



STONES/ENDOUROLOGY

ORIGINAL ARTICLE

# Drug treatment of bothersome lower urinary tract symptoms after ureteric JJ-stent insertion: A contemporary, comparative, prospective, randomised placebo-controlled study, single-centre experience



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## KEYWORDS

Ureteric stent;  
Anti-muscarinic;  
Solifenacin;  
Tropium chloride;  
Alfuzosin

## ABBREVIATIONS

BMI, body mass index;  
ROC, receiver operating characteristic;  
USSQ, Ureteric Stent

**Abstract Objective:** To provide a guide for medication to alleviate bothersome lower urinary tract symptoms (LUTS) in patients after JJ ureteric stenting.

**Patients and methods:** Between June 2011 and June 2015, a prospective randomised placebo-controlled study was conducted on 200 consecutive cases of ureteric stones that required JJ stents. All patients had signed informed consent and JJ-stent placement confirmed by X-ray. The patients were randomised into five groups: A, solifenacin 5 mg; B, tropium chloride 20 mg; C, antispasmodic; and E,  $\alpha$ -blocker; and a placebo group (D). A standard model was created to lessen patient selection bias. Eligible patients were enrolled and assessed for side-effects and bothersome LUTS using the validated Ureteric Stent Symptoms Questionnaire. Appropriate statistical analysis was carried out.

**Results:** In all, 150 male patients in the five groups were compared. LUTS were less in groups A and B ( $P < 0.05$ ), while dry mouth was significantly reported in

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Symptoms  
Questionnaire

Group A. Individual comparisons with the placebo group showed a non-significant difference with Group C, while Group E had significant nocturia improvement. Selective comparison of two best groups (A and B) showed less frequency in Group B, while the other LUTS were less in Group A with comparable side-effects.

**Conclusions:** In symptomatic patients following JJ-stent insertion, anti-muscarinic medication, namely solifenacin 5 mg or trospium chloride 20 mg, was the best. The advantage of trospium over solifenacin is in the control of frequency rather than the other symptoms. Addition of an  $\alpha$ -blocker (alfuzosin 10 mg) is valuable when nocturia is the predominant symptom.

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## Introduction

Insertion of a JJ ureteric stent is a common urological procedure, which was introduced in 1967 [1]. The indications are varied and application has become easier. A JJ stent is widely used temporarily, e.g. as a conduit for pyeloplasty or pyleo- or nephro-lithotomy, stenting of the ureter for oedema due to stone impaction or perforation after endourological procedures, or auxiliary for shockwave lithotripsy. Furthermore, a JJ stent can be used as a permanent solution for ureteric obstruction, e.g. in cases of cervical cancer in women. However, stents may result in irritative LUTS that can negatively impact on quality of life [2].

Many attempts have been made to solve stent-related bother in patients, with the majority concentrating on pharmacological methods. Although there are many publications of various drugs and their results, a randomised study with different medications is lacking.

To the best of our knowledge, no consensus has been achieved regarding the best medical treatment for the symptomatic patient after JJ ureteric stenting.

In the present study, we aimed to find the best drug(s) that can relieve stent-related symptoms with high tolerability and minimal side-effects.

## Patients and methods

A prospective randomised placebo-controlled single-blind study was conducted between June 2011 and June 2015. The study design was approved by the hospital medical committee and all patients signed a written informed consent. We enrolled 200 consecutive patients with ureteric stones for whom a temporary JJ stent was inserted (for  $\geq 7$  days). Patients with single iliac or pelvic ureteric stones, with mild–moderate hydronephrosis, for whom a temporary JJ stent was indicated, were included. Exclusion criteria were elderly people (aged  $> 60$  years), any patient with a previous history of prostate disease or overactive bladder on medications, patients with a body mass index (BMI) of  $> 30$  kg/m<sup>2</sup>,

and any patient with an allergy or contraindications to the tested medications. LUTS were assessed preoperatively using the IPSS.

The indications for JJ-stent insertion in our patients were as follows: after ureteroscopy with stone retrieval, either for oedema at the site of stone impaction, expectant pyuria due to neglected hydronephrosis, or small ureteric perforation that inflected during the procedure. Postoperatively a plain abdominal radiograph of the kidneys, ureters and bladder was taken to ensure JJ-stent positioning. A short course of ciprofloxacin 500 mg (twice daily) was given postoperatively, as routine practice against infection.

All the procedures were performed in one centre, stents were supplied by the same manufacturing company (Coloplast A/S 3050, Denmark), and they were performed by one urologist to lessen bias. To make a standard model of testing, all patients were male, had a body mass index (BMI) of  $\sim 25$  kg/m<sup>2</sup>, and the JJ stent was 6 F in diameter and 24 cm in length.

The patient cohort was randomised in a single-blind, placebo-controlled study. The patients were divided into five groups according to the given medication: Group A, solifenacin 5 mg (once daily); Group B, trospium chloride 20 mg (twice daily); Group C, ordinary anti-spasmodic hyoscine butylbromide (buscopan®) 10 mg (once daily), Group D, placebo; and Group E,  $\alpha$ -blocker alfuzosin 10 mg (once daily). The randomisation was carried out using sealed opaque envelopes; allocation concealment was achieved by using an independent person (assisting nurse).

The patients were assessed for bothersome LUTS, haematuria, and flank/suprapubic pain, as well as for side-effects of the used medications using a simplified questionnaire based on the Ureteric Stent Symptoms Questionnaire (USSQ), as a validated and widely applied questionnaire for stent-related symptoms by Joshi et al. 2003 [3,4]. USSQ scores of 0–2 were considered as no significant bother and scores of 3–5 were considered as significant bother.

The primary endpoint of the study was symptom relief and the secondary endpoint was removal of the

JJ stent or the end of the 2 weeks on the chosen medications.

At the end of the study, to obtain standard patient criteria; female patients and those that missed follow-up or who discontinued their medications were excluded.

For the statistical analyses SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA) was used. Each drug-group was evaluated by means of receiver operating characteristic (ROC) curve analysis. The chi-square test and one-way ANOVA were used to evaluate categorical and continuous variables, respectively. The independent *t*-test for continuous variables was used for comparisons between groups. Statistical significance is considered for a  $P < 0.05$ .

The sample size was calculated and the study was designed to detect a significant difference between groups and basal normal conditions for bothersome LUTS, haematuria, and flank/suprapubic pain (score  $< 3$  on USSQ) with 80% power assuming a significant difference level of 0.05 and two-sided statistical test, and ANOVA test. Sample size was estimated to be 200 patients (40 patients in each group). However, at the end of the study and in order to standardise the examined group and exclude patients that discontinued, 150 patients were included in the final analyses (Fig. 1).

## Results

Among the 200 enrolled patients, the females (14 who were not equally distributed in the groups), those who missed follow-up (28), and those who discontinued their medications (eight) were omitted. Finally, 150 eligible male patients were included. As shown in Table 1, there were no significant statistical differences between the

groups in the measured data. Preoperatively no patient had significant LUTS (IPSS  $< 8$ ).

Postoperatively no patient required readjustment of the stent or had up/down stent migration. No patient needed shockwave lithotripsy and there were no postoperative positive urine cultures. There was no significant difference between the groups for fixation of the JJ stents on right or left sides ( $P = 0.995$ ). The JJ stent was *in situ* for  $\geq 7$  days (range 7–30 days;  $P = 0.325$ ).

Table 2 shows a significant difference in bothersome LUTS in patients in groups A and B compared with the other groups. However, dry mouth was a more common side-effect for patients in Group A ( $P = 0.005$ ).

There was a high incidence of constipation in groups A and B, but this was insignificant in comparison to the other groups. There was no significant difference between the groups for haematuria and headache.

For selective comparison with the placebo group, Group C had a statistically nonsignificant difference vs placebo. Group E had a significant reduction in nocturia compared with the other tested variables vs placebo ( $P < 0.05$ ) including the medication side-effects.

For more consolidation; a selective comparison was made between the groups with the best results against placebo (groups A and B). The comparison showed that frequency was less in Group B ( $P = 0.011$ ), while urgency, incontinence and nocturia were less in Group A but without statistical significance ( $P = 0.429$ ,  $P = 0.632$ , and  $P = 0.461$ , respectively). Moreover flank pain, suprapubic pain, and haematuria were less in Group A, but also did not reach statistically significant values ( $P = 0.171$ ,  $P = 0.452$ , and  $P = 0.625$  respectively). All measured side-effects were comparable without statistical significance in both tested groups ( $P > 0.05$ ).

The ROC analyses for the significant drug-groups and are shown in Table 3 and Figs. 2 and 3.

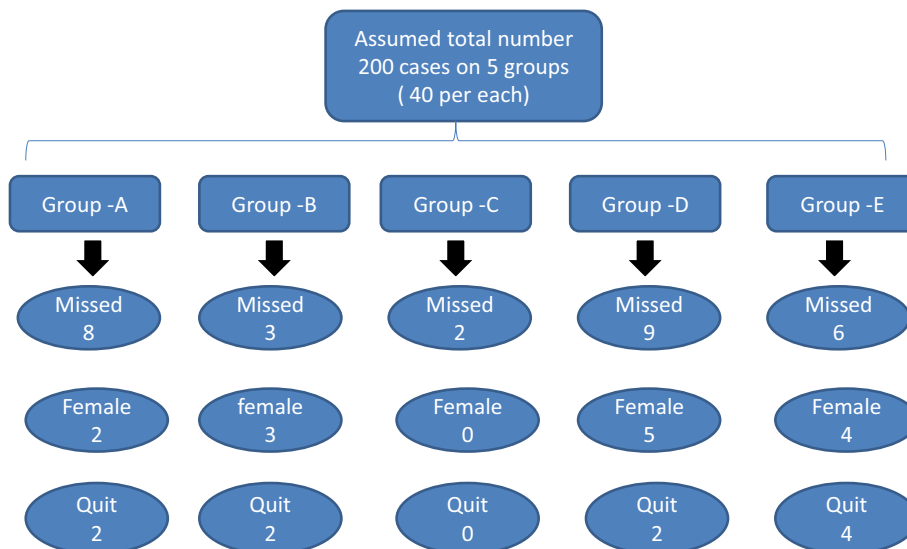


Figure 1 Study flow diagram.

**Table 1** The patients' demographic data.

Variable	Group A	Group B	Group C	Group D	Group E	P
<i>Mean (SD):</i>						
Age, years	40.2 (1.01)	40.9 (1.03)	41.0 (1.25)	37.9 (1.02)	46.4 (1.54)	0.393
Height, m	1.66 (8.27)	1.66 (6.38)	1.64 (5.48)	1.64 (5.48)	1.66 (6.46)	0.820
Weight, kg	78.7 (1.2)	77.4 (1.09)	76.53 (1.49)	74.5 (1.47)	76.06 (9.6)	0.921
BMI, kg/m <sup>2</sup>	28.5 (4.37)	27.7 (2.9)	28.1 (4.7)	26.4 (4.09)	27.8 (3.8)	0.673

**Table 2** Bothersome LUTS and drug side-effects.

	Group A	Group B	Group C	Group D	Group E	P
<i>N (%):</i>						
Frequency	12 (40)	2 (6.7)	20 (66.7)	22 (73.3)	18 (60)	0.002
Urgency	6 (20)	4 (13.3)	20 (66.7)	24 (80)	22 (73.3)	< 0.001
Incontinence	8 (26.7)	8 (26.7)	6 (20)	10 (33.3)	6 (20)	0.162
Nocturia	10 (33.3)	12 (40)	10 (33.3)	16 (53.3)	4 (13.3)	0.237
Flank Pain	12 (40)	18 (60)	12 (40)	16 (53.3)	12 (40)	0.710
Suprapubic pain	12 (40)	10 (33.3)	12 (40)	14 (46.7)	16 (53.3)	0.841
Haematuria	16 (53.3)	16 (53.3)	20 (66.7)	16 (53.3)	18 (60)	0.929
Constipation	14 (46.7)	10 (33.3)	2 (6.7)	4 (13.3)	4 (13.3)	0.048
Dry mouth	10 (33.3)	6 (20)	2 (6.7)	0 (0)	0 (0)	0.005
Headache	6 (20)	4 (13.3)	0 (0)	2 (6.7)	4 (13.3)	0.457

**Table 3** ROC data of significant drug groups.

		Drug group	Group A	Group B	Group E
Bothersome symptom	Area under the curve	Frequency	0.442	0.233	0.567
		Urgency	0.308	0.267	0.642
		Haematuria	0.475	0.084	0.517
	P-value	Frequency	0.487	<b>0.001</b>	0.427
		Urgency	<b>0.022</b>	<b>0.005</b>	<b>0.091</b>
		Haematuria	0.766	<b>0.084</b>	0.843
	95% C.I.*	Frequency	0.279–0.604	0.116–0.350	0.405–0.726
		Urgency	0.165–0.451	0.136–0.398	0.489–0.794
		Haematuria	0.310–0.640	0.310–0.640	0.353–0.680
Side-effect	Area under the curve	Dry mouth	0.642	0.558	0.433
		Constipation	0.650	0.567	0.442
		Headache	0.558	0.517	0.517
	P-value	Dry mouth	<b>0.091</b>	0.487	0.427
		Constipation	<b>0.074</b>	0.427	0.487
		Headache	0.387	0.843	0.843
	95% C.I.*	Dry mouth	0.467–0.816	0.387–0.730	0.282–0.585
		Constipation	0.3482–0.818	0.98–0.736	0.286–0.589
		Headache	0.387–0.730	0.350–0.683	0.350–0.683

P value < 0.05, is consider vacation.

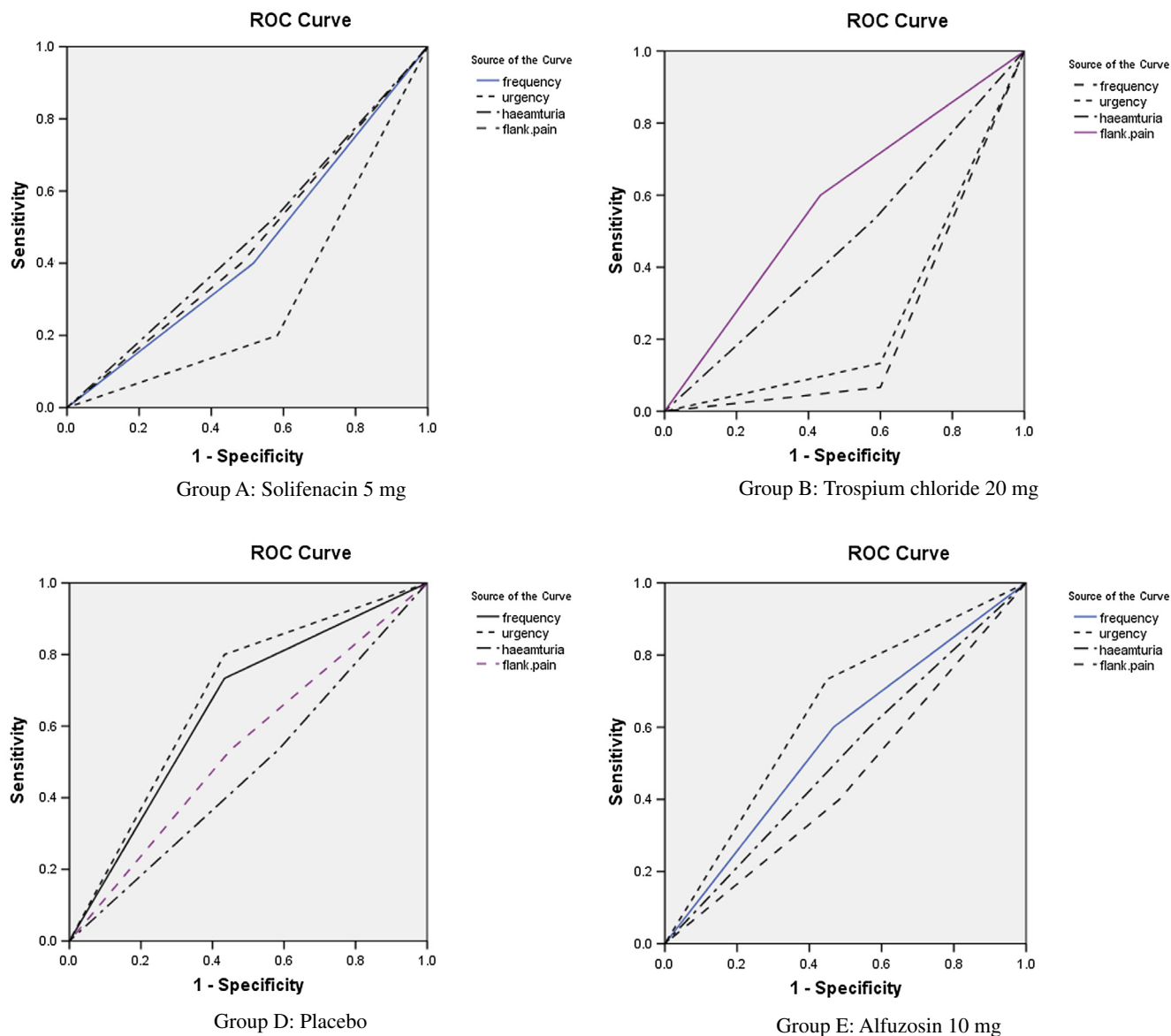
\* CI: Confidence interval.

## Discussion

Ureteric stenting is a widely used urological procedure. However, post-fixation sequelae may be bothersome for the patient and his attending urologist. Furthermore, stent-related sequelae can impact on the patient's quality of life [2] and can result in early

removal in some cases. Usual urinary symptoms (namely; frequency, urgency and haematuria) are related to trigonal irritation or pressure transmitting to the renal pelvis during urination (causing a flank pain) [2,5].

Haematuria is related to stent friction in the collecting system or in the bladder due to physical activity or



**Figure 2** ROC curves for frequency, urgency, pain and haematuria vs medications, solifenacin (A), tropium chloride (B), placebo (D), and alfuzosin 10 mg (E).

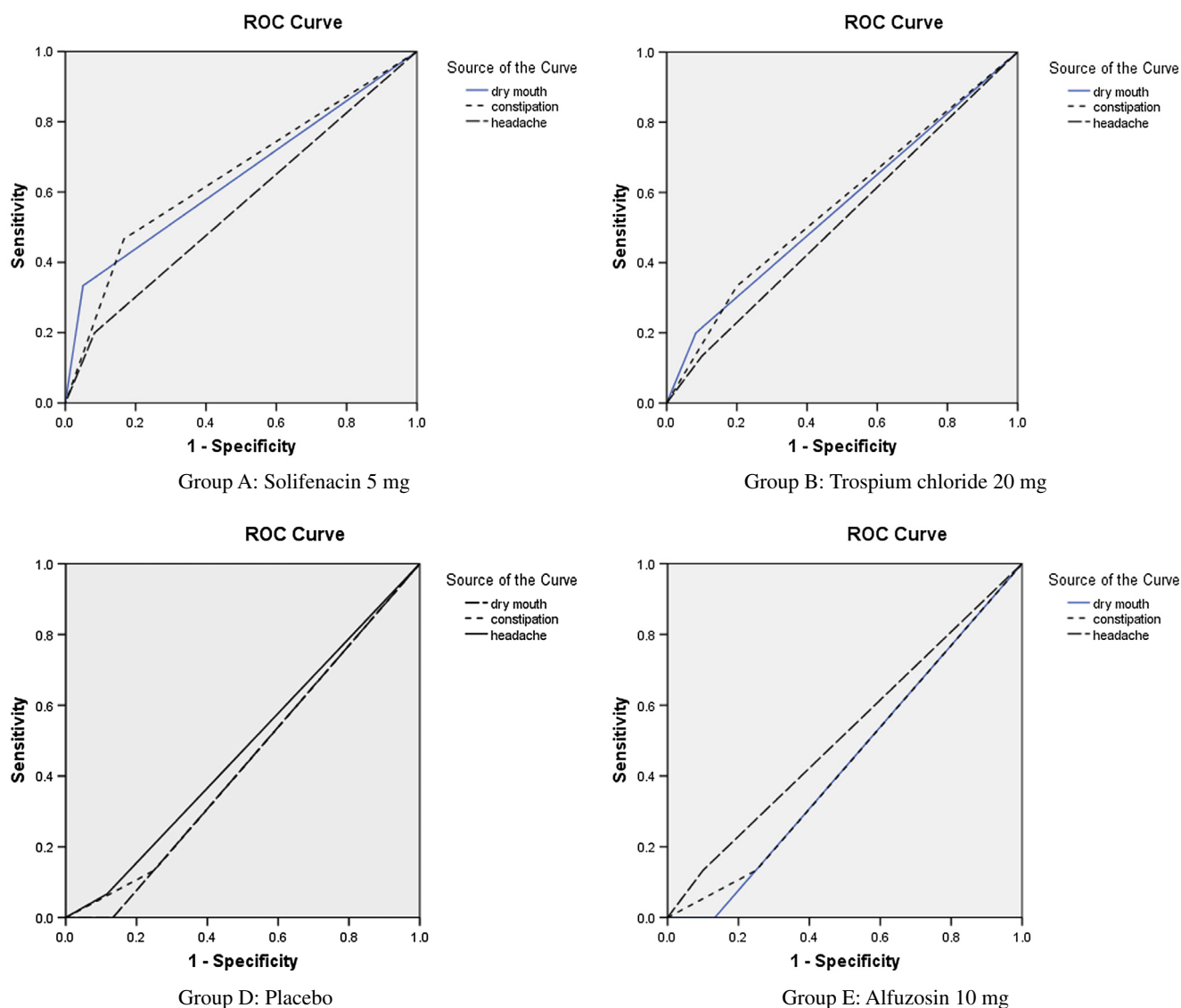
low amount of urine [6]. In a report by Joshi et al. [2], there was an 80% reduction in patient quality of life due to stent-related symptoms after JJ stent insertion.

There have been many studies attempting to resolve this problem with medications, e.g. anti-cholinergics,  $\alpha$ -blockers or combinations, with varying results [7–10]. However, a placebo-controlled study with a multi-drugs comparative protocol is deficient. Furthermore, the bias of stent material effect [5] or sizes of JJ stent [11–13] are contributing factors in many studies. In our present study, we have circumvented these issues by using stents of the same size and from the same manufacturing company.

In order to nullify the bias and for homogeneity of the tested groups, we controlled for JJ-stent material/-

size, patient factors, and urologist factor in the study design. The same urologist inserted all the stents in the same centre. The patient is another important contributing factor, thus in our study; all the patients were male, had the same average age and relatively equal BMI, with no preoperative LUTS. All included patients had no UTIs, significant residual fragments, large ureteric perforations/urinomas, or stent migrations. To strengthen our conclusion we excluded female cases, those who missed follow-up, and those who discontinued their medications.

In our present study we used a simple validated questionnaire based on Ureteric Symptom Score Questionnaire [3,4] to assess LUTS with flank pain and haematuria.



**Figure 3** ROC curves for side-effects vs medications, solifenacin (A), trospium chloride (B), placebo (D), and alfuzosin 10 mg (E).

### The rational of used medications

Stent-related symptoms are similar to overactive bladder symptoms caused by involuntary bladder contraction mediated by muscarinic receptors [7,14]. Solifenacin has proved its effectiveness in many trials with minimal side-effects [8,15]; while there are no studies on trospium chloride in this field. In agreement with other studies, our present results show that the best results were achieved with anti-muscarinic medications (group A and B) compared with the other treated groups and vs placebo. However, side-effects were more pronounced with significant values.

Within the four treated groups, the best results vs placebo were obtained for groups A and B. When we compared group A and B selectively, we found that frequency was less in Group B (trospium) than in Group A (solifenacin;  $P < 0.05$ ), which is in agreement with

the findings of Lee et al. [8]. However, solifenacin is effective in reduction of urgency, urge incontinence and nocturia in the tested groups of patients. Both groups were comparable for effects on haematuria and related side-effects ( $P > 0.05$ ).

Furthermore, in view of the similarity of LUTS and BPH symptoms, an obvious suggestion is the use of an  $\alpha$ -blocker [9]. In agreement with the study by Beddingfield et al. [16] and others [17,18], in our present study frequency, nocturia and flank pain were less in the alfuzosin-treated group in comparison to placebo. However, the results for group E (alfuzosin 10 mg, once daily) were not as good as those for group A and B.

Small sample size and exclusion of female cases could be limitation of our present study. Further studies with large samples and both genders with different age groups would be useful.

## Conclusion

LUTS can be a problem for patients after JJ-stent insertion. Anti-muscarinic medications (solifenacin 5 mg, once daily or trospium chloride 20 mg, twice daily) are the ideal solution to overcome this problem. Trospium chloride is the best choice whenever frequency is the bothersome symptom. Whenever nocturia is the most distressing symptom the addition of an  $\alpha$ -blocker (alfuzosin 10 mg, once daily) is beneficial.

## Conflict of interest

None.

## Source of Funding

None.

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