

ORIGINAL ARTICLES

THE COMPARISON AND EFFICACY OF NIFEDIPINE AND TAMSULOSIN FOR THE MANAGEMENT OF LOWER URETERIC STONES

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Abstract

Purpose: To evaluate and compare the effectiveness of 2 different medical therapies during watchful waiting in patients with lower ureteric stones.

Materials and Methods: A total of 98 patients with stones less than 1 cm located in the lower ureter (juxtavesical or intramural tract) were enrolled in the study and were randomly divided into 3 groups. Group 1 (33) patients received 1 daily oral therapy of 0.4 mg tamsulosin (maximum 28 days), group 2 (33) received 20 mg nifedipine slow-release (maximum 28 days) and group 3 patients (32) were used as controls. Statistical analyses were performed using Student's test, ANOVA test and chi-square test.

Results: Of the 98 enrolled patients 91 completed the study. The average stone size for groups 1 to 3 was 5.89, 6.01 and 5.80 mm, respectively, which was not statistically significant. Expulsion was observed in 27 of 32 patients in group 1 (84.38%), 22 of 31 in group 2 (70.97%) and 13 of 28 in group 3 (46.43%). The difference in groups 1 and 2 with respect to group 3 and between groups 1 and 2 was significant. Average expulsion time for groups 1 to 3 was 7.9, 9.3 and 12.8 days, respectively. A statistically significant difference was noted between groups 1 and 3. Mean diclofenac sodium dosage per patient in groups 1 to 3 was 17.5, 24.5, and 100.5 mg, respectively. A statistical significant difference was observed between groups 1 and 2 with respect to group 3.

Conclusions: Medical treatments with nifedipine and tamsulosin proved to be safe and effective as demonstrated by the increased stone expulsion rate and reduced need for analgesic therapy. Moreover medical therapy, particularly in regard to tamsulosin, increased expulsion rate reduced expulsion time.

Key Words: Ureter, urinary calculi, nifedipine, tamsulosin.

Introduction

Urinary stone disease is a common condition affecting up to 12% of the world population. Among all ureteral stones, 70% are found in the lower third of the ureter.¹⁻³ Ureteral stones occupy an important place in daily

urological practice, and clinicians are frequently asked to choose adequate treatment.⁴ The efficacy of mini-invasive therapies, such as extracorporeal shock wave lithotripsy and ureteroscopy has been proven by several studies.^{5,6} Nevertheless these techniques are not risk-free, are problematic and are quite expensive.⁷ On the other hand, 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 98% for small distal ureteral stones.⁸⁻¹⁰ Moreover, even the simple watchful waiting approach can result in complications, such as infection of the urinary tract, hydronephrosis and renal function effects.⁹ Therefore, it is difficult to choose between mini-invasive therapies and a watchful-waiting approach, especially when patients report few symptoms and/or stones are small. Recently, use of the watchful waiting approach has been extended by using pharmacological therapy, which can reduce symptoms and facilitate stone expulsion.¹¹⁻¹⁴ Several factors thought to influence the spontaneous passage of ureteral stones, such as stone size, configuration and location, smooth muscle spasm, submucosal edema, and anatomy.^{10,15} To achieve the spontaneous passage, α -adrenergic blockers, calcium channel blockers, prostaglandin synthesis inhibitors, glyceryl trinitrate and steroid treatment to relieve edema are being used.^{12,16} The density of α -1-adrenergic receptors in ureteral smooth muscle cells is significantly higher than another adrenergic receptors. Furthermore, α -1-adrenergic antagonists have proved to inhibit basal tone, peristaltic frequency and ureteral contractions even in the intramural tract. Therefore, we decided to perform a comparative study to evaluate the safety and effectiveness nifedipine and tamsulosin therapies for the treatment of lower ureteral stones.

Material and Methods

A total of 98 patients with distal ureteral stones (juxtavesical tract and ureterovesical junction), 1 cm or less in size were included in the study. Study was conducted from July 2007 to December 2008. Of the 90 patients, 51 were men and 39 were women. The patient age range was 15 to 57 years (mean 34.5). The patients who had urinary tract infection, severe hydronephrosis, a solitary kidney, an extra stone in the upper urinary

system, undergone previous surgery for a urinary system stone, a nonopaque stone, or diseases such as diabetes or hypertension; who were pregnant; and those whose renal reserve was reduced by more than 50% were excluded from the study. Stone presence and characteristics were diagnosed with abdominal ultrasonography, x-ray of the kidneys, ureters and bladder and excretory urography were used when necessary. Complete blood cell count, serum creatinine, urinalysis done in every case.

A total of 98 patients were randomly divided into group 1 (33 patients), group 2 (33) and group 3 (32). After randomization to one of 3 groups, the patients received treatment. Group 1 patients received tamsulosin 0.4 mg/day, group 2 patients received nifedipine 20 mg/day (slow release preparation), and group 3 patients did not receive any medical treatment for expulsion (control group). In addition, all patients were treated with prophylactic antibiotic therapy (Ciprofloxacin 500 mg, twice a day) and received 2500 mL hydration daily. The groups received medical treatment for a maximum of 4 weeks. The patients were called for weekly checkups and were followed up weekly with renal ultrasonography, X-ray KUB, urinalysis, and serum creatinine measurements. Diclofenac sodium was recommended for routine use during pain episodes, and patients were requested to record the dose used. During the study, the patients who had attacks of uncontrollable renal colic, whose urosepsis developed, or whose serum creatinine level exceeded 2 mg/dL were excluded from the study. Patients in whom spontaneous passage did not occur by the end of the study underwent ureteroscopy and intracorporeal pneumatic lithotripsy. Statistical analyses were performed with Student's *t* test and chi-square test using the parameters of stone size, expulsion rate and time to expulsion.

Results

Of the 98 enrolled patients 91 completed the study. One patient in group 2 (1.02%) had to cease medical therapy due to side effects. One patient in group 1 (1.02%), and one patient in group 2 (1.02%) four patient in group 3

(4.08%) lost from follow-up therefore, dropped out of this study. Finally group 1 consisted of 20 men and 12 women (mean age 46.6 years), group 2 consisted of 21 men and 10 women (47.4 years) and group 3 consisted of 17 men and 11 women (42.8 years). No significant statistical difference was observed in patient age and gender distribution ($p = 0.3$).

Mean stone size was 5.89 mm (3 to 10) for group 1, 6.01mm (3.5 to 10) for group 2 and 5.80 mm (3.3 to 10) for group 3. ANOVA test and Student's *t* test did not reveal any significant statistical difference among the groups ($p = 0.2$).

Stone expulsion was observed in 27 patients in group 1 (84.38%), 22 in group 2 (70.97%) and 13 in group 3 (46.43%). Group 1 showed a significantly higher stone expulsion rate compared with groups 2 and 3 ($p < 0.05$). Compared with group 3 the higher expulsion rate reported in group 2 was statistically significant ($p < 0.05$).

Average time to expulsion was 7.9 days (1 to 14) in group 1, 9.3 days (3 to 21) in group 2 and 12.8 days (4 to 28) in group 3. A significant statistical difference was observed in times to expulsion between groups 1 and 3 ($p < 0.05$) whereas no significant statistical difference was noted between groups 1 and 2 ($p = 0.2$) and between groups 2 and 3 ($p = 0.09$).

Mean diclofenac sodium dosage was 17.5 mg (0 to 150) per patient in group 1, 24.5 mg (0 to 150) in group 2 and 100.5 mg (0 to 400) in group 3. No significant statistical difference was observed between groups 1 and 2 ($p = 0.03$) while it was noted between groups 1 and 3 and groups 2 and 3 ($p < 0.05$). No patient was hospitalized for recurrent colic, no urosepsis was recorded and no narcotics drugs were administered.

Only 1 group 2 patient experienced serious side effects associated with the medical expulsive therapy (hypotension and palpitations). Patients (5 in group 1, 9 in group 2 and 15 in group 3) who were not stone-free after the 4 weeks of follow up were successfully treated with ureteroscopy and intracorporeal pneumatic lithotripsy.

Table-I
Demographic data of the 3 groups

	Group 1	Group 2	Group 3
Number of patients	32	31	28
Mean age (years)	46.6	47.4	42.8
Sex M/F	20/12	21/10	17/11
Stone size (mm)	5.89 (3 to 10)	6.01 (3.5 to 10)	5.80 (3.3 to 10)
Expulsion rate	84.38% (27)	70.97% (22)	46.43% (13)
Time of expulsion (days)	7.9 (1 to 14)	9.3 (3 to 21)	12.8 (4 to 28)
Mean diclofenac sodium (mg per patient)	17.5 (0 to 150)	24.5 (0 to 150)	100.5 (0 to 400)

Discussion

There are some options for the treatment of distal ureteric stone. ESWL is a noninvasive procedure but it implies relatively high costs and a relevant percent of re-treatments. URS is an invasive procedure that provides the highest success rate and, according to some groups, it represents first choice therapy.^{7,17} However, the choice of treatment for a distal ureteric stone often depends on clinical, socioeconomic, ethical and even business conditions.¹⁸ Furthermore, some conservative pharmacological approaches have been proposed in recent years. Some groups have focused their studies only on the control of analgesic symptoms, whereas others have suggested the use of drugs that can modify ureteric motility. These agents have been used to decrease obstruction induced, phasic peristaltic contractions and maintain tonic contractions, which would allow distal migration of the stone. In addition, some groups also combine antiedemic use to prevent ureteric edema under the stone and/or antibiotic treatment to prevent infection consequent to urinary stasis from causing alterations in ureteric motility.^{11,12,19}

In our randomized trial we compared the clinical efficacy of 2 drugs that can act on ureteric smooth muscle with each other and with control group. Each was associated with the same treatment regimen with antibiotic and analgesics. Nifedipine, is a calcium antagonist. Its use in distal ureterolithiasis has been tested in various studies, which have demonstrated its excellent efficacy for inducing stone expulsion and relieving pain.^{11,12} In this study tamsulosin, a selective α 1A adrenergic antagonist, which we recently used to treat this disease, achieving unexpected and startling results. The rationale for its use for this pathological condition was taken from several studies, as previously described.^{16,20,21}

In our study spontaneous stone expulsion rate is 46.43%. Based on literature data the distal ureteral stone expulsion rate produced by a watchful waiting approach is 25% to 54% with a mean expulsion time of greater than 10 days and considerable analgesic use even for stones less than 4 mm.^{5,6} Ueno et al reported a spontaneous stone expulsion rate of 57% for 5 mm stone.⁹ Francesco et al reported a spontaneous stone expulsion rate of 43% for stone 10 mm or less.²² However, Morse and Resnick reported that a 6 mm stone in the distal ureter was spontaneously expelled in 35% of cases at the expense of recurrent ureteral colic.²³ With regard to the primary end point of our trial all 2 drugs compared in our study proved to be superior to the watchful waiting approach. In addition, the results of

our trial confirm the excellent efficacy of tamsulosin in favoring the rapid expulsion of ureteric stones, clinically supporting the validity of the hypothesis of the role of α -adrenergic receptors in the physiology of ureteric motility and the pathophysiology of renal colic.^{20,21}

The group treated with nifedipine achieved better results than control group thus, confirming the efficacy of this molecule. In particular our trial shows that nifedipine therapy resulted in a decreased need for analgesics and endoscopic procedures compared with control group. Borghi et al demonstrated the beneficial effect of calcium antagonist (nifedipine) in reducing time to stone passage and improving expulsion rates.¹¹ In an experience with nifedipine, this expulsive therapy was safe and effective as demonstrated by the increased expulsion rate, decreased expulsion time and reduced need for analgesic therapy with respect to our control group.¹² Bajor showed that α -blocker reduced the time for stone passage from 11 to 5.2 days in 86 patients with lower ureteric stones without encountering any serious side effects.²⁴

On the basis of the evidence that α -1 receptors have an important role in expulsion of lower ureteral physiology, some authors have more recently proposed the use of α -1 blockers with the aim of facilitating lower ureteral stone expulsion.^{13,14,25,26} In particular Ukhal et al reported positive results in accelerating lower tract ureter stone passage (juxtavesical tract and ureterovesical junction) using α -1 blockers.¹⁴ Cervenakov et al in a randomized study registered a significant statistical difference in stone expulsion rate between the group treated with tamsulosin and the control group.¹³ Similar results have been reported in a recent study.¹⁶

To our knowledge, few studies exist that investigate different expulsive medical therapies, which lead us to our current comparative study of the safety and effectiveness of nifedipine versus tamsulosin for the treatment of lower ureteral stones. We used nifedipine based on our historical positive results and tamsulosin was used based on the literature and α -1 receptors selectivity.¹¹⁻¹⁴ Our study was limited to patients affected by lower ureteral stones (juxtavesical tract and ureterovesical junction) with size equal to or less than 10 mm. The success of these particular medical therapies for this kind of stone was encouraging, and we were further motivated by the positive results with tamsulosin due to the higher density of α -1 receptor in the lower part of the ureter.^{25,26} We decided on a

maximum observation period of 4 weeks because longer periods can increase complication rates by up to 20%.⁸

The medical therapy based on a nifedipine (group 2) demonstrated positive results in 70.97% of patients, whereas tamsulosin (group 1) demonstrated positive results in 84.38% of patients. These figures demonstrate a significant difference. However, differences were also evident in stone expulsion between groups 1 and 3 (84.38% versus 46.43%) and between groups 2 and 3 (70.97% versus 46.43%). These results confirmed that medical therapy with either nifedipine or tamsulosin can improve stone expulsion. As far as expulsion time was concerned, we observed spontaneous stone passage after 7.9 days in group 1, 9.3 days in group 2 and 12.8 days in group 3. A significant statistical difference was noted between groups 1 and 3. The results demonstrate that use of tamsulosin reduced expulsion times significantly in respect to the control group (3) and confirm the positive results obtained in reducing stone passage times by others.^{8, 13, 14} Adding also the fact that the percentage of expulsion rate were greater in group 1, in comparison to group 2, we hypothesize that tamsulosin is more effective for the treatment of this type of ureteric stone than nifedipine. Further evaluation using larger groups will provide an opportunity to confirm these findings.

Moreover, nifedipine and tamsulosin was effective in pain reduction and decreased the amount of analgesic administered as demonstrated by information gathered from groups 1 and 2 with respect to quantities administered to patients in group 3. We encountered one case of serious side effects of medical expulsive therapy (hypotension accompanied by palpitations), which required its suspension. Minor therapy related side effects were observed in patients (2 in group 1, 3 in group 2) but they were able to complete the study. Six patient lost from follow-up (one from group 1, 1 from group 2 and four from group 3). With regard to safety, both combinations were well tolerated by the patients. Patients who were not stone-free after the 4-weeks of follow-up were successfully treated with ureteroscopy and intracorporeal pneumatic lithotripsy. These data demonstrate that neither watchful waiting nor medical therapy seems to negatively affect the success rate of stone removal.

Conclusions

The results of this study indicate that lower tract ureteral stones can be treated with an expulsive medical therapy in patients when a watchful waiting approach is possible.

In our study medical treatments with nifedipine and tamsulosin proved to be safe and effective as demonstrated by the low incidence of side effects and the increased stone expulsion rate. Moreover, medical therapy, particularly tamsulosin, seems better regarding stone expulsion rate and time.

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