Efficacy of Silodosin in Expulsive Therapy for Distal Ureteral Stones: A Randomized Double-blinded Controlled Trial

Chung-Jing Wang, Po-Chao Tsai, Chien-Hsing Chang

Purpose: To evaluate the efficacy of silodosin in the medical expulsive therapy for symptomatic distal ureteral stones.

Materials and Methods: This prospectively randomized controlled trial was carried out from May 2011 to December 2014. In all, 198 patients with radiopaque distal ureteral stones <10 mm in size were eligible: 61 patients in the control group and 62 patients in the silodosin group. The silodosin group received silodosin 8 mg daily, and the control group received lactose tablets. The primary outcome was the expulsion rate. The secondary outcomes the expulsion time, analgesic consumption, lower urinary tract symptoms, colic episodes, and adverse effects. Statistical analyses were performed using a Mann-Whitney U-test and chi-square test.

Results: The final analysis was conducted with 61 control and 62 silodosin patients as the denominator in each randomization arm. The average expulsion times were 6.31 ± 2.13 days for the silodosin group and 9.73 ± 2.76 days for the control group ($P < .001$).

Conclusion: Treatment with silodosin proved to be safe and effective, as demonstrated by the increased stone expulsion rate, the reduced expulsion time, and the reduced analgesics consumption.

Keywords: adrenergic alpha-1 receptor antagonists; dose-response relationship, drug; follow-up studies; prospective studies; treatment outcome; ureteral calculi/drug therapy.

INTRODUCTION

Urolithiasis is a significant and worldwide health problem.[1] Ureteral stones play an important role in daily urological practice, and clinicians are frequently asked to prescribe adequate treatment.[2,3] The efficacy of minimally invasive therapies, such as extracorporeal shock wave lithotripsy (SWL) and ureteroscopy, has been proven in several studies.[4,5] Nevertheless, spontaneous passage of a stone prevents potential pain, related complications, and costs of a surgical intervention.

Recently, the duration of the watchful waiting approach has been extended by using pharmacological therapy that can reduce symptoms and facilitate stone expulsion.[6-9] In the stone migration process, the sympathetic nervous system modulates ureteral activity, as demonstrated by the presence of adrenergic receptors in the ureter.[10] Several studies have shown that the density of α-1A adrenergic receptors in the ureteral smooth muscle cells is greater than that in other adrenergic receptors.[10-12] In addition, α-adrenergic antagonists inhibit basal tone and peristaltic frequency, dilating the ureteral lumen and facilitating stone passage.[13] In general, the main obstacle to the transport of lower ureteral stones is the intramural detrusor tunnel;[7,8] thus, blocking these receptors could allow stone passage. Investigators have reported the effectiveness of pharmacological therapies in increasing ureteral stone expulsion and reducing total analgesic use.[2,6,8,9,14,15] Furthermore, using real-time reverse transcription polymerase chain reactions and immunohistochemical staining, Itoh and colleagues reported that human ureter α-1A and 1D adrenergic receptors are the most commonly expressed subtypes.[16] They also reported that α-1A adrenergic receptors are the main component in phenylephrine-induced ureteral contractions in the isolated human ureters.[17] They found that the selective α-1A adrenergic receptors' antagonist, silodosin, was more effective than the selective α-1D adrenergic receptors' antagonist, BMY-7378, for noradrenaline-induced contractions in the human ureter.[18] Blockage of α-1A adrenergic receptors could accelerate the passage of distal ureteral stones. Therefore, the study was designed to evaluate the clinical role of silodosin in the medical expulsive therapy of symptomatic distal ureteral stones.

Department of Surgery, Division of Urology, Saint Martin De Porres Hospital, Chiayi, Taiwan, R.O.C.
*Correspondence: Department of Surgery, Division of Urology, Saint Martin De Porres Hospital, Chiayi, Taiwan, R.O.C.
Tel: +88 65 2756000 ext. 1013. Fax: +88 65 2788535. E-mail: jing@stm.org.tw.
Received November 2015 & Accepted December 2015

Table 1. Baseline patients' characteristics.*

Characteristics	Control Group (n = 61)	Silodosin Group (n = 62)	*P* Value
Age, years a			.744
Mean ± SD	51.51 ± 10.03	51.42 ± 8.68	
Range	28-72	36-71	
Gender, no (%) b			.741
Male	43 (70.49)	40 (67.74)	
Female	18 (29.51)	22 (32.26)	
BMI, kg/m^2 a	25.09 ± 2.79	25.51 ± 2.62	.389
Male a	24.77 ± 2.91	25.12 ± 2.82	.661
Female a	25.78 ± 2.39	26.23 ± 2.10	.309
No. R/L ureter b	33/28	26/36	.177
Stone size, mm a			
Mean ± SD	6.46 ± 1.31	6.47 ± 1.39	.860
Range	5-10	4-9	

Abbreviations: BMI, Body mass index; R, right; L, Left.
a Mann-Whitney *U* test
b Chi-square test
* Data are presented as mean ± SD.

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 May 2011 to December 2014. The trial was registered at New Zealand Clinical Trials Registry and allocated the ACTRN: ACTRN12611000555954.

Study Population

We assessed the eligibility of 198 patients with radiopaque distal ureteral stones < 10 mm. The presence of stones and characteristics were diagnosed using non-enhanced computed 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 patients were randomly divided into two groups: patients who received silodosin 8 mg daily and patients who received lactose tablets as the control. 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,[14] as determined from an outpatient visit, plain kidney-ureter-bladder radiography, abdominal ultrasonography, and non-enhanced CT, when necessary.

Randomization

In all, 198 patients were eligible, and 164 were prospectively randomized into two groups (using a random numbers table) before they were enrolled in the study. In all, 164 patients were available for consideration in each group. Among them, 12 patients, who were unwilling to be randomized in the control group, and 11 patients, who were unwilling to be randomized in the silodosin group, were excluded from the trial. Of the remaining patients, 70 were allocated to the control group, and they received lactose tablets. Among them, five missed the primary outcome and four withdrew their informed consent; thus, they were eliminated from

Table 2. Randomization results.

Variables	Control Group	Silodosin Group	*P* Value
Expulsion time, days a			< .0001
Mean	9.73 ± 2.76	6.31 ± 2.13	
Range	6-14	3-11	
Expulsion rate, no (%) b	33/61 (54.10)	48/62 (77.42)	.006
Lower urinary tract symptoms, no (%) b	26/61 (42.62)	22/62 (35.48)	.417
Ketorolac consumption, mg a			< .0001
Mean	343.77 ± 109.90	255.97 ± 112.48	
Range	90-480	90-420	
Buprenorphine consumption, mg a			.771
Mean	0.49 ± 0.29	0.47 ± 0.27	
Range	0.2-1.2	0.2-1.0	
Colic episodes a			.160
Mean	2.75 ± 1.38	2.39 ± 1.30	
Range	1-6	1-5	
Adverse effects, no (%) b	2/61 (3.28)	10/62 (16.13)	.016
Adjuvant therapy, no (%) b	28/61 (45.90)	14/62 (22.58)	.006
SWL/URSL, no	14/14	4/10	-----
Stone location b			.177
Right	33/61 (54.10)	26/62 (41.94)	
Left	28/61 (45.90)	36/62 (58.06)	

Abbreviations: SWL, Extracorporeal Shock Wave Lithotripsy; URSL, Ureterorenoscopic stone lithotripsy
a Mann-Whitney *U* test.
b Chi-square test.

the analysis. Another 71 patients were allocated to the silodosin group. Among them, five missed the primary outcome and four withdrew their informed consent; thus, they were eliminated from the analysis. The final analysis was conducted with 61 patients in the control group and 62 in the silodosin group patients, as the denominator in each randomization arm (**Figure**).

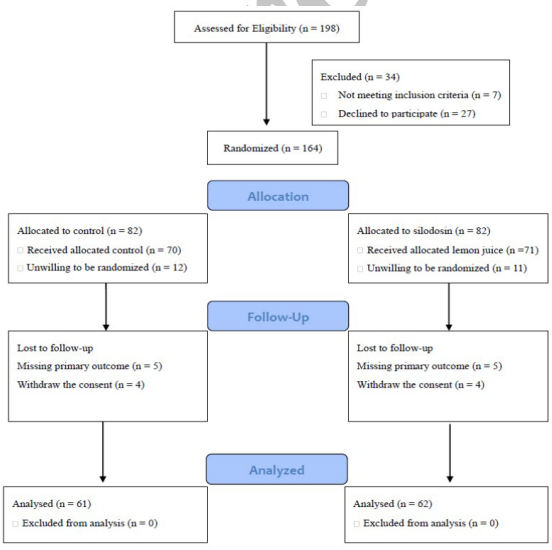

Figure. Study flowchart

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 Sys-

tems survey software; a sample size of 55 patients per group was needed. All analyses were conducted using Statistical Package for the Social Science (SPSS Inc, Chicago, Illinois, USA) 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

In all, 123 patients completed the study protocol: 61 patients in the control group and 62 patients in the silodosin group. No significant statistical difference was observed in patients' ages, gender distribution, or laterality. The Mann-Whitney *U*-test did not reveal any significant statistical difference in the average stone size among the groups ($P = .860$) (**Table 1**).

A significant statistical difference in the stone expulsion rate was noted between the two groups ($P = .006$). The average time to expulsion was significantly different ($P < .001$). No significant differences were observed in the mean sublingual buprenorphine dosages or the number of colic episodes between male and female patients or between the right and left sides. The mean ketorolac consumption was significantly difference ($P < .0001$).

No significant statistical difference was observed in the incidence of lower urinary tract symptoms between the two groups ($P = .417$). No patients were hospitalized for recurrent colic, and no urosepsis was recorded. Only two patients in the control group experienced adverse effects associated with the medical expulsive therapy, whereas 10 patients in the silodosin group reported adverse effects (transient hypotension, asthenia, syncope, and palpitations), and a significant statistical difference in the incidence rate of complications was noted between the groups ($P = .016$) (**Table 2**). No patients discontinued medical therapy, and the adverse effects disappeared. Patients (28 in the control group and 14 in the silodosin group) who were not stone-free after the two-week follow-up were successfully treated with ureteroscopy[17] or SWL[9]. All ureteroscopic findings revealed moderate-to-severe inflammatory reactions of stone-impacted mucosa with edematous bullous changes.

DISCUSSION

During the last two decades, minimally invasive therapies, such as SWL and ureteroscopy, have been widely used for the treatment of ureteral stones. The efficacy of these treatments has been proven by several studies. Although such procedures are rather effective, they are predisposed to the risk of related complications or cause inconveniences and are quite expensive.[2,5,15]

In the European Association of Urology Guidelines on Urolithiasis, several trials have demonstrated the α-blocker class effect on stone expulsion rates.[19] Tamsulosin is one of the most commonly used α-blockers. However, one small study suggested that tamsulosin, terazosin, and doxazosin are equally effective, indicating a possible class effect.[20] This has also been indicated in several trials that demonstrated increased stone expulsion rates using doxazosin, terazosin, alfuzosin, naftopidil, and silodosin.

According to our study, the medical therapy based on silodosin demonstrated positive results in 77.42% patients, with a significant statistical difference in the control group (54.10%). These results confirm that medical therapy with α-1 blockers can improve stone expulsion, as reported previously.[20]

Moreover, α-1 blockers limit analgesic usage by decreasing the frequency of phasic peristaltic contractions in the obstructed ureteral tract, thus decreasing the frequency of ureteral colic.[8] Meanwhile, silodosin was effective for pain reduction and decreased the amount of analgesics administered in our study. In addition, no relationship between stone size and expulsion time was evident. Gender and stone size did not influence the stone expulsion rate. As previously reported, these data suggest that stone size is not the only factor that influences expulsion times; other factors stone shape and edema around the stone also influence expulsion times.[7] Patients who were not stone-free after the two-week follow-up were successfully treated with ureteroscopy. This demonstrates that neither watchful waiting nor medical therapy seems to have a negative effect on the success rates of stone removal. From our ureteroscopic manipulation of the failed cases, all ureteroscopic findings revealed moderate-to-severe inflammatory reactions of stone-impacted mucosa with edematous bullous changes. Therefore, medical therapy is not effective for impacted lower ureteral stones if they can be judged in advance. In other words, if the stone did not impact the ureter due to marked inflammatory changes of the surrounding tissue, perhaps medical therapy could be effective.

We encountered three cases of serious adverse effects of medical expulsive therapy (postural hypotension in the silodosin group) that did not require its discontinuation. Minor therapy-related side effects (dizziness, asthenia, postural hypotension) were observed in 10 pa-

tients (in the silodosin group), but those patients completed the study. These results are similar to those of benign prostatic hyperplasia patients treated with α-1 blockers. Regarding safety, α-1 blockers were well tolerated by the patients.

Lower urinary tract symptoms (frequency, residual sensation, difficulty, urine retention, and tenesmus) are other troublesome issues for distal ureteral stone patients. Although our study did not demonstrate how α-1 blockers can alleviate lower urinary tract symptoms effectively, and did not show a significant statistical difference, it implies that silodosin is an α-1A specific blocker and more potent α-1 blocker for the relaxation of the lower ureter than other α-1 blockers.

Our study had one important limitation; namely, a highly homogenous population was included. All included patients had their first episode of distal ureteral stone, which is unachievable for most researchers and hence, may limit the scope of this study.

CONCLUSIONS

The results of this study indicate that distal ureteral stones can be treated with expulsive medical therapy in patients when the watchful waiting approach is possible. In our study, medical treatments with silodosin proved to be safe and effective, as demonstrated by the low incidence of side effects, the increased stone expulsion rate, and the reduced expulsion times. Moreover, medical therapy, particularly in regard to the α-1A-1D specific blocker-silodosin seems to decrease the incidence of adverse effects.

ACKNOWLEDGEMENTS

We would like to thank Jui-Fang Huang, from the Department of Research and Education, St Martin De Porres Hospital, Chia-Yi, Taiwan, for his support with statistical methods. E-mail:h102_2@stm.org.tw

Contributions: Research idea and study design: CJW and PCT; data acquisition: CJW, PCT, CHC; data analysis/interpretation: CJW, PCT, and CHC; statistical analysis: CJW; and supervision or mentorship: CJW. Each author contributed important intellectual content during this manuscript's drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. CJW, PCT, and CHC take responsibility for ensuring that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study, as planned and registered, have been explained.

There are no financial or commercial interests that should be acknowledged. The work has not already been published and has not been submitted simultaneously to any other journal. The corresponding author takes on the above responsibilities.

CONFLICT OF INTEREST

None declared.

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