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A Prospective Randomized Controlled Trial of the Efficacy of Tamsulosin After Extracorporeal Shock Wave Lithotripsy for a Single Proximal Ureteral Stone

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Purpose: The objective of this study was to evaluate the efficacy of tamsulosin on stone clearance after extracorporeal shock wave lithotripsy (ESWL) in patients with a single proximal ureteral stone.

Materials and Methods: This prospective randomized controlled trial was performed on 88 patients with a single proximal ureteral stone. After consenting with a doctor, the patients were allocated to the treatment (tamsulosin 0.2 mg once a day) or control (no medication) group, and the efficacy of tamsulosin was evaluated. The primary outcome of this study was the stone-free rate, and the secondary outcomes were the period until clearance, pain intensity, analgesic requirement, and incidence of complications.

Results: A stone-free state was reported in 37 patients (84.1%) in the treatment group and 29 (65.9%) in the control group (p=0.049). The mean expulsion period of the stone fragments was 10.0 days in the treatment group and 13.2 days in the control group (p=0.012). There were no statistically significant differences in aceclofenac requirement or pain score between the two groups. Only one patient in the treatment group experienced transient dizziness associated with medical expulsive therapy, and this adverse event disappeared spontaneously.

Conclusions: The results of this prospective randomized controlled trial of the efficacy of tamsulosin after ESWL for a single proximal ureteral stone suggest that tamsulosin helps in the earlier clearance of stone fragments and reduces the expulsion period of stone fragments after ESWL.

Keywords: *Lithotripsy; Tamsulosin; Urolithiasis*

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INTRODUCTION

The lifetime prevalence of urinary stones is estimated to be 1% to 15%, with the probability of having a stone varying according to age, gender, race, and body mass index (BMI) [1]. Acute colic due to a ureteral stone is the most common situation encountered by urologists in an emergency setting [2]. Ureteral stones have been treated by different modalities depending on location, size, and urgency of clearance. Besides watchful waiting, management of ureteral stones is undertaken with extracorporeal shock wave lithotripsy (ESWL) or ureteroscopic lithotripsy [1,3]. ESWL has advantages such as low morbidity, no need for hospitalization or anesthesia, and avoidance of initial stone manipulation. Currently, ESWL has been recommended as the first-line treatment for ureteral stones with a success rate of 80% to 90% [4-6]. However, a recent meta-analysis showed that, compared with ureteroscopic lithotripsy, stone-free rates were lower and re-treatment rates were higher in patients who underwent ESWL [5]. Thus, interest has increased in adjunctive treatment to enhance the passage of stone fragments after ESWL. We

aimed to evaluate the efficacy of tamsulosin as an adjunctive treatment on stone clearance after ESWL in patients with a single proximal ureteral stone.

MATERIALS AND METHODS

Since March 2011, an open-label, prospective randomized controlled trial was performed to evaluate the efficacy of tamsulosin on stone clearance after ESWL in patients with a single proximal ureteral stone in an outpatient setting. The study protocol was approved by the Institutional Review Board of Seoul National University Hospital, and written informed consent was obtained from eligible patients. Patients in the age range of 18 to 70 years with symptomatic, unilateral, and single proximal ureteral stones ranging from 6 to 20 mm in the longest axis proved on plain abdominal kidney, ureter, and bladder (KUB) radiography and nonenhanced kidney computed tomography (CT) were included in this trial. Exclusion criteria were as follows: active urinary tract infection; severe hydronephrosis; pregnancy; inadequate renal function (serum creatinine, >2.0 mg/dL); concomitant treatment with alpha-blockers, calcium channel blockers, or steroids; hypotension; multiple urinary stones; morbid obesity (BMI, >30 kg/m^2); stone on nonfunctioning kidney; history of previous failed ESWL; history of urinary tract surgery; or uncorrected urinary tract obstruction. After consenting, patients were allocated to the treatment (tamsulosin 0.2 mg once a day) or control (no medication) group by computer-generated randomization concealed in a sealed envelope until the day of ESWL. Patients in the treatment group received tamsulosin 0.2 mg once a day just before the session of ESWL until the clearance of the ureter stone. All lithotripsy sessions were performed by using the Sonolith Praktis electroconductive lithotripter (EDAP TMS S.A., Lyons, France) with a shock wave frequency of 2 Hz by the same team of radiographers under the supervision of a urologist. The power was gradually increased during the initial minute of treatment with steps from 25% to 70%. All patients were allowed to use aceclofenac 100 mg on demand and were asked to drink 1.5 to 2.0 L of water per day.

The primary outcome of this study was the stone-free rate, and the secondary outcomes were the time until stone clearance, pain intensity, analgesic requirement, and incidence of complications. Stone-free state was defined as the complete absence of any stone or the presence of residual fragments smaller than 3 mm in diameter. Patients were assessed at 1, 2, and 3 weeks for these outcomes by means of KUB and/or kidney ultrasonography when it was required, urinalysis, serum level of creatinine, and visual analogue scale.

All demographics and follow-up data were analyzed by using the IBM SPSS ver. 19.0 (IBM Co., Armonk, NY, USA). Comparisons of all available variables were performed by Student t-test, Mann-Whitney U test for continuous or ordinal scales, and chi-square test for categorical scale. All p-values were 2-sided, and data were considered statistically significant at $p<0.05$.

RESULTS

Ninety-six patients with a mean age of 46.7 years (range, 22 to 67 years) were randomly assigned to the treatment (n=48) and control (n=48) groups. Of the 96 patients, 88 patients completed the study. Four patients in the treatment group and 4 in the control group dropped out of the trial owing to withdrawal of consent (n=3) or loss of follow-up for an unknown reason (n=5). Patient characteristics are presented in Table 1. There were no significant differences between the two groups in terms of age, gender, BMI, affected side, or stone diameter. The mean stone diameter before ESWL was 9.2 and 9.6 mm in the treatment and control groups, respectively.

A stone-free state was reported in 37 of 44 patients

TABLE 1. Comparison of patient demographics

Demographic	Treatment group	Control group	p-value
No. of patients	44	44	-
Gender, n (%)			0.823
Male	29 (65.9)	28 (63.6)	
Female	15 (34.1)	16 (36.4)	
Age (y)			0.588
Mean	46.2	47.6	
Median (interquartile range)	49.5 (34.25–57.75)	50.5 (39.25–55.75)	
Body mass index (kg/m^2)			0.871
Mean	24.1	24.3	
Median (interquartile range)	24.6 (21.9–26.7)	24.4 (22.3–26.9)	
Affected side, n (%)			0.669
Right	20 (45.5)	22 (50.0)	
Left	24 (54.5)	22 (50.0)	
Stone size (mm)			0.455
Mean	9.2	9.6	
Median (interquartile range)	8.5 (8.0–10.0)	9.0 (8.0–10.0)	

TABLE 2. Results of the study

Variable	Treatment group	Control group	p-value
Stone-free, n (%)	37 (84.1)	29 (65.9)	0.049
Expulsion duration (d)			0.012
Mean	10.0	13.2	
Median (interquartile range)	7 (7-14)	14 (7-14)	
Aceclofenac consumption (mg)			0.096
Mean	384.1	447.7	
Median (interquartile range)	350 (200-475)	400 (325-475)	
Steinstrasse, n (%)	4 (9.1)	5 (11.4)	0.725
Pain score (VAS)			0.416
Mean	3.2	3.4	
Median (interquartile range)	3 (2-4)	3 (3-4)	

VAS, visual analogue scale.

(84.1%) in the treatment group and 29 of 44 (65.9%) in the control group (p=0.049). The mean expulsion period of the stone fragments was 10.0 days in the treatment group and 13.2 days in the control groups (p=0.012). There were no statistically significant differences between the two groups in aceclofenac requirement or pain score (Table 2).

Steinstrasse developed in 4 patients in the treatment group and in 5 patients in the control group, without statistical significance. All of these patients had stones in the range of 11 to 20 mm. Four patients passed stone fragments by conservative management, whereas 5 patients required auxiliary ureteroscopic lithotripsy. No patient was hospitalized for recurrent colic, bleeding, or urinary tract infection. Only one patient in the treatment group experienced transient dizziness associated with medical expulsive therapy. The medication was not discontinued, however, and the adverse event disappeared spontaneously.

Patients who were not stone-free after 3 weeks of follow-up (7 in the treatment group and 15 in the control group) were successfully treated with watchful waiting (n=9), repeated ESWL (n=8), or ureteroscopic lithotripsy (n=5).

DISCUSSION

ESWL is now accepted as the gold standard for ureteral stones because it is minimally invasive [1]. It should be noted that ESWL for ureteral stones often achieves excellent results after repeated treatments and secondary procedures such as ureteral stenting [5]. In a recent Cochrane Library review, compared with the rates after ureteroscopic lithotripsy, stone-free rates were lower (risk ratio [RR], 0.84; 95% confidence interval [CI], 0.73 to 0.96) and re-treatment rates were higher (RR, 6.18; 95% CI, 3.68 to 10.38) in patients who underwent ESWL [5]. As a result, a study to evaluate the treatment modalities that enhance the clearance of stones would be of particular interest.

Evidence that ureteral stone clearance may be enhanced with medical expulsive therapy has been accumulating for several years. Furosemide, calcium channel blockers, α-blockers, and corticosteroids have been widely investigated as effective therapies to promote stone clearance [7]. Among these medications, α-blockers are a particularly promising class of medical expulsive therapy, including tamsulosin, alfuzosin, doxazosin, terazosin, and naftopidil [8-11]. With the identification of large populations of $\alpha 1_A$ and $\alpha 1_D$ adrenoreceptors in the human ureter [12-14], medical expulsive therapy with tamsulosin, a selective $\alpha 1_A$ and $\alpha 1_D$ adrenoreceptor antagonist, has been widely investigated as a potential treatment strategy that may lead to ureteral relaxation and enhance the passage of stone fragments after ESWL. The present study was designed to prospectively investigate the role of tamsulosin as an adjunctive therapy after ESWL of proximal ureter stones. The study results showed that tamsulosin helps in the earlier clearance of stone fragments and reduces the expulsion duration of stone fragments after ESWL. Also, tamsulosin was well tolerated without significant adverse events.

Numerous clinical trials have been performed to investigate the efficacy of tamsulosin. Also, several systematic reviews and meta-analyses have already reported the clinical effectiveness of tamsulosin in stone clearance after ESWL. Zhu et al. [15] reported that the pooled absolute risk difference of the stone clearance rate was 16% (95% CI, 5% to 27%) and the pooled mean difference of the expulsion time was 8 days (95% CI, −3 to 20 days) in favor of the tamsulosin medication [15]. In another meta-analysis by Zheng et al. [16], tamsulosin had an overall benefit for stone clearance (RR, 1.24; 95% CI, 1.12 to 1.37) and expulsion time (mean difference, −0.34; 95% CI, −0.56 to 0.11) compared with the control group [16]. In addition, lower analgesic requirements and fewer colic episodes and adverse effects were demonstrated. However, information on the efficacy of tamsulosin in stone clearance after ESWL in Korean populations is sparse.

In the Korean population, this issue is still under debate. Han et al. [17] reported a higher expulsion rate (90.9 vs. 65.2%, p=0.038) and lower analgesic requirement (0.23 injections vs. 0.78 injections, p=0.042) with tamsulosin treatment compared with the control. Choi et al. [18] evaluated

the effect of tamsulosin and nifedipine in stone clearance after ESWL and reported that the total stone expulsion rate was significantly higher in the tamsulosin group (84.4%) than in the nifedipine (67.7%) and control (60.6%) groups (p=0.032). However, another multicenter, prospective, randomized trial by Kang et al. [19] demonstrated that there were no significant differences in expulsion rate (50.4% vs. 39.1%, $p > 0.05$) and mean distance of stone migration (7.1 cm vs. 5.5 cm, $p > 0.05$) between the tamsulosin and control groups. Kim et al. [20] also reported similar negative results for the complete stone expulsion rate between the tamsulosin and control groups. On the basis of these studies, Lee et al. [21] performed a meta-analysis and demonstrated that tamsulosin had an overall benefit for ureteral stone clearance over the control after ESWL (RR, 1.38; 95% CI, 1.14 to 1.68). However, several limitations of their meta-analysis, such as poor quality of included studies and publication bias, could have affected the pooled analysis. In that respect, well-designed randomized controlled trials are needed to confirm these findings.

CONCLUSIONS

The results of this prospective randomized controlled trial concerning the efficacy of tamsulosin after ESWL for a single proximal ureteral stone suggest that tamsulosin helps in the earlier clearance of stone fragments and reduces the expulsion period of the stone fragments after ESWL. In addition, tamsulosin was well tolerated without significant adverse events.

CONFLICTS OF INTEREST

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