

Efficacy of tolterodine for medical treatment of intramural ureteral stone with vesical irritability

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Abstract We evaluated the clinical results of tolterodine in treating impacted stones in the intramural ureter with symptoms of vesical irritability. A total of 80 patients with intramural ureter stones were included in the study from December 2007 to November 2009. Patients were randomly divided into two groups. The 41 patients in group A were given a watchful waiting and served as control group. Group B received 2 mg tolterodine (twice a day). Both groups were followed up for 2 weeks. The stone expulsion rate and time and the number of pain episodes were obtained. Subjects rated the urgency associated with each micturition using the Urinary Sensation Scale (USS). Pain descriptions were recorded by the patients using the Visual Analog Scale (VAS). The stone expulsion rate in groups A and B was 56.1 and 56.4%, respectively ($P = 0.98$). The mean numbers of renal colic episodes of patients in groups A and B had experienced 4.5 and 1.7, respectively. The USS for groups A and B in 3 and 7 days were 2.89 ± 0.56 , 1.29 ± 0.60 ; 1.98 ± 0.79 , 1.09 ± 0.3 , respectively ($P < 0.001$). Statistically significant difference was found between groups A and B in relation to the VAS score on days 3 and 7, respectively ($P < 0.001$). While our study demonstrated no improvement in expulsion rate, Tolterodine reduced the common symptoms of frequency, urgency, intensity of the pain episodes and discomfort often associated with intramural ureter stone.

Keywords Intramural ureter · Stone · Tolterodine

Abbreviations

SWL	Shock wave lithotripsy
URS	Ureteroscopy
MET	Medical expulsive therapy
KUB	X-rays of the kidneys, ureters and bladder
IVU	Intravenous urogram
CT	Computer tomography
SD	Standard deviation
IQR	Interquartile range
USS	Urinary Sensation Scale
VAS	Visual Analog Scale
HRQL	Health-related quality of life
OAB	Overactive bladder

Introduction

The intramural ureter is the narrowest segment of ureter. If stones are impacted in it, the patient would complain of vesical irritability with pain, urinary urgency and frequency, which is similar to overactive bladder (OAB). Urinary urgency is the hallmark symptom of intramural ureter stone. Anticholinergic medications and alpha-blockers may be used to reduce symptoms of vesical irritability.

Tolterodine is the first muscarinic receptor antagonist that has been specifically developed for the treatment of OAB. There are little data on whether tolterodine can be associated with minimization of symptoms of frequency, urgency, and discomfort often associated with intramural ureter stone. In this study, we evaluate the clinical results of tolterodine in treating impacted stones in the intramural ureter with symptoms of vesical irritability.

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Materials and methods

A total of 80 patients with intramural ureter stones were included in the study from December 2007 to November 2009. Of the 80 patients, 54 were men and 26 were women. All the patients underwent evaluation including blood and urine analyses, urine culture and biochemical test. The stone sizes and characteristics were assessed with abdominal, ultrasonography and KUB. IVU or unenhanced CT scan is performed when necessary. Stone size was registered as the maximum diameter measured on a plain abdominal film.

After local ethical committee approval and informed consent from each subject, those patients with vesical irritability for intramural ureteral stone (<10 mm) were included in the study. The exclusion criteria were multiple stones, severe incarcerated stones, history of distal ureteral surgery, renal colic for more than 24 h, urinary tract infection, severe hydronephrosis, voiding dysfunction, hypotension, cardiovascular and cerebrovascular diseases, hepatic and renal dysfunction, pregnancy, diabetes and ulcer disease.

Eighty patients were randomly divided into two groups. The 41 patients in group A were given a watchful waiting and served as control group. They did not receive any expulsive medical therapy. Group B received 2 mg tolterodine (twice a day). All the patients in group A and B were instructed to drink a minimum of 2 L of water daily. Both groups were followed up for 2 weeks. Ultrasonography or KUB was performed on day 7 and 14. An indomethacin suppository was recommended for routine use during pain episodes, and patients were required to record the dose used.

The stone expulsion rate and time, the number of pain episodes and requirements for pain medication were obtained. Potential side effects of tolterodine were also documented during the treatment period. The criteria for treatment discontinuation were stone expulsion and treatment failure including hypersensitivity to tolterodine, uncontrollable pain (colic for more than 24 h), patient desire to remove the stone, and loss to follow-up or study withdrawal. At the end of the follow-up period, patients who failed to expel the stone were scheduled to undergo SWL or ureteroscopy.

Subjects rated the urgency associated with each micturition using the Urinary Sensation Scale (USS), a five-point scale with established content validity (1, no urgency; 2, mild urgency; 3, moderate urgency; 4, severe urgency; 5, UII) [4]. Pain descriptions were recorded by the patients using the Visual Analog Scale (VAS).

Discrete variables were presented as counts (or frequencies) and were evaluated by the Chi-square or Fisher exact test. Continuous variables with normal distribution

were presented as mean $\pm$ standard deviation (SD) and were compared by Student's *t* test, whereas skewed data were summarized as median and interquartile range (IQR) and analyzed with Mann–Whitney *U* test. STATA Version 8.0 was used for all the analyses. All statistical tests were based on 2-tailed probability. A *p* value of <0.05 was considered statistically significant. The sample size was enough to achieve a statistical power of 95% at 5% type I error.

Results

All the patients in both groups completed the study. No significant difference was found between the groups in age, sex and stone size or location ($P > 0.05$; Table 1). The stone expulsion rate in groups A and B was 56.1 and 56.4%, respectively ($P = 0.98$, Table 1). The mean numbers of renal colic episodes of patients in groups A and B had experienced 4.5 and 1.7, respectively (Fig. 1).

The USS for groups A and B in 3 and 7 days were 2.89 ± 0.56 , 1.29 ± 0.60 ; 1.98 ± 0.79 , 1.09 ± 0.3 , respectively ($P < 0.001$, Fig. 2, Table 2). Statistically significant difference was found between groups A and B in relation to the VAS score on days 3 and 7, respectively ($P < 0.001$, Fig. 2).

No significant side effect of tolterodine was encountered, except only 6 of the 43 treatment group patients experienced dry mouth, headache, constipation slight dizziness, and fatigue.

Table 1 Demographic information and results of two groups

	Group A	Group B	<i>P</i> Value
No.	41	39	
Mean age $\pm$ SD (years)	34.3 ± 6.7	35.5 ± 6.4	0.18
No. male/female	27/14	27/12	
Stone location			
Right	9	17	
Left	32	22	
Stone size (mm)			
Mean	6.5	6.8	0.75
Range	5–9	5–9	
No. expulsion (%)	23 (56.1)	22 (56.4)	0.98
Time to expulsion (days)			
Median	6	7	
IQR	4–8	3–8	0.53
Colic episodes (mean)	4.5	1.7	
No. side effects	0	6	

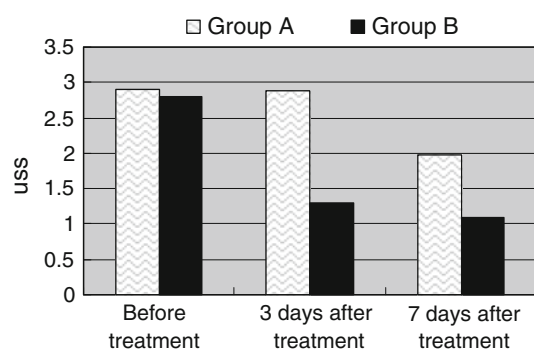


Fig. 1 USS comparison of patients with and without tolterodine

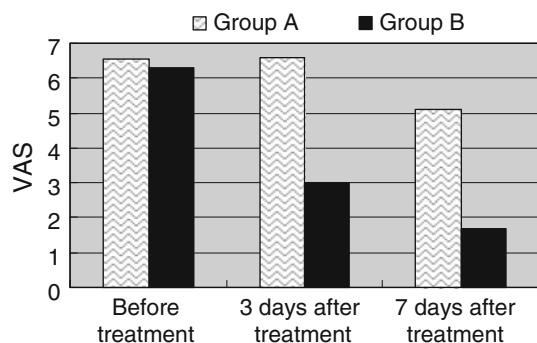


Fig. 2 VAS comparison of patients with and without tolterodine

Table 2 Results of two groups for the USS and VAS

	Group A	Group B	P Value
Urinary Sensation Scale			
Before treatment	2.90 ± 0.74	2.80 ± 0.75	
3 days after treatment	2.89 ± 0.56	1.29 ± 0.60	<0.001
7 days after treatment	1.98 ± 0.79	1.09 ± 0.3	<0.001
Visual Analog Scale			
Before treatment	6.56 ± 0.95	6.31 ± 1.17	
3 days after treatment	6.59 ± 0.89	3.02 ± 0.82	<0.001
7 days after treatment	5.10 ± 1.18	1.7 ± 0.75	<0.001

Discussion

Urolithiasis is one of the most common urologic diseases. Among all urinary tract stones, 20% are ureteral stones, of which 70% are found in the lower third of the ureter [1]. The effectual factors for the spontaneous expulsion of ureteral stones are stone location, size, number, and structure; spasm in the ureteral smooth muscles; mucosal edema or inflammation and the ureteral anatomy [2, 3]. The most important blockage of spontaneous expulsion is at the terminal ureter, especially the part of the intramural ureter.

The spontaneous expulsion rate of ureteral stones <5 mm is almost 85%. The rate of spontaneous passage diminish as stone size increases [5]. Stones of 5–10 mm pass spontaneously from the proximal ureter in 10–53% and from the distal ureter in 25–53% of the patients. Consequently, observation treatment is recommended for distal ureter stones of 5–10 mm, including the part of the intramural ureter. However, some problems can also develop in the observation treatment, such as emerge renal colic and symptoms of vesical irritability for intramural ureteral stone. To prevent such symptoms and accelerate spontaneous expulsion, various medical expulsive therapies (MET) have been used in previous years, such as anticholinergic agent, nonsteroidal anti-inflammatories, hormones, corticosteroids, calcium channel blockers and α 1-adrenergic receptor antagonists [6–9].

There are little data on whether anticholinergic agent can accelerate spontaneous passage of the stones and minimize symptoms of frequency, urgency, and discomfort associated with intramural ureter stone. Urgency is the hallmark symptom of intramural ureter stone. Although there are many scales to measure urgency, none has been adopted as the standard measure. We categorized micturitions according to urgency level based on the 5-point USS, which has since been used in several other studies [4].

Tolterodine is the first muscarinic receptor antagonist that has been specifically developed for the treatment of OAB, it is non-selective with respect to the muscarinic M1–M5 receptor subtypes, but has a greater effect on the bladder than on salivary glands in vivo, in both animals and humans [10]. It can effectively reduce urgency, micturition frequency, urgency urinary incontinence (UI) and improves decreased health-related quality of life (HRQL) [10, 11] in patients with overactive bladder.

Erturhan [12] evaluated the activity of the therapeutic agents (tamsulosin and/or tolterodine) used to accelerate the expulsion of stones and to reduce the probable complications during observation of the medical treatment of distal ureteral stones to allow spontaneous passage. The stone expulsion rate in tolterodine groups was 46.6%, in his study, the use of tamsulosin for the expulsion of distal ureteral stones was effective; however, the use of tolterodine provided no additional advantages.

Because the tolterodine can reduce symptoms of frequency and urgency, we used it to treat intramural ureteral stone. Our data demonstrated that the use of tolterodine was not effectual in increasing the expulsion rate or reducing the expulsion time. However, the USS, the pain episodes and VAS scores of the patients were evaluated for the Urgency and bladder pain, the use of tolterodine contributed significantly. There was statistical difference between post treatment and pre -treatment in group B for USS and the VAS score, respectively.

Conclusions

While our study demonstrated no improvement in expulsion rate, Tolterodine can reduce the symptoms of frequency, urgency, intensity of the pain episodes and discomfort often associated with intramural ureter stone.

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