Urol Res (2012) 40:605–609
DOI 10.1007/s00240-012-0482-2

ORIGINAL PAPER

Effects of alfuzosin with methylprednisolone for spontaneous expulsion and pain control of lower ureteral stone

Eu Chang Hwang · In Sang Hwang · Ho Song Yu · Sun-Ouck Kim · Seung Il Jung · Taek Won Kang · Dong Deuk Kwon · Kwangsung Park · Soo Bang Ryu · Myung Ki Kim · Ji Wan Lu

Received: 9 January 2012 / Accepted: 2 May 2012 / Published online: 25 May 2012

Abstract The aim of this study is to evaluate the efficacy of alfuzosin with methylprednisolone on expulsion and pain control of lower ureteral stones <10 mm in size. Between June 2005 and June 2007, 113 patients with lower ureteral stones <10 mm in size were enrolled in the study. The patients were divided into a control group (group I) and medical expulsive therapy group (group II). Group I ($n = 66$) received oral analgesics daily and group II ($n = 47$) received the same analgesics along with 10 mg alfuzosin and 8 mg methylprednisolone for 4 weeks orally once a day. The treatment was continued until stone expulsion or to a maximum of 4 weeks. All patients were allowed 25 mg pethidine hydrochloride intramuscular injections if needed for suboptimal pain control. The average stone size was 6.15 mm in group I and 5.42 mm in group II. Of the 113 patients, 80 became stone free (70.7 %). Group II had significantly higher stone free rates (82.9 vs. 62.1 %, $p = 0.014$), fewer expulsion times (mean 4.4 vs. 7.3 days, $p = 0.001$), and mean number of intramuscular analgesic injections (0.8 vs. 2.1) compared to group I. Alfuzosin with methylprednisolone treatment seems safe and effective for lower ureteral stones <10 mm in size as demonstrated by the increased stone free rate, earlier expulsion, and reduced additional analgesic therapy.

Keywords Urinary calculi · Alfuzosin · Methylprednisolone

E. C. Hwang · I. S. Hwang · H. S. Yu · S.-O. Kim · S. I. Jung (✉) · T. W. Kang · D. D. Kwon · K. Park · S. B. Ryu
Department of Urology, Chonnam National University Medical School, 160, Baeseok-ro, Dong-gu, Gwangju 501-757, Republic of Korea
e-mail: drjsi@yahoo.co.kr

M. K. Kim
Chonbuk National University, Jeonju, Republic of Korea

J. W. Lu
Yanbian Tumor Hospital, Jilin, China

Introduction

The development of endourology, represented by extracorporeal shock wave (ESWL) and ureteroscopic lithotripsy (URSL), has made it possible to clinically treat urinary stones faster and easier than the past. However, in clinical practice, most patients still prefer medical expulsive therapy (MET) with the anticipation of spontaneous stone passage.

For MET, the location, size, and number of stones are important factors related to spontaneous passage, which can be influenced by spasm of ureteral smooth muscle and edema in ureter mucosa [1, 2]. The alpha-receptor in ureter smooth muscle mainly comprises α1D receptor [1, 2]. Therefore, α-blockers are considered to be the most effective drugs for MET. Several studies have promoted the effect of tamsulosin, a selective blocking agent for α1A and α1D, on the spontaneous passage of ureteral stones [3–5]. In addition, corticosteroids are helpful in spontaneous passage by reducing the edema and inflammation of ureter mucosa [6].

Compared to tamsulosin, alfuzosin exhibits no pharmacological uroselectivity for any of the α1 subtypes (α1A, α1B, and α1D) [7], however, alfuzosin has the lack of adverse effect and blood pressure changes, it has been claimed to be uroselective drug [8]. Thus, it is expected to have the same effect in promoting the spontaneous stone passage. However, this is unclear, given the paucity of studies to date. Also, studies concerning the influence of

corticosteroids on stone passage have mainly involved combinations with tamsulosin [9, 10]. Therefore, we investigated the effect of combination therapy with alfuzosin and methylprednisolone on spontaneous passage of lower ureteral stones.

Patients and method

The study was carried out in accordance with the Declaration of Helsinki.

Study population

Between June 2007 and June 2009, patients with lower ureteral stone <10 mm in size diagnosed by kidney–ureter–bladder (KUB) X-ray, intravenous urography (IVU), and non-enhanced computed tomography (CT) were reviewed. The criteria for case exclusion were radiolucent stone, urinary tract infection, severe hydronephrosis, pregnancy, underlying disease such as hypotension, medication with calcium channel blockers, diabetes, multiple urinary stones, ulcer disease, and renal insufficiency (serum creatinine >1.5 mg/dL). In addition, we had excluded those patients who received additional treatment of ESWL or URSL before the 4 week waiting period as they complained about severe pains. As a result, 113 patients were enrolled in this retrospective analysis.

Patients were divided into two groups by physician preference, a control group (group I) and medical expulsive therapy (MET) group (group II). All the patients were checked by routine laboratory test and blood pressure measurement before drug treatment. Group I ($n = 66$) received oral analgesics (10 mg ketorolac tromethamine twice a day) daily and group II ($n = 47$) received the same analgesics along with 10 mg alfuzosin and 8 mg methylprednisolone for 4 weeks orally once a day. If pain control by oral analgesics was not sufficient, 25 mg pethidine hydrochloride intramuscular injections on demand were additionally given. Follow-up examinations were done weekly for 4 weeks, during which KUB was checked to identify whether a stone passed or not. The date of stone passage from treatment initiation, side effects of drugs, and frequency of intramuscular analgesic usage were recorded. If no spontaneous stone passage was confirmed on KUB until week 4, we performed ESWL or URSL within 2 weeks. In analgesics only group and alfuzosin with methylprednisolone group, three patients and one patient received additional treatment, respectively.

Statistical analyses

SPSS version 19.0 (SPSS, Chicago, IL, USA) was used for statistical analysis. We compared the stone size, success rate of stone passage, date of stone passage from treatment initiation, and frequency of intramuscular analgesic usage between the two groups. Blood pressure changes before and after MET were also compared. The continuous variables were analyzed by Student's t test (two-tailed) and Paired t test (two-tailed), and Chi-square test was used for categorical variables. $p < 0.05$ was considered significant for all analyses.

Results

Baseline demographics

Group I, who received oral analgesics only, was comprised of 66 patients (36 males, 30 females) whose mean age was 53.8 ± 9.04 years (range 18–74 years). Group II, who received MET therapy, was comprised of 47 patients (27 males, 20 females) whose mean age was 52.3 ± 9.79 years (range 16–80 years). The mean stone size was 6.15 ± 0.61 mm (range 3.4–10.0) in group I and 5.42 ± 0.81 mm (range 2.5–10.0) in group II. There was no significant difference in age, sex ratio, and stone size between the two groups (Table 1, $p > 0.05$). For stones <5 mm and 5–10 mm in size, the stone size between the two groups also showed no significant difference (Table 1, $p > 0.05$).

Comparison of stone passage according to treatment

Eighty of the 113 patients (70.7 %) successfully passed the stone spontaneously. Overall, the stone expulsion rate was increased in group II (39 of 47, 82.9 %) compared to group I (41 of 66, 62.1 %) ($p = 0.014$, Table 2). In addition, when subdivided by stone size in each group (<5 vs. 5–10 mm), there was no significant difference in stone

Table 1 Baseline patient characteristics

	Group I	Group II	p value
Number of patients	66	47	
Mean age ± SD (years)	53.8 ± 9.04	52.3 ± 9.79	0.134
Sex			
Male:female	36:30	27:20	0.616
Laterality			
Left:right	37:29	22:25	0.069
Mean stone size ± SD (mm)			
Overall	6.15 ± 0.61	5.42 ± 0.81	0.125
<5 mm	3.85 ± 0.36	3.65 ± 0.67	0.144
5–10 mm	6.76 ± 1.75	6.74 ± 1.67	0.472

Group I: oral analgesics only; group II: medical expulsion therapy (alfuzosin with methylprednisolone)

SD standard deviation

Table 2 Comparison of the clinical results between the two groups

	Group I	Group II	*p* value
Stone expulsion rate, % (expulsion cases/total)	62.1 (41/66)	82.9 (39/47)	0.014
Stone expulsion rate, % according to stone size			
<5 mm	78.5 (11/14)	90.0 (18/20)	0.185
5–10 mm	57.6 (30/52)	77.7 (21/27)	0.032
Stone expulsion interval from treatment initiation (mean days ± SD)			
Overall	7.3 ± 4.87	4.4 ± 3.23	0.001
Size <5 mm	5.7 ± 3.28	2.9 ± 1.96	0.004
Size 5–10 mm	7.9 ± 5.27	5.7 ± 3.57	0.053
Additional analgesic use (mean times ± SD)	2.1 ± 1.17	0.8 ± 0.36	0.021

Group I: oral analgesics only; group II: medical expulsion therapy (alfuzosin with methylprednisolone)

SD standard deviation

expulsion rate between group I (11 of 14, 78.5 %) and group II (18 of 20, 90 %) ($p = 0.185$, Table 2). In contrast, for 5–10 mm sized stones, the expulsion rates were 57.6 % (30 of 52) for group I and 77.7 % (21 of 27) for group II, which were statistically significantly different ($p = 0.032$, Table 2). Concerning the overall stone expulsion interval from treatment initiation, group II was shorter than the group I (4.4 ± 3.23 vs. 7.3 ± 4.87 days, Table 2, $p = 0.001$). Analgesic usage was less in group II than in group I (0.8 ± 0.00 vs. 2.1 ± 0.00 times, Table 2, $p = 0.021$).

Blood pressure changes after medical expulsive therapy

In group II, no clinically significant drop in blood pressure was found after MET (Table 3).

Adverse effect of each group

In group II, slight headache (8.5 %, 4 of 47) and dizziness (6.3 %, 3 of 47) developed more often compared to group I (1.5 %, 1 of 66; 3 %, 2 of 66, respectively). All documented side effects did not require stopping the administration of the drugs and could be managed by conservative therapy also; none of the patients have steroid-related adverse effect.

Table 3 Blood pressure changes after medical expulsive therapy (group II)

	MET (before)	MET (after)	*p* value
Erect systolic (±SD)	129.1 ± 2.28	127.1 ± 1.59	0.096
Erect diastolic (±SD)	78.6 ± 1.26	77.3 ± 1.33	0.051

MET medical expulsive therapy, *SD* standard deviation

Discussion

The present study demonstrates that alfuzosin with methylprednisolone for the treatment of lower ureteral stones increases stone expulsion rate, shortens the stone expulsion interval from treatment initiation and reduces usage of analgesics, compared to treatment with oral analgesics.

In urological clinical practice, the determination of the treatment method for lower ureteral stones in patients presenting with acute pain remains challenging. Traditionally, therapy has consisted of a conservative approach that includes MET and endourological surgery represented by ESWL and URSL. In cases of ureteral stones <5 mm in size, we recommend MET first [1]. The reported success rate of this approach varies widely, from 5 to 70 %, in accordance with the lower ureteral stone [2]. The most important factors that influence spontaneous passage of ureter stone are its size and location [2]. Other influential factors include spasm of ureteral smooth muscle, edema of ureteral mucosa, degree of hydronephrosis, and activity of adrenalin receptor in the ureter [11].

Given the possibility of renal function damage, a conservative approach exceeding 6 weeks is not recommended [12]. Accordingly, many studies have been undertaken to evaluate MET in the accelerated passage of ureteral stones. Studies of calcium antagonists and alpha blocking agents have shown the prowess of alpha blocking agents in reducing contractility during peristaltic movement of ureteral smooth muscle [3, 4]. Also, the edema and inflammation of ureteral mucosa due to ureter stone can block the expulsion passage of the stone; the use of an anti-edema drug such as a corticosteroid can aid in the passage of the stone in this case [6, 9].

Alpha receptor in ureter smooth muscle localized mainly in the one-third of the lower ureter is involved in ureter contraction and peristaltic movement [1, 11]. As such, alpha blocking agents may be helpful in assisting stone passage by decreasing peristaltic movement, contractility and pressure in the ureter. Consistent with this idea, the administration of alpha blocking agents including tamsulosin and doxazosin increases the spontaneous passage of stones, reduces pain and shortens the period to stone expulsion, which can decrease the need for analgesics [3–5].

The rationale for using a steroid drug is based on the principle that the presence of a stone in the ureter causes an inflammatory reaction of the mucosa, which causes various grades of edema [13]. The use of steroids stabilizes neutrophil lysosomes, therefore decreasing inflammation and treat edematous reaction, which is an additional obstacle to the descent of the stone [14]. Based on this, steroids have been linked to a high spontaneous stone expulsion rate (88 %) compared to patients not treated with steroids [6]. A

study of the effect of steroid in combination with tamsulosin increased overall stone expulsion rate by 14 %, and by 22 % for stones >5 mm in size compared to tamsulosin alone [9]. But, another study reported no difference in the stone expulsion rate between the tamsulosin with steroid (97 %) compared to tamsulosin only (90 %, $p = 0.612$) [10]. Thus, the efficacy of steroids on stone expulsion is equivocal. In addition, most studies used methylprednisolone 40 mg [6] and deflazacort 30 mg [9, 10], but we selected twofold physiological dose (8 mg) of methylprednisolone to avoid steroid-related adverse effect.

As most studies on MET have focused on tamsulosin alone or combination with other drugs, we evaluated the effect of alfuzosin with methylprednisolone for stone expulsion compared to analgesics. Only a few reports have compared alfuzosin to tamsulosin. One study found no significant difference in the stone expulsion rate between alfuzosin and placebo (77.1 vs. 73.5 %, respectively). However, alfuzosin was effective in shortening the time for stone passage and in lessening pain [15]. In another study [16], 102 patients with ureter stone <10 mm in size were allocated to receive divided tamsulosin, alfuzosin or placebo. The rate of stone passage was 82.3, 70.5, and 35.2 % ($p = 0.003$), respectively, and the mean time for expulsion was 12.3, 14.5, and 24.5 days ($p = 0.001$), respectively. The data were consistent with the view that alfuzosin was relatively less effective than tamsulosin in stone expulsion, although there was no statistical difference between the two drugs ($p = 0.25$), and supported the conclusion that alfuzosin could significantly increase the rate and decrease the time for stone expulsion. A recent study revealed that alfuzosin with analgesic therapy was effective in promoting the ureteral stone expulsion rate, particularly for upper ureter stones <10 mm in size [17]. Similarly, the present results indicated that alfuzosin combined with methylprednisolone was effective on increasing the rate of stone expulsion (82.9 vs. 62.1 %, $p = 0.014$) and shortening the time (4.4 ± 3.23 vs. 7.3 ± 4.87 days, $p = 0.001$). In addition, alfuzosin with methylprednisolone was more effective in the expulsion of stones 5–10 mm in size compared to stone <5 mm ($p = 0.032$). However, since we did not compare alfuzosin monotherapy with combination therapy (alfuzosin with methylprednisolone), we cannot definitively conclude that alfuzosin is truly the best option for stones exceeding 5 mm. Future works must address this shortcoming.

During a 4-week MET regimen, there were no specific side effects, except slight dizziness in four patients and headache in three patients. In all cases, symptoms were not sufficient to halt the treatment. Additional analgesic (pethidine hydrochloride) was administered 0.8 ± 0.36 times for group II and 2.1 ± 1.17 times for group I ($p = 0.021$).

The 2007 American Urological Association guideline, which reflects the relatively newest trend regarding conservative therapy for spontaneous stone expulsion, recommends MET for ureter stones <5 mm in size routinely and for stones <10 mm in size as long as pain is well controlled [18]. In this regard, alfuzosin combined with methylprednisolone therapy may be useful in aiding spontaneous stone passage and reducing pain. The result could be increased patient compliance relative to the conservative approach.

Conclusions

With MET for lower ureter stones <10 mm in size, alfuzosin combined with methylprednisolone improves stone expulsion rate, shortens expulsion time, and reduces pain. Especially, in case of stone 5–10 mm in size, alfuzosin with methylprednisolone is expected to be markedly more effective.

References

1. Hollingsworth JM, Rogers MA, Kaufman SR et al (2006) Medical therapy to facilitate urinary stone passage: a meta-analysis. Lancet 368:1171–1179
2. Coll DM, Varanelli MJ, Smith RC (2002) Relationship of spontaneous passage of ureteral calculi to stone size and location as revealed by unenhanced helical CT. AJR Am J Roentgenol 178:101–103
3. Yilmaz E, Batislam E, Basar MM, Tuglu D, Ferhat M, Basar H (2005) The comparison and efficacy of 3 different alpha-1 adrenergic blockers for distal ureteral stones. J Urol 173:2010–2012
4. Han MC, Park YY, Shim BS (2006) Efficacy of tamsulosin on the expectant treatment of lower ureteral stones. Korean J Urol 47:708–711
5. Kim JW, Cho DY, Lee JG (2007) Effect of tamsulosin on the expected treatment of upper and lower ureteral stones. Korean J Urol 48:724–730
6. Salehi M, Fouladi MM, Shier H, Mokhtari G, Dejabad V (2005) Does methylprednisolone acetate increase the success rate of medical therapy for patients with distal ureteral stones. Eur Urol 4(Suppl 3):25
7. Andersson KE, Lepor H, Wyllie MG (1997) Prostatic alpha 1-adrenoceptors and uroselectivity. Prostate 30:202–215
8. Kirby RS (1998) Clinical uroselectivity of alfuzosin in the treatment of benign prostatic hyperplasia. Eur Urol 33(Suppl 2):19–27
9. Jang WK, Hong YK (2008) The efficacy of furosemide-based medical expulsive therapy with tamsulosin and deflazacort for symptomatic distal ureter stones. Korean J Urol 49:1013–1017
10. Dellabella M, Milanese G, Muzzonigro G (2005) Medical-expulsive therapy for distal ureterolithiasis: randomized prospective study on role of corticosteroids used in combination with tamsulosin simplified treatment regimen and health-related quality of life. Urology 66:712–715
11. Cervenakov I, Fillo J, Mardiak J, Kopecny M, Smirala J, Lepies P (2002) Speedy elimination of ureterolithiasis in lower part of

ureters with the alpha1-blocker tamsulosin. Int Urol Nephrol 34:25–29
12. Tiselius HG, Ackermann D, Alken P et al (2001) Guidelines on urolithiasis. Eur Urol 40:362–371
13. Yamaguchi K, Minei S, Yamazachi T, Kaya H, Okada K (1999) Characterization of ureteral lesions associated with impacted stones. Int J Urol 6:281–285
14. Saita A, Bonaccorsi A, Marchese F, Condorelli SV, Motta M (2004) Our experience with nifedipine and prednisolone as expulsive therapy for ureteral stones. Urol Int 72(Suppl 1): 43–45
15. Pedro RN, Hinck B, Hendlin K, Feia K, Canales BK, Monga M (2008) Alfuzosin stone expulsion therapy for distal ureteral calculi: a double-blind, placebo controlled study. J Urol 179: 2244–2247
16. Agrawal M, Gupta M, Gupta A, Agrawal A, Sarkari A, Lavania P (2009) Prospective randomized trial comparing efficacy of alfuzosin and tamsulosin in management of lower ureteral stones. Urology 73:706–709
17. Chau LH, Tai DC, Fung BT, Li JC, Fan CW, Li MK (2011) Medical expulsive therapy using alfuzosin for patient presenting with ureteral stone less than 10 mm: a prospective randomized controlled trial. Int J Urol 18(7):510–514
18. Preminger GM, Tiselius HG, Assimos DG et al (2007) 2007 Guideline for the management of ureteral calculi. Eur Urol 52:1610–1631