Urol Res (2011) 39:361–365
DOI 10.1007/s00240-010-0357-3

ORIGINAL PAPER

Randomized controlled trial of the efficacy of isosorbide-SR addition to current treatment in medical expulsive therapy for ureteral calculi

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Received: 1 August 2010 / Accepted: 15 December 2010 / Published online: 5 January 2011

Abstract It has been suggested that nitrates are potent smooth muscle relaxants that may reduce pain and facilitate ureteral stone passage; therefore it may be an option for medical expulsive therapy in ureteral stones. In a prospective randomized controlled clinical trial, we evaluated the efficacy of medical expulsive therapy with isosorbide-SR 40 mg in patients with ureteral stones (≤10 mm). The patients with ureteral stones in KUB or urinary tract ultrasonography were randomized to receive methylprednisolone plus celecoxib without (control group), and with isosorbide-SR 40 mg (treatment group) for 21 days. 66 patients [33(50%) in control, 33(50%) in treatment group] were entered randomly to our study. The stone expulsion rate was not significantly different between two groups (54.5 vs. 45.5%) ($P = 0.497$). The need for surgical procedures were more common in control group within 21 days (9.4 vs. 6.1%) and more common in treatment group after 21 days (33.3 vs. 21.9%) ($P = 0.756$).Patients in the treatment group experienced more intractable pain (27.3 vs. 6.1%), intractable vomiting (3 vs. 0%) ($P = 0.046$) and hospitalization (3 vs. 0%) ($P = 0.314$). Drug side effects including headache and dizziness were more common in treatment group (39.4 vs. 9.1%) ($P = 0.004$). In our study, the use of isosorbide-SR in treatment group did not improve the stone expulsion rate in patients with ureteral stones (≤10 mm) but developed more side effects. Then it may not an appropriate alternative for medical expulsive therapy. Of course, further trials are recommended.

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Keywords Isosorbide-SR · Medical expulsive therapy · Ureteral stones

Introduction

Urolithiasis is the third most common urologic disease [1]. In the United States, the prevalence of stone disease has been at 10–15% [2]. Current therapeutic options for ureteral stones include active intervention as well as conservative watch and wait approaches. Endoscopic treatment of ureteral stones has a high success rate and reliable results in immediate stone removal [3, 4], however surgical as well as anesthetic risks are not negligible and serious complications, although rare, are possible [5]. Extracorporeal shock wave lithotripsy (ESWL) is preferred for small proximal ureteral stones; however, it has a significant rate of complications and is quite expensive [6]. Thus, for many patients, a conservative treatment without immediate invasive procedures is an appealing option. If a conservative approach proves to be unsuccessful, interventional treatment becomes necessary [7]. To date, non-steroidal anti-inflammatory drugs (NSAIDs), hormones, corticosteroids, calcium channel blockers and α_1-adrenergic receptor antagonists have been evaluated as medical expulsive agents to increase the stone passage rate.

Although earlier intervention is required in the presence of urinary tract infection, renal function deterioration or intractable pain, failure to pass the stone spontaneously within a specified time usually result in some form of intervention. It has been suggested that up to 4 weeks of conservative management is safe in patients with complete obstruction [8]. Therefore our study was performed for 3 weeks duration.

It has been suggested that nitrates have relaxation effect on vessels and ureter's smooth muscles [9]. Our hypothesis was that the smooth muscle relaxation effect of nitric oxide can facilitate stone passage by producing ureteral dilation at the site of stone impaction and may reduce the pain by diminishing ureteral spasm. However, to our knowledge there is no report on effects of long acting nitrates, including oral isosorbide-SR, on ureteral stone passage. Therefore, we performed the current prospective randomized controlled trial on medical expulsion therapy of ureteral stones with oral isosorbide-SR (40 mg) as long acting smooth muscle relaxant in ureter.

Materials and methods

This prospective randomized controlled trial was performed in Razi university hospital, Rasht (from June 2008 to December 2009) with subjects in an out patient setting. All male and female patients >18 years presenting with documented ureteral stone (<10 mm) in KUB and/or ultrasonography were randomized as control group who received methyl prednisolone-SR (40 mg-IM-stat and 10 days later) plus celecoxib (100 mg—PO-BD) and treatment group who received isosorbide-SR (40 mg, every night) with methyl prednisolone plus celecoxib for 21 days. Lab data (CBC-U/A-U/C-BUN-Cr) were checked in the first visit.

Within 21 days, the physician and the patients had close communication together by phone and the patients received advice or admission for interventional procedures if required.

After 21 days, if the patient did not return to revisit, the physician called on the patient and received the relevant data for completion of questionnaire. If stone expulsion did not occur after 21 days, interventional procedures were performed. The ethical committee approved the study design and all patients signed informed consent form.

Patients older than 18 years, with stones larger than 10 mm, Cr >2 mg/dl, urinary tract infection, solitary kidney or pregnancy were excluded from our study. Other exclusion criteria were current α-blockers, calcium channel blockers, nitrate and PDE-5 inhibitor or corticosteroid use, known allergic reaction to the study drugs or history of ureteral stricture or ureteral surgery.

The primary end point was stone expulsion within 21 day and secondary end points of study were time to spontaneous stone expulsion, additional need to analgesic drugs, the intervention and hospitalization, workday lost rate, side effects of administered drugs and safety of the therapy.

Statistical analysis

Participants were allocated to the two groups using random block method with a 1:1 ratio and collectors were unaware about patient's treatment in either group.

Stone free rate determined with difference of 17% between two groups with confidence of 95% and power 80% and 33 subjective were calculated and statistical analysis was performed using the chi-square in SPSS (2003) software.

Results

From June 2008 to December 2009, 66 patients were randomly assigned in control and treatment groups. 33 patients (50%) in control group and 33 patients (50%) in treatment group entered the final analysis. There were 45 males and 21 females in our study with the mean age of 41.61 years in control group and 43.8 years in treatment group ($P = 0.378$). Mean stone size was 7.45 mm in control group and 7 mm in treatment group. No statistically significant differences were found between the two groups in age, gender, stone location and degree of hydronephrosis. Location of stones was stratified as 11 (33.3%) upper, 3 (9.1%) middle and 19 (57.6%) lower ureter in control group and 8 (24.2%), 2 (6.1%) and 23 (69.7%), respectively, ($P = 0.59$) in the treatment group. The side of stones was 35 (53%) right and 31 (47%) left ureter ($P = 0.084$). Hydronephrosis was absent in 5 (15.2 %) of patients in control and 8 (24.2%) of patients in treatment group.

Mild or moderate hydronephrosis was seen in 13 (39.4%) and 15 (45.4%) of control group and 14 (42.4%) and 11 (33.3%) of treatment group respectively, ($P = 0.554$).

In control group, 4, 4–7 and 7–10 mm stone size and in treatment group, 3 (9.1%), 7 (21.2%) and 23 (69.7%), respectively, were stratified. 3 (9.1%), 17 (51.5%) and 13 (39.4%), respectively, ($P = 0.031$).

16.4% of patients had normal urinalysis while microscopic hematuria was present in 83.6% of patients.

The overall rate of spontaneous stone passage was 49.9%. There was no significant difference in spontaneous stone passage between the control and treatment groups (54.5 vs. 45.5%), respectively, ($P = 0.497$) (Fig. 1).

Surgical intervention requirement was more common in control group within 21 days (9.4 vs. 6.1%) and more common in treatment group after that (33.3 vs. 21.9%) ($P = 0.756$).

Finally, surgical procedures were performed for 10(30%) patients in control group and 13 (39%) patients in treatment group.

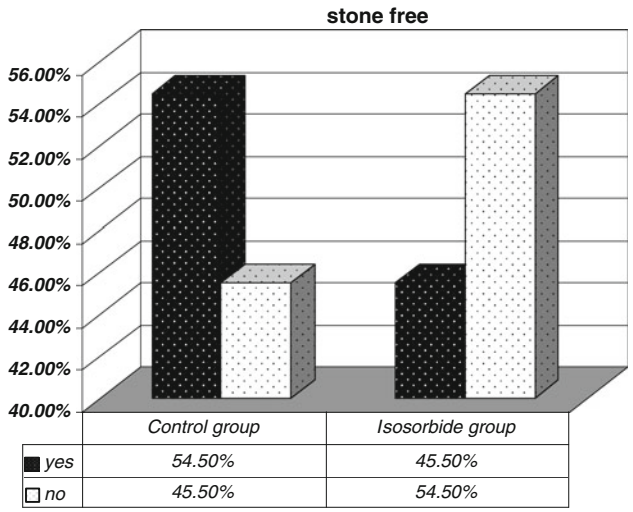

Fig. 1 Stone free rates in the treatment and control groups

Stones with size of 4, 4–7, and 7–10 mm were expulsed spontaneously in 83.4, 54.2, and 41.7% of patients, respectively.

In stone-passed patients, it occurred more common (45.4%) within 21 days and only 4.5% of stone passage occurred after 21 days ($P = 0.152$).

Side effects of isosorbide including headache and dizziness were more common and statistically significant in treatment group (39.4 vs. 9.1%) ($P = 0.004$).

Hospitalization occurred more common in treatment group (3% vs. 0) ($P = 0.314$).

Blood pressure did not change in both groups. Colicky pain episodes was more common in treatment group (24.5 vs. 11.1%) ($P = 0.055$) and additional requirement of analgesic drug injections were more common in treatment group (21.2 vs. 9.1%) ($P = 0.026$) and prolonged colicky pain episodes were more common in treatment group (24.2 vs. 12.1%) ($P = 0.142$) but workdays lost rate were more common in control group (12.1 vs. 0%) ($P = 0.119$) (Table 1).

Table 1 The study groups characteristics

	Control group	Isosorbide group	*P* value
Number (%)	33 (50)	59 (50)	
Mean age (SD)	41.61 (11.29)	43.8 (11.41)	0.378
Mean BMI (SD)	24.79 (3.9)	24.88 (3.57)	0.91
Sex			
Male *n* (%)	22 (66.7)	23 (69.7)	0.792
Female	11 (33.3)	10 (30.3)	
Previous renal operation (SD)	2 (6.1)	1 (3)	
Location			
Upper ureter *n* (%)	11 (33.3)	8 (24.2)	0.59
Middle ureter *n* (%)	3 (9)	2 (6.1)	
Lower ureter *n* (%)	19 (57.5)	23 (69.7)	
Right ureter *n* (%)	21(63.6)	14 (42.4)	0.084
Left ureter *n* (%)	12 (36.4)	19 (57.6)	
Hydronephrosis			
No *n* (%)	5 (15.2)	8 (24.2)	0.554
Mild *n* (%)	13 (39.4)	14 (42.4)	
Moderate *n* (%)	15 (45.4)	11 (33.3)	
Size			
4>mm *n* (%)	3 (9.1)	3 (9.1)	0.031
4–7 mm *n* (%)	7 (21.2)	17 (51.5)	
7–10 mm *n* (%)	23 (69.7)	13 (39.4)	
Stone free *n* (%)	18 (54.5)	15 (45.5)	0.497
No stone free *n* (%)	15 (45.5)	18 (54.5)	
Headache–dizziness *n* (%)	3 (9.1)	13 (39.4)	0.004
Intractable pain *n* (%)	2 (6.1)	9 (27.3)	0.046

Discussion

This study was the first prospective randomized controlled trial for assessment of the efficacy of medical expulsive therapy with oral isosorbide-SR (40 mg).

Several studies have shown that α-blockers expedite the time to stone passage. Previous studies have evaluated the efficacy of tamsulosin, doxazosin and trazosin for medical expulsive therapy [10, 11].

Because of lack of trials on nitrates for medical expulsive therapy, we compared our study with trial results on α-blockers and calcium channel blockers.

Data obtained from our study showed that the spontaneous stone expulsion rate was not significantly difference between the isosorbide-SR (45.5%) and control (54.5%) groups in 21 days ($P = 0.497$). Since it has been suggested that spontaneous stone expulsion occurred in 80–97% with tamsulosin [10, 11] and 81% with nifedipine [12], then, isosorbide treatment in combination with methylprednisolone plus celecoxib did not improve spontaneous expulsion rate of ureteral stones (≤10 mm).

Multiple trials have revealed the efficacy of tamsulosin in medical expulsive therapy of ureteral stones [13]. They have suggested that tamsulosin decreased episodes of colicky pain and analgesic requirement and hospitalization rate. Park et al. [14] reported that nitrate spray decreased acute colicky pain that was intractable to narcotic drugs.

But in the present study, colicky pain was more common in isosorbide group (27.3 vs. 6.1%) ($P = .046$).

Hospitalization (3 vs. 0%) ($P = 0.314$), prolonged and intractable colicky pain (27.3 vs. 6.1%) ($P = 0.046$) were more in the isosorbide group. Further, the side effects of

drugs, such as headache and dizziness (39.4 vs. 9.1%) ($P = 0.004$) were more common in isosorbide-SR group. Also analgesic requirement was more common in isosorbide group (21.2 vs. 9.1%) ($P = 0.026$).

Papadoukakis et al. [15] reported that upper, middle and lower ureteral stones were expulsed spontaneously in 25, 45 and 75%, respectively. In the current clinical trial, the stones were expulsed 15.2, 6.1 and 78.8% ($P = 0.09$), respectively.

It has been reported that stones with size of 4, 4–6 and >6 mm were expulsed spontaneously in 80, 59 and 21%, respectively, [16] and present study revealed that stones with size of 4, 4–7 and 7–10 mm expulsed spontaneously 83.4, 54.2 and 41.7%, respectively.

Hussain et al. [8] in study with glycerin trinitrate patch, reported that headache occurred in 25% of patients who had to discontinue this drug, but in our study, headache and dizziness occurred in 39.4% of treatment patients against 9.1% of control patients ($P = 0.004$) who continued this drug.

It has been suggested that surgical procedures were performed in 50% of patients with ureteral stone >4 mm [16] but in present study surgical procedures were performed in 30% of control and 39.3% of isosorbide-SR groups.

Early onset surgical procedures (<21 days) were performed in 6.1% of isosorbide and 9.4% of control group in the present study but in Hussian's study, no patient had intervention during the 6 week study period.

Stone expulsive rate was more common in right ureter (54.5 vs. 45.5%) in our study, but this difference was not statistically significant ($P = 0.56$).

Recent work investigating the role of nitric oxide in obstructive uropathy has demonstrated a beneficial antifibrotic effect. Although some uncertainly remains as to whether reducing the resultant tubointerstitial fibrosis attenuates renal scaring, isosorbide may be protective in the context of acute renal obstruction [8].

Our preliminary results did not demonstrate a significant advantage in using isosorbide-SR in terms of spontaneous stone passage within 21 days. However because of the small differences observed in this study, it may be an error due to small number of patients. We believe that additional research is required to evaluate fully the potential of nitric oxide in the treatment of patients with ureteral stone.

The probable explanation of our finding is that the nitrate has a high metabolic rate with rapid first pass effect during oral ingestion and it may affect the efficacy of this drug in medical expulsive therapy. Perhaps a sublingual or spray form of nitrate compound may facilitate medical expulsive therapy. Further trials are recommended.

Conclusion

The data revealed that oral isosorbide-SR did not only improve the stone expulsion rate in patients with ureteral stone (≤10 mm), but also that patients developed more side effects in treatment group. Thus, isosorbide-SR may not be a proper alternative for known α- blockers and calcium channel blockers in medical expulsive therapy for ureteral stones.

Conflict of interest The authors of this article have no conflict of interest for this manuscript and do not have a financial relationship with any organization.

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