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ORIGINAL PAPER

Naftopidil and tolterodine in the medical expulsive therapy for intramural ureteral stones: a prospective randomized study

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Abstract We performed a randomized, prospective study to assess the possible role of combined naftopidil and tolterodine for facilitating the spontaneous expulsion of intramural ureteral stones. A total of 76 patients with intramural ureter stones were included in the study from December 2007 to February 2011. Patients were randomized to one of three treatment groups. Group A patients received naftopidil 25 mg/day, group B patients received naftopidil 25 mg/day plus tolterodine 2 mg (twice a day), and group C patients received tolterodine 2 mg (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). A significant difference was shown for the expulsion rate between the group C and the other two groups ($P < 0.001$ by log rank test). In groups A, B and C, the mean number of pain episodes was 2.25 ± 0.90, 1.38 ± 1.37 and 1.54 ± 1.18, respectively. The USS score for groups A, B and C at 3 days was 2.32 ± 0.55, 1.4 ± 0.58 and 1.34 ± 0.49, respectively. It was 1.75 ± 0.44, 1.2 ± 0.41 and 1.22 ± 0.42, respectively, at 7 days. On the other hand, a statistically significant difference was found between groups A and B, and groups A and C in relation to the visual analog scale score on days 3 and 7, respectively. Treatment with naftopidil and tolterodine appears to be beneficial in intramural ureteral stones clearance, particularly in the intramural ureter with symptoms of vesical irritability.

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Introduction

The intramural ureter is the narrowest segment of the ureter. The most important blockage of the spontaneous expulsion rate of the distal ureter stones of 5–10 mm is at this part [1]. Medical expulsive therapy for intramural ureter stones has gained increasing attention in the last few years. Numerous clinical trials have been performed to investigate the efficacy of the $\alpha 1_{A/D}$ selective a-blocker tamsulosin [2–10]. Most of these studies were randomized and revealed that tamsulosin treatment significantly improved the expulsion rate of distal ureteral stones. Currently, tamsulosin represents a noninvasive and cost-effective alternative to interventional approaches.

However, $\alpha 1_D$ receptors are found prevalently in the distal ureter [8]. $\alpha 1_D$ receptor may be a promising target for medical expulsive therapy. Compared with tamsulosin, naftopidil had a greater selectivity for $\alpha 1_D$ subtype, with approximately 3- and 17-fold higher potency for $\alpha 1_D$ than for $\alpha 1_A$ and $\alpha 1_B$, respectively [11]. Naftopidil could also be used as a medical expulsive agent with higher efficacy and lower side effects for distal ureteral stones than tamsulosin. On the other hand, if stones are impacted in the intramural ureter, the patient often complains of vesical irritability with pain, urinary urgency and frequency, similar to overactive bladder (OAB). Urinary urgency is the hallmark symptom of intramural ureter stone. Anticholinergic medications and alpha blockers, such as tolterodine (the first muscarinic receptor antagonist that has been specifically developed for the treatment of OAB), may be used to reduce symptoms of vesical irritability.

For these reasons, we performed a randomized, prospective study to assess the possible role of combined naftopidil and tolterodine for facilitating the spontaneous expulsion of intramural ureteral stones.

Materials and methods

A total of 76 patients with intramural ureter stones were included in the study from December 2007 to February 2011. Of the 76 patients, 39 were men and 37 were women. All the patients underwent evaluation including blood and urine analyses, urine culture and biochemical test. The distal ureteral stones were initially diagnosed by abdominal ultrasound and plain abdominal X-ray for kidney, ureter and bladder (KUB). IVU (intravenous urogram) 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 ($\leq$9 mm $>$4 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. Also, subjects with a history of hypersensitivity to naftopidil and subjects receiving treatment with cardiovascular drugs, α receptor antagonists or calcium antagonists were excluded from the study. Also, individuals who withdrew from the study or were lost to follow-up were excluded from this study.

Patients were randomized to one of three treatment groups. Treatment group A patients received naftopidil 25 mg/day, group B patients received naftopidil 25 mg/day plus tolterodine 2 mg (twice a day), and group C patients received tolterodine 2 mg (twice a day). All patients were instructed to drink at least 2 L of fluids daily. An indomethacin suppository was recommended for routine use during pain episodes and patients were required to record the dose used.

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 = UUI) [26]. Pain descriptions were recorded by the patients using the visual analog scale (VAS).

The patients were advised to filter their urine, and those who had passed their stones were asked to stop taking the medication. All patients were followed up for 2 weeks. Ultrasonography and KUB were performed on days 7 and 14. The stone expulsion rate and time, the number of pain episodes and requirements for pain medication were recorded. The potential side effects of naftopidil and tolterodine were also documented during the treatment period. At the end of the follow-up period, patients who failed to expel the stone were scheduled to undergo ESWL or ureteroscopy.

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. Kaplan–Meier curves were plotted to describe time to stone expulsion in patients in each group, and the differences between the curves were assessed using log rank analysis. The Cox proportional hazards regression model was applied to estimate the effects of different variables on stone expulsion, including age, sex, stone size and therapy. STATA Version 8.0 was used for all the analyses. All statistical tests were based on two-tailed probability. A P value of <0.05 was considered to be statistically significant. The sample size was enough to achieve a statistical power of 95 % at 5 % type I error.

Results

All patients completed the study. No statistically significant differences were observed with regard to patient age, gender distribution or the stone side (right or left). Average stone size for groups A, B and C were 6.96 $\pm$ 1.31, 7.08 $\pm$ 1.44 and 7.36 $\pm$ 1.26 mm, respectively. ANOVA did not reveal any statistically significant difference in size among the groups ($P = 0.671$) (Table 1).

Thirty-eight patients found their stones to have passed, and 17 patients were considered to be stone free by KUB and abdominal ultrasound test after 2 weeks. Stone expulsion was observed in 22 patients in group A (22 of 28, 78.6 %), 21 patients in group B (21 of 25, 84.0 %) and 12 patients in group C (12 of 23, 52.2 %). A statistically significant difference was noted with Chi-square testing between groups A and C, and groups B and C ($P = 0.000$ and $P = 0.000$, respectively). Average time to expulsion for groups A, B and C was 7.63 $\pm$ 2.28, 7.90 $\pm$ 2.31 and 10.71 $\pm$ 2.72 days, respectively ($P = 0.000$) (Fig. 2). Kaplan–Meier curves were plotted to access the expulsion rate of each group over time (Fig. 1). A significant difference was shown for the expulsion rate between the tolterodine group and the other two groups. ($P < 0.001$ by log rank test). In groups A, B and C, the mean number of pain episodes was 2.25 $\pm$ 0.90, 1.38 $\pm$ 1.37and 1.54 $\pm$ 1.18, respectively ($P = 0.023$) Fig. 3.

The side effects encountered in the study groups were generally mild and did not require cessation of therapy in any patient (Table 2). The USS score for groups A, B and

Table 1 Demographic information and results of the two groups

Parameter	Group A	Group B	Group C	*P* value
No.	28	25	23	
Mean age ± SD (years)	32.19 ± 6.42,	33.67 ± 6.47	34.32 ± 6.36	0.485
No. of male/female	15/13	13/12	11/12	0.918
Mean stone size ± SD (mm)	6.96 ± 1.31	7.08 ± 1.44	7.36 ± 1.26	0.671
Ureteral stone side (L/R)	12/16	14/11	13/10	0.534
Expulsion rate (%)	78.6 (22 of 28)	84.0 (21 of 25)	52.2 (12 of 23)	0.031

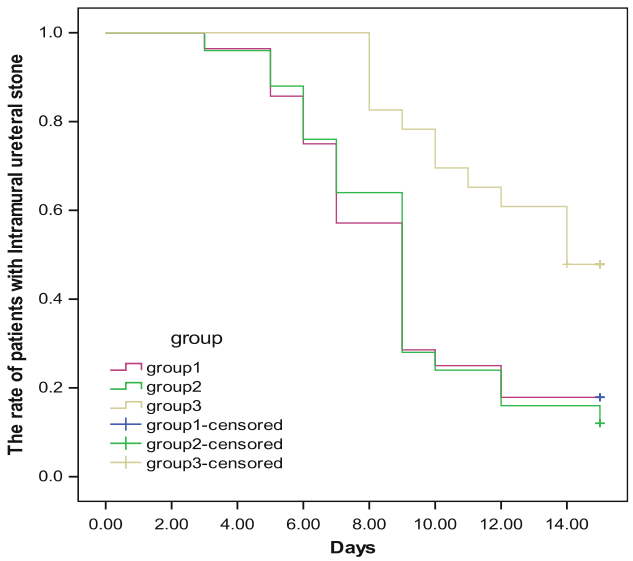

Fig. 1 Kaplan–Meier curves for the expulsion rate of each group over time (the difference between the curves was significant, $P < 0.001$ by log rank test)

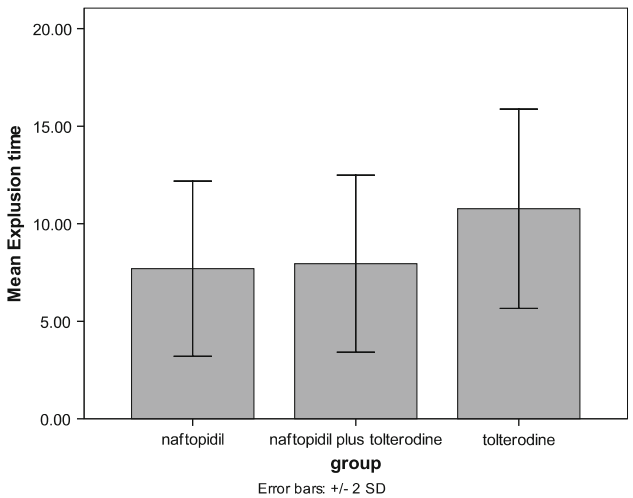

Fig. 2 Mean expulsion time (d) comparison of three groups (group A: 95 % CI (7.728–10.272), group B: 95 % CI (7.762–10.398), group C: 95 % CI (11.499–13.806))

C at 3 day was 2.32 ± 0.55, 1.4 ± 0.58 and 1.34 ± 0.49, respectively. It was 1.75 ± 0.44, 1.2 ± 0.41, and 1.22 ± 0.42, respectively, at 7 days (Fig. 4; Table 3). On the other hand, a statistically significant difference was found between groups A and B, and groups A and C in relation to the visual analog scale score on days 3 and 7, respectively. ($P = 0.000$ and $P = 0.000$, respectively, Fig. 5; Table 3).

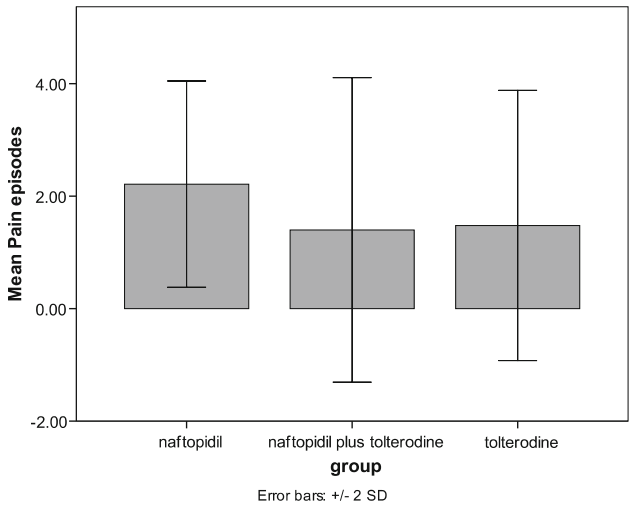

Fig. 3 Mean pain episode comparison of the three groups

Table 2 Side effects

Side effect	Group A	Group B	Group C
Dizziness	3	5	6
Headache	3	4	0
Fatigue	1	2	1
Postural hypotension	0	0	0
Rhinitis	1	0	2
Dry mouth	4	7	12
Constipation	0	3	4

Any patient who was not stone free after 2 weeks of follow-up was first treated with ESWL. If shock wave lithotripsy treatment failed, ureteroscopy was performed. Twenty-one patients (6 in group A, 4 in group B and 11 in group C) had ESWL performed (Xixin Compact lithotripter, electromagnetic lithotripter, China). Four patients in whom primary ESWL failed underwent repeat ESWL for two times and subsequently became stone free. Three patients in whom repeat ESWL treatment failed required

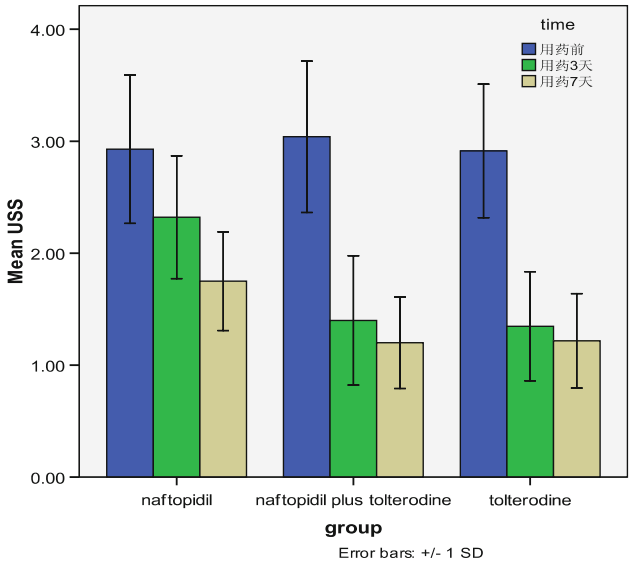

Fig. 4 USS comparison of the three groups

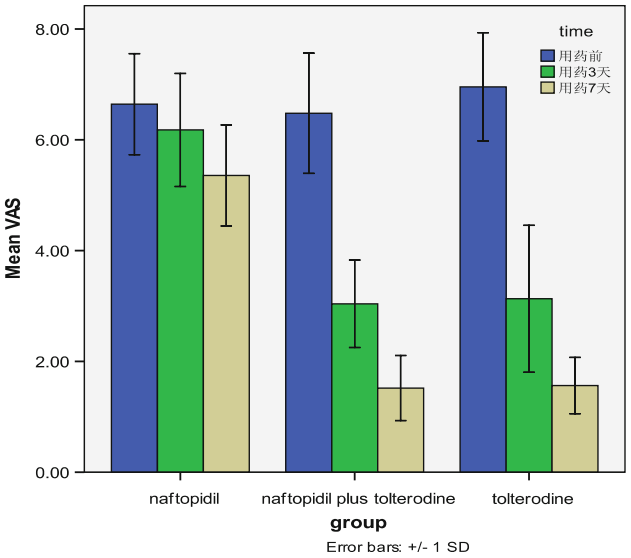

Fig. 5 VAS comparison of the three groups

secondary treatment with ureteroscopy (Wolf, Knittlingen, Germany) and subsequently became stone free. Ureteroscopic findings revealed a moderate to severe stone-induced mucosal inflammatory reaction with polypoid change.

Discussion

Ureteral stones occupy an important place in daily urological practice, and clinicians are frequently asked to choose adequate treatment. A watchful waiting approach can be used in a large number of cases, as demonstrated by several studies that revealed spontaneous passage rates of up to 85 % for distal ureteral stones less than 5 mm [12–14]. However, watchful waiting does not always result in stone clearance and may be associated with recurrent renal colic [15]. Use of the watchful waiting approach has been extended by using pharmacological therapy, which can reduce symptoms and facilitate stone expulsion [16, 17].

A cost-effective strategy, medical expulsive therapy (MET), has been developed over the past few years for small distal ureteral stones, especially in the juxtavesical or intramural tract [1]. The α1-adrenergic receptor antagonists have been used to accelerate the expulsion of stones and to reduce probable complications. The α_1 receptors have been classified into three subtypes ($\alpha1_A$, $\alpha1_B$ and $\alpha1_D$). The $\alpha1_A$ receptors predominate in the proximal urethra, prostate and bladder outflow, and $\alpha1_B$ receptors are distributed widely in the vascular smooth muscles, while $\alpha1_D$ receptors are found prevalently in the distal ureter where it passes through the detrusor muscle. The distribution of these receptors in the distal ureter was $\alpha1_D > \alpha1_A > \alpha1_B$ [18]. So, $\alpha1_D$ receptor may be a promising target for medical expulsive therapy. Some research revealed that naftopidil had approximately threefold stronger affinity for $\alpha1_D$ receptor than for $\alpha1_A$ [19]. Sun et al. had evaluated that a total of 60 patients with distal ureteral stones were randomly divided into groups A and B. Group A acted as the control group and was provided watchful waiting, while group B received 50 mg of naftopidil daily in the morning.

Table 3 Results of the three groups for the USS and VAS

	Group A	Group B	Group C	*P* value
Urinary sensation scale				
Before treatment	2.57 ± 0.50	3.0 ± 0.58	2.91 ± 0.60	0.754
3 days after treatment	2.32 ± 0.55	1.4 ± 0.58	1.34 ± 0.49	0.000
7 days after treatment	1.75 ± 0.44	1.2 ± 0.41	1.22 ± 0.42	0.000
Visual analog scale				
Before treatment	6.67 ± 0.91	6.48 ± 1.08	6.96 ± 0.98	0.247
3 days after treatmen	6.15 ± 1.03	3.04 ± 0.79	3.13 ± 1.32	0.000
7 days after treatment	5.33 ± 0.92	1.52 ± 0.58	1.56 ± 0.51	0.000

The stone expulsion rate was observed to be significantly higher in group B (90.0 %) compared with that in group A (26.7 %) [19]. Zhou et al. [1] observed a 72.1 % stone expulsion rate in patients who received $\alpha 1_D$ receptor antagonist naftopidil, which was significantly higher than that of the watchful waiting group (30.2 %).The stone expulsion rate of naftopidil was similar for tamsulosin(70–85 %) [8–21].

On the other hand, the intramural ureter is the narrowest segment of the ureter. If stones are impacted in it, the patient would complain of vesical irritability with pain, urinary urgency and frequency, is similar to overactive bladder (OAB) [22]. Tolterodine is the muscarinic receptor antagonist that has been specifically developed for the treatment of overactive bladder (OAB); however, there are little data on whether anticholinergic agent can accelerate spontaneous passage of the intramural ureter stones and minimize symptoms of frequency, urgency and discomfort associated with contractions of smooth muscles of the intramural part of the ureter or detrusor muscle. Tolterodine can reduce these muscle contractions by acting on M_1–M_5 subtypes of muscarinic receptors, whereas modern antimuscarinic treatments for overactive bladder only act on M_2 and M_3 receptors making them more selective [23]. Tolterodine can effectively reduce urgency, micturition frequency and urgency urinary incontinence (UUI) and improve decreased health-related quality of life (HRQL) in patients with overactive bladder [23, 24].

Erturhan evaluate 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 [25]. Lu et al. used tolterodine to treat intramural ureteral stone in the previous years. While their study demonstrated no improvement in the expulsion rate, it could reduce the common symptoms of frequency, urgency, intensity of the pain episodes and discomfort often associated with intramural ureter stone [23].

In this study we use naftopidil plus tolterodine to treat impacted stones in the intramural ureter with symptoms of vesical irritability. Our data demonstrated that the use of only tolterodine was not effectual in increasing the expulsion rate or reducing the expulsion time, but there was statistical difference between post-treatment and pre-treatment in this group in the Urinary Sensation Scale and the visual analog scale score, respectively. On the contrary, the use of only naftopidil could increase the expulsion rate and decrease average expulsion time, but there was no statistical difference between post-treatment and pre-treatment in this group in Urinary Sensation Scale and the visual analog scale score, respectively. However, the Naftopidil plus tolterodine group have a similar expulsion rate or the expulsion time with the use of only naftopidil group and a similar Urinary Sensation Scale and the visual analog scale score with the use of only tolterodine group. We think intramural ureter smooth muscle or bladder detrusor muscle contractions are an important effect factor for intramural ureter stone expulsion. Naftopidil plus tolterodine could not only reduce muscle contractions, but also decrease peristalsis below the ureter and induce an increase in the intraureteral pressure gradient around the stone. The effect result will induce a strong urge to expel the stone and reduce the vesical irritability symptoms.

Conclusions

Treatment with naftopidil and tolterodine appears to be beneficial in intramural ureteral stone clearance, particularly in intramural ureter stone with symptoms of vesical irritability.

Conflict of interest There is no conflict of interest.

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