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Outcome of α-blockers, with or without methylprednisolone combination, in medical expulsive therapy for lower ureteric stones: A prospective randomised study

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KEYWORDS

α-Blockers;
Methylprednisolone;
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Urolithiasis

ABBREVIATIONS

KUB, plain abdominal radiograph of the kidneys, ureters and bladder;
MET, medical expulsive therapy;

Abstract ***Objectives:*** To compare the safety and efficacy of tamsulosin, alfuzosin, and their combinations with methylprednisolone, in the medical management of lower ureteric stones.

Patients and methods: Between September 2012 and June 2014, patients diagnosed with a single lower ureteric stone of ⩽10 mm (longest dimension) were enrolled. Patients with urinary tract infection, severe hydronephrosis, pregnancy, hypertension, diabetes, ulcer disease, or renal insufficiency were excluded. According to the medication added to the analgesic anti-inflammatory, patients were stratified into four groups, with 53 patients in each. Group I patients received tamsulosin 0.4 mg and those in Group II received tamsulosin 0.4 mg and methylprednisolone 8 mg. Group III patients received alfuzosin 10 mg and those in Group IV received alfuzosin 10 mg and methylprednisolone 8 mg. Treatment was continued until stone expulsion or to a maximum of 2 weeks. The patients' demographics, stone criteria, and stone-free rates were calculated and analysed.

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SWL, shockwave lithotripsy;
URS, ureteroscopy

Results: The mean (SD) maximum stone dimension was 7.8 (1.5), 8.1 (1.3), 7.9 (1.6) and 8.0 (1.4) mm in Groups I, II, III and IV, respectively. Groups II and IV had significantly higher stone-free rates than Groups I and III ($P < 0.05$), whilst there were no statistically significant differences between Groups I and III or between Groups II and IV. There was no statistical difference among the four groups for the time to stone expulsion. Three patients in Group II and two patients in Group IV developed transient hyperglycaemia, which resolved after cessation of methylprednisolone.

Conclusions: The combination of alfuzosin or tamsulosin with methylprednisolone seems to be effective and safe for managing lower ureteric stones of < 1 cm.

Introduction

Urolithiasis is an international problem affecting ≈12% of the population. About 70% of stones at the time of diagnosis are located in the lower ureter [1]. Treatment options for ureteric stones range from non-invasive procedures, such as medical expulsive therapy (MET), to more invasive, such as shockwave lithotripsy (SWL) or ureteroscopy (URS) for stone extraction. The rational of MET is to enhance fluid intake to increase urine volume and hydrostatic pressure, with subsequent increasing ureteric peristaltic activity. Many pharmaceutical agents have been introduced for the medical management of stones, e.g. α_1-adrenergic receptor blockers, prostaglandin synthesis inhibitors, calcium channel blockers, and steroids [2]. The α_1-adrenergic receptors are found predominately in the distal ureter. They inhibit smooth muscle contraction with subsequent ureteric relaxation. Corticosteroids are useful for the expulsion of ureteric stones via their anti-oedematous effect by reducing the inflammation of the ureteric mucosa [3]. Numerous reports exist signifying improved spontaneous stone expulsion using alfuzosin [4,5], terazosin [6], naftopidil [7], doxazosin [8], and silodosin [9]. Yilmaz et al. [10] proposed a possible class effect for α-adrenergic receptor blockers with equal efficacy for all class members. There is insufficient published data on the effect of corticosteroid alone or combined with α-blockers for MET. In the present study, we aimed to compare the safety and efficacy of tamsulosin, alfuzosin and their combinations with methylprednisolone in the medical management of lower ureteric stones.

Patients and methods

This prospective randomised study enrolled patients diagnosed with a lower ureteric stone between September 2012 and June 2014, and it was conducted in the Department of Urology, Zagazig University, Egypt. Local Ethics Committee approval and an informed consent from all patients were obtained. Eligible patients were required to have: (i) a single radiopaque stone of ⩽10 mm by plain abdominal radiograph of the kidneys, ureters and bladder (KUB), (ii) the stone located below the sacroiliac joint, and (iii) agree to participate in the study. Patients with UTI, severe hydronephrosis, pregnancy, hypertension, diabetes, ulcer disease, previous pelvic surgery or renal insufficiency (creatinine > 1.5 mg/dL) were excluded from the study. Patients were evaluated by routine laboratory testing (random blood sugar, renal, and liver functions) and blood pressure measurement before starting treatment and at the end of the treatment period.

Study design

Sample-size was calculated by estimating that the difference in the rate of stone expulsion between α-blockers and their combination with corticosteroid was 25% based on a prior study [2], and the power of the test to be 80% at a CI of 95%. The calculated sample was 48 in each group. After allowing for a 20% attrition rate, 60 patients were finally enrolled in each group. Patients were randomly divided into four groups by a simple randomisation method (shuffled cards). Group I patients received tamsulosin 0.4 mg daily and those in Group II received tamsulosin 0.4 mg and methylprednisolone 8 mg daily. Group III patients received alfuzosin 10 mg daily and those in Group IV received alfuzosin 10 mg and methylprednisolone 8 mg daily.

Intervention

Patients received 10 mg ketorolac (oral tablet) twice daily, as well as 75 mg diclofenac sodium (i.m.) as needed for pain. Patients were instructed to accurately report the time of stone expulsion if any. Treatment was evaluated 2 weeks later by KUB for those who did not have clear evidence of complete stone expulsion. Occurrence of and time to stone expulsion were

recorded in each group. In cases of unsuccessful MET, another treatment option was offered, e.g. SWL or URS. Fasting blood sugar, blood pressure, and possible steroid-related side-effects were monitored before and after the treatment course. Need of additional analgesic was calculated in each group. The patients' demographics, stone criteria, stone-free rate, and time to stone expulsion were calculated and statistically analysed.

Endpoints

The primary endpoint of this study was the rate and time of stone expulsion. The secondary endpoint was occurrence of treatment side-effects and drawbacks of the used drug in each group.

Statistical analysis

Data were checked, entered and analysed using MedCalc Software (version 14.8.1). The one-way ANOVA test was used for quantitative data and the chi-squared test for qualitative data, with a $P < 0.05$ considered to indicate statistical significance. Time to stone expulsion was plotted using a Kaplan–Meier curve and log-rank test.

Results

Seven patients in each group were lost during follow-up, resulting ultimately in each group comprising of 53 patients (Fig. 1). The mean (SD) age of the patients was 53(1.5), 51 (3.6), 49 (2.7) and 48 (4.1) years in Groups I, II, III and IV, respectively. The mean (SD) maximum stone dimension was 7.8 (1.5), 8.1 (1.3), 7.9 (1.6), and 8.0 (1.4) mm in Groups I, II, III and IV, respectively. There were no significant differences in gender, body mass index or stone length between the four groups (Table 1). There were significantly higher stone-free rates in Groups II (38/53, 71.9%) and IV (39/53, 73.6%) compared with Groups I (29/53, 54.7%) and III (28/53, 52.8%) ($P < 0.05$). The median time to stone expulsion was 13, 10, 12 and 9 days in Groups I, II, III and IV, respectively, with no statistically significant difference between the four groups (Table 2 and Fig. 2). The mean (SD) time of additional analgesic use was 2.3 (1.1), 1.9 (0.9), 2.1 (1.3) and 1.8 (1) days in Groups I, II, III and IV, respectively ($P = 0.33$). Three (5.7%) patients in Group II and two (3.8%) in Group IV developed transient hyperglycaemia, which resolved after cessation of methylprednisolone. Those five patients had neither a family history of diabetes mellitus nor were they overweight. There were no

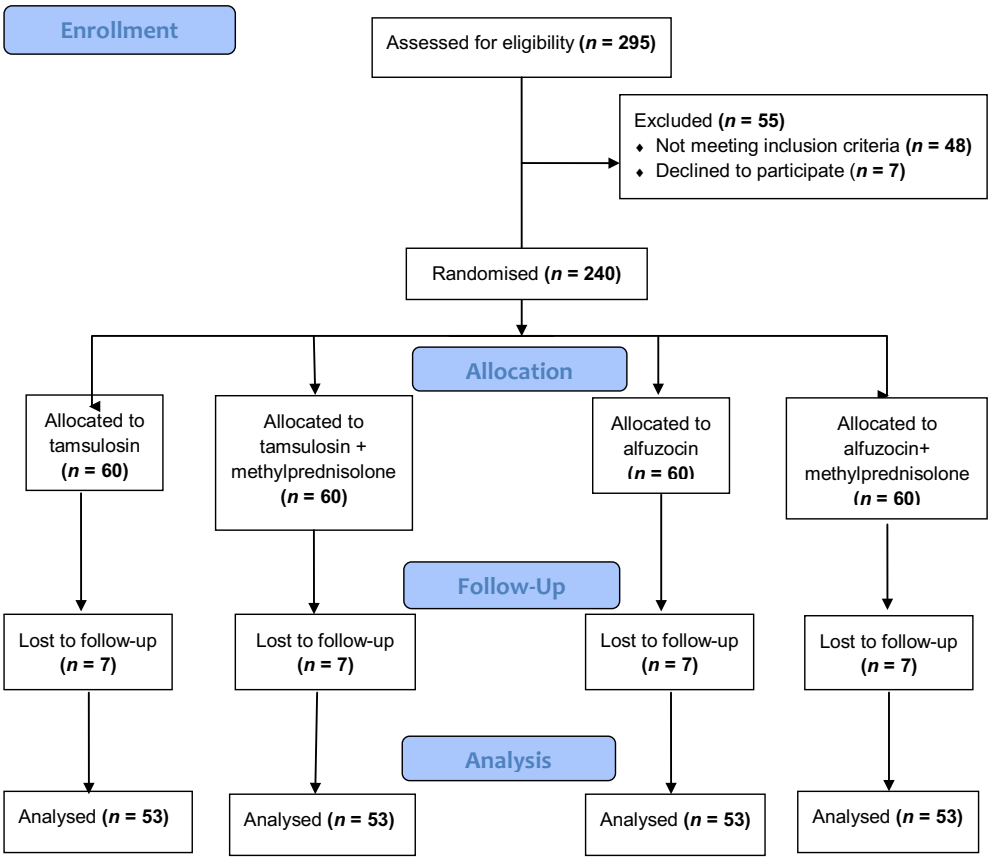

Figure 1 Consolidated Standards Of Reporting Trials (CONSORT) flow diagram.

Table 1 Patients' demographics and stone criteria.

Variable	Group I (tamsulosin)	Group II (tamsulosin + methylprednisolone)	Group III (alfuzosin)	Group VI (alfuzosin + methylprednisolone)	*P*
Number of patients	53	53	53	53	
Mean (SD) age, years	53 (1.5)	51 (3.6)	49 (2.7)	48 (4.1)	0.049
Mean (SD) BMI, kg/m^2	29.5 (2.4)	30.3 (3.1)	30.1 (3.9)	31.4 (3.2)	0.165
Gender: M/F, *n*	30/23	29/24	31/22	27/26	0.88
Laterality: right/left, *n*	31/22	27/26	30/23	28/25	0.858
Mean (SD) stone length, mm	7.8 (1.5)	8.1 (1.3)	7.9 (1.6)	8.0 (1.4)	0.37

BMI, body mass index.

Table 2 Outcomes and complications of treatment.

Variable	Group I (tamsulosin)	Group II (tamsulosin + methylprednisolone)	Group III (alfuzosin)	Group VI (alfuzosin + methylprednisolone)	*P*
Number of patients	53	53	53	53	
Stone-free rate, *n* (%)	29 (54.7)	38 (71.9)	28 (52.8)	39 (73.6)	0.042
Median time to stone expulsion, days	13	10	12	9	0.082
Hyperglycaemia, *n* (%)	–	3 (5.7)	–	2 (3.8)	0.137

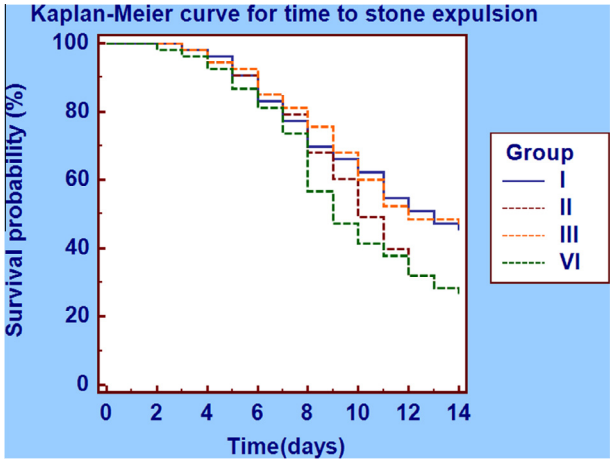

Figure 2 Kaplan–Meier analysis of time to stone expulsion.

increases in blood pressure compared with pretreatment values.

Discussion

There is currently an increasing interest in using pharmacological agents to facilitate stone expulsion and reduce expected pain attacks. Stone factors and the drugs used for MET influence stone passage [11]. Various drugs are used, e.g. α-blockers, calcium channel blockers, and corticosteroids. The spontaneous expulsion rate for lower ureteric stones with MET ranges from 5% to 70%. Successful passage of a stone is affected by stone-related factors, e.g. size and location [12], or ureter-related factors, e.g. mucosal oedema and degree of ureteric dilatation [13]. In a randomised double-blind study, Al-Ansari et al. [14] studied the efficacy of tamsulosin in 100 patients and reported an 82% stone expulsion rate vs 61% in the control group ($P = 0.02$). Kaneko et al. [15] reported a 77% stone expulsion rate after using low-dose tamsulosin. Although tamsulosin has been extensively studied for MET, other α-blockers have also shown great efficacy. In a prospective randomised controlled trial, Chau et al. [16] reported a 51.3% increase in the overall expulsion rate with alfuzosin. In our present study, we have comparable results with tamsulosin (54.7%) and alfuzosin (52.8%). The concomitant usage of corticosteroids and α-blockers has been discussed in the literature with favourable results. Porpiglia et al. [2] studied the combined effect of corticosteroid and tamsulosin in MET in 114 patients. They reported an 84.8% stone expulsion rate in the combination arm (deflazacort and tamsulosin). Conversely, Dellabella et al. [17] found no statistically significant difference in the stone expulsion rate when they compared tamsulosin alone to its combination with steroids ($P = 0.612$). In our present study, we found a significant increase in the stone expulsion rate when using the combination of methylprednisolone and tamsulosin compared with tamsulosin alone, with no significant difference for the time to stone expulsion. There is diversity in the steroid agent used, as some authors have used methylprednisolone 40 mg [3], deflazacort 30 mg [17,18], and methylprednisolone 8 mg [19]. Lack of a standard medication and dosing regimen precludes its routine usage in MET. Our present study was not devoid of limitations as the time to stone expulsion was reported subjectively by the patients, which carries some risk of inaccuracy.

In conclusion, the combination of alfuzosin or tamsulosin with methylprednisolone seems to be effective and safe for managing lower ureteric stones of < 1 cm.

Conflict of interest

The authors have no conflict of interest to declare.

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None.

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