Efficacy of a highly selective $\alpha$-1 adrenoceptor antagonist in expulsive therapy of distal ureteral stones: A randomized controlled study

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ABSTRACT

The objective of this study was to evaluate the clinical role of a specific $\alpha$-1 blocker in medical expulsive therapy of symptomatic distal ureteral stones. Two hundred four patients with symptomatic distal ureteral stones with a diameter of <10 mm were enrolled in this prospective study. The patients were randomly divided into three groups: tamsulosin treatment (Group 1, n=67), silodosin treatment (Group 2, n=68), or a placebo (Group 3, n=69). The patients recorded the number of colic episodes, lower urinary tract symptoms, analgesics dosages, and number of days for spontaneous passage of the stones through the ureter in a diary. Expulsion was observed in 85.11% in group 1, 79.17% in Group 2, and 59.18% in Group 3. The expulsion time was significantly shorter in Groups 1 and 2 compared to that in Group 3. The average expulsion time in Groups 1, 2, and 3 was 6.28±2.41, 6.03±2.72, and 9.79±2.71 days, respectively. The average expulsion time was significantly shorter in Groups 1 and 2 compared to that in Group 3. The occurrence of adverse effects was significantly different in the three groups, with 12.50% of patients in Group 2 reporting adverse effects compared to 2.13 and 0% in Groups 1 and 3, respectively. Adverse effects were noted in 12.50% of the patients in Group 2, with a statistically significant difference compared to Groups 1 and 3. Medical expulsion therapy with $\alpha$-1A blockers is safe and effective, as demonstrated by the increased stone expulsion rate, reduced expulsion time, and reduced need for analgesics.

Key words: $\alpha$-1 blocker, distal ureteral stone, tamsulosin, silodosin, expulsive therapy

INTRODUCTION

Urolithiasis is a significant worldwide health problem (Pak, 1998). Patients with ureteral stones are a common occurrence in urological practice. Ureteral stones play an important role in daily urological practice and clinicians are frequently asked to prescribe an adequate treatment (Carstensen, 1993). Several studies have proven the efficacy of mini-invasive therapies, such as extracorporeal shock wave lithotripsy (ESWL) and ureteroscopy (Carstensen, 1999; Segura, 1997). However, noninvasive therapies that aid the spontaneous passage of ureteral stones would prevent the potential pain, risk, and expense associated with invasive interventions.

Recently, the use of a watchful waiting approach has been extended to ureteral stones, using pharmacological therapy to reduce symptoms and facilitate stone expulsion (Borghi, 1994; Porpiglia, 2000; Cervenakov, 2002; Ukal, 1999). In the stone migration process, the sympathetic nervous system modulates ureteral activity, as demonstrated by the presence of adrenergic receptors in the ureter (Latifpour, 1989). Several studies have shown that the number of $\alpha$-1A-adrenergic receptors in the ureteral smooth muscle cells is greater than in other adrenergic receptors (Latifpour, 1989;
Materials and Methods

Study design

The study was approved (10B-015) by the Institutional Review Board of St. Martin De Porres Hospital, Chiayi City, where the work was undertaken. All procedures involving human participants were performed in accordance with the ethical standards of the institutional and national research committee and in compliance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This prospectively randomized controlled trial was carried out from October 2010 to March 2013. The trial was registered at New Zealand Clinical Trials Registry and allocated the ACTRN: ACTRN12611000571976.

Study population

We assessed the eligibility of 296 patients with radiopaque distal ureteral stones <10 mm. The presence of stones and characteristics were diagnosed using non-enhanced computerized tomography (CT). The stones were classified according to their diameter along the ureteral axis. No patients who had undergone previous ureteral surgery were included in this study. All patients signed an informed consent form before participating.

Exclusion criteria included: urinary tract infections, high-grade hydronephrosis, diabetes, peptic ulcers, history of hypersensitivity to α-1 blockers, pregnancy, or nursing. Patients with a history of spontaneous stone expulsion, hypotension, or those with systolic blood pressure <110 mmHg were also excluded.

Study Interventions

The presence and characteristics of stones were diagnosed by nonenhanced computerized tomography (CT). The stones were classified according to their diameter along the ureteral axis. All patients were prospectively randomized (using a random numbers table) into three groups (tamsulosin, silodosin, or placebo) before they were enrolled in the study. All patients were prescribed 10 mg of ketorolac three times per day as an analgesic and were allowed to use 0.2 mg of sublingual buprenorphine on demand; they were encouraged to drink a minimum of 2 L of water per day. To highlight any possible fragment or stone expulsion, all patients were asked to filter their urine. All patients were evaluated within two weeks because most studies in the literature have shown positive results within the first 10 days of medical therapy (Delabella et al, 2003), as determined from an outpatient visit, plain kidney-ureter-bladder radiography, abdominal ultrasonography, and non-enhanced CT, when necessary.

Randomization

Two hundred ninety-six patients were eligible, and 88 in the tamsulosin group, 76 patients were available. Among these, six patients missed primary outcome, and three patients refused consent and were eliminated from the study. Thus, 67 patients (group 1) received tamsulosin (0.4 mg) daily. In the silodosin group, 91 patients were available. Among these, seven patients missed primary outcome, and four patients refused consent and were eliminated from the study. Sixty eight (68) patients (group 2) received silodosin (8 mg daily). In the placebo group, 82 patients were available. Among these, seven patients missed primary outcome, and four patients refused consent. Thus, 69 patients (group 3) acted as controls (Figure 1).

Study outcomes

The primary outcome was the stone expulsion rate. The secondary outcomes were expulsion time, analgesics consumption, lower urinary tract symptoms, colic episodes, and adverse effects. The stone expulsion rate was defined by determining the number of stones passed and dividing by the total number of patients in each group. Only patients without any residual fragments were considered to have successful outcomes. The expulsion time was defined as the date of stone passage, as reported by patients. The number of colic episodes, lower urinary tract symptoms (frequency,
residual sensation, difficulty, urine retention, and tenesmus), the amount of analgesic consumption, and adverse effects of medical therapy were recorded in a diary and evaluated.

**Sample size and statistical analysis**

We detected a 30% difference in the stone expulsion rate in the treatment groups at a significance level of 0.05 and a power of 80% via Creative Research Systems survey software; a sample size of 55 patients per group was needed. All analyses were conducted using SPSS® version 14.0.1. Age, body mass index, stone size, expulsion time, ketorolac consumption, buprenorphine consumption, and colic episodes were evaluated using the Mann-Whitney U-test. The gender, stone laterality, stone expulsion rate, lower urinary tract symptoms, and adverse effects were evaluated using the chi-square test.

**RESULTS**

Two hundred four patients completed the study. No statistically significant difference was observed in the patient’s age, gender distribution, or laterality. The average stone size was 6.70±1.30 mm (5–9 mm) in group 1, whereas it was 6.46 ± 1.25 mm (4–9 mm) and 6.59 ± 1.37 mm (4–9) in groups 2 and 3, respectively. The Kruskal-Wallis test did not reveal any statistically significant difference among the groups ($p>0.050$) (Table 1).

Stone expulsion was observed in 40 (85.11%) patients in group 1 and in 38 (79.17%) and 29 (59.18%) patients in groups 2 and 3, respectively. The chi-square test revealed a statistically significant difference in stone expulsion between group 1 vs. 3 and group 2 vs. 3 ($p=0.02$ 1 vs. 3, $p=0.05$ 2 vs. 3, respectively). The average time to expulsion was 6.28±2.41 days (range 2–12) in group 1, whereas it was 6.03±2.72 days (2–14) in group 2 and 9.79±2.70 days (1–14) in group 3. According to the Kruskal-Wallis test, there...
was a statistically significant difference in the time to expulsion between group 1 vs. 3 and group 2 vs. 3 (p<0.05 and p<0.0001, respectively). There were no statistically significant differences in the mean sublingual buprenorphine dosages and colic episodes between males and females and between the right and left sides. The mean ketorolac consumption was 230.87±94.42 mg (range 90–420) per patient in group 1, whereas it was 221.56±94.22 mg (90–420) in group 2 and 331.96±106.47 mg (90–480) in group 3. The mean ketorolac consumption was significantly different between group 1 vs. 3 and group 2 vs. 3 (p<0.0001 and p=0.001, respectively) according to the Kruskal-Wallis test. With regard to lower urinary tract symptoms, there was a statistically significant difference between groups 1 and 3 (p=0.040). No patient was hospitalized for recurrent colic, and no urosepsis was recorded. Only one patient in group 1 experienced adverse effects associated with the medical expulsive therapy, whereas six patients in group 2 reported adverse effects (transient hypotension, asthenia, syncope, and retrograde ejaculation), with a statistically significant difference in adverse effects noted in group 2 compared to group 3 (p=0.009) (Table 2). The medical therapy was not suspended in any of the patients, and the adverse effects disappeared. Patients (7 in group 1, 10 in group 2, and 10 in group 3) who were not stone free after the 2 weeks of follow-up were successfully treated with ureteroscopy (Sasaki et al, 2011) or ESWL (Ukhal et al, 1999). All the ureteroscopic findings revealed moderate-to-severe inflammatory reactions to stone-impacted mucosa and polypoid changes.

**DISCUSSION**

Several studies have demonstrated the efficacy of these treatments (Carstensen, 1999; Segura, 1997). Although such procedures are generally effective, they are invasive and are not risk free. They are also relatively expensive (Segura, 1997; Dellabella, 2003).

Several trials have demonstrated the benefit of drugs belonging to the α-blocker class for the treatment of urolithiasis, as defined by the European Association of Urology (Türk, 2015). Tamsulosin is one of the most commonly used α-blockers. One small study suggested that tamsulosin, terazosin, and doxazosin were equally effective, indicating a possible class effect (Yilmaz, 2005). A possible class effect was also indicated by several trials, which demonstrated increased stone expulsion using doxazosin, terazosin, alfuzosin, naftopidil, and silodosin.

A previous comparative study of three different α1-blockers reported that tamsulosin, terazosin and doxazosin were equally effective, indicating a possible class effect (Yilmaz, 2005). Based on the findings of that study, the present research compared the safety and effectiveness of tamsulosin and silodosin for the treatment of distal ureteral stones. The present study selected tamsulosin and silodosin based on the previous literature, which showed both α1-blockers had α1 A/D receptor selectivity (Porpiglione, 2000; Cervenakova, 2002; Ukhal, 1999; Sasaki, 2011). The present study was limited to patients affected by distal ureteral stones with a diameter of <10 mm. A maximum observation period of 2 weeks was selected because longer periods can increase complication rates by up to 20% (Dellabella, 2003). Furthermore, most studies have reported positive results of medical therapy within the first 10 days of commencing the treatment (Dellabella, 2003).

Positive outcomes were observed in 85.11% of patients in the tamsulosin group (group 1), 79.17% of patients in the silodosin group (group 2), and only 59.18% of patients in the
Table 2. Randomization results.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Tamsulosin group</th>
<th>Silodosin group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expulsion time (days) a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>6.28±2.41</td>
<td>6.03±2.72</td>
<td>9.79±2.7</td>
</tr>
<tr>
<td>Range</td>
<td>2–12</td>
<td>2–14</td>
<td>1–14</td>
</tr>
<tr>
<td>Expulsion rate b</td>
<td>40/47 (85.11)</td>
<td>38/48 (79.17)</td>
<td>29/49 (59.18)</td>
</tr>
<tr>
<td>Lower urinary tract symptoms b</td>
<td>6/47 (12.77)</td>
<td>11/48 (22.92)</td>
<td>17/49 (34.69)</td>
</tr>
<tr>
<td>Mean</td>
<td>0.36±0.19</td>
<td>0.37±0.19</td>
<td>0.45±0.20</td>
</tr>
<tr>
<td>Range</td>
<td>0.2–0.8</td>
<td>0.2–0.8</td>
<td>0.2–1.0</td>
</tr>
<tr>
<td>Ketorolac consumption (mg) a</td>
<td>230.87±114.69</td>
<td>221.56±94.22</td>
<td>331.96±106.47</td>
</tr>
<tr>
<td>Adverse effects c</td>
<td>2.13 (1/47)</td>
<td>12.50 (6/48)</td>
<td>0/49 (0)</td>
</tr>
<tr>
<td>Adjuvant therapy b</td>
<td>7/47 (20.41)</td>
<td>20.83 (10/48)</td>
<td>10/49 (14.89)</td>
</tr>
<tr>
<td>Stone location b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>23/47 (48.94)</td>
<td>21/48 (43.75)</td>
<td>23/49 (46.94)</td>
</tr>
<tr>
<td>Left</td>
<td>24/47 (51.06)</td>
<td>27/48 (56.25)</td>
<td>26/49 (53.06)</td>
</tr>
</tbody>
</table>

The values are presented as the mean±standard deviation or number (%). *p<0.05, **p<0.01, *Kruskal-Wallis test, *Chi-square test, *Fisher’s exact test.

control group, with the difference statistically significant in stone expulsion rate. These results confirmed that medical therapy with a specific α1-blocker can improve stone expulsion rate, as reported by others (Sasaki, 2011).

Obara et al. (1996) stated that the presence of the α1-D adrenoceptor subtype was demonstrated in the human ureter. In an obstructed ureter, it is possible that tamsulosin induces an increase in the intraureteral pressure gradient around the stone (i.e., an increase in the urine bolus above the stone), thereby increasing the intraureteral pressure above the stone and decreasing the peristalsis below the ureter. This may reduce the intraureteral pressure below the stone, as well as the basal and micturition pressure, even at the bladder neck. This would result in a stronger urge to expel the stone.

With regard to analgesic consumption, α1-blockers limit usage by decreasing the frequency of phasic peristaltic contractions in the obstructed ureteral tract and, thus, decreasing the frequency of ureteral colic (Cervenakov, 2002). In the present study, the α1-blockers were effective in pain reduction and decreasing the amount of analgesics consumed, as demonstrated by the consumption in groups 1 and 2 compared to that in group 3. There was no statistically significant difference between the average size of expelled and not expelled stones in the treated patients. In addition, there seemed to be no relationship between the size of the stone and time to expulsion. Neither gender nor the stone side appeared to influence the stone expulsion rate. As reported by Porpiglia (2000), these data suggest that expulsion times are affected not only by the size of the stone but also by other factors, such as the shape of the stone and edema around the stone. In the present study, patients who were not stone free after the 2-week follow-up were successfully treated with ureteroscopy. These data demonstrate that neither watchful waiting nor medical therapy seems to negatively affect the success rate of stone removal. In the ureteroscopic manipulation for those failed cases, all the ureteroscopic findings revealed moderate-to-severe inflammatory reactions to stone-impacted mucosa and polypoid changes. Thus, medical therapy is not effective for impacted lower ureteral stones. However, such therapy may be effective for unimpacted ureteral stones, which are accompanied by marked inflammatory changes in the surrounding tissue.
In the present study, there was one serious adverse side effect of the medical expulsive therapy (postural hypotension in group 1), but the therapy did not have to be suspended. Minor therapy-related side effects (dizziness, asthenia, postural hypotension, and retrograde ejaculation) were observed in six patients (group 2), but they were able to complete the study. These results are similar to those reported for patients with BPH who were treated with α-1 blockers (Kihara, 1992). With regard to safety, both tamsulosin and silodosin were well tolerated by the patients (Madersbacher, 2007).

Lower urinary tract symptoms (urinary frequency, residual sensations, difficulty, urine retention, and tenusmus) cause additional problems for patients with lower ureteral stones. The current study does not demonstrate that α-1 blockers significantly alleviate lower urinary tract symptoms. However, the incidence of lower urinary tract symptoms was significantly lower in group 1 (12.77%) compared to group 2 (22.92%) and group 3 (34.69%) (p=0.040, group 1 vs. group 3). This finding implies that silodosin, a specific α-1A blocker, is more potent than α-1 D blockers for relaxation of the lower ureter.

Conclusions

The results of this study indicate that distal ureteral stones can be treated with expulsive medical therapy in patients when a watchful waiting approach is possible. In the present study, medical treatment with α-1 specific blockers proved to be safe and effective, as demonstrated by the low incidence of side effects, increased stone expulsion rates, and shorter expulsion times. The findings of the current study also suggest that tamsulosin and silodosin are equally effective, pointing to a possible class effect. In particular, the α-1A/D specific blocker tamsulosin seems to decrease the incidence of adverse effects.

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