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ORIGINAL ARTICLE

The efficacy of tamsulosin vs. nifedipine for the medical expulsive therapy of distal ureteric stones: A randomised clinical trial

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KEYWORDS

Ureteric calculi;
Pain;
Tamsulosin;
Nifedipine;
Renal colic

ABBREVIATIONS

MET, medical expulsive therapy;
JVT, juxtavesical tract;
VUJ, vesico-ureteric junction;
US, ultrasonography

Abstract ***Objectives:*** To assess and compare, in a randomised clinical trial, the efficacy of tamsulosin and nifedipine as medical expulsive therapy for distal ureterolithiasis.

Patients and methods: In all, 128 symptomatic patients with stones in the juxtavesical tract of the ureter were randomly divided into group 1 (64 patients) receiving oral nifedipine sustained-release 30 mg/day, and group 2 (64 patients) receiving tamsulosin 0.4 mg/day. Both groups received oral prednisolone 30 mg/day for 10 days and diclofenac 75 mg intramuscularly on demand. Patients were assessed by weekly ultrasonography with or with no abdominal computed tomography, during a follow-up of 4 weeks. The stone passage rate and time, analgesic use, hospitalisation and endoscopic interventions were evaluated. The results were analysed statistically using appropriate tests.

Results: The stone expulsion rate was 55% for group 1 and 80% for group 2 ($P = 0.004$). The mean stone size was 8.59 and 8.85 mm in groups 1 and 2, respectively. The mean expulsion time was 23 days for group 1 and 9 days for group 2 ($P < 0.001$). The mean number of diclofenac injections was 1.19 for group 1 and 0.42 for group 2 ($P < 0.001$). Eleven patients in group 1 vs. two in group 2 were

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hospitalised ($P = 0.001$). Twenty-six patients in group 1 and 13 in group 2 underwent ureteroscopy ($P < 0.001$).

Conclusions: Medical expulsive therapy with tamsulosin should be considered as a first-line treatment for index cases of distal ureterolithiasis with no complications. The use of tamsulosin provides better stone expulsion than does nifedipine.

Introduction

Urolithiasis affects 8–15% of the world population [1]. Urinary stones are the result of various metabolic, environmental and nutritional conditions, and are most commonly composed of calcium oxalate, with the precipitation of other calcium salts, uric acid, struvite or other compounds [2]. Of all types of urinary stones, ureteric stones account for 20%, and almost 70% of these are distal ureteric stones [3].

The likelihood that stones will pass through the ureter mainly depends on stone size and their location within the ureter [4–6]. Smaller stones, particularly those of <5 mm, are far more likely to pass spontaneously and might require only observation and the management of symptoms. Stones up to 6 mm might require up to 42 days to pass spontaneously [7]. This conservative approach to treatment is based on the pharmacological control of pain, oedema, ureteric spasm, and infection, all factors trying to favour stone expulsion [1].

Urolithiasis is a chronic disease with substantial economic consequences and of great importance to public health [2,3]. Thus if ureteric stones could be expelled with pharmacotherapy, surgical procedures and their associated costs could be avoided. Also, the efficacy of surgical procedures could be improved pharmacologically, and the cost of further and repeat procedures could also be reduced [8]. Currently there are two groups of drug therapy, i.e., α1-adrenergic receptor antagonists and calcium-channel blockers, that are the main treatments of choice for LUTS caused by distal ureteric stones [9].

The rationale and aim of the present study was to implement the growing evidence from trials of effective medical expulsive therapy (MET) into clinical practice, and thus to minimise the use of minimally invasive surgical techniques, such as ESWL and ureteroscopy, used to remove the stone burden. The surgical methods have measurable risks and are costly, and thus effective MET should reduce the use of surgery, hospitalisation rates, treatment costs, and the morbidity associated with distal ureterolithiasis and its surgical management.

Patients and methods

The study was conducted in the Department of General Surgery at the B.P. Koirala Institute of Health Sciences, Dharan, Nepal, between June 2009 and May 2010. The study was approved by 'The Institute Protocol and Ethical Committees', Dharan, Nepal.

Index patients with a solitary stone in the distal ureter, at the juxtavesical tract (JVT) or vesico-ureteric junction (VUJ) of 5–15 mm were included in the study. Patients with a UTI, gross hydronephrosis, diabetes, peptic ulcer disease, hypersensitivity to nifedipine or corticosteroid, or a history of spontaneous stone expulsion and hypotension, pregnant women, and children, were excluded from the study. The stone was located using abdominal ultrasonography (US), IVU or plain CT when necessary.

In all, 128 patients were randomised equally to two groups of 64. According to the previously reported 20% difference between such study groups in the rate of stone expulsion, and with an expectation that the proportion of subjects with spontaneous stone expulsion would increase from 70% (nifedipine) to 90% (tamsulosin), a sample size of 128 patients was calculated. The power of the study was 80%, with an α error of 5%, a withdrawal rate of 10%, and a two-sided test was used. Patients were randomised to the two groups using appropriate software.

Patients in both groups received oral prednisolone 30 mg/day for a maximum of 10 days. In addition, patients in group 1 received 30 mg nifedipine (slow-release) daily for a maximum of 28 days, while patients in group 2 received 0.4 mg tamsulosin for a maximum of 28 days. Each patient in groups 1 and 2 also received diclofenac 75 mg intramuscularly on demand. All patients were required to drink $\geqslant 2$ L of water daily. The follow-up was limited to 4 weeks. Patients in whom the stone was not expelled within 4 weeks were treated with ureteroscopy. To highlight possible stone expulsion, all patients were required to filter their urine. All patients were examined weekly using a plain abdominal film, or US, or plain CT during the follow-up. The adverse effects of the drugs were recorded during the follow-up.

Primary data were analysed after entering all collected data into a spreadsheet, and the per protocol data were analysed with appropriate software. The measured variables of each group were compared using the Pearson chi-square test or Mann–Whitney *U*-test (for non-normally distributed variables), and Student's *t*-test for comparing the means of normally distributed variables. anova was used to compare the means of stone size and

age between the treatment groups. The Kaplan–Meier test was used to assess the time to stone expulsion with stone expulsion rate, and the log-rank analysis was used for comparing treatment groups. The level of significance of factors (age, gender, stone size and therapy) which could explain the outcome of time-related endpoints was evaluated using a Cox proportional regression model, with the level of significance set at $P < 0.05$, and with 95% CI. A sensitivity analysis was also used for a 'best-case/worst-case' analysis for tamsulosin, in which all unknown patients in the nifedipine group were assumed to have passed their stones and no unknown subjects in the nifedipine group to have passed their stones at 42 days (6 weeks).

Results

Of 319 patients diagnosed as having distal ureteric stones and attending the surgical or emergency department, 101 did not fulfil the exclusion criteria and were not offered enrolment in the study. The remaining 218 patients were informed of the available methods of managing distal ureteric stones and asked for their consent to enter the study; 90 refused consent for drug therapy and chose surgical management in first instance. However, 128 patients gave informed written consent for the observational approach (medical therapy), and were enrolled and randomised. Six patients in group 1 were lost to follow-up for unknown reasons after the allocation of drug therapy, and had no follow-up.

In all, 122 patients completed the study protocol, 64 in group 2 and 58 in group 1. None of the patients in either group discontinued the therapy after randomisation. Of all patients enrolled in the study, stones were identified in 60 using simple US, as the stones were in the VUJ, 20 on IVU, and by CT in 42 because the stones were in the JVT. Fig. 1 shows the flow of patients in the study.

The demographic variables of the patients are given in Table 1. There were no significant statistical differences in patient age, gender, stone size, and side (right/left) between the groups. A univariate analysis is also shown in Table 1; the stone expulsion rate was significantly greater in group 2 than group 1 ($P = 0.004$). Also the time to stone expulsion from the start of therapy was less in group 2 ($P = 0.001$). The difference between the mean size of expelled and retained stones was not statistically significant between the groups ($P = 0.18$). The mean analgesic consumption was significantly less in group 2 ($P = 0.001$), and the hospitalisation rate and number of auxiliary procedures (ureteroscopy) were lower in group 2. Patients (26 in group 1, 13 in group 2) who were not stone-free after the 4 weeks of follow-up were treated successfully with ureteroscopy ($P = 0.004$). Minor therapy-related adverse effects were reported in 13 patients (11 in group 1, two in group 2) but they were able to complete the study.

There were no serious side-effects of MET (hypotension accompanied by heart palpitations, and severe asthenia), which required its suspension. Table 1 also shows the distribution of side-effects in both groups. All patients with adverse effects were given symptomatic treatment, and they continued and completed the study.

For the best-case sensitivity analysis, we assumed that all six patients in nifedipine group with unknown stone passage had passed their stones. Under this scenario, 80% (51) of those in group 2 and 59% (38) in group 1 would have successfully passed their stone, with a difference between the groups of ≈20% ($P = 0.021$). Similarly, assuming the worst-case analysis, that no patients with unknown stone passage in group 1 passed their stones, then 80% (51) in group 2 and 50% (32) in group 1 would have successfully expelled the stone, giving a difference between the groups of 30% ($P = 0.001$). Thus there was a decrease in the percentage of spontaneous stone expulsion in group 1 from 60% to 50%, with no change in group 2 in both scenarios. The difference between the groups also increased by 10% between the scenarios, which is statistically significant, confirming that patients receiving tamsulosin had a greater chance of spontaneous stone expulsion than had patients receiving nifedipine in either of the scenarios.

A multivariate analysis for predicting stone expulsion also showed that patients receiving tamsulosin had 2.1 times more chance of spontaneous stone expulsion than those taking nifedipine ($P < 0.001$). Patient gender and stone lateral location were not predictive factors for determining the spontaneous stone expulsion rate ($P = 0.892$ and 0.557, respectively). However, stone size was a strong predictive factor for determining spontaneous stone expulsion, with smaller stones (5–10 mm) having a higher chance of being expelled than larger stones (> 10 mm).

The time to spontaneous stone expulsion was also evaluated using Kaplan–Meier analysis (Fig. 2). When the number of days to stone passage was compared between the groups using the log-rank test, there was a statistically significant difference ($P < 0.001$), confirming a higher stone expulsion rate and quicker stone expulsion in group 2 than group 1 (Table 1).

Discussion

In several 28-day trials [8] with stones of < 15 mm, the rates of distal ureteric stone passage were 35–70% in a control group, 77.1–80% in patients treated with nifedipine and 79.3–100% in patients treated with tamsulosin. The mean time for stone expulsion was 4.6–20 days in a control group, 5–9.3 days in a nifedipine group and 2.7–7.9 days in those receiving tamsulosin. The benefits of MET using α1-blockers and calcium-channel antagonists on quality-of-life endpoints, such as recurrent hospitalisation rates because of uncontrollable

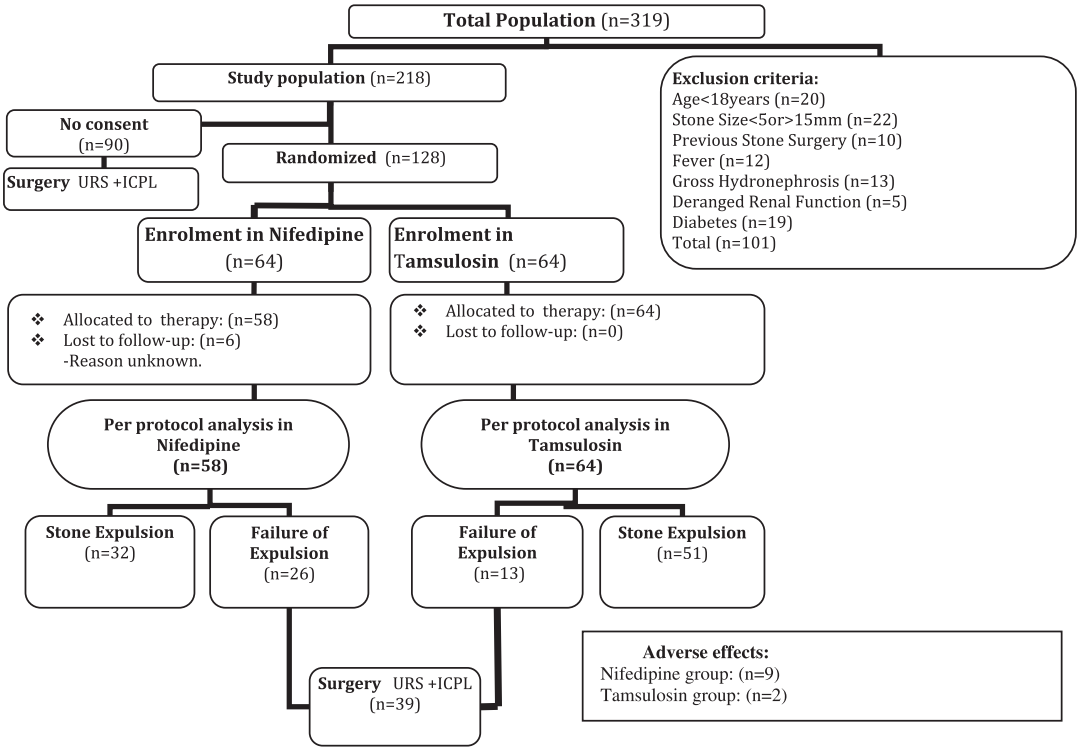

Figure 1 A flow diagram of the total population of the study.

Table 1 The demographic variables, study results, expulsion times and rate, and adverse effects.

Mean (SD) variable[a]	Nifedipine	Tamsulosin	*P*
Age (range), years	30.4 (11.36, 18–74)	34.0 (12.83, (18–74)	0.107
Gender (M:F)	1.48:1	1.28:1	0.765
Median duration of pain (days)	10	10	0.793
Serum creatinine level (mg/dL)	0.96 (0.21)	0.98 (0.22)	>0.05
Stone size (mm)	8.59 (2.25)	8.85 (2.50)	0.18
% Expulsion (*n* patients)	55.2 (32)	79.7 (51)	0.004
Median duration to expulsion (days)	23	9	<0.001
Analgesic use	1.19 (0.59)	0.42 (0.14)	<0.001
Follow-up assessments (*n*)	2.21 (0.85)	1.59 (0.83)	<0.001
Adverse events, *n* (%)	11 (19)	2 (0.2)	0.001
Surgery[b], *n*	26	13	0.004
Stone expulsion time, n (%)			
⩽10	16 (50)	40 (78)	<0.001
11–20	13 (40)	8 (16)	
21–30	2 (6)	3 (6)	
31–42	1 (3)	0	
Total	32 (100)	51 (100)	
Adverse events (%)			
Headache	43	50	
Gastric upset	0	25	
Loose stool	24	0	
Dizziness	5	25	
Fatigue	5	0	
Flushing	5	0	
Palpitation	9	0	
Muscle cramps	9	0	

[a] Unless stated otherwise.
[b] Ureteroscopy or intracorporeal pneumatic lithotripsy.

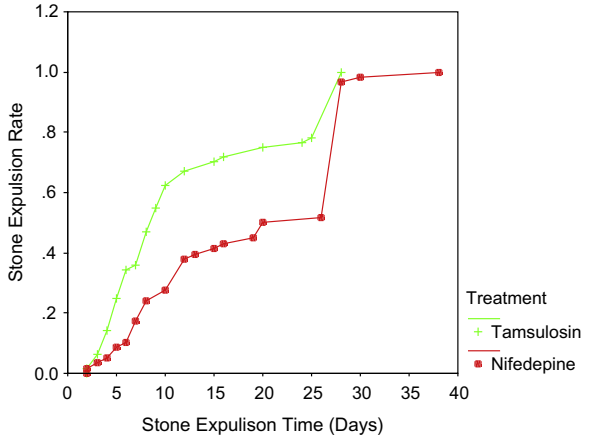

Figure 2 The Kaplan–Meier analysis of the stone expulsion rate vs. stone expulsion time in both groups.

pain, were significantly reduced from 9% to 34% for the control group to only 0–9% for the tamsulosin group and 20% for the nifedipine group. The need for surgery to remove distal ureteric stones also reduced from 30–31% in controls to only 0–1.4% in the tamsulosin and 20% in the nifedipine groups [10].

Various medications have been used to assist the passage of ureteric stones. Bajor [11] showed that an α-blocker reduced the time for stone passage from 11 to 5.2 days in 86 patients with lower ureteric stones, and with no serious side-effects. Similarly Borghi et al. [10] showed the beneficial effect of a calcium antagonist (nifedipine) in reducing the time to stone passage and improving the expulsion rates. Propiglia et al. [12] reported their experience with nifedipine and a corticosteroid agent (deflazacort). This MET was safe and effective, as shown by the increased expulsion rate, decreased expulsion time and less need for analgesic therapy than in a control group. The rationale of the present MET is to use prednisolone to reduce the oedema, and use nifedipine to inhibit the stone-induced ureteric spasm, thus maintaining the peristaltic ureteric rhythm.

On the basis of the evidence that α-1 receptors have an important role in expulsion associated with lower ureteric physiology, many authors proposed the use of α-blockers with the aim of facilitating stone expulsion from the lower ureter [13–17]. In particular Ukhal et al. [14] reported positive results in accelerating lower-tract ureteric stone passage (JVT and VUJ) using α1-blockers. Cervenakov et al. [15], in a randomised study, reported a significant statistical difference in the stone expulsion rate between the group treated with tamsulosin and a control group. Similar results were reported by Dellabella et al. [1]. To our knowledge, there are very few comparative studies that investigated different METs, which led us to devise the current comparative study of the safety and effectiveness of nifedipine and prednisolone vs. tamsulosin and prednisolone for treating lower ureteric stones.

The present study was limited to patients with lower ureteric stones (JVT and VUJ) of α 15 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 α1-receptors in the lower part of the ureter [16,17]. We chose a maximum observation period of 4 weeks because longer periods can increase the complication rates by up to 20% [9]. In the present study the MET was based on a combination of nifedipine and prednisolone (group 1), and gave positive results in 55% of patients, whereas the combination of tamsulosin and prednisolone (group 2) gave positive results in 80% of patients, a significant difference. These results confirmed that MET with tamsulosin provides better stone expulsion than with nifedipine. For the expulsion time, there was spontaneous stone passage after 23 days in group 1, and 9 days in group 2, a significant statistical difference. These results confirm the positive results obtained in reducing stone passage times by others [16,18,19]. Also, the stone size in group 2 was not significantly different to that in group 1, showing that tamsulosin was more effective for treating this type of ureteric stone than was nifedipine. A further evaluation using larger groups should provide confirmation of these findings.

Moreover, the combination of tamsulosin and prednisolone was more effective than nifedipine and prednisolone in pain reduction, and decreased the amount of analgesic administered. There was no statistically significant difference between the mean size of expelled and retained stones in the treated patients. There was also a relationship between stone size and time to expulsion, but gender and stone laterality appeared not to influence the stone expulsion rate. As previously reported, these data suggest that not only stone size, but also other factors, such as stone shape and oedema around the stone, can influence expulsion times [20]. There were no cases of serious adverse events of MET (hypotension accompanied by heart palpitations, and severe asthenia), which required its suspension. There were minor therapy-related adverse effects in 13 patients (11 in group 1, two in group 2) but they were able to complete the study. There were no clinical side-effects related to use of the corticosteroid drug. As to safety, both combinations were well tolerated by the patients. Ibrahim et al. [21] similarly reported minor therapy-related side-effects in five patients taking tamsulosin and in six taking alfuzosin, which were mild and did not require the withdrawal of treatment in any patient. Patients who were not stone-free after the 4 weeks of follow-up were treated successfully with ureteroscopy. These data show that neither watchful waiting nor MET seems to negatively affect the success rate of stone removal.

In conclusion, tamsulosin was more effective than nifedipine for the MET of distal ureteric stones, with a

higher rate of spontaneous stone expulsion by 24% (a difference of >20%) and quicker stone expulsion, lower doses of analgesic consumption, fewer emergency visits, minimal follow-up, fewer adverse drug reactions, fewer auxiliary operations, and less need of hospitalisation for recurrent pain.

Conflict of interest

None.

Source of funding

None.

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