Impact of Tamsulosin on Ureter Stone Expulsion in Korean Patients: A Meta-Analysis of Randomized Controlled Studies

Jung Keun Lee, Chang Wook Jeong, Seong Jin Jeong, Sung Kyu Hong, Seok-Soo Byun, Sang Eun Lee

Department of Urology, Seoul National University Bundang Hospital, Seongnam, Korea

Purpose: Using meta-analysis, the study's aim was to evaluate the efficacy of tamsulosin, an alpha-blocker, in the treatment of ureteral stones with or without shockwave lithotripsy (SWL) in Korean patients.

Materials and Methods: Relevant randomized controlled studies published through June 2011 were identified in a search of MEDLINE, KoreaMed, and the Korean Medical Database. No language restriction was applied. Only randomized controlled trials conducted with Korean patients were eligible for the analysis. The primary outcome assessed was the stone clearance rate. Two reviewers independently assessed the quality of the study and extracted the data. Meta-analysis was conducted by using R, version 2.13.0.

Results: A total of 6 articles were selected as being suitable for evaluation. Pooling of the trials demonstrated a 43% higher expulsion rate for tamsulosin treatment compared to a control group (risk ratio [RR], 1.43; 95% confidence interval [CI]: 1.24 to 1.65). Similar results were obtained in all subgroup analyses according to stone location (upper: RR, 1.31; 95% CI, 1.02 to 1.68, lower: RR, 1.50; 95% CI, 1.20 to 1.88) or concomitant SWL (yes: RR, 1.38; 95% CI, 1.14 to 1.68, no: RR, 1.48; 95% CI, 1.21 to 1.83).

Conclusions: This meta-analysis of randomized controlled studies provides a high level of evidence supporting the suggestion that treatment with tamsulosin augments the stone expulsion rate for ureter stones with or without SWL in a Korean population. However, a high-quality, large-scale, multicenter, randomized controlled trial is warranted to fully support this hypothesis.

Key Words: Adrenergic alpha-antagonists; Extracorporeal shock wave lithotripsy; Meta-analysis; Tamsulosin; Ureteral calculi

INTRODUCTION

Urinary stone disease affects 5 to 10% of the world's population, and it is one of the most common reasons for patients to visit a urologic clinic [1]. Furthermore, several studies have shown a worldwide trend toward an increasing prevalence of stone disease [2]; a trend that is also observed in Korea [3].

The goal of treating ureter stones is to achieve complete stone clearance with minimal patient morbidity. The standard treatment of ureter stones today is observation, medical therapy, shockwave lithotripsy (SWL), and ureteroscopic ureterolithotomy [4]. Medical expulsive therapy (MET) for ureter stones has especially gained increasing attention in the past decade, and there is growing evidence that MET can be efficacious to facilitate stone passage [5,6]. Various medications, such as calcium channel blockers (nifedipine and verapamil), α-blockers (tamsulosin, alfuzosin, doxazosin, and terazosin), and corticosteroids have been investigated [5,6]. Among these drugs, tamsulosin seems to be the most effective in facilitating stone clearance, both in patients undergoing expectant management...
and in those undergoing SWL. Several reports based on meta-analyses of randomized controlled trials (RCTs) support this fact [4-7].

However, the effectiveness of tamsulosin in Korean patients remains controversial. Although there are several RCTs on this subject, the majority of them were small, single-center studies [8-12]. Thus, even if the study showed a trend favoring tamsulosin, the results would be statistically insignificant or partly significant by subgroup analysis. There is currently no conclusive evidence that tamsulosin augments stone clearance in the Korean population.

The aim of this study was to conduct a meta-analysis of evidence from RCTs to assess the efficacy of tamsulosin in the treatment of ureter stones with or without SWL in Korean patients. Such evidence can aid physicians in making decisions in their clinical practice for the Korean population.

MATERIALS AND METHODS

1. Search strategy
MEDLINE, KoreaMed, and the Korean Medical Database were searched through June 30, 2011, without a time limit. All RCTs were identified in which patients were randomly selected to receive either tamsulosin or standard therapy with or without placebo to treat ureter stones. Only RCTs conducted with Korean patients were eligible for the analysis. No language restriction was applied. The search was conducted by exploring and combining the following medical terms: (urolithiasis OR urinary calculi OR ureterolithiasis OR stone) AND (alpha-antagonists OR tamsulosin). The primary outcome assessed was the stone clearance rate.

2. Quality assessment
Two reviewers independently extracted data from each study by using a standardized form. The quality of the included randomized studies was assessed by using the Jadad scale score reporting for each study, which ranged from 0 to 5 points [13]. The Jadad score is assigned according to randomization and the quality of randomization,

![FIG. 1. Search results: trial flow diagram. RCTs, randomized controlled trials; METs, medical expulsive therapy.](image)

### Table 1. Characteristics and quality assessment of the included studies

| Study          | Total patient no. | Stone location       | Standard therapy                  | Treatment vs. control (n) | Mean stone size (mm) | Expulsion rate (%) | Follow-up | Jadad score |
|----------------|-------------------|----------------------|-----------------------------------|--------------------------|----------------------|-------------------|-----------|-------------|
| Han et al. 2006 [8] | 67                | Lower ureter         | Ketorolac 30 mg IM on demand     | Tamsulosin 0.2 mg qd (35) | 4.4                  | 29/35 (82.8)     | 4 wk      | 1           |
| Han et al. 2006 [9] | 45                | Upper ureter         | Ketorolac 30 mg IM on demand     | Tamsulosin 0.2 mg qd (22) | 8.2                  | 20/22 (90.9)     | 2 wk      | 1           |
| Bak et al. 2007 [10] | 192               | Upper and lower ureter | Ketorolac 10 mg bid Diclofenac 90 mg IM on demand | Tamsulosin 0.2 mg qd (75) | 4.3                  | 57/75 (76.0)     | 2 wk      | 2           |
| Choi et al. 2008 [11] | 96                | Upper and lower ureter | SWL 1 time Trospium chloride 5 mg bid | Tamsulosin 0.2 mg qd (32) | 7.6                  | 27/32 (84.4)     | 2 wk      | 1           |
| Kim et al. 2008 [12] | 76                | Upper and lower ureter | SWL Tramadol 50 mg PO or IV on demand | Tamsulosin 0.2 mg qd (42) | 5.7                  | 18/42 (42.9)     | 1 wk      | 1           |
| Kang et al. 2009 [14] | 247               | Renal, upper and lower ureter | With/without SWL Diclofenac 100 mg PO | Tamsulosin 0.2 mg qd (134) | 7.0                  | 67/134 (50.0)    | 1 wk      | 1           |

SWL, shockwave lithotripsy; PO, per os.
blinding, quality of allocation concealment, and description of dropouts.

3. Statistical analysis
All of the statistical analyses were performed with R for Windows, ver. 2.11.0 (http://www.r-project.org/). Meta-analyses were performed mainly by using the package Meta. For all statistical comparisons, differences with a p < 0.05 were considered significant. The Mantel-Haenszel test pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for the effects of tamsulosin. The chi-squared ($\chi^2$) test was used to detect statistical heterogeneity. When heterogeneity was present (p < 0.1), the data were analyzed by using the random effects model. In the absence of heterogeneity, a fixed effects model was applied. An inverted funnel plot was used to assess the presence of publication bias. The risk differences (RDs) for stone clearance were plotted against the standard error (SE) of the RD. Forest plots were applied by visualizing the RR in each square with the area proportional to the number of events; 95% CIs were visible as horizontal lines. Pooled RRs and corresponding 95% CIs were plotted as a diamond. Subgroup meta-analyses were performed by stone location (upper or lower ureter stone) and whether SWL was applied or not.

RESULTS
The initial search strategy identified 191 possible articles. Of these retrieved publications, 10 studies were conducted with Korean patients. Finally, a total of 6 articles were identified by our search strategy that met the eligible criteria (Fig. 1). There were no placebo-controlled studies. Two studies were for expectant treatment [8,10], three studies were for concomitant use with SWL [9,11,12], and one multicenter study was for both situations [14]. All studies used 0.2 mg tamsulosin per day. The characteristics and the Jadad scale scores of the 6 included studies are summarized in Table 1.

Funnel plot analysis demonstrated a mild publication bias (Fig. 2). No significant heterogeneity of the studies was detected ($\chi^2=0.52$, p=0.991). The forest plot represented in Fig. 3 shows that tamsulosin had an overall benefit for ureteral stone clearance over the control (RR, 1.43; 95% CI, 1.24 to 1.65). Subgroup analyses also demonstrated this significant effect in all situations (Figs. 4, 5). Tamsulosin treatment for lower ureter stones (RR, 1.50; 95% CI, 1.20 to 1.88) showed a relatively higher RR than for upper ureter stones (RR, 1.31; 95% CI, 1.02 to 1.68).

DISCUSSION
Tamsulosin is a combined $\alpha_{1A}$- and $\alpha_{1D}$-selective adrenergic antagonist. The adrenoceptors of these subtypes exist in the smooth muscle cells of the human ureter [15,16]. $\alpha_1$-Blockers decrease tension, release the spasm of smooth muscles, lessen obstructions, and, consequently, enhance stone elimination in the ureter [17]. The distal ureter has the highest density of adrenoceptors, and the $\alpha_{1D}$-receptor is the most common receptor present in all portions of the ureter [16,18]. Thus, tamsulosin, which is more selective for the $\alpha_{1D}$-subtype, can be considered the most effective drug for MET among the $\alpha$-blockers. Distal ureter stones in particular may be more affected by tamsulosin, because

| Study or subgroup | Tamsulosin | Control | Risk ratio (95% CI) | Year |
|------------------|------------|---------|---------------------|------|
| Han et al. [8]   | 29         | 35      | 1.56 (1.09-2.23)    | 2006 |
| Han et al. [9]   | 20         | 22      | 1.39 (1.01-1.93)    | 2006 |
| Bak et al. [10]  | 57         | 75      | 1.50 (1.15-1.96)    | 2007 |
| Choi et al. [11] | 27         | 32      | 1.39 (1.02-1.90)    | 2008 |
| Kim et al. [12]  | 18         | 42      | 1.32 (0.73-2.41)    | 2008 |
| Kang et al. [14] | 61         | 116     | 1.37 (1.01-1.87)    | 2009 |
| Total (95% CI)   | 322        | 283     | 1.43 (1.24-1.65)    |      |
| Total events     | 212        | 133     |                     |      |

Heterogeneity: $\chi^2=0.52$, DF=5 (p=0.991)
the highest density of $\alpha_{1D}$-receptors can be found in the distal ureter. In this study, the RR for lower ureter stones (RR, 1.50; 95% CI, 1.20 to 1.88) was higher than that for upper ureter stones (RR, 1.31; 95% CI, 1.02 to 1.68) in the subgroup meta-analysis.

Several systematic reviews and meta-analyses have already demonstrated the effectiveness of tamsulosin in facilitating stone clearance in both patients being managed...
by watchful waiting and patients after SWL. Seitz et al. [5] reported a higher rate of stone expulsion in watchful waiting patients treated with either 0.2 mg (RR, 1.56; 95% CI, 1.21 to 2.03) or 0.4 mg (RR, 0.40; 95% CI, 1.28 to 1.54) of tamsulosin. They also demonstrated that SWL plus tamsulosin (0.4 mg) was more effective than SWL alone (RR, 1.38; 95% CI, 1.22 to 1.56) by meta-analysis [5]. In the meta-analysis performed by Zheng et al. [19], a 24% (RR, 1.24; 95% CI, 1.12 to 1.37) improvement was demonstrated in stone clearance by tamsulosin after SWL for renal and ureteral stones. The tamsulosin group had a shorter expulsion time, lower analgesic requirements, and fewer colic episodes and adverse effects. A meta-analysis performed by Zhu et al. [7] showed a 16% RD of stone clearance after SWL, favoring the tamsulosin group over the control group. In addition, the expulsion time was shortened by 8 days in the tamsulosin group. However, no conclusive evidence exists of the effectiveness of tamsulosin for stone clearance in Korean patients.

The results of the present meta-analysis showed that a 0.2-mg dose of tamsulosin is effective in enhancing stone expulsion in Korean patients. The pooled analysis showed a 43% higher expulsion rate in the tamsulosin group than in the control group. Furthermore, similar results were obtained regardless of stone location or concomitant SWL. The RCTs included were mostly small, single-center studies; therefore, the results were inconclusive or partly significant. However, more conclusive evidence can be generated by a meta-analysis of these RCTs.

Similar to Korea, low-dose tamsulosin of 0.2 mg is the usual accepted dose in Japan. Two RCTs have evaluated the efficacy of a 0.2-mg tamsulosin dose in MET for ureteral stones in a Japanese population [20,21]. The low dose of tamsulosin shortened the stone expulsion time (15.66±6.14 days vs. 35.47±53.70 days, p=0.0424) in Japanese men with ureteral stones after SWL [20]. However, the stone expulsion rates were not significantly different (84.21% vs. 88.24%, p=0.34). Concerning the watchful waiting setting, 0.2 mg of tamsulosin significantly facilitates ureteral stone clearance (77% vs. 50%, p=0.002) in Japanese men [21]. These data further support our results, because all studies were conducted with the 0.2-mg dose of tamsulosin in a Far East Asian population.

Nevertheless, this meta-analysis could have possible limitations. Most studies were predominantly small, single-center trials that did not present the power calculations needed. Again, only one report described the randomization method used, and none of the reports presented dropouts. Owing to the qualities of the included studies, the pooled analysis could be affected. The other limitation was the publication bias. As the funnel plot suggested, studies with a negative result seemed to be unpublished.

We could not compare the duration of stone expulsion or the degree of colic pain. Only one study described the expulsion duration, and there was no standardized reporting protocol for pain. Furthermore, a study that evaluates pain and adverse events should be placebo-controlled and double-blinded. All included studies used an open-label protocol. We could not evaluate the dose-response relationship of tamsulosin in stone clearance that was suggested by other articles [7,19]. There is some evidence that a combination of tamsulosin and other agents, such as corticosteroids, might be more effective than α-blockers alone [22,23]. Future studies should focus on the dose-response relationship of tamsulosin and its combination with other drugs.

Despite the abovementioned potential limitations, this study provides the highest level of evidence to date from RCTs conducted with Korean patients. To the best of our knowledge, this is the first well-performed meta-analysis that has incorporated RCTs conducted with only Korean patients in a urologic field. These results support the use of tamsulosin for the ureteral stone patients who are commonly encountered in the urologic clinic.

CONCLUSIONS

The results of the present meta-analysis suggest that treatment with tamsulosin facilitates the stone expulsion rate for ureter stones with or without SWL in the Korean population. Despite the high level of evidence provided by this meta-analysis of RCTs, there was a lack of well-designed, high-quality prospective studies. More information should be assessed, and large-scale, multicenter, placebo-controlled RCTs should be performed in the future.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

ACKNOWLEDGEMENTS

We thank Soyeon Ahn, Ph.D. at the Medical Research Collaboration Center of Seoul National University Bundang Hospital for providing statistics consultation and support.

REFERENCES

1. Ramello A, Vitale C, Marangella M. Epidemiology of nephrolithiasis. J Nephrol 2000;13 Suppl 3:845-50.
2. Stamate lou KK, Francis ME, Jones CA, Nyberg LM, Curhan GC. Time trends in reported prevalence of kidney stones in the United States: 1976-1994. Kidney Int 2003;63:1817-23.
3. Lee HN, Yoon HN, Shim BS. The trend change of incidence and treatment of urolithiasis between the 1980s and 2000s. Korean J Urol 2007;48:40-4.
4. Preminger GM, Tiselius HG, Assimos DG, Alken P, Buck AC, Gallucci M, et al. 2007 Guideline for the management of ureteral calculi. Eur Urol 2007;52:1610-31.
5. Seitz C, Liatsikos E, Porpiglia F, Tiselius HG, Zuwergel U. Medical therapy to facilitate the passage of stones: what is the evidence? Eur Urol 2009;56:455-71.
6. Singh A, Alter HJ, Littapeage A. A systematic review of medical therapy to facilitate passage of ureteral calculi. Ann Emerg Med 2007;50:552-63.
7. Zhu Y, Djujves D, Rovers MM, Lock TM. alpha-Blockers to assist stone clearance after extracorporeal shock wave lithotripsy: a meta-analysis. BJU Int 2010;106:256-61.
8. Han MC, Park YY, Shim BS. Effect of tamsulosin on the expectant treatment of lower ureteral stones. Korean J Urol 2006;47:708-11.
9. Han MC, Jeong WS, Shim BS. Additive expulsion effect of tamsulosin after shock wave lithotripsy for upper ureteral stones. Korean J Urol 2006;47:813-7.
10. Bak CW, Yoon SJ, Chung H. Effects of an alpha-blocker and terpene mixture for pain control and spontaneous expulsion of ureter stone. Korean J Urol 2007;48:517-21.
11. Choi NY, Ahn SH, Han JH, Jang IH. The effect of tamsulosin and nifedipine on expulsion of ureteral stones after extracorporeal shock wave lithotripsy. Korean J Urol 2008;49:150-4.
12. Kim TH, Oh SY, Moon YT. The effect of tamsulosin on expulsion of ureteral stones after extracorporeal shock wave lithotripsy. Korean J Urol 2008;49:1100-4.
13. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996;17:1-12.
14. Kang DI, Cho WY, Kim TH, Chung JM, Park J, Yoon JH, et al. Effect of tamsulosin 0.2 mg on the short-term treatment of urinary stones: multicenter, prospective, randomized study. Korean J Urol 2009;50:586-90.
15. Morita T, Ando M, Kihara K, Oshima H. Function and distribution of autonomic receptors in canine ureteral smooth muscle. Neurourol Urodyn 1994;13:315-21.
16. Park HK, Choi EY, Jeong BC, Kim HH, Kim BK. Localizations and expressions of alpha-1A, alpha-1B and alpha-1D receptors in human ureter. Urol Res 2007;35:325-9.
17. Cervenakov I, Fillo J, Mardiak J, Kopecy M, Smirala J, Lepes P. Speedy elimination of ureterolithiasis in lower part of ureters with the alpha 1-blocker–Tamsulosin. Int Urol Nephrol 2002;34:25-9.
18. Signala S, Dellabella M, Milanese G, Fornari S, Faccoli S, Palazzolo F, et al. Evidence for the presence of alpha1 adrenoceptor subtypes in the human ureter. Neurourol Urodyn 2005;24:142-8.
19. Zheng S, Liu LR, Yuan HC, Wei Q. Tamsulosin as adjunctive treatment after shockwave lithotripsy in patients with upper urinary tract stones: a systematic review and meta-analysis. Scand J Urol Nephrol 2010;44:425-32.
20. Kobayashi M, Naya Y, Kino M, Awa Y, Nagata M, Suzuki H, et al. Low dose tamsulosin for stone expulsion after extracorporeal shock wave lithotripsy: efficacy in Japanese male patients with ureteral stone. Int J Urol 2008;15:495-8.
21. Kaneko T, Matsushima H, Morimoto H, Tsuzaka Y, Homma Y. Efficacy of low dose tamsulosin in medical expulsive therapy for ureteral stones in Japanese male patients: a randomized controlled study. Int J Urol 2010;17:462-5.
22. Dellabella M, Milanese G, Muzzonigro G. 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 2005;66:712-5.
23. Porpiglia F, Vaccino D, Billia M, Renard J, Cracco C, Ghignone G, et al. Corticosteroids and tamsulosin in the medical expulsive therapy for symptomatic distal ureter stones: single drug or association? Eur Urol 2006;50:339-44.