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Urolithiasis

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

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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*

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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,

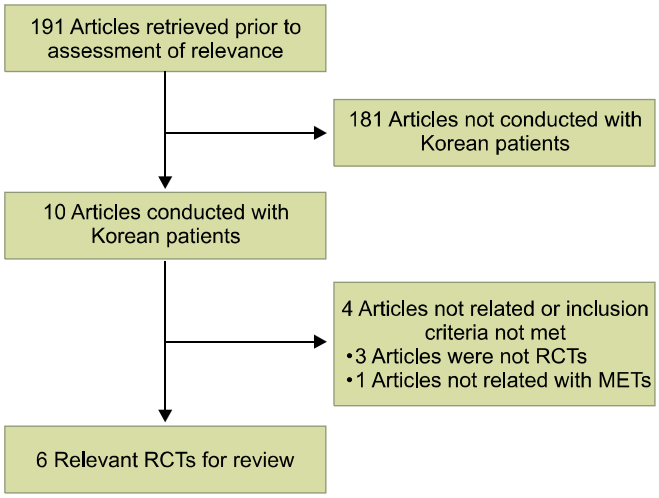


FIG. 1. Search results: trial flow diagram. RCTs, randomized controlled trials; METs, medical expulsive therapy.

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) Caroverine 20 mg tid (32)	4.4 4.3	29/35 (82.8) 17/32 (53.1)	4 wk	1
Han et al. 2006 [9]	45	Upper ureter	SWL 1 time Ketorolac 30 mg IM on demand	Tamsulosin 0.2 mg qd (22) Caroverine 20 mg tid (23)	8.2 7.9	20/22 (90.9) 15/23 (65.2)	2 wk	1
Bak et al. 2007 [10]	192	Upper and lower ureter	Ketorolac 10 mg bid Diclofenac 90 mg IM on demand	Tamsulosin 0.2mg qd (75) Rowatinex 3C tid (50) Control (67)	4.3 4.1 4.0	57/75 (76.0) 33/50 (66.0) 34/67 (50.7)	2 wk	2
Choi et al. 2008 [11]	96	Upper and lower ureter	SWL 1 time Trospium chloride 5 mg bid Ketorolac 30 mg IM on demand	Tamsulosin 0.2 mg qd (32) Nifedipine 30 mg qd (31) Control (33)	7.6 7.3 7.4	27/32 (84.4) 21/31 (67.7) 20/33 (60.6)	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) Control (34)	5.7 6.1	18/42 (42.9) 11/34 (32.4)	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) Control (113)	7.0 7.5	67/134 (50.0) 44/113 (38.9)	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 (χ^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.

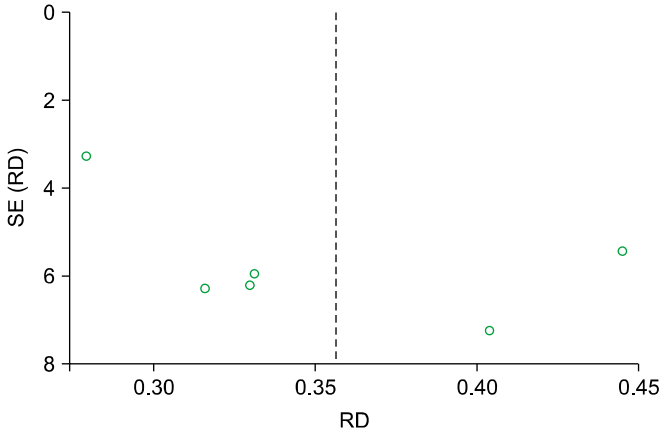


FIG. 2. Funnel plot of the included studies. SE (RD), standard error (risk differences).

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 (χ^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 α_{1A}- and α_{1D}-selective adrenergic antagonist. The adrenoceptors of these subtypes exist in the smooth muscle cells of the human ureter [15,16]. α_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 α_{1D}-receptor is the most common receptor present in all portions of the ureter [16,18]. Thus, tamsulosin, which is more selective for the α_{1D}-subtype, can be considered the most effective drug for MET among the α-blockers. Distal ureter stones in particular may be more affected by tamsulosin, because

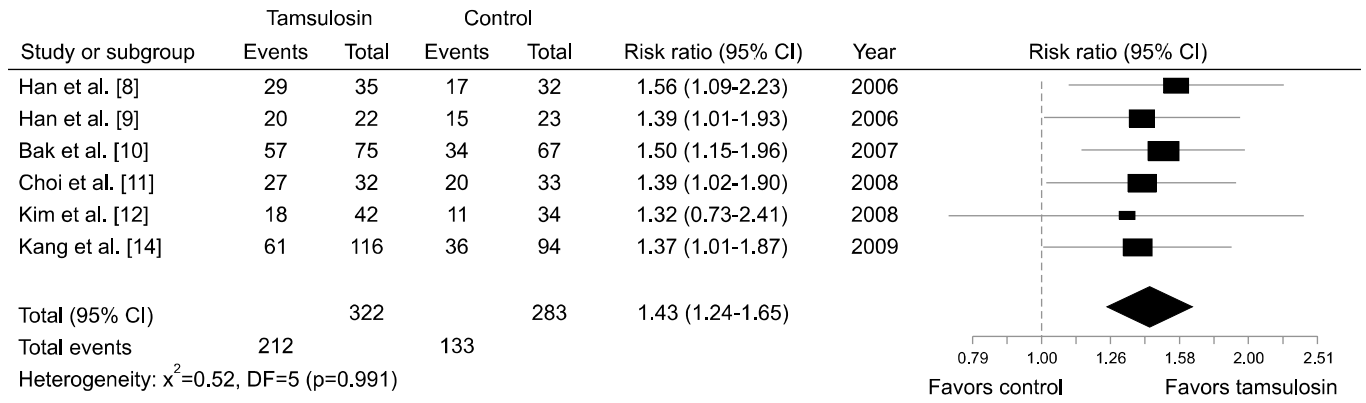
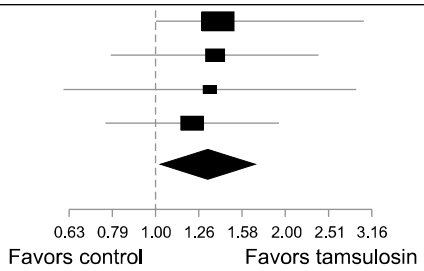


FIG. 3. Forest plot of comparison: tamsulosin vs. control. CI, confidence interval.

A

Study or subgroup	Tamsulosin Events	Tamsulosin Total	Control Events	Control Total	Risk ratio (95% CI)	Year
Han et al. [9]	20	22	15	23	1.39 (1.01-1.93)	2006
Choi et al. [11]	11	15	8	15	1.38 (0.78-2.41)	2008
Kim et al. [12]	8	18	7	21	1.33 (0.60-2.95)	2008
Kang et al. [14]	27	59	17	45	1.21 (0.76-1.93)	2009
Total (95% CI)		114		104	1.31 (1.02-1.68)	
Total events	66		47			

Heterogeneity: X^2=0.28, DF=3 (p=0.964)



B

Study or subgroup	Tamsulosin Events	Tamsulosin Total	Control Events	Control Total	Risk ratio (95% CI)	Year
Han et al. [8]	29	35	17	32	1.56 (1.09-2.23)	2006
Choi et al. [11]	16	17	12	18	1.41 (1.00-2.00)	2008
Kim et al. [12]	10	24	4	13	1.35 (0.53-3.48)	2008
Kang et al. [14]	34	57	19	49	1.54 (1.02-2.32)	2009
Total (95% CI)		133		112	1.50 (1.20-1.88)	
Total events	89		52			

Heterogeneity: X^2=0.22, DF=3 (p=0.974)

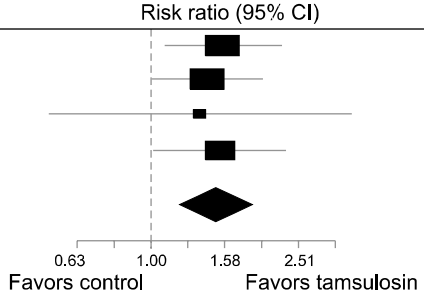
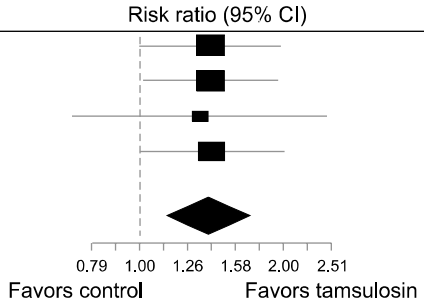


FIG. 4. Forest plots grouped by stone locations. (A) Upper ureter stone. (B) Lower ureter stone. CI, confidence interval.

A

Study or subgroup	Tamsulosin Events	Tamsulosin Total	Control Events	Control Total	Risk ratio (95% CI)	Year
Han et al. [9]	20	22	15	23	1.39 (1.01-1.93)	2006
Choi et al. [11]	27	32	20	33	1.39 (1.02-1.90)	2008
Kim et al. [12]	18	42	11	34	1.32 (0.73-2.41)	2008
Kang et al. [14]	52	97	28	73	1.40 (0.99-1.87)	2009
Total (95% CI)		193		163	1.38 (1.14-1.68)	
Total events	117		74			

Heterogeneity: X^2=0.03, DF=3 (p=0.999)



B

Study or subgroup	Tamsulosin Events	Tamsulosin Total	Control Events	Control Total	Risk ratio (95% CI)	Year
Han et al. [8]	29	35	17	32	1.56 (1.09-2.23)	2006
Bak et al. [10]	57	75	34	67	1.50 (1.15-1.96)	2007
Kang et al. [14]	9	19	8	21	1.24 (0.60-2.56)	2009
Total (95% CI)		129		120	1.48 (1.21-1.83)	
Total events	95		59			

Heterogeneity: X^2=0.31, DF=2 (p=0.857)

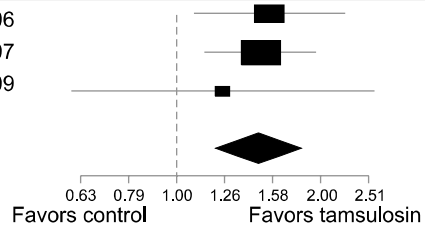


FIG. 5. Forest plots grouped by whether SWL was applied or not. (A) After SWL. (B) No SWL (expectant treatment). SWL, shock wave lithotripsy; CI, confidence interval.

the highest density of α_{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 ureter 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.

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