African Journal of Urology (2017) **23**, 28–32

African Journal of Urology

Official journal of the Pan African Urological Surgeon's Association
web page of the journal

www.ees.elsevier.com/afju
www.sciencedirect.com

Original article

Impact of Tamsulosin, Tolterodine and drug-combination on the outcomes of lower urinary tract symptoms secondary to post-ureteroscopy ureteral stent: A prospective randomized controlled clinical study

O. Abdelkader [a], K. Mohyelden [b,*], M.H. Sherif [a], A.H. Metwaly [a], H. Aldaqadossi [b], A. Shelbaya [c], H. Khairy [d], A. Elnashar [a]

[a] *Department of Urology, Suez Canal University, Ismailia, Egypt*
[b] *Department of Urology, Fayoum University, Fayoum, Egypt*
[c] *Student Hospital, Cairo University, Cairo, Egypt*
[d] *Department of Urology, Cairo University, Cairo, Egypt*

Received 17 March 2016; received in revised form 23 June 2016; accepted 23 June 2016
Available online 18 November 2016

KEYWORDS
Anticholinergics;
α-Adrenergic blockers;
Ureter stent;
Ureteroscopy

Abstract
Objectives: To compare the role of alpha-blocker (Tamsulosin) monotherapy, anticholinergic (Tolterodine) monotherapy or combination of both drugs *versus* analgesics in improving post-ureteroscopy (URS) lower urinary tract symptoms related to double-J ureteral stent.
Patients and methods: Between January 2009 and June 2013, 160 consecutive patients with ureteric stones were included in this study at 2 tertiary care centers'. Patients were randomized into 4 groups; group A ($n=40$) received 0.4 mg Tamsulosin once a day, group B ($n=40$) received 4 mg Tolterodine once a day, group C ($n=40$) received Tamsulosin 0.4 mg and Tolterodine 4 mg once a day and group D ($n=40$) as a control group, received placebo once a day. All patients received analgesics on demand. Pre-treatment evaluation was done followed by among-groups comparison after 14 days including ureteral stent symptom questionnaire (USSQ) [Urinary symptom index (USI), pain symptom index (PSI), general health index (GHI), work perform index (WPI), need for pain killer (PK), need for analgesia, visual analogue scale (VAS) for pain and quality of life (QOL)]. Side effects were recorded and compared.

* Corresponding author.
E-mail addresses: osmanco3247@yahoo.com (O. Abdelkader), kma02@fayoum.edu.eg (K. Mohyelden), mh_sherief68@yahoo.com (M.H. Sherif), aldaqados@yahoo.com (H. Aldaqadossi), ashelbaia@yahoo.com (A. Shelbaya), dr_hosni@yahoo.com (H. Khairy), ahmedelnashar@gmail.com (A. Elnashar).
Peer review under responsibility of Pan African Urological Surgeons' Association.

http://dx.doi.org/10.1016/j.afju.2016.06.001

Results: Out of 160 patients, 153 patients (40, 38, 37 and 38 patients in groups A, B, C and D, respectively) completed the study with a mean age of 34.3 ± 7.6 (20–50) years. All groups were comparable in terms of age, gender, stone size and stone location, USSQ items and QOL. After 14 days, the USSQ and QOL were significantly lower in group A, B and C in comparison with group D ($p < 0.05$). Patients in group C had significantly much improvement than those of groups A and B ($p < 0.05$).
Conclusion: Combination of alpha blockers (Tamsulosin) and Anticholinergics (Tolterodine) seems to significantly improve post-URS lower urinary tract symptoms secondary to ureteral stents with lower need for analgesia and better quality of life. Adverse effect of used drugs mentioned as transient and tolerated by the patients without need for auxiliary medication.

Introduction

Ureteral stenting is a widespread procedure with variable indications in urology, including post endoscopic procedures, prior to SWL in selected cases, intolerable renal colic, and ureteral injury during ureteroscopy [1].

However, ureteral stent placement might be associated by bothersome lower urinary tract symptoms (LUTS) including bladder irritation, pain, frequency and dysuria. These symptoms usually affect the patient's quality of life and consequently the general health and work [2]. Alpha adrenergic blockers have been widely used to manage such stent related symptoms with encouraging results [3,4].

Similarly, anticholinergics alone or in combination with α-blockers have been used successfully to treat LUTS related symptoms associated with benign prostate hyperplasia (BPH) and overactive bladder (OAB) syndrome [5,6]. These latter pathologies usually presented by LUTS/storage symptoms which mimic that of the stent placement. Moreover, there are sparse of literature with level-1 evidence which compare the outcomes of these drugs, monotherapy or in combination, in the management of those bothersome symptoms.

Therefore, the aim of the present study was to evaluate the efficacy and safety of Tamsulosin and Tolterodine, either monotherapies or in combination, for improving LUTS/storage bladder symptoms secondary to post-ureteroscopy (URS) double-J ureteral stenting.

A great effort has been done by Joshi et al. [7] to develop USSQ as psychometrically valid measure to evaluate the stent related symptoms and QOL. USSQ explores six areas (sections) containing 38 items, the answers of which are based on a rating scale from 0 to 5 and the scoring system consists of a simple sum of the scores of individual questions in each section. Those sections include (Urinary symptom index, pain symptom index, general health index, work performance index, sexual matter and additional problem index) which contain 11, 8, 6, 7, 1 and 5 items, respectively. This USSQ is considered the as the first valid objective tool to evaluate stent related symptoms and their effect on QOL. Following this score, different versions has been published in Italian, Korean, Spanish and Turkish language. Recently, the validated Arabic version of the USSQ was introduced by El-Nehas et al. [8] that can be used to evaluate the stent related symptoms and QOL in Arabic patient.

Patients and methods

After institutional board approval of the study protocol, 160 patients who underwent URS for management of ureteric stones were included after giving an informed consent to participate in the study. Before URS, all patients were evaluated by history taking, clinical examination, laboratory investigations and radiological imaging including intravenous urography (IVU) and non-contrast spiral computer tomography (CT).

Patients between 20 and 50 years old (to avoid LUTS due to BPH), who had been managed for a single ureteral stone less than 10 mm in their longest diameter, were included in the current randomized cohort study. Patients with complicated URS, concurrent urinary tract infection (UTI), ongoing medication with alpha blockers, anticholinergics or chronic analgesics, bilateral ureteric stents, open ureteral surgery, previous pelvic or prostatic surgery, pregnancy or bleeding disorders were excluded from the study.

Procedure

Ureteroscopic lithotripsy using pneumatic lithotripter with removal of the stones was performed in all patients and double J ureteric stent, (consisting from polyurethane), 6 F, 26–28 cm (according to ureter length) polyurethane material was inserted for 2 weeks postoperatively. The ureteral stent symptom questionnaire (USSQ) was used to evaluate lower urinary tract symptoms and impact on quality of life of ureteral stents. The patients were prospectively randomized into four groups using a computer software; group A ($n = 40$) received 0.4 mg Tamsulosin once a day, group B ($n = 40$) received 4 mg Tolterodine once a day, group C ($n = 40$) received Tamsulosin 0.4 mg and Tolterodine 4 mg once a day and group D ($n = 40$) as a control group, received placebo once a day. All patients received pain killer on demand.

The patients used Diclofenac potassium Tab. 50 mg when needed (up to twice per day), and paracetamol Tab. 500 mg when needed as analgesic medication.

Pre-treatment evaluation was done followed by among-groups comparison after 14 days including ureteral stent symptom questionnaire (USSQ), using urinary symptom index (USI), pain symptom index (PSI), general health index (GHI), work performance index (WPI), need for pain killer (PK), visual analogue scale (VAS) and quality of life (QOL). Side effects were recorded and compared.

Collected data included patient's age, sex, stone size, stone location and laterality. Follow up consisted of urine analysis, plain kidney, ureter and bladder (KUB) film after one week to evaluate stone-free status and to confirm the position of the stents.

Statistical analysis

Data analysis was done using the commercially available Statistical Package for Social Sciences for Windows, version 20 (SPSS, Chicago, IL). Descriptive data were presented in terms of numbers, percentages, and means with standard deviations. Categorical variables were compared using Fisher exact test while continuous variables were compared by the analysis of variance (ANOVA) test. A two-sided level of significance under 0.05 was adopted.

Results

Out of 160 patients, 153 patients completed the study, whereas 40, 38, 37, 38 patients in groups A, B, C, D, respectively with a mean age of 34.3 ± 7.60 (20–50) years, including 87 (56.9%) males and 66 (43.1%) female. Demographic data and stone characteristics of all groups are presented in Table 1. All groups were comparable in terms of age, gender, stone size and stone locations (Table 1).

Patient's symptoms after stent insertion included dysuria, urgency, urge incontinence, loin pain, suprapubic pain, frequency, and/or nocturia. Similarly, patients of all groups were comparable in terms of the baseline ureteral stent symptom questionnaire (USSQ), using urinary symptom index (USI), pain symptom index (PSI), general health index (GHI), work performance index (WPI), need for pain killer (PK), visual analogue scale (VAS) and quality of life (QOL) ($p > 0.05$) (Table 2).

After 14 days of stent insertion evaluation based on USSQ items VAS and impact on QOL revealing symptom scores were significantly lower in group A, B and C in comparison with the control group, with much better improvement in group C in comparison with either group A or group B alone (*P* value 0.011, 0.001, 0.001, 0.005, 0.005, 0.001 and 0.001) (Table 2).

The mean analgesic tablets consumption was 11, 7, 12.3, 10.8 and 16.4 in group A, B, C, D, respectively, which was comparable in the first two groups and significantly higher in group D and lower in group C.

There was no statistical significant difference between group A and group B in improvement of symptoms scores at day 14.

In group A, three patients (7.5%) suffered from dizziness and two patients (5%) had headache. In group B, 18.4% had dry mouth and 5.2% had dizziness. In group C, dry mouth and headache were reported in 13.5% and 2.7% of patients, respectively. Anejaculation was reported in 25% in group A (10/40) and in 5.4% in group C (2/37). Otherwise, no other adverse events were detected in all groups (Table 3).

Discussion

Post-URS ureteral stents help in preventing ureteral obstruction and assisting stone passage [2]. However, those indwelling ureteral stents are usually associated with bothersome symptoms such as urgency, renal colic, suprapubic pain, incontinence and haematuria [9]. These symptoms might result from irritation of the trigone and the high pressure transmitted to the renal pelvis during micturition after ureteral stenting or detrusor muscle spasm in and around the intramural ureter [10,11].

Moreover, stent-related pain and urinary frequency might be related to spasm of the lower ureter or local trigone sensitivity as [3] therefore, the idea beyond adding anticholinergics to the α-blockers in the current study was to relief the irritation of the trigone and to decrease the ureteral spasm and or local trigonal sensitivity caused by the lower end of the ureteral stent.

In the current study, we prospectively evaluated the impact of α-adrenergic blockers monotherapy or anticholinergic monotherapy or in combination on the outcome of these post-URS stent-related symptoms.

Several studies have compared the efficacy of α-adrenergic blockers with or without anticholinergics for improvement of stent-related LUTS and QOL [3,4,12,13]. Moreover, both Alfuzosin and Tolterodine monotherapy had significantly improved lower urinary symptoms and pain related to double-J stent according to USSQ Questionnaire [12].

However, other studies found no improvement in LUTS except with phenazopyridine *versus* control 2-days post-stenting [13]. In the current cohort USI, PSI, GHI, WPS, PK, VAS and QOL were comparable at baseline. However, after 14 days, these scores significantly changed in groups A, B, and C in comparison to the control group, indicating improvements of the post-stenting symptoms in these groups. This symptom improvement was better in group C than either group A or B alone, indicating the superiority of combination therapy over the monotherapy. The α-adrenergic blockers seem to improve the stent-related symptoms due to the similarity of these symptoms to benign prostate hyperplasia (BPH)-related

Table 1 Patient's characteristics.

Variable	Group A*n* = 40	Group B*n* = 38	Group C*n* = 37	Group D*n* = 38	*P* value
Sex (Male:Female)	24/16	22/16	19/18	22/16	0.885
Age (Mean)	32.2 ± 10	34.3 ± 9.8	32.6 ± 9.2	31 ± 9.2	0.922
Mean stone size (mm)	9.5 ± 2.2	9.5 ± 1.8	9.6 ± 2.6	7.8 ± 1.1	0.141
Stone location(Middle/lower) ureter	8/32	7/31	10/27	8/30	0.816
Stent character					
6 fr/26 cm	12	18	21	17	1
6 fr/28 cm	18	20	16	21	
Sexual active (+/−)	30/10	24/14	26/11	30/8	0.456

Table 2 Overall results of the study in 4 groups at days 0, 14.

			A alpha blockers	B anticholinergics	C combined	D control	*P* value*
US[1]	Day 0	Median	22	22	21	21.5	0.011
		IQR	4.75	4	3.75	3.5	
	Day 14	Median	23	23	21	25	
		IQR	5.75	6.75	2.75	6.5	
PSI[2]	Day 0	Median	13.5	13	13.5	14	<0.001
		IQR	1.75	1	1	2	
	Day 14	Median	18	19	15	20.5	
		IQR	1.75	2	2.75	3	
GH[3]	Day 0	Median	14.5	14.5	14	14.5	<0.001
		IQR	3.75	3	2	3.75	
	Day 14	Median	16	16	13	17.5	
		IQR	3.75	3.75	2.75	3.75	
WPS[4]	Day 0	Median	12.5	12	12.5	12	0.005
		IQR	3	4.5	3	3.5	
	Day 14	Median	11	11	9	11	
		IQR	2	1.75	1.75	2.75	
PK[5]	Day 0	Median	1	1	1	1	0.005
		IQR	0	1	0	0	
	Day 14	Median	2	3	1	7	
		IQR	1	1	0	1.75	
VAS[6]	Day 0	Median	4	4	4	4	<0.001
		IQR	1.75	1	1	2	
	Day 14	Median	2	3	2	2.5	
		IQR	1	1	1	2	
QOL[7]	Day 0	Median	4	4	5	5	<0.001
		IQR	0.75	1	1	1	
	Day 14	Median	3	3	1	4	
		IQR	2	1	1	1	
USSQ[8]	Day 0	Median	72	72	71	72	<0.001
		IQR	8	14.5	4.5	7	
	Day 14	Median	75	79	62	87.5	
		IQR	10	4	4.5	8.5	

USSQ, ureteral stent symptom questionnaire; USI, urinary symptom index; PSI, pain symptom index; GHI, general health index; WPI, work performance index; PK, need for pain killer; VAS, visual analogue scale; QOL, quality of life.

LUTs caused by involuntary contraction of the detrusor muscle [3]. Moreover, the randomized controlled trials have proved the role of α-blockers in improvement of stent-related LUTS and supported their use in routine clinical practice [7,14–16].

In addition, Lamb et al. have reported that alpha-blockers reduce stent-related symptoms assessed by the ureteral stent symptoms questionnaire (USSQ) [14].

No significant difference was noted between groups A, B at day 14 in symptoms scores improvement. After 14-days, USSQ maintained their significant improvement in groups A, B, and C in comparison to that of the control group with evident effect in group C than the other monotherapy groups.

Adverse effect of drugs used in our study mentioned as transient and tolerated by the patient without need for auxiliary medication 32 patients (21%) from total presented in group A, B and C by 15 (10%), 9 (6%) and 8 (5%), respectively.

Despite being a prospective study, the current study is limited by the relatively small sample size per each group, and short time of stenting, also ESWL cases, post open surgery stenting, and permanent stent in cases of (tumor or obstructive uropathy) were not included.

Table 3 Adverse effect.

Adverse effect	Group A α-blocker	Group B Anticholinergic	Group C combined	Group D control	*P* value
Dizziness	3	2	0	0	0.104
Headache	2	0	1	0	0.561
Dry mouth	0	7	5	0	0.046
Anejaculation	10	0	2	0	0.006

Conclusion

Combination of α-adrenergic blockers and anticholinergics seems to have a better efficacy than either drug as a monotherapy in improving the lower post-URS stent-related symptoms and quality of life and is associated with lower needs for analgesia. Adverse effect of used drugs mentioned as transient and tolerated by the patients without need for auxiliary medication.

Author's contribution

Osman Abdel Kader shared in performing the procedures and collecting data and was responsible for the design and edits the manuscript. Khaled Mohyelden shared in performing the procedures and was responsible for the design and edits the manuscript. Mahmoud H. Sherif shared in performing the procedures and collecting data and responsible for statistics and data analysis. Adel H. Metwally shared in performing the procedures and collecting data. Hussein Adbelhameed shared in performing the procedures and collecting data. Hosni Khairy was responsible for revising the manuscript. Ahmed Shelbaya and Ahmed Elnashar were responsible for interpretation of data.

Ethical approval

Ethical committee of Faculty of Medicine Fayoum University approved the protocol of this study. Informed consent was obtained in all cases.

Conflicts of interest

The authors declared that there was no conflict of interest.

Funding

None declared.

Acknowledgment

To Dr. Keely and all member of USSQ: As he is the first one to develop and assess the USSQ by its satisfactory validity with good evaluative and discriminate properties.

The authors would like to thank Dr. Mohammed Aly Elkoushy for his kind help in editing this manuscript.

References

[1] Jeong H, Hwak C, Lee SE. Ureteric stenting after ureteroscopy for ureteric stones: a prospective randomized study assessing symptoms and complications. BJU Int 2004;93:173–80.
[2] Chew BH, Knudsen BE, Denstedt D. The use of stents in contemporary urology. Curr Opin Urol 2004;14:111–5.
[3] Deliveliotis C, Chrisofos M, Gougousis E, Papatsoris A, Dellis A, Varkarakis IM, et al. Is there is a role for alpha blockers in treating double J stent related symptoms. Urology 2006;67:35–9.
[4] Damiano R, Autorino R, Desio M, Giacobbe A, Palumbo IM, D'Armiento M, et al. Effect of tamsulosin in preventing ureteral stent related morbidity: a prospective study. J Endourol 2008;22:651–6.
[5] Kaplan SA, Roehrborn CG, Rovner ES, Carlsson M, Bavendam T, Guan Z, et al. Tolterodine and tamsulosin for treatment of men with lower urinary tract symptoms and overactive bladder: a randomized controlled trial. J Am Med Assoc 2006;296:2319–28.
[6] Chung DE, Te AE. Tolterodine extended-release for overactive bladder. Expert Opin Pharmacother 2009;10:2181–94.
[7] Joshi HB, Newns N, Stainthorpe A, MacDonagh R, Keeley JRFX, Timoney AG. Ureteral stent symptom questionnaire. Development and validation of a multidimensional quality of lifemeasure. J Urol 2003;169:1060–4.
[8] El-Nahas AR, Elsaadany MM, Tharwat M, Mosbah AA, Metwally H, Hawary A, et al. Validation of the Arabic linguistic version of the ureteral stent symptoms questionnaire. Arab J Urol 2014:1–4.
[9] Clayman RV. Ureteric stenting after ureteroscopy for ureteric stones: a prospective randomized study assessing symptoms and complications. J Urol 2005;173(June (6)):2022.
[10] Thomas R. Indwelling ureteral stents: impact of material and shape on patient comfort. J Endourol 1993;7:137–40.
[11] Gupta M, Patel T, Xavier K, Maruffo F, Lehman D, Walsh R, et al. Prospective randomized evaluation of periureteral botulinum toxin type A injection for ureteral stent pain reduction. J Urol 2010;183:598.
[12] Park SC, Jung SW, Lee JW, Rim JS. The effects of tolterodine extended release and alfuzosin for the treatment of double-J stent-related symptoms. J Endourol 2009;23:1913–7.
[13] Norris RD, Sur RL, Springhart WP, Marguet CG, Mathias BJ, Pietrow PK, et al. A prospective randomized double blind placebo controlled comparison between extended release oxybutinin versus phenazopyridine for management of ureteral stent related discomfort. Urology 2008:71–92.
[14] Lamb AD, Vowler SL, Johnston R, Dunn N, Wiseman OJ. Meta-analysis showing the beneficial effect of alpha-blockers on ureteric stent discomfort. BJU Int 2011;108(11):1894–902.
[15] Yakoubi R, Lemdani M, Monga M, Villers A, Koenig P. Is there a role for α-blockers in ureteral stent related symptoms? A systematic review and meta-analysis. J Urol 2011;186(September (3)):928–34.
[16] El-Nahas AR, El-Assmy AM, Shoma AM, Eraky I, El-Kenawy MR, El-Kappany HA. Self-retaining ureteral stents: analysis of factors responsible for patient discomfort. J Endourol 2006;20(January (1)):33–7.