

## STONES/ENDOUROLOGY

### ORIGINAL ARTICLE

# Efficacy and safety of tamsulosin vs. alfuzosin as medical expulsive therapy for ureteric stones

Ahmed K. Ibrahim <sup>a,\*</sup>, Isam H. Mahmood <sup>b</sup>, Nada S. Mahmood <sup>c</sup>

<sup>a</sup> Urology Division, Department of Surgery, University of Mosul, Mosul, Iraq

<sup>b</sup> Department of Pharmacology, College of Pharmacy, University of Mosul, Mosul, Iraq

<sup>c</sup> Department of Pharmacology, College of Medicine, University of Mosul, Mosul, Iraq

Received 29 December 2012, Received in revised form 18 February 2013, Accepted 22 February 2013

Available online 6 April 2013

#### KEYWORDS

Ureteric stones;  
Medical expulsive therapy;  
Tamsulosin;  
Alfuzosin

#### ABBREVIATIONS

MET, medical expulsive therapy;  
US, ultrasonography

**Abstract Objective:** To evaluate and compare the efficacy of tamsulosin and alfuzosin as medical expulsive therapy for ureteric stones.

**Patients and methods:** In all, 112 patients with ureteric stones of  $\leq 10$  mm, located along the ureter, were randomly divided into three groups. In group I, 32 patients received no  $\alpha$ -blockers (controls), in group II 40 patients received tamsulosin 0.4 mg daily, and in group III 40 patients received alfuzosin 10 mg daily. All patients were given analgesia and antibiotics when indicated. The follow-up was weekly for 4 weeks.

**Results:** The mean stone size and age were comparable in the three groups. The stone expulsion rate was 44%, 85% and 75% in groups I, II and III, respectively. Half of the stones in group II passed within 2 weeks, half in group III passed within 3 weeks, while more than half of the stones in group I did not pass even after 4 weeks. The mean number of painful episodes was 2.45, 1.38 and 1.64 in groups

\* Corresponding author. Address: Urology Division, Department of Surgery, College of Medicine, Mosul University, Alshifaa Street, Mosul, Iraq. Tel.: +964 7708224454.

E-mail address: ahmed\_khalil5@yahoo.com (A.K. Ibrahim).

Peer review under responsibility of Arab Association of Urology.



Production and hosting by Elsevier

I, II and III, respectively. The drug-related side-effects reported by patients were mild and transient.

**Conclusion:** The use of tamsulosin or alfuzosin as medical expulsive therapy for ureteric stones in the three sections of the ureter (upper, middle and lower) was safe and effective, as shown by the increased overall stone expulsion rate, reduced stone expulsion time and fewer pain episodes. Tamsulosin was associated with a greater rate of stone expulsion than was alfuzosin.

© 2013 Production and hosting by Elsevier B.V. on behalf of Arab Association of Urology.

## Introduction

Urinary tract stones are one of the most common urological conditions worldwide. The prevalence is estimated to be 1–5% in Asia, 5–9% in Europe and 13% in the USA [1]. Ureteric stones represent one of the major causes for attendance at the emergency and outpatient departments in urology, and are associated with considerable morbidity.

Current therapeutic options for ureteric stones include active intervention and conservative ‘watch and wait’ approaches. Recent advances in endoscopic stone management have allowed upper tract stones to be treated using minimally invasive techniques, which have increased the success rates and decreased treatment-related morbidity. These advances include ESWL, ureteroscopy and percutaneous approaches. Although these procedures are less invasive than traditional open surgery they are more expensive and have inherent risks [2], but the surgical and anaesthetic risks are not negligible, and serious complications, although rare, are possible [3]. Thus, for many patients, a conservative treatment with no invasive procedures is an appealing option. However, watchful waiting does not always result in stone clearance and can be associated with recurrent renal colic [4].

The 2007 Guideline for the Management of Ureteral Calculi of the AUA [3], and the European Association of Urology guideline, recommend watchful waiting with medical treatment for patients with a stone of < 10 mm in diameter and with well-controlled pain.

Medical expulsive therapy (MET) has been investigated as a supplement to observation in an effort to improve spontaneous stone-passage rates, which can be unpredictable. Because ureteric oedema and ureteric spasm have been postulated to affect stone passage, these effects have been targeted by pharmacological intervention. Therefore, the primary agents that have been evaluated for MET are calcium-channel blockers, steroids, NSAIDs and  $\alpha$ 1-adrenergic receptor antagonists [2].

The human ureter contains  $\alpha$ -adrenergic receptors along its length, with the highest concentration in the distal ureter. Three subtypes of  $\alpha$ 1 receptor have been described, i.e.,  $\alpha$ 1a,  $\alpha$ 1b and  $\alpha$ 1d, with the last having

the highest density in the distal ureter [5]. Stimulation of the receptors increases the force of ureteric contraction and the frequency of ureteric peristalsis, whereas antagonism of the receptors has the opposite effects. The  $\alpha$ 1-adrenoreceptor antagonists ( $\alpha$ 1-blockers) inhibit contractions of the ureteric musculature, reduce the basal tone, and decrease the peristaltic frequency and colic pain, facilitating the expulsion of ureteric stones [6].

The aim of the present study was to compare tamsulosin and alfuzosin for their efficacy and safety as MET in patients with a symptomatic uncomplicated ureteric stone that was located in one of the three sections of the ureter. We also assessed the effect of these two drugs in reducing the pain episodes in these patients.

## Patients and methods

This was a prospective randomised controlled trial. The inclusion criterion was a symptomatic ureteric stone of < 10 mm in diameter. The exclusion criteria were acute infection, a solitary kidney, elevated levels in renal functional tests at presentation, severe hydronephrosis, bilateral ureteric stones, pregnancy or lactation, current use of  $\alpha$ -blockers, calcium-channel blockers or steroids, age < 18 years, and any allergic reaction to the study medication.

The study was conducted between July 2012 and December 2012, and was approved by the Department of Surgery and authorities of the Mosul College of Medicine. In all, 112 patients fulfilled the above criteria and completed the follow-up. All of the eligible patients had signed an informed consent.

At the initial visit the patients had a complete history taken, a physical examination, urine analysis, and blood urea nitrogen and serum creatinine levels were measured. All patients were assessed with urinary ultrasonography (US) and a plain abdominal X-ray. IVU or CT was used in a few patients depending on specific indications.

## Study design

In consultation with a statistician, the sample size was scheduled to be 50 patients in each of three groups, taking into consideration previous similar studies, and the

patients were randomised systematically at a ratio of 1:1. The fate of the patients through the various stages (enrolment, follow-up and analysis) is shown in the consort chart (Fig. 1).

Accordingly, the patients were divided into three groups, i.e. group I (control, 32 patients, no  $\alpha$ -blockers), group II, (40 patients) taking a tamsulosin capsule of 0.4 mg daily, group III (40 patients) receiving alfuzosin 10 mg daily. The patients were followed-up weekly for 4 weeks, and every visit comprised a focused history, a physical examination and urinary US, with pain episodes and any drug-related side-effects also reported. Significant pain episodes were defined as an acute pain episode that necessitated the use of parenteral analgesia and/or hospitalisation. (All the patients were given diclofenac potassium orally 50 mg and/or diclofenac sodium as an intramuscular injection of 75 mg on demand). The date of stone passage (if any) was recorded.

The criteria for treatment discontinuation and the need for intervention (ESWL or endoscopy) were uncontrolled pain, fever, severe hydronephrosis, or lack of successful stone expulsion after 4 weeks.

anova was used to compare between age and ureteric stone size among the groups, with differences considered significant at  $P < 0.05$ ; other data are presented as percentages or proportions if the totals were small.

## Results

The three groups were matched for age and stone size (Table 1). Most stones were in the lower ureter (Fig. 2). Among the 40 patients in group II, 34 (85%) successfully passed the stone spontaneously, and in group III, 30 (75%) did so, whereas in group I only 14 (44%) patients passed the stone spontaneously. The differential rate of stone passage for each part of the ureter is shown in Table 2; the difference was significant for the lower ureteric stones and overall stone passage.

The stone expulsion time is also shown in Table 2, where half the stones in group II passed within 2 weeks, half in group III passed within 3 weeks, but more than half of the stones in group I did not pass even after 4 weeks. The mean number of painful episodes was 2.45, 1.38 and 1.64 for groups I, II and III, respectively.

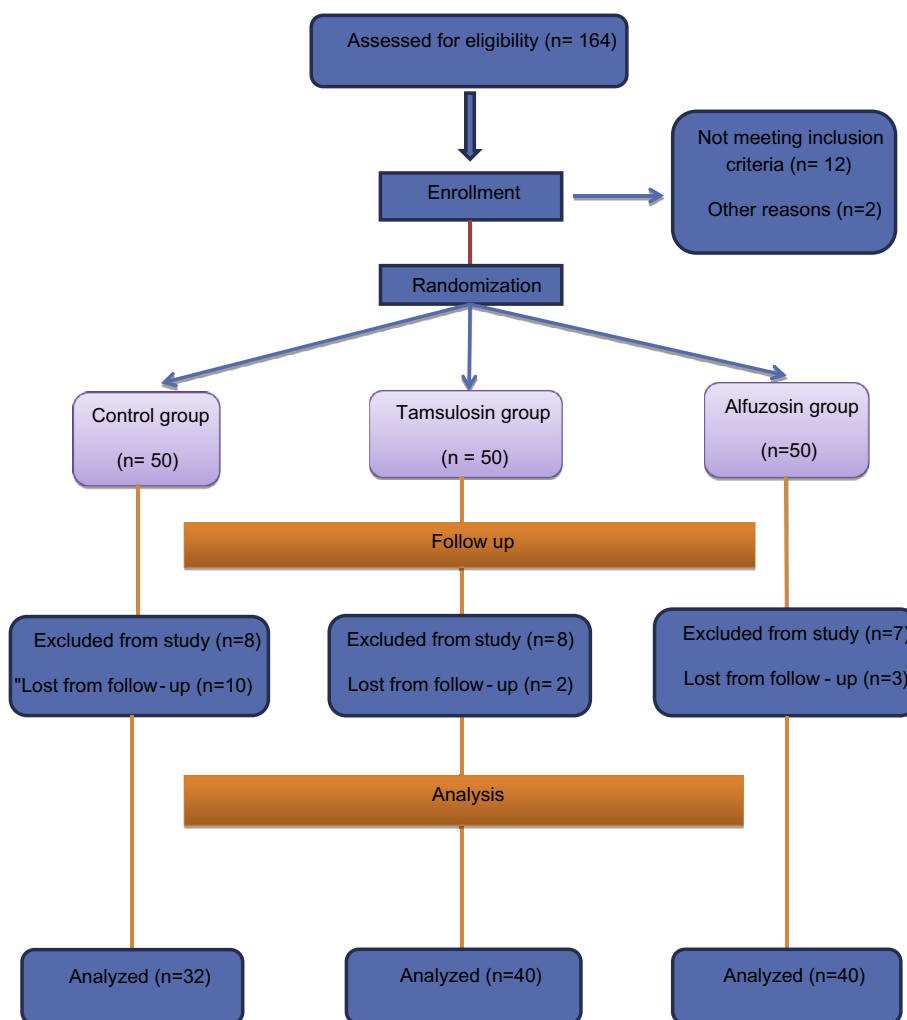
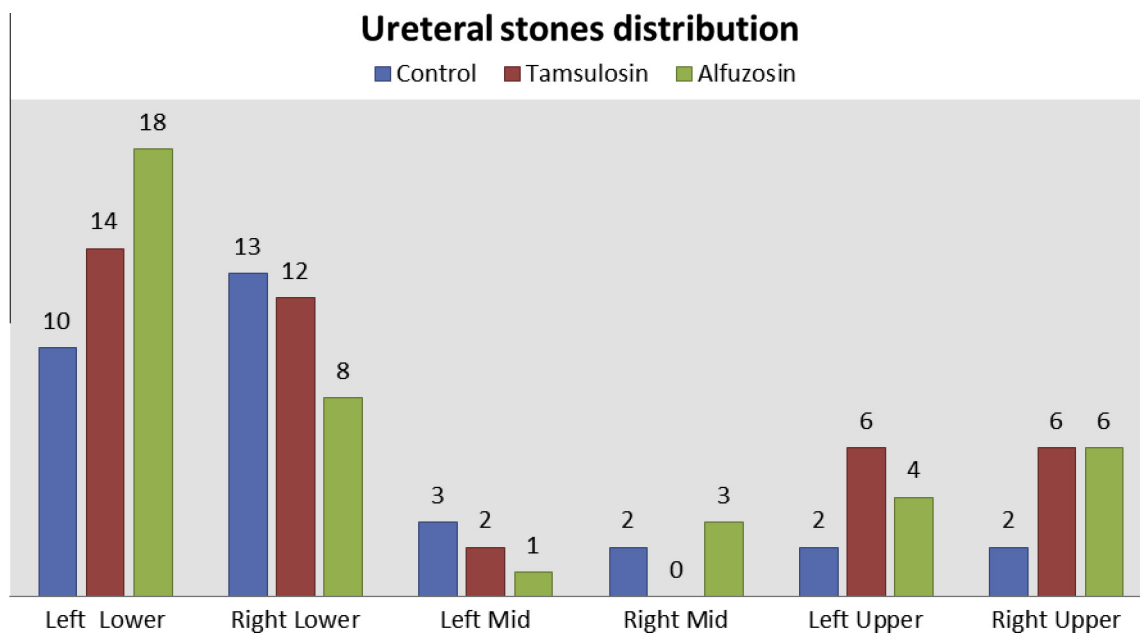


Figure 1 The consort chart.

**Table 1** The patients' characteristics.

Mean (SD) or <i>n</i> (%)variable	Group			<i>P</i>
	I (Control)	II (Tamsulosin)	III (Alfuzosin)	
Age (years)	36.71 (11.64)	38.17 (14.54)	36.5 (11.54)	0.819
Stone size (mm)	5.65 (1.25)	5.58 (0.93)	5.94 (1.66)	0.441
<i>Sex</i>				
M	25 (78)	32 (80)	34 (85)	
F	7 (22)	8 (20)	6 (15)	
Total	32	40	40	



**Figure 2** The distribution of the ureteric stones within the ureter in the three groups.

**Table 2** Location and rate of the spontaneous passage of stones, and the duration before passage.

<i>n/N</i> (%) or <i>n/N</i> at location	Group			<i>P</i>	<i>P</i>
	I	II	III		
<i>Upper</i>					
Passed	1/4	8/12	5/10	0.192	0.406
Not passed	3/4	4/12 5/10	5/10		
<i>Mid</i>					
Passed	1/5	2/2	3/4	0.143	0.167
Not passed	4/5	-/-	1/4		
<i>Lower</i>					
Passed	12/23 (52)	24/26 (92)	22/26 (85)	0.002	0.014
Not passed	11/23 (48)	2/26 (8)	4/26 (15)		
Total passed	14/32 (44)	34/40 (85)	30/40 (75)	0.002	0.007
Not passed	18/32 (56)	6/40 (15)	10/40 (25)		
<i>Weeks to stone passage, n (%)</i>					
1	2 (6)	12 (30)	11 (28)	-	
2	4 (13)	9 (23)	8 (20)	-	
3	6 (19)	8 (20)	7 (18)	-	
4	2 (6)	5 (13)	4 (10)	-	

Of those patients in whom the stone failed to pass after 4 weeks, 12 (from all groups) who had an upper ureteric stone were managed successfully with ESWL, two of seven patients on  $\alpha$ -blockers (groups II and III) needed more than one session, while two of five in the control group needed more than one session. Five patients had mid-ureteric stones, three of whom were managed successfully with two sessions of ESWL, and the remaining two (from the control group) were treated with ureteroscopy and lithotripsy, respectively. Finally, 17 patients had lower ureteric stones, and all were treated successfully with ureteroscopy and lithotripsy.

Side-effects were reported in five patients in group II (13%), including retrograde ejaculation in three and postural hypotension in two. In group III, six patients reported side-effects (15%), two complaining of retrograde ejaculation, three of postural hypotension and one had nasal congestion. None of these patients stopped the MET because of the side-effects.

## Discussion

Tamsulosin is the most commonly used  $\alpha$ -blocker for the medical treatment of ureteric stones, because of its excellent tolerability, the lack of need for dose titration on initiation of treatment (which allows a fully effective dose to be administered immediately) and its uroselectivity for  $\alpha$ 1a and  $\alpha$ 1d. This results in relaxation of the smooth muscles of the lower ureter, facilitating stone passage and relieving pain [7]. However, other  $\alpha$ -blockers were also found to be effective in promoting the expulsion of ureteric stones. Yilmaz et al. [8] showed that tamsulosin, terazosin and doxazosin were equally effective in increasing the frequency of spontaneous passage of ureteric calculi. Wang et al. [9] showed that tamsulosin was associated with an expulsive rate of 81%, and terazosin of 78%. Another study from China [10] reported that MET using alfuzosin slow-release 10 mg daily was effective in increasing the spontaneous passage rate of ureteric stones (81.8%) and reducing analgesic use. Those authors concluded that MET with an  $\alpha$ -blocker was safe and effective, as shown by the increased stone expulsion rate and reduced expulsion time, and the reduced need for analgesics.

The present study showed that tamsulosin was associated with an overall spontaneous expulsion rate of 85%, greater than with alfuzosin (75%) or in the control group (44%). The efficacy of tamsulosin or alfuzosin has been studied in many previous trials. Agrawal et al. [11] compared the efficacy of tamsulosin and alfuzosin for treating ureteric stones and reported expulsion rates of 82.3%, 70.5% and 35.2% for tamsulosin, alfuzosin and a control group, values lower than the rates obtained in the present study. Ahmed and Al-Sayed [7]

reported that 25 of 29 patients in a tamsulosin group (86%), 23 of 30 in an alfuzosin group (77%), and 14 of 28 in a control group (50%) expelled the stones by the end of the study, results similar to those in the present study. A recent Korean study [12] showed that calculi passed through the ureter spontaneously in 32 patients (78% of the group) treated with tamsulosin 0.2 mg, in 23 (77%) treated with tamsulosin 0.4 mg, in 27 (75%) treated with alfuzosin 10 mg, and in 16 (47%) treated with tiroprium chloride. Comparison between the two tamsulosin doses and the 10 mg alfuzosin dose showed no significant differences in expulsion rate or expulsion time for lower ureteric calculi.

The present study showed that treatment with an  $\alpha$ -blocker gave better results than in the control group. Stone size, location and symptom duration are the most important variables for predicting spontaneous stone expulsion, in addition to patient-dependent factors such as pain tolerance and the development of infection, that determine the need for active stone removal or decompression of the renal collecting system [13]. Miller and Kane [14] reported that the mean time to spontaneous stone passage of stones of  $\leq 2$  mm, 2–4 mm and 4–6 mm was 8.2, 12.2 and 22.1 days, respectively, and 95% of those that passed did so by 31, 40 and 39 days, respectively. Coll et al. [15] reported that the spontaneous passage rate for stones of 1 mm in diameter was 87%, for 2–4 mm was 76%, for 5–7 mm was 60%, for 7–9 mm was 48% and for stones of  $> 9$  mm was 25%. The spontaneous passage rate as a function of stone location was 48% for those in the proximal ureter, 60% for mid-ureteric stones, 75% for distal stones and 79% for stones at the vesico-ureteric junction.

In the present study we included patients with ureteric stones in the upper, middle and lower ureter; both tamsulosin and alfuzosin facilitated the expulsion of ureteric stones from all parts of the ureter, and tamsulosin was slightly better. The two treatments had a better effect than in the control group. A review of previous reports showed that most studies tested the effects of  $\alpha$ -blockers as MET when the stones were in the distal ureter. Ahmed and Al-Sayed [7] and Agrawal et al. [10] compared the effects of tamsulosin and alfuzosin in patients with ureteric stones in the distal ureter, and Yilmaz et al. [8] compared the effects of tamsulosin, terazosin and doxazosin on lower ureteric stones. Al-Ansari et al. [16] assessed the effect of tamsulosin on the spontaneous passage rate of distal ureteric stones. However, Chau et al. [10] used alfuzosin for upper ureteric stones, with a spontaneous passage rate of 72.7% vs. 21.4% for the control. In the present study the respective rates of spontaneous stone passage for upper ureteric stones were one of four in the control, 8/12 for tamsulosin and 5/10 for alfuzosin.

An additional benefit to the use of  $\alpha$ -blockers in patients with ureteric stones, especially those who are can-



didates for surgical intervention, is the emerging role of these drugs in relieving symptoms related to an indwelling JJ stent, as reported by other studies [17,18].

In the present study there were minor therapy-related side-effects in five patients taking tamsulosin and in six taking alfuzosin. The side-effects were mild and did not require the withdrawal of treatment in any patient. The side-effects included retrograde ejaculation, postural hypotension and nasal congestion. Previous reports also showed that treatment with tamsulosin or alfuzosin produced no or only mild adverse effects [7,10,19]. Furthermore, a recent study by Mokhless et al. [20] showed that tamsulosin is a safe and effective treatment option for lower ureteric stones in children.

The limitations of the present study were the relatively few patients, which should be increased in future studies, and the absence of a placebo arm.

In conclusion, the use of tamsulosin 0.4 mg or alfuzosin 10 mg as MET for ureteric stones in all three sections of the ureter was safe and effective, as shown by the increased overall stone expulsion rate, reduced stone expulsion time and fewer pain episodes. Tamsulosin was associated with a greater rate of stone expulsion than was alfuzosin. Both drugs can be used safely for managing uncomplicated ureteric stones of  $\leq 10$  mm in any part of the ureter, before undertaking any invasive intervention.

### Conflict of interest

No conflict of interest to declare.

### Funding

Not funded.

### References

- [1] Ramello A, Vitale C, Marangella M. Epidemiology of nephrolithiasis. *J Nephrol* 2000;**13**(Suppl. 3):45–50.
- [2] Lipkin M, Shah O. The use of alpha-blockers for the treatment of nephrolithiasis. *Rev Urol* 2006;**8**(Suppl. 4):35–42.
- [3] Priminger GM, Tiselius HG, Assimos DG, Alken P, Buck C, Gallucci M, et al. 2007 Guidelines for the management of ureteral calculi. *Eur Urol* 2007;**52**:1549–814.
- [4] Shokeir AA. Renal colic. Pathophysiology, diagnosis and treatment. *Eur Urol* 2001;**39**:241–9.
- [5] Sigala S, Dellabella M, Milanese G, Fornari S, Faccoli S, Palazollo F, et al. Evidence for the presence of alpha1 adrenoceptor subtypes in the human ureter. *NeuroUrol Urodyn* 2005;**24**:142–8.
- [6] Seitz C. Medical expulsive therapy of ureteral calculi and supportive therapy after extracorporeal shock wave lithotripsy. *Eur Urol* 2010(Suppl.);807–13.
- [7] Ahmed AA, Al-Sayed AS. Tamsulosin versus alfuzosin in the treatment of patients with distal ureteral stones: prospective, randomized, comparative study. *Korean J Urol* 2010;**51**:193–7.
- [8] Yilmaz E, Batislam E, Basar MM, Tuglu D, Ferhat M, Basar H. The comparison and efficacy of three different alpha1-adrenergic blockers for distal ureteral stones. *Int J Urol* 2005;**173**:2010–2.
- [9] Wang CJ, Huang SW, Chang CH. Efficacy of an alpha1 blocker in expulsive therapy of lower ureteral stones. *J Endourol* 2008;**22**:41–6.
- [10] Chau L, Tai D, Fung B, Man Li J, Fan C, Wah Li M. Medical expulsive therapy using alfuzosin for patient presenting with ureteral stone less than 10 mm: a prospective randomized controlled trial. *Int J Urol* 2011;**18**:510–4.
- [11] Agrawal M, Gupta M, Gupta A, Agrawal A, Sarkari A, Lavania P. Prospective randomized trial comparing efficacy of alfuzosin and tamsulosin in management of lower ureteral stones. *Urology* 2009;**73**:706–9.
- [12] Cha WH, Choi JD, Kim KH, Seo YJ, Lee K. Comparison and efficacy of low-dose and standard-dose tamsulosin and alfuzosin in medical expulsive therapy for lower ureteral calculi: prospective, randomized, comparative study. *Korean J Urol* 2012;**53**:349–54.
- [13] Dal Moro F, Abate A, Lanckriet GR, Arandjelovic G, Gasparella P, Bassi P, et al. *Kidney Int* 2006;**69**:157–60.
- [14] Miller OF, Kane CJ. Time to stone passage for observed ureteral calculi: a guide for patient education. *Int J Urol* 1999;**162**:688–90.
- [15] Coll DM, Varanelli MJ, Smith RC. Relationship of spontaneous passage of ureteral calculi to stone size and location as revealed by unenhanced helical CT. *AJR* 2002;**178**:101–3.
- [16] Al-Ansari A, Al-Naimi A, Alobaidy A, Assadiq K, Azmi MD, Shokeir AA. Efficacy of tamsulosin in the management of lower ureteral stones: a randomized double-blind placebo-controlled study of 100 patients. *Urology* 2010;**75**:4–7.
- [17] Deliveliotis C, Chrisofos M, Gougousis E, Papatsoris A, Dellis A, Varkarakis IM. Is there a role for alpha1-blockers in treating double-J stent-related symptoms? *Urology* 2006;**67**:35–9.
- [18] Lamb A, Vowler S, Johnston R, Dunn N, Wiseman O. Meta-analysis showing the beneficial effect of  $\alpha$ -blockers on ureteric stent discomfort. *BJU Int* 2011;**108**:1894–902.
- [19] Abdel-Meguid TA, Tayib A, Al-Sayyad A. Tamsulosin to treat uncomplicated distal ureteral calculi: a double blind randomized placebo-controlled trial. *Can J Urol* 2010;**17**:5178–83.
- [20] Mokhless I, Zahran A, Youssif M, Fahmy A. Tamsulosin for the management of distal ureteral stones in children: a prospective randomized study. *J Pediatr Urol* 2012;**8**:544–8.