibin B and FSH ($P < 0.001$ and $P = 0.000$, respectively) after taxane administration, which was maintained throughout the follow-up (6 months).[33] Authors conclude that the above changes in combination with the observed bilateral decrease in testicular size indicate a significant gonadal damage following the administration of chemotherapeutic agents such as docetaxel. The results of the above study, if combined with

the results of studies demonstrating the direct correlation of inhibin B values with spermatogenesis,[33,34] can lead to the indirect conclusion that chemotherapy for prostate cancer can cause infertility in patients receiving it.

Conclusions

As the age of the first diagnosis of prostate cancer decreases, the need for clear answers and solutions for the possible infertility that the treatments potentially cause will increase. Both prostate cancer itself and its treatments, predominantly radiation, can cause long-term azoospermia; however, the data in the literature are sparse, mainly derived from small series, and based on these, no safe conclusions can be drawn.

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Conflicts of interest

There are no conflicts of interest.

References

1. American Cancer Society. Cancer Facts & Figures 2017 Atlanta: American Cancer Society; 2017. Available form: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2017/cancer-facts-and-figures-2017.pdf. [Last assesed on 2017 Mar 01].
2. Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, *et al*. SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD. Available from: https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site. [Last accessed on 2017 Apr 01].
3. Huyghe E, Sui D, Odensky E, Schover LR. Needs assessment survey to justify establishing a reproductive health clinic at a comprehensive cancer center. J Sex Med 2009;6:149-63.
4. Boyd BG, McCallum SW, Lewis RW, Terris MK. Assessment of patient concern and adequacy of informed consent regarding infertility resulting from prostate cancer treatment. Urology 2006;68:840-4.
5. Williams DH 4th, Karpman E, Sander JC, Spiess PE, Pisters LL, Lipshultz LI. Pretreatment semen parameters in men with cancer. J Urol 2009;181:736-40.
6. Ragni G, Somigliana E, Restelli L, Salvi R, Arnoldi M, Paffoni A. Sperm banking and rate of assisted reproduction treatment: Insights from a 15-year cryopreservation program for male cancer patients. Cancer 2003;97:1624-9.
7. Meseguer M, Molina N, Garcia-Velasco JA, Remohi J, Pellicer A, Garrido N. Sperm cryopreservation in oncological patients: A 14-year follow-up study. Fertil Steril 2006;85:640.
8. Carroll PR, Whitmore WF Jr., Herr HW, Morse MJ, Sogani PC, Bajorunas D, *et al*. Endocrine and exocrine profiles of men with testicular tumors before orchiectomy. J Urol 1987;137:420-3.
9. Meirow D, Schenker JG. Cancer and male infertility. Hum Reprod 1995;10:2017-22.
10. Miller LR, Partin AW, Chan DW, Bruzek DJ, Dobs AS, Epstein JI, *et al*. Influence of radical prostatectomy on serum hormone levels. J Urol 1998;160:449-53.
11. Olsson M, Ekström L, Schulze J, Kjellman A, Akre O, Rane A, *et al*. Radical prostatectomy: Influence on serum and urinary androgen levels. Prostate 2010;70:200-5.
12. Bantis A, Zissimopoulos A, Athanasiadou P, Gonidi M, Agelonidou E, Strataki A, *et al*. Serum testosterone, dihydrotestosterone, luteinizing hormone and follicle-stimulating hormone versus prostate specific antigen in patients with localized prostate adenocarcinoma who underwent radical prostatectomy. Radioimmunoassays measurements. Hell J Nucl Med 2007;10:56-61.
13. Klingmüller D, Haidl G. Inhibin B in men with normal and disturbed spermatogenesis. Hum Reprod 1997;12:2376-8.
14. Andersson AM, Petersen J, Jorgensen N, Jensen TK, Skakkebaek NE. Serum inhibin B and follicle-stimulating hormone levels as tools in the evaluation of infertile men: Significance of adequate reference values from proven fertile men. J Clin Endocrinol Metab 2004;89:2873-9.
15. Zagars GK, Pollack A. Serum testosterone levels after external beam radiation for clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 1997;39:85-9.
16. Seal US. The Veterans Administration Uro-Oncology Research Group. Investigative Urol 1978;16:278-80.
17. Tomić R, Bergman B, Damber JE, Littbrand B, Löfroth PO. Effects of external radiation therapy for cancer of the prostate on the serum concentrations of testosterone, follicle-stimulating hormone, luteinizing hormone and prolactin. J Urol 1983;130:287-9.
18. Grigsby PW, Perez CA. The effects of external beam radiotherapy on endocrine function in patients with carcinoma of the prostate. J Urol 1986;135:726-7.
19. Fransson P, Widmark A. Self-assessed sexual function after pelvic irradiation for prostate carcinoma. Comparison with an age-matched control group. Cancer 1996;78:1066-78.
20. Talcott JA, Rieker P, Clark JA, Propert KJ, Weeks JC, Beard CJ, *et al*. Patient-reported symptoms after primary therapy for early prostate cancer: Results of a prospective cohort study. J Clin Oncol 1998;16:275-83.
21. Fransson P, Widmark A. Late side effects unchanged 4±8 years after radiotherapy for prostate carcinoma: A comparison with age-matched controls. Cancer 1999;85:678-88.
22. Daniell HW. A worse prognosis for men with testicular atrophy at therapeutic orchiectomy for prostate carcinoma. Cancer 1998;83:1170-3.
23. Meistrich ML, Vassilopoulou-Sellin R, Lipshultz LI. Adverse effects of treatment: Gonadal dysfunction. In: DeVita VT, Hellman S, Rosenberg SA, editors. Cancer: Principles and Practice of Oncology. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 2560-74.
24. Colpi GM, Contalbi GF, Nerva F, Sagone P, Piediferro G. Testicular function following chemo-radiotherapy. Eur J Obstet Gynecol Reprod Biol 2004;113 Suppl 1:S2-6.
25. Howell SJ, Shalet SM. Spermatogenesis after cancer treatment: damage and recovery. J Natl Cancer Inst Monogr. 2005:12-7.
26. Wu Q, Liang J, Yan D. Application of dose compensation in image-guided radiotherapy of prostate cancer. Phys Med Biol 2006;51:1405-19.
27. Steinsvik EA, Fosså SD, Lilleby W, Eilertsen K. Fertility issues in patients with prostate cancer. BJU Int 2008;102:793-5.
28. Mydlo JH, Lebed B. Does brachytherapy of the prostate affect sperm quality and/or fertility in younger men? Scand J Urol Nephrol 2004;38:221-4.
29. Hall MC, Fritzsch RJ, Sagalowsky AI, Ahrens A, Petty B, Roehrborn CG. Prospective determination of the hormonal response after cessation of luteinizing hormone-releasing hormone agonist treatment in patients with prostate cancer.

Urology 1999;53:898-902.
30. Pedraza R, Kwart AM. Hormonal therapy for patients with advanced adenocarcinoma of the prostate: Is there a role for discontinuing treatment after prolonged androgen suppression? Urology 2003;61:770-3.
31. Kostanski JW, Jiang G, Dani BA, Murty SB, Qiu W, Schrier B, *et al*. Return to fertility after extended chemical castration with a GnRH antagonist. BMC Cancer 2001;1:18.
32. Dohle GR. Male infertility in cancer patients: Review of the literature. Int J Urol 2010;17:327-31.
33. Chatzidarellis E, Makrilia N, Giza L, Georgiadis E, Alamara C, Syrigos KN. Effects of taxane-based chemotherapy on inhibin B and gonadotropins as biomarkers of spermatogenesis. Fertil Steril 2010;94:558-63.
34. Kumanov P, Nandipati K, Tomova A, Agarwal A. Inhibin B is a better marker of spermatogenesis than other hormones in the evaluation of male factor infertility. Fertil Steril 2006;86:332-8.

Review Article

Antioxidants and Oligoasthenoteratozoospermia: A Review of the Literature

Abstract

The present review examines whether and to which extent the antioxidant drugs have a role in the management of patients with oligoasthenoteratozoospermia (OAT). Subfertility and especially semen parameters disorders presented as OAT have been associated with increased oxidative stress and on this basis, several studies of antioxidants administration toward its treatment have been carried out. In the limits of this literature review and by using scientific publications search engines (PubMed, Medscape, Cochrane Library, Google Scholar), 285 related studies were found in total. Among them, the 34 more relevant to the investigated topic, with a complete statistical analysis, were isolated and included in the present review. It seems that there is a significant positive impact of antioxidants on semen parameters' improvement and childbearing. However, these studies are quite heterogeneous and more studies are required, for safe conclusions to be extracted. Administration of antioxidants to those men should be a matter of individualized approach.

Keywords: *Antioxidants, oligoasthenoteratozoospermia, subfertility*

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Introduction

Infertility is defined by the WHO as the inability of a sexually active, noncontracepting couple to achieve pregnancy in 1 year.[1] It affects 15% of couples globally. The malefactor participates in 50% of infertile couples, whereas it is exclusively responsible for 20%–30% of the cases.[2] The main cause of male infertility is idiopathic oligoasthenoteratozoospermia (OAT).[2] Reactive oxygen species (ROS) are unstable oxygen molecules that derive from the incomplete reduction of molecular oxygen at the end stage of oxidative phosphorylation.[3] Under normal circumstances, ROS plays a key role in sperm's chromatin condensation, spermatozoa activation, and spermatozoa number regulation via apoptosis.[4] Extra modifications occur during spermatozoa transit through the epididymis, leading to their maturation.[5] When ROS concentration exceeds the total antioxidant capacity (TAC) of spermatozoa, oxidative stress occurs. Spermatozoa are vulnerable to oxidative stress.[6] Genetic causes, varicocele, genitourinary infections and trauma, cancer and the treatments against it, obesity, nutrients deficiency, smoking, drugs, pollution, high temperature, and radiation lead to oxidative stress, which cause protein damage, lipid peroxidation, DNA damage, and apoptosis, resulting to sperm damage and infertility.[2] Lower TAC has been associated with impaired sperm motility and infertility.[5] Oxidative stress has been associated further with impairment of all semen parameters and microscopic defects, associated mostly with impaired sperm motility.[5] Higher ROS concentrations have been associated with semen parameters disorders, such as OAT. A cutoff concentration value of 91.95 relative light units has been proposed as a diagnostic tool for oxidative stress and as a prognosis index in assisted reproductive technology (ART) procedures.[7]

Methods

PubMed, Medscape, Cochrane Library, and Google Scholar were used as search engines. The following keywords – alone and in combinations – were used: "OAT," "oral antioxidants," "antioxidant treatment," "male infertility," "coenzyme Q10," "zinc," "vitamin C," "vitamin E," "glutathione," "pentoxifylline," 'carnitines," "folic acid," "lycopene," "selenium," and "N-acetyl cysteine (NAC)." Studies were selected based on whether they were randomized,

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included a target population of infertile men with OAT and if they measured the outcome based on the effect on semen parameters, spontaneous pregnancy rate, outcome of ART, or live birth rate (LBR).

The titles and abstracts extracted from the electronic searches were scrutinized and full manuscripts of relevant citations that met the search predefined selection criteria were obtained. Final study inclusion was made following the examination of the full manuscripts.

The selected studies were assessed for methodological quality by using the components of study design that are related to internal validity,[8] including method of randomization, allocation concealment, double-blinding, intention-to-treat analysis, and follow-up (or drop-out) rate. Study characteristics, participant features, study inclusion and exclusion criteria, and nature of intervention (type and dose of antioxidant(s) used and duration of treatment) were extracted from each study.

Results

Out of 285 studies retrieved from the electronic search, 34 (11.9%) were included in this review. Semen parameters were examined in 32 studies. A statistically significant improvement was observed in 27 of them (84.3%). Spontaneous pregnancy and/or LBR were examined in 18 of these studies (52.9%), showing a positive effect on outcome in 12 of them (66.6%). Five of these studies (27.7%) assessed the outcome of ART procedures following antioxidant treatment, with 3 of them (60%) showing a statistically significant improvement of LBR. Thirteen studies examined the spontaneous pregnancy rate (38.2%) and a statistically significant improvement was observed in 9 of them (69.2%).

Coenzyme Q10

Lower levels of this molecule have been associated with higher concentrations of organic peroxides in seminal plasma.[9] A meta-analysis of three double-blind randomized clinical trials in 2013 showed a significant improvement in all semen parameters of men receiving CoQ10, without any effect on pregnancy rate. LBR was not examined. Heterogeneity of the trials is the most prominent drawback of this meta-analysis.[10] Spontaneous pregnancy rate = 34.1% and LBR = 92.9% were observed in men with OAT, who received 600 mg CoQ10 daily for 12 months (n = 287), in a trial lacking a control group.[11] Its effectiveness seems dose and time dependent.[11,12] CoQ10 produced superior results on sperm motility, morphology, and oxidative status – as depicted by superoxide dismutase activity and catalase (CAT)-in comparison with selenium ($P < 0.01$ vs. $P < 0.05$), while sperm concentration and CAT activity were improved only by CoQ10 administration ($P < 0.01$ and $P < 0.05$, respectively).[4] However, in most cases, the baseline values were extremely low and even after their statistically significant improvement remained lower than lower reference values.

Vitamin C

Its use has been studied in combination with other antioxidants, mostly Vitamin E. No significant effect on semen parameters or pregnancy rate was observed by Rolf *et al*.[13] A double-blind randomized clinical trial by Greco *et al*. showed a significant improvement of sperm DNA fragmentation, leading to improved outcomes of ICSI, even if semen parameters were not affected.[14] Vitamin C has been used as an adjuvant means of treatment to the surgical treatment of varicocele, showing a statistically significant improvement in sperm motility and morphology ($P < 0.01$).[15]

Vitamin E

Administration of Vitamin E as a monotherapy was associated with an improvement in the sperm's oxidative status and motility, resulting in a pregnancy rate of 21% in men with AT (n = 52).[16] Its use in combination with clomiphene citrate (400 mg + 25 mg, respectively) was shown to result in significant improvement of sperm concentration and forward motility, leading to an improved pregnancy rate (36.7% vs. 13.3%) in a double-blind randomized clinical trial by Ghanem *et al*.[17] A similar effect on semen parameters appeared in a study carried by ElSheikh *et al*., which indicated that the combination of clomiphene citrate and Vitamin E produced better results than each component alone.[18]

Glutathione

Glutathione is poorly absorbed by the gastrointestinal tract, making its intramuscular administration necessary, which is a less convenient option compared to per os administration. Therefore, other per os administered antioxidants are preferable to it and there are few associated data. Lenzi *et al*. observed a significant improvement of sperm motility and morphology in a study of few participants, lacking a control group.[19]

Carnitines

Carnitines' concentration in the epididymis is 2000 times higher than the concentration in plasma, significantly lower in men with OAT. Carnitines' administration (2 g LC/day + 1 g LAC/day) was associated with a significant improvement of semen parameters in men with OAT and Grade I–III varicocele. This improvement was more prominent – including also Grade IV varicocele patients – when 30 mg cinonxicam/4 day was added. Pregnancy rates were 1.7%, 21.8%, and 38%.[20] Another double-blind randomized clinical trial demonstrated a significant improvement of sperm motility, especially in cases of low baseline values and four spontaneous pregnancies.[21] A study by Cavallini *et al*. showed significantly improved Intracytoplasmic Sperm Injection (ICSI) outcomes in patients with OAT, who responded well to carnitines' administration – response was evaluated by the reduction of aneuploidy percentage.[22]

Zinc

Combined administration of zinc and folic acid produced a significant improvement in sperm concentration, while zinc plasma concentration was associated with sperm concentration and motility.[23] Another double-blind randomized clinical trial demonstrated a significant improvement of all semen parameters and DNA integrity in patients who received zinc, regardless of the co-administration of Vitamins C and E.[24] Raigani *et al*. failed to demonstrate any improvements in semen parameters following the administration of zinc and/or folic acid. Only a marginally significant DNA Fragmentation Index (DFI) was observed in patients receiving zinc as monotherapy.[25]

Folic acid

Mutations in genes related to folic acid metabolism have been associated with idiopathic OAT, whereas its concentration in plasma has been found lower in infertile men.[26] Folic acid has not been associated with improvement of semen parameters, sperm oxidative status, and DNA integrity,[25] but its combination with zinc seems to have a positive effect on sperm motility[23] and concentration.[27]

Lycopene

Two studies[28,29] have observed a statistically significant improvement of sperm concentration and motility, along with spontaneous pregnancy rates of 36% and 20% respectively, but they are highly restricted due to small number of participants and lack of control group.

Polyunsaturated fatty acids

Omega-3 fatty acids' concentration was found lower in men with OAT, whereas the omega-6 to omega-3 ratio was significantly higher in these men.[30] In a double-blind randomized clinical trial,[31] omega-3 fatty acids' administration was associated with improved sperm concentration – baseline values were already marginally below normal – and increased antioxidant enzymes' activity.

Selenium

Administration of selenium as a monotherapy or in combinations with Vitamins A, C, and E has produced a nonstatistically significant improvement of sperm motility in men with OAT, along with five (11%) spontaneous pregnancies, null in the placebo group.[32] All semen parameters statistically significantly improved after the administration of selenium and/or NAC, while the improvement was more prominent under the combination treatment.[33] A review of selenium concludes on its administration being proposed only for men with proven selenium deficiency, in areas with soil poor in selenium.[34] Its effect on semen parameters was lower than this of CoQ10.[23]

N-acetyl cysteine

NAC has been associated with improved sperm viability[35] and reduction of oxidative stress[36] when used *in vitro*. Administration of 600 mg NAC/day for 3 months in men with AT was associated with improved sperm volume, viscosity, and motility.[37] All semen parameters statistically significantly improved after the administration of selenium and/or NAC, while the improvement was more prominent under the combination treatment.[33]

Pentoxifylline

Its use, along with folic acid and zinc, in men with OAT and grade 3 or higher varicocele has been associated with improvement in sperm morphology.[38] A double-blind randomized clinical trial of 254 participants with OAT demonstrated a statistically significant improvement in all semen parameters, TAC, and acrosome reaction following the administration of 400 mg pentoxifylline twice daily for 24 weeks. The pregnancy rate was not examined in this trial.[39]

Multiple antioxidants

In a double-blind randomized clinical trial carried by Galatioto *et al*., a statistically significant improvement of sperm motility was observed following the administration of a mixture of NAC, antioxidant vitamins, and nutrients to men with impaired semen parameters after the surgical treatment of varicocele. No significant effect was observed on pregnancy rate.[40] Another double-blind randomized clinical trial by Tremellen *et al*. demonstrated a nonsignificant improvement of implantation rate (46.2% vs. 24%) and a statistically significant improvement of LBR following the administration of a mixture of multiple antioxidants (lycopene, Vitamins C and E, zinc, selenium, folic, and garlic) 3 months prior to ICSI.[41] The administration of a similar regimen to – both OAT and non-OAT – men prior to ICSI resulted in a statistically significant improvement of sperm concentration and motility. However, the new values were still pathological and the procedure's outcome was not examined.[42] A significant improvement of DFI was observed in another study, regarding only men with higher baseline DFI values. However, its statistical value is limited.[43] A double-blind randomized clinical trial by Gopinath *et al*. regarding the use of LC, zinc, CoQ10, and lycopene in two different dosages demonstrated a significant dose-dependent effect on sperm concentration and motility – with the new values being above the reference values. Spontaneous pregnancy rate also increased following the administration of this regimen. However, this increase was not statistically significant.[44] Busetto *et al*. demonstrated a statistically significant improvement of all semen parameters in 104 men with OAT, with or without varicocele, who received a mixture of LC, LAC, fructose, CoQ10, zinc, folic acid, and Vitamins C and B12. The improvement was more prominent

in patients with varicocele. The pregnancy rate was 19.2% versus 3.8% in the placebo group. 90% of pregnancies that occurred in the first group and 50 % of pregnancies that occurred in the placebo group regarded patients without varicocele.[45] A mixture of L-arginine, CoQ10, Vitamins C, B3 and E, inositol, ginseng, and Tribulus was associated with improvement of all semen parameters in men with OAT prior to ICSI. Even if fertilization rate and number and quality of embryos improved, LBR was not affected.[46] Joseph *et al*. observed no significant improvement of semen parameters, live pregnancy rate, or LBR in a double-blind randomized clinical trial regarding men with OAT, who received a mixture of Vitamins C and E and zinc prior to *in vitro* fertilization procedures.[47]

Discussion

The role of oxidative stress and ROS concentration in the pathophysiology of male infertility has been demonstrated in several studies.[2,4,6,7] One study showed that antioxidant treatment is more efficient when combined with lifestyle modifications (avoiding red meat, soy, saturated fats and high temperatures, smoking, drugs, and alcohol cessation along with limited exposure to pollutants). The outcome of childbearing efforts was not measured in this study.[48] Another study demonstrated a greater benefit from antioxidant treatment in patients younger than 35 having a body mass index (BMI) <25. Given the increased oxidative stress in older and heavier men, it was expected that older men of an increased BMI would benefit the most. These findings imply that either the oxidative stress exceeded the antioxidant capacities of the treatment or other mechanisms are also involved.[49] During all the studies included, no incident of dropping out of the study because of adverse effects of the administered drugs was observed. Adverse effects were dyspeptic complaints of low statistical significance. The overuse of antioxidants – mostly due to an inappropriate estimation of oxidative status – could lead to "antioxidant paradox" – a nonsignificant effect of large quantities of antioxidants on semen parameters – or even reductive stress, which is associated with male infertility and multisystemic disorders that mostly pertain to animal models.[50]

This review incudes a large number of heterogeneous studies, as far as administered drug, study methodology, and statistical analysis are concerned. Due to this heterogeneity, the conduction of a meta-analysis was not possible. The results of the studies above imply a significant improvement of sperm parameters in men with OAT, while the effect on the outcome of childbearing outcomes is more controversial, seeming that ART procedures are more likely to benefit from such interventions. However, the semen parameters' improvement seems to be more intense in patients with extremely low baseline values and – even after their statistically significant improvement – the parameters' values remain below reference values, with only a few exceptions.[31,46] It is clear – and pointed in most of the included studies – that more precise and homogeneous studies are required to clarify the role of antioxidant treatment in men with OAT.

Conclusions

The present studies are quite heterogeneous as far as many of their features are concerned and there is a distinct need for more research on this subject. It seems that an improvement of semen parameters – especially in more severe situations – may occur. The effect on the outcome of childbearing efforts is more controversial. The administration of such drugs should be individualized to men under oxidative stress and proved deficiency of specific antioxidant substances. Finally, the selection of the appropriate reproduction technique should be the result of the interdisciplinary approach of the infertile couple, taking into account their wishes and their needs.

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Conflicts of interest

There are no conflicts of interest.

References

1. World Health Organization. WHO laboratory manual for the examination and processing of human semen, 5th ed. World Health Organization. 2010.
2. Hirsch A. ABC of subfertility: Male subfertility. BMJ 2003;327:669-72.
3. Berg JM, Tymoczko JL, Stryer L. Biochemistry. 5th ed. USA: W. H. Freeman and Company; 2001.
4. Alahmar AT, Sengupta P. Impact of coenzyme Q10 and selenium on seminal fluid parameters and antioxidant status in men with idiopathic infertility. Biol Trace Elem Res 2021;199:1246-52.
5. El-Taieb MA, Herwig R, Nada EA, Greilberger J, Marberger M. Oxidative stress and epididymal sperm transport, motility and morphological defects. Eur J Obstet Gynecol Reprod Biol 2009;144:199-203.
6. Ahmadi S, Bashiri R, Ghadiri-Anari A, Nadjarzadeh A. Antioxidant supplements and semen parameters: An evidence based review. Int J Reprod Biomed 2016;14:729-36.
7. Agarwal A, Sharma RK, Sharma R, Assidi M, Abuzenadah AM, Alshahrani S, *et al*. Characterizing semen parameters and their association with reactive oxygen species in infertile men. Reprod Biol Endocrinol. 2014;12:33-41.
8. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, *et al*. Assesssing the quality of reports of randomised clinical trials. Is blinding necessary? Control. Clin. Trials. 1996;17:1-12.
9. Alleva R, Scararmucci A, Mantero F, Bompadre S, Leoni L, Littarru GP. The protective role of ubiquinol-10 against formation of lipid hydroperoxides in human seminal fluid. Mol Aspects Med 1997;18:221-8.
10. Lafuente R, González-Comadrán M, Solà I., López G, Brassesco M, Carreras R *et al*.Coenzyme Q10 and male infertility: a meta-analysis. J Assist Reprod Genet. 2013;30:1147-56.
11. Safarinejad MR. The effect of coenzyme Q_{10} supplementation

on partner pregnancy rate in infertile men with idiopathic oligoasthenoteratozoospermia: An open-label prospective study. Int Urol Nephrol 2012;44:689-700.
12. Alahmar AT. The impact of two doses of coenzyme Q10 on semen parameters and antioxidant status in men with idiopathic oligoasthenoteratozoospermia. Clin Exp Reprod Med 2019;46:112-8.
13. Rolf C, Cooper TG, Yeung CH, Nieschlag E. Antioxidant treatment of patients with asthenozoospermia or moderate oligoasthenozoospermia with high-dose Vitamin C and Vitamin E: A randomized, placebo-controlled, double-blind study. Hum Reprod 1999;14:1028-33.
14. Greco E, Iacobelli M, Rienzi L, Ubaldi F, Ferrero S, Tesarik J. Reduction of the incidence of sperm DNA fragmentation by oral antioxidant treatment. J Androl 2005;26:349-53.
15. Cyrus A, Kabir A, Goodarzi D, Moghimi M. The effect of adjuvant Vitamin C after varicocele surgery on sperm quality and quantity in infertile men: A double blind placebo controlled clinical trial. Int Braz J Urol 2015;41:230-8.
16. Suleiman SA, Ali ME, Zaki ZM, El-Malik EM, Nasr MA. Lipid peroxidation and human sperm motility: Protective role of Vitamin E. J Androl 1996;17:530-7.
17. Ghanem H, Shaeer O, El-Segini A. Combination clomiphene citrate and antioxidant therapy for idiopathic male infertility: A randomized controlled trial. Fertil Steril 2010;93:2232-5.
18. ElSheikh MG, Hosny MB, Elshenoufy A, Elghamrawi H, Fayad A, Abdelrahman S. Combination of Vitamin E and clomiphene citrate in treating patients with idiopathic oligoasthenozoospermia: A prospective, randomized trial. Andrology 2015;3:864-7.
19. Lenzi A, Culasso F, Gandini L, Lombardo F, Dondero, F. Andrology: Placebo-controlled, double-blind, cross-over trial of glutathione therapy in male infertility. Hum Reprod 1993;8:1657-62.
20. Cavallini G, Ferraretti AP, Gianaroli L, Biagiotti G, Vitali, G. Cinnoxicam andl-carnitine/acetyl-l-carnitine treatment for idiopathic and varicocele-associated oligoasthenospermia. J Androl 2004;25:761-70.
21. Lenzi A., Sgrò P., Salacone P., Paoli D, Gilio B, Lombardo F *et al.* A placebo-controlled double-blind randomized trial of the use of combined l-carnitine and l-acetyl-carnitine treatment in men with asthenozoospermia. Clinical Trial Fertil Steril. 2004; 81:1578-84.
22. Cavallini G, Magli MC, Crippa A, Ferraretti AP, Gianaroli L. Reduction in sperm aneuploidy levels in severe oligoasthenoteratospermic patients after medical therapy: A preliminary report. Asian J Androl 2012;14:591-8.
23. Ebisch IM, Pierik FH, De Jong FH, Thomas CM, Steegers-Theunissen RP. Does folic acid and zinc sulphate intervention affect endocrine parameters and sperm characteristics in men? Int J Androl 2006;29:339-45.
24. Omu AE, Al-Azemi MK, Kehinde EO, Anim JT, Oriowo MA, Mathew TC. Indications of the mechanisms involved in improved sperm parameters by zinc therapy. Med Princ Pract 2008;17:108-16.
25. Raigani M, Yaghmaei B, Amirjannti N, Lakpour N, Akhondi MM, Zeraati H *et a*l. The micronutrient supplements, zinc sulphate and folic acid, did not ameliorate sperm functional parameters in oligoasthenoteratozoospermic men. Randomized Controlled Trial Andrologia. 2014;46:956-62.
26. Murphy LE, Mills JL, Molloy AM, Qian C, Carter TC, Strevens H, *et al.* Folate and vitamin B12 in idiopathic male infertility. Asian J Androl 2011;13:856-61.
27. Wong WY, Merkus HM, Thomas CM, Menkveld R, Zielhuis GA, Steegers-Theunissen RP. Effects of folic acid and zinc sulfate on male factor subfertility: A double-blind, randomized, placebo-controlled trial. Fertil Steril 2002;77:491-8.
28. Mohanty NK, Kumar S, Jha AK, Arora RP. Management of idiopathic oligoasthenospermia with lycopene. Indian J Urol 2001;18:57-61.
29. Gupta NP, Kumar R. Lycopene therapy in idiopathic male infertility – A preliminary report. Int Urol Nephrol 2002;34:369-72.
30. Safarinejad MR, Hosseini SY, Dadkhah F, Asgari MA. Relationship of omega-3 and omega-6 fatty acids with semen characteristics, and anti-oxidant status of seminal plasma: A comparison between fertile and infertile men. Comp Study Clin Nutr 2010;29:100-5.
31. Safarinejad MR. Effect of omega-3 polyunsaturated fatty acid supplementation on semen profile and enzymatic anti-oxidant capacity of seminal plasma in infertile men with idiopathic oligoasthenoteratospermia: A double-blind, placebo-controlled, randomised study. Andrologia 2011;43:38-47.
32. Scott R, MacPherson A, Yates RW, Hussain B, Dixon J. The effect of oral selenium supplementation on human sperm motility. Br J Urol 1998;82:76-80.
33. Safarinejad MR, Safarinejad S. Efficacy of selenium and/or N-acetyl-cysteine for improving semen parameters in infertile men: A double-blind, placebo controlled, randomized study. J Urol 2009;181:741-51.
34. Ahsan U, Kamran Z, Raza I, Ahmad S, Babar W, Riaz MH *et al.* Role of selenium in male reproduction—A review. Animal Reproduction Science. 2014;146:55-62.
35. Erkkilä K, Hirvonen V, Wuokko E, Parvinen M, Dunkel L. N-acetyl-L-cysteine inhibits apoptosis in human male germ cells *in vitro*. J Clin Endocrinol Metab 1998;83:2523-31.
36. Oeda T, Henkel R, Ohmori H, Schill WB. Scavenging effect of N-acetyl-L-cysteine against reactive oxygen species in human semen: A possible therapeutic modality for male factor infertility? Andrologia 1997;29:125-31.
37. Ciftci H, Verit A, Savas M, Yeni E, Erel O. Effects of N-acetylcysteine on semen parameters and oxidative/antioxidant status. Urology 2009;74:73-6.
38. Oliva A, Dotta A, Multigner L. Pentoxifylline and antioxidants improve sperm quality in male patients with varicocele. Fertil Steril 2009;91:1536-9.
39. Safarinejad MR. Effect of pentoxifylline on semen parameters, reproductive hormones, and seminal plasma antioxidant capacity in men with idiopathic infertility: A randomized double-blind placebo-controlled study. Int Urol Nephrol 2011;43:315-28.
40. Galatioto PG, Gravina GL, Angelozzi G, Sacchetti A, Innominato PF, Pace G *et al*. May antioxidant therapy improve sperm parameters of men with persistent oligospermia after retrograde embolization for varicocele? World Journal of Urology. 2007; 26:97-102.
41. Tremellen K, Miari G, Froiland D, Thompson J. A randomised control trial examining the effect of an antioxidant (Menevit) on pregnancy outcome during IVF-ICSI treatment. Aust N Z J Obstet Gynaecol 2007;47:216-21.
42. Wirleitner B, Vanderzwalmen P, Stecher A, Spitzer D, Schuff M, Schwerda D *et al*. N.H. Dietary supplementation of antioxidants improves semen quality of IVF patients in terms of motility, sperm count, and nuclear vacuolization. Int J Vitam Nutr Res. 2012;82:391-8.
43. Abad C, Amengual MJ, Gosalvez J, Coward K, Hannaoui N, Benet J *et al*. Effects of oral antioxidant treatment upon the dynamics of human sperm DNA fragmentation and

subpopulations of sperm with highly degraded DNA. Andrologia. 2013;45:211-6.

44. Gopinath PM, Kalra B, Saxena A, Malik S, Kochhar K, Kalra S *et al*. Fixed dose combination therapy of antioxidants in treatment of idiopathic oligoasthenozoospermia: results of a randomized, double-blind, placebo-controlled clinical trial. Int J Infertil Fetal Med. 2013;4:6-13.
45. Busetto GM, Agarwal A, Virmani A, Antonini G, Ragonesi G, Del Giudice F *et al*. Effect of metabolic and antioxidant supplementation on sperm parameters in oligo-astheno-teratozoospermia, with and without varicocele: A double-blind placebo-controlled study. Randomized Controlled Trial Andrologia. 2018;50:e12927.
46. Gambera L, Stendardi A, Ghelardi C, Fineschi B, Aini R. Effects of antioxidant treatment on seminal parameters in patients undergoing *in vitro* fertilization. Arch Ital Urol Androl 2019;91:187-90.
47. Joseph T, Mascarenhas M, Karuppusami R, Karthikeyan M, Kunjummen AT, Kamath MS. Antioxidant pretreatment for male partner before ART for male factor subfertility: A randomized controlled trial. Hum Reprod Open 2020;16:1-10.
48. Magdi Y, Darwish E, Elbashir S, Majzoub A, Agarwal A. Effect of modifiable lifestyle factors and antioxidant treatment on semen parameters of men with severe oligoasthenoteratozoospermia. Andrologia 2017;49:e12694.
49. Busetto GM, Del Giudice F, Agarwal A, Micic S, Virmani A, De Berardinis E. Body mass index and age correlate with antioxidants supplementation effect on sperm quality: A double blind place controlled trial on patients with varicocele and oligoasthenoteratozoospermia. J Urol 2019;201:e769.
50. Henkel R, Sandhu S, Agarwal A. The excessive use of antioxidant therapy: A possible cause of male infertility? Andrologia 2019;51:e13162.

Case Report

A 36-Year-Old Patient with Acute Urinary Retention Due to an Anterior Midline Prostatic Cyst: A Case Report and Review of the Literature

Abstract

During the years, there have been no more than a few reports (with ours being so far the sixth) of prostatic cysts prolapsing into the bladder and thus causing urinary obstruction. Most of those cystic formations are generally asymptomatic and are found during random controls. In our case, the cyst was located in the anterior midline of the prostate in a 36-years-old patient presenting at the E. R with severe suprapubic pain and urinary retention after 3 months of constantly deteriorating lower urinary tract symptoms. Transabdominal ultrasonography and magnetic resonance imaging revealed a projecting prostatic cyst that like a valve was blocking the bladder neck at 12 o'clock position. It was successfully removed by transurethral resection leaving the patient free of symptoms.

Keywords: *Bladder obstruction, prostate, prostatic cyst, transurethral resection, urinary retention*

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Introduction

Cysts of the lower male genitourinary tract are not a common feature and usually are found to be benign.[1,2] Their discovery has been the result of the increasing use of transrectal ultrasound, computed tomography, and magnetic resonance imaging.

Embryology

Both sex embryos have two pairs of genital ducts: The paramesonephric ducts (Müllerian) and the mesonephric ducts (Wolffian). When it comes to the male genital tract development this is considered to be a result of the differentiation of the components on the Wolffian duct and the involution of the müllerian ones. Sometimes those remnants persist on adult males despite the degeneration of the müllerian ducts leading to the presence of certain formations or anatomic disorders.[3]

Classification

In the literature, prostatic cysts are usually classified as either median, paramedian, and lateral cysts, or intraprostatic and periprostatic cysts.[4,5] Median cysts (prostatic utricle cysts and Müllerian duct cysts) are located in the midline behind the upper half of the prostatic urethra [Table 1].

Prostatic utricle cysts are an embryologic remnant of the Müllerian duct system, results of an incomplete regression of this structure during embryologic development. They are most commonly found in males under 20 years of age. Their reported occurrence in the general population is about 1%–5%.[6,7] They are associated with various genitourinary abnormalities, including hypospadias, intersex disorders, cryptorchidism, and ipsilateral renal agenesis and they may manifest with various signs and symptoms, including urinary tract infection, pain, postvoiding incontinence, recurrent epididymitis, and hematospermia.[6,8,9] Since utricle cysts communicate with the urethra, they may result in postvoiding dribbling. Prostatic utricle cysts can become infected and may contain pus or hemorrhage, which can confuse imaging because their appearances overlap with those of abscesses and cystic tumors of the prostate.[4] Utricle cysts are pear-shaped structures that, unlike müllerian duct cysts, do not extend above the base of the prostate. They communicate freely with the prostatic urethra.[8] Utricle cysts are typically smaller than müllerian cysts and are usually 8–10 mm long. They contain fluid, which has high signal intensity on T2-weighted images.[4] At the transrectal US, they manifest as a midline anechoic cystic cavity posterior to the urethra.

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Müllerian duct cysts result from focal failure of regression and focal saccular dilatation of the mesonephric duct. They are occasionally associated with renal agenesis, but external genitalia is normal.[9] The peak incidence of müllerian duct cysts is between the ages of 20 and 40 years. A few cases have been reported to occur in infancy.[10] According to an older autopsy series, the reported prevalence in men is 1%. However, the frequency of occurrence may be underreported, since some authors found a prevalence of 5% in urologic patients.[4] Müllerian duct cysts are usually asymptomatic but may manifest in early adulthood with urinary retention and urinary tract infection.[7] They may also cause ejaculatory impairment by obstructing the ejaculatory duct in the midline. Such as utricle cysts, Müllerian cysts can become infected; their imaging appearance resembles that of abscesses or cystic tumors of the prostate.[5] At aspiration, müllerian duct cysts never contain spermatozoa, but they do commonly contain calculi. There have been case reports of müllerian duct cysts and prostatic utricle cysts containing carcinoma.[5] Surgical excision of a müllerian duct cyst may be performed depending on the size and location of the cyst and the presence of clinical symptoms.[8] Transurethral resection and percutaneous aspiration are used to treat small müllerian duct cysts. The use of laparoscopic excision has also been reported. For a large pelvic or abdominal cyst, open surgical excision is the treatment of choice.[4] Müllerian duct cysts appear as teardrop-shaped midline cysts extending above the prostate. They do not communicate with the posterior urethra[10] [Table 2].

Case Report

A 36-year-old patient presented at the E. R with severe suprapubic pain and urinary retention after 3 months of constantly deteriorating lower urinary tract symptoms including frequency, weak urinary stream, and a sensation of residual urine that became really important 1 week before. Our patient presented a form of coronal hypospadias [Figure 1] and besides that, he was a healthy male, free of other medical problems.

The clinical examination revealed a dilated bladder. We performed a transabdominal ultrasound [Figure 2] and the volume of residual urine was >500 ml. At the same time, we noted the presence of a midline cystic formation elapsing from the prostate with an approximate diameter of 1,5 cm that projected on the bladder neck. The volume of the prostate was normal for the patient's age.

A simple 16fr foley catheter was put in place and the patient was further controlled with an MRI [Figure 3] suggesting the presence of a ureterocele, or a cyst of prostatic origin

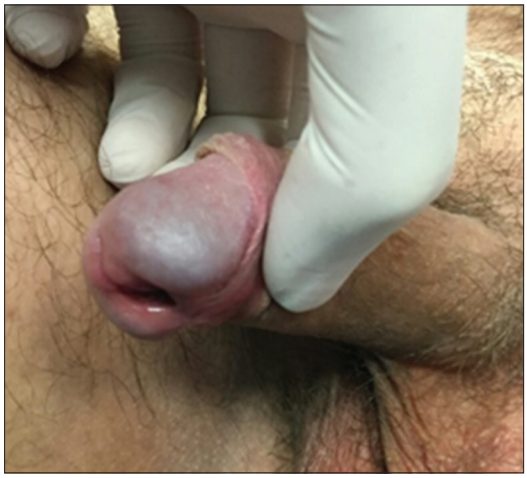

Figure 1: Coronal hypospadias

Table 1: Cystic lesions of the lower male urogenital tract (source: Reference[18])

Intraprostatic cysts			Extraprostatic cysts	Mimics of prostatic and paraprostatic cysts
Median	**Paramedian**	**Lateral**		
Prostatic utricle cysts	Ejaculatory duct cysts	Prostatic retention cysts	Seminal vesicle cysts	Ureteroceles
Müllerian duct cysts		Cystic degeneration of BHP	Cysts of vas deferens	Defect resulting from TURP
		Cysts associated with tumors	Cowper duct cysts	Bladder diverticula
		Prostatic abscess		Hydroureter and ectopic insertion of ureter

TURP: Transurethral resection of the prostate, BPH: Benign prostatic hyperplasia

Table 2: Prostatic utricle cysts versus müllerian duct cysts (source: Reference[18])

Parameters	Utricle cysts	Müllerian cysts
Patient age (years)	0-20	10-30
Origin	Embryologic remnant of the müllerian duct system	Failure of regression and focal saccular dilatation of the müllerian duct
Configuration	Pear shape	Teardrop shape
Extension above the base of the prostate	No	Yes
Communication with prostatic urethra	Yes	No
Spermatozoa present	Yes	No
Malignancy reported	Yes	Yes

such as a müllerian duct cyst. A preoperative cystoscopy revealed a cystic mass located in the anterior prostate, in the precise 12 o'clock position, closing the bladder neck like a checking valve [Figure 4]. There was not any other abnormality either from the bladder mucosa or the prostatic urethra.

The patient underwent transurethral surgery under general anesthesia and the cyst was excised with the transurethral resector [Figure 5]. No bleeding or other incidences were noted after the operation.

Discussion

Prostatic cysts are rather uncommon with a percentage of incidence varying from 0.5% to 7.9%. According to current classification, there can be intraprostatic cysts, extraprostatic, and mimics of prostatic and periprostatic cysts. Intraprostatic cysts can be either median (1%–5% prostatic utricle and 1%–5% müllerian duct cysts), either paramedian or lateral.[4,6,7] On studies among patients with symptomatic cysts up to 40% complained of obstructive urinary tract symptoms, while according to other studies patients with a medial prostatic cyst complained of prostatitis-like symptoms (77%), scrotal pain (62%), impaired micturition (32%), small volume ejaculation (35%), painful ejaculation (24%), hemospermia (24%), and infertility (12%).[2,11] When it comes to the location of midline cysts these are mostly found posteriorly rather than anteriorly.[12] Most of the references so far have to do with posterior cysts or infravesical formations, while so far only a few cases with involvement of the bladder neck are presented including our case.[11-17]

In our case, being the sixth on a series of similar cases so far, transurethral unroofing and excision of the cyst seem like the way to go.[11,16,17] No complications were noted including any level of erectile dysfunction and recession of LUTS. In our case, the patient mentioned a complete relief of his symptoms the first few hours since the removal of the postoperational catheter. The most important complication of transurethral resection includes injury of the urethra or bladder, which is located near the thin base of the cystic mass.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have

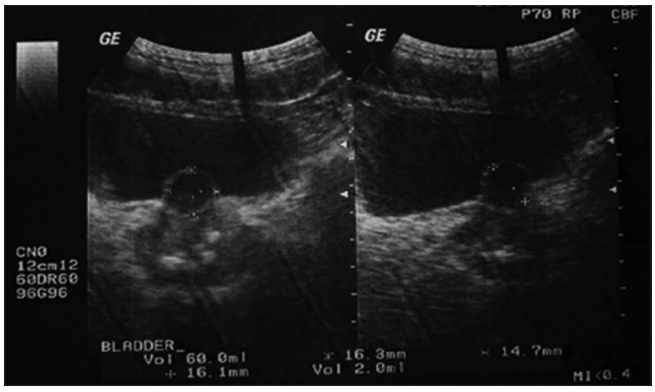

Figure 2: Ultrasound revealing a cyst at the level of the bladder neck and urinary retention

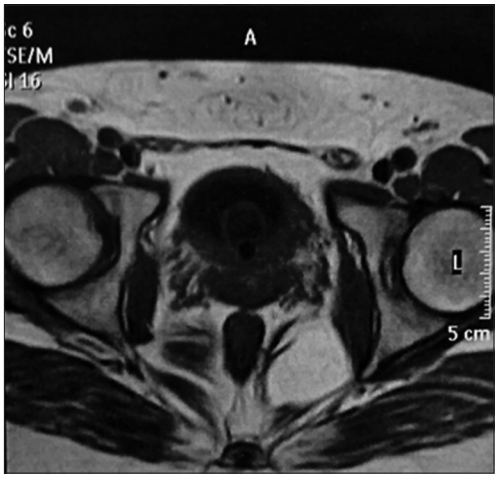

Figure 3: T1 MRI image of the lower abdomen, revealing an anterior prostatic cyst

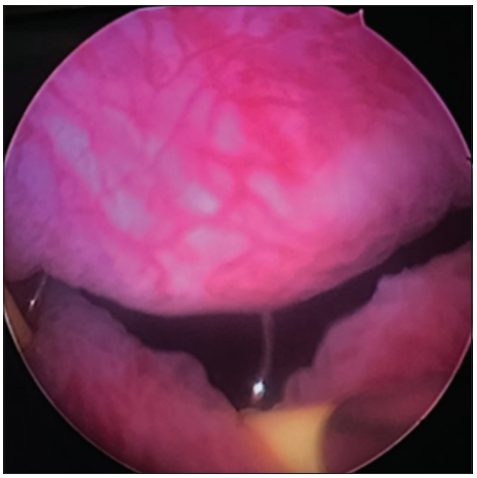

Figure 4: Intra-operative cystoscopy with the anterior prostatic cyst, blocking almost completely the bladder neck opening

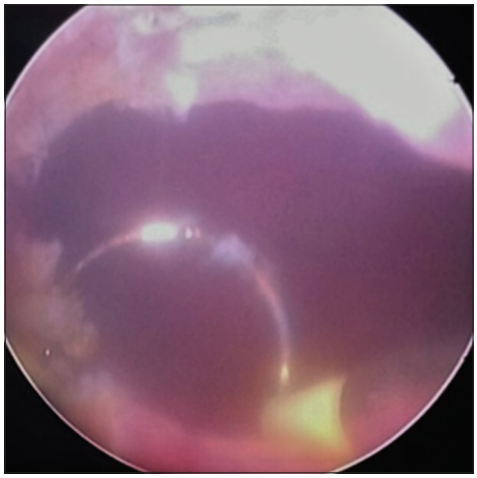

Figure 5: The channel created after minimal resection of the prostatic cyst

given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Ishikawa M, Okabe H, Oya T, Hirano M, Tanaka M, Ono M, *et al.* Midline prostatic cysts in healthy men: Incidence and transabdominal sonographic findings. AJR Am J Roentgenol 2003;181:1669-72.
2. Dik P, Lock TM, Schrier BP, ZeijlemakerBY, Boon TA. Transurethral marsupialization of a medial prostatic cyst in patients with prostatitis-like symptoms. J Urol 1996;155:1301-4.
3. Sajjad Y. Development of the genital ducts and external genitalia in the early human embryo. J Obstet Gynaecol Res 2010;36:929-37.
4. McDermott VG, Meakem TJ 3rd, Stolpen AH, Schnall MD. Prostatic and periprostatic cysts: Findings on MR imaging. AJR Am J Roentgenol 1995;164:123-7.
5. Curran S, Akin O, Agildere AM, Zhang J, Hricak H, Rademaker J. Endorectal MRI of prostatic and periprostatic cystic lesions and their mimics. AJR Am J Roentgenol 2007;188:1373-9.
6. Paudel K, Kumar A. Unusually large prostatic utricle cyst. Kathmandu Univ Med J (KUMJ) 2009;7:73-5.
7. Jaidane M, Hidoussi A, Slama A, Hmida W, Sorba NB, Mosbah F. An acute urinary retention in an old man caused by a giant müllerian duct cyst: A case report. Cases J 2009;2:203
8. Parsons RB, Fisher AM, Bar-Chama N, Mitty HA. MR imaging in male infertility. Radiographics 1997;17:627-37.
9. Trigaux JP, Van Beers B, Delchambre F. Male genital tract malformations associated with ipsilateral renal agenesis: Sonographic findings. J Clin Ultrasound 1991;19:3-10.
10. Simpson WL Jr, Rausch DR. Imaging of male infertility: Pictorial review. AJR Am J Roentgenol 2009;192:S98-11.
11. Tambo M, Okegawa T, Nutahara K, Higashihara E. Prostatic cyst arising around the bladder neck-cause of bladder outlet obstruction: Two case reports. Hinyokika Kiyo 2007;53:401-4.
12. Nayyar R, Dogra PN. Anteriorly placed midline intraprostatic cyst. J Endourol 2009;23:595-7.
13. Issa MM, Kalish J, Petros JA. Clinical features and management of anterior intraurethral prostatic cyst. Urology 1999;54:923.
14. Yildirim I, Kibar Y, Sümer F, Bedir S, Deveci S, Peker AF. Intraurethral prostatic cyst: A rare cause of infravesical obstruction. Int Urol Nephrol 2003;35:355-6.
15. Tamaki M, Isogawa Y, Ohmori K. A case of prostatic cyst. Hinyokika Kiyo 1994;40:537-40.
16. Lee JY, Kang DH, Park HY, Park JS, Son YW, Moon HS, *et al.* An anteriorly positioned midline prostatic cyst resulting in lower urinary tract symptoms. Int Neurourol J 2010;14:125-9.
17. Diaz RR, Lee JY, Choi YD, Cho KS. Unroofed midline prostate cyst misled into a stricture with obliterative bladder neck contracture following a laser prostatectomy. Int Neurourol J 2013;17:34-7.
18. Shebel HM, Farg HM, Kolokythas O, El-Diasty T. Cysts of the lower male genitourinary tract: Embryologic and anatomic considerations and differential diagnosis. Genitourin Imaging 2013;33:1125-43. doi: 10.1148/rg.334125129.

Case Report

Conservative Management of Hemodynamically Stable Patient with Grade V Renal Trauma: Case Presentation and Review of the Literature

Abstract

Renal trauma is a major health problem involving mostly young patients. It is estimated that renal trauma is diagnosed in almost 5% of all trauma patients. Patients diagnosed with Grade V renal trauma require surgical intervention and usually nephrectomy. The aim of this study is to present a case of Grade V renal trauma in a hemodynamically stable patient treated conservatively in our department. A 24-year-old male was admitted to the urology department due to Grade V left renal trauma after a motor accident. The patient presented with hematuria and was hemodynamically stable. A conservative approach was performed with close monitoring of hemodynamic status. Two red blood cells units was transfused. The patient remained hemodynamically stable and renal hematoma reduced in size in follow-up computed tomography. The patient was discharged in excellent clinical status after 17 days of hospitalization. Although Grade V renal trauma involving vascular injury requires immediate surgical intervention, in selected patients diagnosed with shattered kidney, a conservative approach may be successful provided that the patient remains hemodynamically stable and under close monitoring. Hemodynamic instability is an absolute indication for surgical exploration and possible nephrectomy.

Keywords: *Grade V renal trauma, renal injury, shattered kidney*

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Introduction and Background

Renal trauma is a major health problem involving mostly young patients and more often males rather than females. It is estimated that renal trauma is diagnosed in almost 5% of all trauma patients.[1] All patients are classified according to the American Association for the Surgery of Trauma (AAST) renal injury scale to receive appropriate treatment, as it provides information about morbidity and predicts the risk for surgical intervention and nephrectomy.[2] As far as it concerns treatment, the absolute indication for surgical exploration is hemodynamic instability, the need to explore associated abdominal injuries, and the discovery of an expanding or pulsatile perirenal hematoma at laparotomy. Grade V renal trauma includes patients with vascular injury of the renal pedicle including avulsion or cases presenting with shattered kidney. As a result, Grade V renal vascular trauma is an absolute indication for exploration; however, in clinical practice, all Grade V cases (parenchymal and vascular) undergo surgical exploration.[3] In this paper, we present a case of Grade V renal trauma in a hemodynamically stable patient treated conservatively in our department.

Case Presentation

A 24-year-old male was transferred to the emergency department after a motor accident. During initial resuscitation, a Foley catheter was placed, and visible hematuria was present. The patient was hemodynamically stable, and according to the current protocol, he underwent full-body computed tomography (CT) which revealed left kidney Grade V parenchymal trauma (shattered kidney) [Figure 1]. Neither there was sign of vascular trauma nor was concomitant injury recorded. The patient remained hemodynamically stable with hemoglobin level of 12.2 ng/dl and was admitted to the urology department. The decision was to conservatively manage the patient with close monitoring of hemodynamic status. A transfusion of two units of red blood cells was performed when hemoglobin levels dropped to

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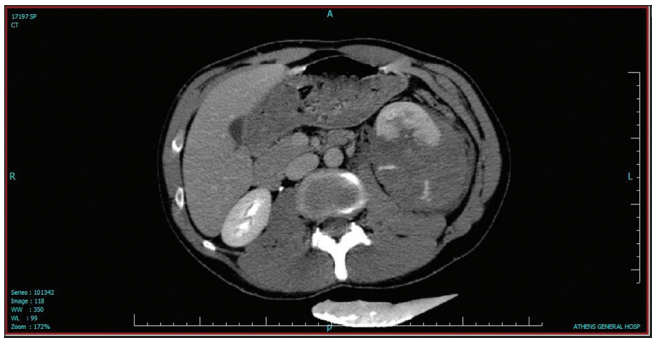

Figure 1: Grade V renal trauma (shattered kidney)

9 ng/dl. The patient remained hemodynamically stable, and 48 h postadmission, a repeat CT was performed which revealed a large perirenal hematoma and signs of shattered kidney. No further transfusion was required, and a follow-up CT was performed 15 days after initial evaluation in which hematoma was reduced in size. The patient was discharged after 17 days of hospitalization, and another CT was performed 1 month later. Hematoma had almost disappeared, and the kidney appeared to be functional [Figure 2]. No signs of hypertension were recorded at follow-up.

Discussion

Assessment of overall renal injury severity is classified according to the AAST renal injury scale. This classification is based on the degree of renal parenchyma and blood vessel rupture and the extent of the subcapcapsular or perirenal hemorrhage. Grade V trauma is diagnosed in cases of shattered kidney or vascular injury of the renal pedicle or avulsion.[2] In clinical practice, most patients suffering from renal trauma are hemodynamically stable, and according to the current protocols, they undergo abdominal CT to evaluate trauma severity.[4] On the other hand, Grade V renal trauma usually presents with hemodynamic instability, and it is quite common that the patient also suffers from severe concomitant injuries; thus, the possibility of surgical exploration is remarkably high.[5]

Nowadays, based on modern imaging techniques and growing experience in the conservative management of renal trauma, the trend is toward a more conservative approach even in cases of severe renal trauma. Despite the fact that Grade V vascular trauma is an absolute indication for surgical intervention, in cases of hemodynamic stable patients diagnosed with shattered kidney (Grade V parenchymal trauma), a more conservative approach may be performed.[3,6] In a case series presented by van der Wilden *et al*., including a total of 206 patients presenting with Grade IV or V renal trauma, 74.8% were managed nonoperatively (with the assistance of angiographic embolization for 25 patients). Nonoperative management failed for 12 of the 154 patients (7.8%).[7] In addition, Lanchon *et al*. presented their experience in nonoperative

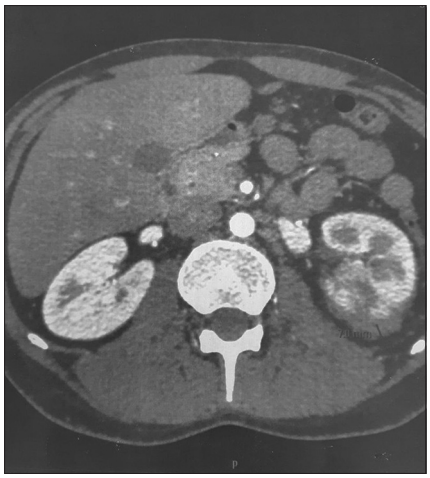

Figure 2: Follow-up computed tomography (1 month later)

management of Grade IV/V patients with a total success rate of 82%. Severity of renal trauma influenced success rates with patients suffering from Grade V trauma presenting a success rate of 52% compared with 89% for Grade IV patients.[8]

In the current clinical practice, hemodynamic instability is an absolute indication for surgical exploration regardless of trauma severity. Surgical exploration is influenced by etiology and grade of injury, transfusion requirements, the need to explore associated abdominal injuries, and the discovery of an expanding or pulsatile perirenal hematoma at laparotomy.[9]

Conclusion

Isolated Grade V renal trauma is extremely rare. In selected cases, in patients with hemodynamic stability and provided that renal pedicle vascular trauma is excluded, a conservative management may be possible under very close monitoring of vital signs. In any sign of hemodynamic instability, surgical exploration should be performed.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

References

1. Meng MV, Brandes SB, McAninch JW. Renal trauma: Indications and techniques for surgical exploration. World J Urol

1999;17:71-7.
2. Moore EE, Shackford SR, Pachter HL, McAninch JW, Browner BD, Champion HR, *et al.* Organ injury scaling: Spleen, liver, and kidney. J Trauma 1989;29:1664-6.
3. Shariat SF, Roehrborn CG, Karakiewicz PI, Dhami G, Stage KH. Evidence-based validation of the predictive value of the American Association for the Surgery of Trauma Kidney Injury Scale. J Trauma 2007;62:933-9.
4. Santucci RA, Wessells H, Bartsch G, Descotes J, Heyns CF, McAninch JW, *et al.* Evaluation and management of renal injuries: Consensus statement of the renal trauma subcommittee. BJU Int 2004;93:937-54.
5. Moudouni SM, Hadj Slimen M, Manunta A, Patard JJ, Guiraud PH, Guille F, *et al.* Management of major blunt renal lacerations: Is a nonoperative approach indicated? Eur Urol 2001;40:409-14.
6. Dantanarayana N, Ting F, Symons J, Evans D, Graham A. Isolated grade 5 renal trauma in a hemodynamically stable patient. Urol Case Rep 2016;4:30-2.
7. van der Wilden GM, Velmahos GC, Joseph DK, Jacobs L, Debusk MG, Adams CA, *et al.* Successful nonoperative management of the most severe blunt renal injuries: A multicenter study of the research consortium of New England Centers for Trauma. JAMA Surg 2013;148:924-31.
8. Lanchon C, Fiard G, Arnoux V, Descotes JL, Rambeaud JJ, Terrier N, *et al.* High grade blunt renal trauma: Predictors of surgery and long-term outcomes of conservative management. A prospective single center study. J Urol 2016;195:106-11.
9. Husmann DA, Gilling PJ, Perry MO, Morris JS, Boone TB. Major renal lacerations with a devitalized fragment following blunt abdominal trauma: A comparison between nonoperative (expectant) versus surgical management. J Urol 1993;150:1774-7.