Effect of α1-Adrenergic Antagonists on Lower Ureteral Stones With Extracorporeal Shock Wave Lithotripsy

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OBJECTIVE: To evaluate the efficiency of α1-adrenergic antagonists on stone clearance after extracorporeal shock wave lithotripsy (ESWL) in patients with lower ureteral stones.

METHODS: A total of 107 patients with solitary lower ureteral stones and who underwent single ESWL sessions were divided into two groups. Group 1 received our standard medical therapy, and group 2 was treated with 0.4 mg/day tamsulosin for a maximum of 2 weeks. All patients were re-evaluated with plain film radiography and ultrasound each week during treatment.

RESULTS: Twenty-four of the 52 patients in group 1 (46.2%) and 41 of 55 patients in group 2 (74.5%) (p = 0.002) were found to be stone-free. Among patients with stones 10–15 mm in diameter, the stone-free rate was 36.4% in group 1 and 73.0% in group 2 (p = 0.003). Average stone expulsion time was 11.6 days and 8.1 days in groups 1 and 2, respectively (p = 0.000). Ureteral colic occurred in 10 patients (19.2%) in group 1 but only 3 patients (5.5%) in group 2 (p = 0.043). The only side effect of tamsulosin was slight dizziness in 2 of the 55 (3.6%) patients in group 2.

CONCLUSION: Adjunctive therapy with α1-adrenergic antagonists after ESWL is more effective than, and equally as safe as lithotripsy alone in the treatment of patients with lower ureteral stones. The use of α1-adrenergic antagonists is more useful for stones with a large dimension, and can also reduce stone expulsion time and episodes of ureteral colic. [Asian J Surg 2010;33(1):37–41]

Key Words: α1-adrenergic antagonists, lithotripsy, lower ureteral stone

Introduction

Symptomatic ureteral stone disease is one of the important issues that urologists face in emergency clinical settings. Although extracorporeal shock wave lithotripsy (ESWL) is accepted in many institutions as the first-line treatment option for patients with ureteral stones, this approach does not seem to work efficiently when the stone size increases. Recently, however, ESWL have been reconsidered for the treatment of larger ureteral stones. Some authors1,2 have reported positive results in accelerating lower ureteral stone passage using α1-adrenergic antagonists, on the basis that α1-adrenergic receptors play an important physiological role in lower ureteral excretion.3 Here, we perform a comparative study to evaluate the safety and effectiveness of α1-adrenergic antagonists for the treatment of lower ureteral stones.

Material and methods

Patients

Between January 2005 and June 2008, 110 patients who had lower ureteral stones were evaluated by physical examination, serum creatinine measurement, plain abdominal...
X-rays, intravenous pyelography and abdominal B-mode ultrasound. Patients were excluded from the study if they had any of the following: urinary tract infection, multiple stones, severe hydronephrosis, solitary kidney, congenital urinary anomalies, or previous ureteral surgery. Patients with severe obesity, pregnancy, lactation, or previous treatment with α1-adrenergic antagonists were also excluded. A total of 107 patients met these requirements and were enrolled in the study.

Treatment
Patients were treated using an HB-ESWL-V (Zhanjiang, Jiangsu, China) lithotripter. The number of shocks given to each patient was decided empirically according to the diameter of the stone. Patients were in the supine position and no analgesics were used during ESWL. After ESWL, the patients were assigned to two groups by simple random allocation, and placebo-controlled medical treatment was initiated immediately and continued for a maximum of 2 weeks, or until an alternative treatment was applied. Standard treatment of 25 mg indomethacin and 5 g paishi granules (Chinese herbal medicine) was given three times daily to group 1, the control group. Group 2 received the standard medical treatment in addition to 0.4 mg tamsulosin (α1-adrenergic antagonist) once daily. Furthermore, all patients were instructed to drink a minimum of 2 L of water daily and were asked to keep a diary about ureteral colic, stone expulsion and side effects of medical therapy. Follow-up included clinical examination, abdominal B-mode ultrasound and/or intravenous pyelography repeated every week after lithotripsy.

Statistical analysis
Data were analysed using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA).

Results
Patient characteristics are summarized in Table 1. Group 1 consisted of 14 women and 38 men, with a mean age of 40.9 ± 10.3 years (range: 19–62), whereas group 2 consisted of 19 women and 36 men, with a mean age of 42.2 ± 12.6 years (range: 21–69). Stone diameter was 8.6 ± 3.0 and 9.3 ± 2.6 mm for groups 1 and 2, respectively. The groups were not significantly different in their demographic and clinical characteristics (p > 0.05).

![Table 1. Demographic and clinical characteristics of patients](image)

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n = 52)</th>
<th>Group 2 (n = 55)</th>
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<tbody>
<tr>
<td>Mean age (yr)</td>
<td>40.9 ± 10.3</td>
<td>42.2 ± 12.6</td>
</tr>
<tr>
<td>Mean weight (kg)</td>
<td>72.4 ± 6.2</td>
<td>73.2 ± 6.1</td>
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<tr>
<td>Stone diameter</td>
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<tr>
<td>5–9 mm</td>
<td>19</td>
<td>18</td>
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<tr>
<td>10–15 mm</td>
<td>33</td>
<td>37</td>
</tr>
<tr>
<td>Mean diameter (mm)</td>
<td>8.6 ± 3.0</td>
<td>9.3 ± 2.6</td>
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</table>

All patients underwent one session of ESWL. A mean of 2955.8 ± 256.1 shocks per patient in group 1 was delivered at a mean voltage of 7.7 ± 0.6 kV, and a mean of 2902.0 ± 241.8 shocks per patient in group 2 was delivered at a mean voltage of 7.9 ± 0.8 kV, with no significant difference between the groups (p > 0.05). Twenty-four of the 52 patients in group 1 (46.2%) and 41 of the 55 patients in group 2 (74.5%) were found to be stone free. The difference between groups was statistically significant (p = 0.002; Figure 1A). Among patients with stones 10–15 mm in diameter, we found a significant difference in the stone-free rate between the two groups (36.4% in group 1 and 73.0% in group 2; p = 0.003; Figure 1B). In contrast, we found no significant difference in stone-free rate among patients with stones 5–9 mm in diameter (63.2% in group 1 and 77.8% in group 2; p = 0.345; Figure 1B). Average stone expulsion time for groups 1 and 2 was 11.6 ± 1.4 days and 8.1 ± 1.6 days, respectively (p < 0.001). Ureteral colic occurred in 19.2% of patients in group 1 but in only 5.5% of patients in group 2 (p = 0.043; Figure 1C).

The only side effect of tamsulosin was slight dizziness in two of 55 patients in group 2 (3.6%).

Discussion
Urinary stone disease is a significant worldwide health problem. Of all urinary tract stones, 20% are ureteral, and 70% of these are located in the distal portion of the ureter. If the diameter of a ureteral stone is less than 4 mm, spontaneous passage is generally possible. Ureteral stones greater than 6 mm in diameter have a ≤5% chance of spontaneous passage.4,5 Currently, ESWL represents the first-line therapeutic option for lower ureteral stones, but it implies a certain percentage of re-treatments. The major goal in treating...
patients with lower ureteral stones is achieving a stone-free state. Stone fragment expulsion after ESWL is probably not dissimilar to spontaneous passage. Several variables play a fundamental role in the migration of calculi: stone size, intrinsic areas of narrowing within the ureter, ureteral peristalsis, hydrostatic pressure of the column of urine proximal to the stone and oedema, urinary tract infection, and spasm of the ureteral site in which the stone is lodged.6,7

Oedema, urinary tract infection, spasm and ureteral peristalsis can be modified by appropriate medical therapy. If the friction between the intramureral wall and the stone decreases, ureteral relaxation occurs and promotes stone passage at the site of obstruction. Two factors that appear to be most useful in facilitating stone passage are increase in hydrostatic pressure proximal to the stone, and relaxation of the ureter in the region of the stone. The primary functional anatomical unit of the ureter is the ureteral smooth muscle cell.4

The sympathetic nervous system appears to modulate ureteral activity as shown by the presence of adrenergic receptors in the ureter. Hancock8 has reported the presence of α- and β-adrenergic receptors in the human ureter. Several studies have shown that the density of α1-adrenergic receptors in the ureteral smooth muscle cells is greater than that of other adrenergic receptors.9 According to the general consensus, α1-adrenergic receptor agonists tend to stimulate ureteral activity. β-Adrenergic receptor agonists tend to inhibit ureteral activity. α-Adrenergic receptors are found in trigone, prostatic urethra and ureters. These receptors cause contraction of the smooth muscles in these regions.10 It is suggested that α-adrenergic stimulation reduces the volume of urine flow through the ureter and causes ureteral spasm.

In contrast, α-adrenergic antagonists can decrease ureteral peristaltic frequency, which reduces ureteral spasm. These changes are accompanied by an increase in

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**Figure 1.** Comparison of stone-free rate between groups 1 (control) and 2 (tamsulosin). (A) Percentage of patients found to be stone free in groups 1 and 2 (p = 0.002). (B) Percentage of patients found to be stone free in groups 1 and 2 with stone diameter of 5–9 mm (p = 0.345) and 10–15 mm (p < 0.003). (C) Percentage of patients with episodes of ureteral colic (p < 0.001).
the rate of fluid transport.\textsuperscript{1} Based on the evidence that $\alpha$-adrenergic antagonists have an important physiological role in lower ureteral excretion, some researchers have more recently proposed the use of $\alpha$-1-adrenergic antagonists for facilitating lower ureteral stone expulsion.\textsuperscript{11} Sofa et al\textsuperscript{12} have reported the spontaneous passage of lower ureteral stones in 86.6% of patients who were treated with an $\alpha$1-adrenergic antagonist, and a significant difference in the stone-free rate between patients treated with tamsulosin and the control group. Koppel et al\textsuperscript{13} have reported favourable impact of 15-day tamsulosin treatment on the clearance of residual fragments after ESWL. Porpiglia et al\textsuperscript{14} have also shown that the stone-free rate was significantly greater with nifedipine and deflazacort supplementation than without it. In our study, the stone-free rate was 46.2% and 74.5% in patients who underwent ESWL alone and ESWL plus tamsulosin treatment, respectively ($p = 0.002$). For stones larger than 10 mm in diameter, however, the success rate was significantly greater in the patients who underwent ESWL plus tamsulosin treatment compared with those receiving ESWL alone. We propose that this might be attributed to the effect of tamsulosin in improving the passage of larger fragments generated after ESWL. During ESWL, larger stones often generate larger fragments that migrate less easily. In such cases, tamsulosin could promote the passage of these fragments by increasing the intraretinal flow and the intraretinal pressure gradient above the stone, or by decreasing the peristalsis above the stone. As far as expulsion time was concerned, we observed stone passage after 11.6 days in group 1 and 8.1 days in group 2 ($p < 0.001$). Our results demonstrated that the use of tamsulosin significantly reduced expulsion times in comparison with the control group.

Ureteral stones usually cause severe colic pain as a result of increasing intraretinal pressure above the site of ureteral obstruction. The goal of treatment of ureteral colic is to relieve the pain and release the ureteral obstruction. Experimental and clinical studies have shown that antispasmodic drugs are effective for the relief of ureteral colic and possibly for the promotion of stone passage, but such drugs are generally considered unsatisfactory in term of efficacy and safety.\textsuperscript{15} Dellabella et al\textsuperscript{1} have found that treatment with tamsulosin provides relief of ureteral colic pain, as indicated by significantly less analgesic use. In our study, ureteral colic occurred in 19.2% of patients in group 1 but in only 5.5% of patients in group 2 ($p = 0.043$) demonstrating that that tamsulosin probably worked to decrease the frequency of peristaltic contractions within the ureter.

The side effects with tamsulosin treatment after ESWL were mild. In the study by Porpiglia et al,\textsuperscript{11} the incidence of side effects with adjunctive medication was 10%, while it was only 3.6% in our study. The rates of side effects, such as dizziness, rhinitis and diarrhea have been reported to be 14.9%, 13.1% and 6.2% respectively.\textsuperscript{13} However, these rates were recorded after at least 13 weeks of tamsulosin treatment for benign prostatic hyperplasia. In the present study, only 3.6% of patients (2/55) receiving tamsulosin reported slight dizziness within the 2-week treatment period. However, this low number of side effects was probably due to the short follow-up period.

The results of our study demonstrate that adjunctive therapy with $\alpha$-1-adrenergic antagonists following ESWL is more effective than lithotripsy alone, while equally as safe, for the treatment of lower ureteral stones. Our results also indicate that $\alpha$-1-adrenergic antagonists are more useful for stones with a larger diameters. Finally, adjunctive therapy with $\alpha$-1-adrenergic antagonists could significantly reduce stone expulsion time and the number of ureteral colic episodes after ESWL.

References


