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Silodosin in the treatment of distal ureteric stones in children: A prospective, randomised, placebo-controlled study

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KEYWORDS

Silodosin;
Distal ureteric stone (DUS);
Children;
Medical expulsive therapy

ABBREVIATIONS

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

Abstract ***Objectives:*** To evaluate the possible role of silodosin (a highly selective α_{1A}-adrenoceptor antagonist) in facilitating the passage of distal ureteric stones (DUS) in children, as the role of α-blockers as medical expulsive therapy is well known in adults.

Patients and methods: In all, 40 paediatric patients (27 boys and 13 girls) diagnosed with unilateral, single, radiopaque DUS of <10 mm were included in the study. Their mean (SD, range) age was 8.1 (2.7, 5–17) years. The patients were randomly divided into two groups: Group A, received silodosin 4 mg as a single bedtime dose; and Group B, received placebo as a single bedtime dose. Ibuprofen was prescribed to both groups on-demand for pain episode relief. Patients were followed up biweekly for 4 weeks. The stone expulsion time and rate, pain episodes, analgesic use, and any adverse effects were recorded.

Results: The mean (SD) stone size in Group A was 6.6 (1.7) mm and in Group B was 6.7 (1.4) mm ($P = 0.4$). Two patients were lost to follow-up (one from each group), and one patient in Group A refused to complete the study. The stone-free rate at end of the 4-week treatment period was 88.8% in Group A vs 73.6% in

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SFR, stone-free rate;
SWL, shockwave lithotripsy;
URS, ureteroscopy

Group B ($P = 0.4$). The mean (SD) stone expulsion time was 7.0 (4.3) vs 10.4 (4.7) days in groups A and B, respectively ($P = 0.02$). The mean (SD) number of pain episodes requiring ibuprofen was 2.3 (1.4) vs 4.7 (2.6) episodes in groups A and B, respectively ($P < 0.001$). Adverse effects (headache and dizziness) were recorded in three patients (16.7%) in Group A, which were mild and none of them discontinued treatment, whilst no adverse effects were recorded in Group B.

Conclusions: The data in the present study show that silodosin can be safely used in the treatment of DUS in children for decreasing time to stone expulsion, pain episodes, and analgesic requirement.

Introduction

The estimated incidence of urolithiasis in children is reported to be between 0.1% and 5% [1–3]. Various factors may contribute to the formation of urinary stones in children including metabolic, environmental, and nutritional factors [4,5].

Ureteric calculi represent ~20% of urinary stones at the time of diagnosis, of which ~70% of the stones are found in the distal third of the ureter [6]. Microscopic haematuria, UTI, and pain are typical presentations in children [7]. The treatment strategy depends on different factors including: stone location, size, and the anatomy of the urinary tract [8].

In recent years, the management of paediatric ureteric stones has shifted from open surgery to minimally invasive procedures, as the entire urinary tract can be accessed by miniature endoscopes and shockwaves. Medical expulsive therapy (MET) may be of benefit in reducing the need for surgical intervention by eliminating pain and/or enhancing stone passage [6,9]. In adults, different drugs have been used to enhance spontaneous stone passage and decrease the time to stone expulsion; however, the use of α-blockers in children has recently expanded to involve treatment of neurogenic bladder, voiding dysfunction, and idiopathic urethritis [6,10,11]. Silodosin, a selective α_{1A}-adrenoceptor antagonist, has been used as MET in adults with distal ureteric stones (DUS) and has achieved a significantly greater stone expulsion rate compared with placebo [12]. In the present study, we aimed to evaluate the possible role of silodosin in facilitating the passage of DUS in paediatric patients.

Patients and methods

The present study was a prospective placebo-controlled randomised study, conducted after obtaining approval from the Ethics Committee in our centre and written informed consent from all patients and/or their guardians. A clear statement was made about silodosin, as a selective α_{1A}-adrenoceptor antagonist, and its off-label use in the treatment of children with DUS, emphasising its possible effects and adverse reactions. In all, 40 paediatric patients (27 boys and 13 girls) who presented with single, radiopaque DUS were included in the present study between September 2014 and October 2015. Inclusion criteria were: age <18 years, single unilateral radiopaque DUS, and largest stone diameter of ≤ 10 mm.

Exclusion criteria were: multiple, bilateral or recurrent stones, radiolucent stone, largest stone diameter >10 mm, UTI or urosepsis, anomalies of the ureter or the kidney, previous urinary tract endoscopy or surgery, marked hydronephrosis, and abnormal renal function. All patients were evaluated by complete history taking and a thorough physical examination. Laboratory investigations included urine analysis and serum creatinine. Radiological assessment with plain abdominal radiograph of the kidneys, ureters and bladder (KUB) and abdomino-pelvic ultrasonography was done.

This single-blinded study included 40 patients with mean (SD, range) age of 8.1 (2.7, 5–17) years. Fig. 1 shows the study flow chart. Treatment was assigned on a randomised basis using the closed envelope randomisation method into two equal groups, i.e. 20 patients in each group. As there were no known published data on the role of silodosin in the treatment of DUS in children, we performed a pilot study prior to the present study, in children who were not included in the present study. The results of the pilot study were used to calculate the sample size by assuming that the mean (SD) stone expulsion time in Group A was 7.2 (2) days and in Group B was 8.6 (0.9) days (pilot data). Using Open Epi 2.3, to detect a 15% difference between the two groups with 80% power and a threshold of significance of 0.05, the sample size was estimated to be 40 patients (20 in each group).

In Group A, children received silodosin 4 mg at bedtime, whilst those in Group B received placebo. Medications (placebo or silodosin) were supplied according to the randomisation list by a registered outpatients-clinic nurse that had a registry for these patients. A pill counter was given to every patient to confirm adequate com-

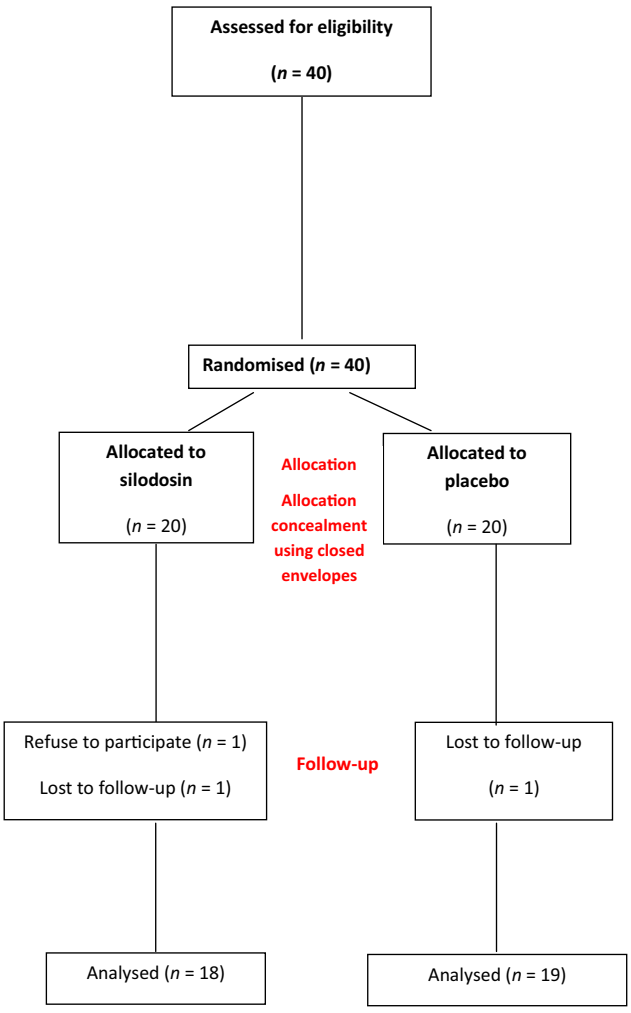

Fig. 1 Study flow chart.

pliance to the given medication. For those who could not swallow the capsule, the capsule contents were emptied into a small amount of water or juice. Ibuprofen (20 mg/kg/day) was divided into two doses for pain episodes. Children were encouraged to take plenty of fluids. Follow-up included two assessments at 2 and 4 weeks from starting the treatment. At the follow-up assessments history, physical examination (blood pressure, pulse rate, and body temperature), urine analysis, KUB and ultrasonography were undertaken (to confirm stone passage). The stone expulsion time and rate, number of pain episodes, need of analgesia, and any adverse effects were recorded in both groups. The primary outcomes were time to stone passage and the secondary outcomes were stone-free rate (SFR), pain, and incidence of adverse effects. For time to stone passage (stone-expulsion time): children were advised to urinate in a potty under parent or guardian observation to ensure the exact time of stone passage by visual confirmation of the stone or a part of it which was subsequently confirmed radiologically. The stone-expulsion time was calculated from the day of starting the treatment until the visual confirmation of stone passage in days. The SFR was calculated at two time points (2 and 4 weeks of starting the treatment), regardless of the time to stone passage and it was defined by visual confirmation of a stone passage, which was confirmed radiologically or absence of the stone on radiological assessment at the 2- or 4-week follow-up. A pain episode was defined as any form of abdominal pain (either typical renal colic or atypical abdominal pain) occurring in our patients during the study period that required treatment with ibuprofen. Failure of treatment was defined as failure to achieve a stone-free status at the 4-week follow up. Patients were referred either for shockwave lithotripsy (SWL) or ureteroscopy (URS).

The statistical analysis was carried out using the Statistical Package for Science (SPSS® version 16, SPSS Inc., Armonk, NY, USA). For quantitative variables the means and standard deviations (SDs) were calculated, for categorical variables numbers and percentages were calculated. The Student's *t*-test was used for quantitative data of normal distribution, for data that were not normally distributed we used the Wilcoxon Mann–Whitney test; for qualitative variables the chi-squared test and Fisher's exact test were used. All tests were used at a level of significance of $< 5\%$.

Results

Our study included 40 patients with radiopaque single DUS randomised into groups A and B. Three patients were excluded from our study, two were lost to follow-up (one in each group) and one refused to complete the study in Group A. Regarding age, sex, DUS size, and patients' weight, there was no significant difference between the groups (Table 1).

In the present study, all patients who passed their stone could visually confirm stone passage. The mean (SD) stone expulsion time was 7.0 (4.3) and 10.4 (4.7) days in groups A and B, respectively ($P = 0.02$). The mean (SD) number of pain episodes requiring ibuprofen was 2.3 (1.4) and 4.7 (2.6) episodes in groups A and B, respectively ($P < 0.001$) (Table 2). In Group A, the failure rate was 11.1% (two of 18), in which one patient was scheduled for URS and the other was scheduled for SWL. In Group B, the failure rate was 26.3% (five of 19) in which three patients were scheduled for URS and two were scheduled for SWL. Adverse drug effects

Table 1 Patient and stone characteristics.

Variable	Group A (silodosin)	Group B (placebo)	*P*
Male:female, *n*	12:8	15:5	0.3
Mean (SD):			
Age, years	8.4 (3.1)	7.7 (2.3)	0.2
Weight, kg	24.8 (5.9)	23.5 (4.7)	0.2
Stone size, mm	6.6 (1.7)	6.7 (1.4)	0.4

Table 2 Outcomes and results.

Variable	Group A (silodosin)	Group B (placebo)	*P*
% (*n*/*N*):			
SFR at 2 weeks	72.2 (13/18)	57.8 (11/19)	0.4
SFR at 4 weeks	88.8 (16/18)	73.6 (14/19)	0.4
Mean (SD):			
Time to stone expulsion, days	7.0 (4.3)	10.4 (4.7)	0.02
Number of pain episodes	2.3 (1.4)	4.7 (2.6)	<0.001

included headache and dizziness, which were recorded in three patients (16.7%) in Group A, these were mild and no patients discontinued treatment, whilst no adverse effects were recorded in Group B.

Discussion

Paediatric urolithiasis is considered endemic in certain developing countries, e.g. Turkey, Pakistan, India, and the Far East [13]. Children who have urinary stones are more likely to have recurrent stones, so they may need multiple interventions for stone removal during their lives [14]. Different treatment methods are used for managing urinary stones in children including: open surgery, SWL, URS (rigid or flexible), percutaneous nephrolithotomy, laparoscopic or robot-assessed ureteropyelolithotomy, and MET [8]. Interventional treatment has been reported to be successful in 98–100% of cases; however, they are not complication free. The reported incidence of complications for URS is 10–20% (including 3–5% major complications, such as ureteric perforation, avulsion, and stricture). Complications related to SWL range between 15% and 32%, e.g. subcapsular haematoma, perirenal fluid collection, and retreatment sessions in up to 50% [8,15].

In contrast to adults, the natural history of paediatric urolithiasis in not well-defined; however, the management of paediatric stones has changed dramatically in the last two decades, with the increasing use of less invasive treatment methods [9,10,16]. The main aim of any conservative treatment is to reduce pain, decrease ureteric smooth muscles spasm and mucosal oedema, speed stone passage, and increase rate of stone passage [17]. Recently, several studies have evaluated the possible role of different drugs in accelerating the passage of DUS. Analgesic anti-inflammatory drugs, calcium channel blockers, and α-adrenoceptor blockers represent the most commonly used agents [18].

As shown in many studies, the α_{1A}-adrenoceptors are located mainly in the distal ureteric smooth muscles, with blockade of these receptors the intraureteric constrictions decrease and thus stones passage increases [5,19]. With the introduction of silodosin, as a highly selective α_{1A}-adrenoceptor blocker, ureteric smooth muscle relaxation can be achieved with a lesser influence on α_{1B}-adrenoceptors and thus a lesser effect on blood pressure. Therefore, selective α_{1A}-adrenoceptor antagonism should prevent uncoordinated smooth muscle contractions, without prohibiting ureteric peristalsis, hence facilitating stone passage in a short time and decrease the need for analgesics [20].

A large multicentre randomised prospective trial to examine silodosin vs placebo for MET in adults with ureteric stones showed that silodosin significantly improves SFR in patients with DUS. In that study, they recommended further studies on different stone sizes and locations [12]. In the present study, the stone expulsion rate was higher in the silodosin group (Group A) than in the placebo group (Group B), at 88.8% vs 73.6%, respectively; however, this was not statistically significantly different. Mokhless et al. [21] studied tamsulosin in the treatment of DUS in children and reported a SFR of 88% vs 64% in the tamsulosin group and placebo group, respectively ($P < 0.01$). Aydogdu et al. [22] studied doxazosin in the treatment of DUS in children and reported a SFR of 84% and 70% in the doxazosin and ibuprofen groups, respectively (statistically non-significant).

Erturhan et al. [23] studied doxazocin in the management of DUS in paediatric patients, their study included 45 patients with single lower ureteric stones that were randomly divided into two groups, Group 1 received ibuprofen and Group 2 received doxazocin in addition to ibuprofen, and reported stone-expulsion rates of 28.5% and 70.8%, respectively ($P = 0.001$). Tasian et al. [24] performed a multi-institutional retrospective study including 274 paediatric patients with ureteric stones of ≤ 10 mm, where 99 patients received tamsulosin and 175 patients received analgesics alone, and reported a SFR of 55% in the tamsulosin cohort compared to 44% in the analgesic alone cohort ($P = 0.03$).

In the present study, the mean (SD) stone expulsion time was significantly shorter in the silodosin group vs the placebo group, at 7.0 (4.3) vs 10 (4.7) days. Mokhless et al. [21] reported a mean (SD) stone expulsion time of 8.2 (3.4) and 14.5 (4.5) days in the tamsulosin group and placebo group, respectively ($P = 0.001$). Whilst, Aydogdu et al. [22], reported no statistically significant difference between doxazocin and ibuprofen alone, with a mean (SD) stone expulsion time of 6.1 (2.3) vs 5.9 (2.1) days. In the present study, for the number of pain episodes and analgesic use, there was a statistically significant difference in favour of silodosin in decreasing the frequency of pain episodes and analgesic use. Mokhless et al. [21], Aydogdu et al. [22] and Erturhan et al. [23] reported fewer pain episodes and less analgesic use with tamsulosin and doxazosin than placebo or ibuprofen alone, respectively. In contrast, a study performed by Pickard et al. [25] showed no statistically significant ben-

efit between active treatment [α-blockers or nifedipine] vs placebo for pain reduction during episodes of ureteric colic. In the present study, adverse effects occurred in only three patients in the silodosin group, these were mild (headache or dizziness) and none of them discontinued treatment, whilst there were no adverse effects reported in the placebo group.

The main limitation of the present study is the relatively few participants limiting the generalisability of our results for DUS in children. Another limitation is the use of KUB and ultrasonography during follow-up, which may have limited sensitivity and specificity. Also fluid intake among children was difficult to calculate. To our knowledge, the present study is the first to evaluate the possible role of silodosin as a selective α_{1A}-adrenoceptor antagonist in facilitating the passage of DUS in children.

Conclusion

The data in the present study show that silodosin can be used safely for treating DUS in children for decreasing time to stone expulsion, pain episodes, and analgesic requirement.

Conflict of interest

None.

Source of Funding

None.

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