Urol Res (2011) 39:491–495
DOI 10.1007/s00240-011-0380-z

ORIGINAL PAPER

Tamsulosin does not have greater efficacy than conventional treatment for distal ureteral stone expulsion in Mexican patients

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Received: 12 October 2010 / Accepted: 7 April 2011 / Published online: 24 April 2011
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Abstract The objective of the study was to evaluate tamsulosin (TAM) efficacy in distal ureteral stone expulsion in Mexican patients. A double-blind clinical trial was carried out for a period of 4 weeks on 65 patients assigned to the following treatment groups: Group A, 32 patients receiving conventional treatment + TAM; and Group B, 33 patients receiving conventional treatment + placebo. Patients of both groups were checked every 14 days to evaluate treatment adherence and clinical progression through plain abdominal film and abdominal ultrasonogram. There was no significant difference in stone expulsion percentage between groups: Group A 69% ($n = 22$) versus Group B 70% ($n = 23$), $P = 0.9$. There was no significant difference in mean expulsion time comparison between groups: Group A 22 ± 6.7 days (11–30 days interval) versus Group B 23 ± 6.3 days (11–30 days interval), $P = 0.3$. Tamsulosin did not demonstrate greater efficacy in distal ureteral stone expulsion in Mexican patients.

Keywords Stone · Tamsulosin · Ultrasonogram · Ureteral · Plain film

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Introduction

In the United States, it is estimated that urolithiasis will present in 8–15% of the population and approximately 50% of these individuals will spontaneously expel the stones and the remaining 50% will present with reno-ureteral colic [1]. Conventional treatment for kidney stones is endoscopic ureterolithotomy and lithotripsy. However, these procedures are costly and not risk-free [2–6]. Treatment with anti-inflammatory and antispasmodic medication as well as analgesics and antibiotics is used to reduce edema, spasm and infection [1, 7, 8].

Tamsulosin (TAM) is an alpha 1 adrenergic drug that has been reported as a therapeutic alternative in stone expulsion and reno-ureteral colic reduction. Early studies have stated that the combination of TAM with corticosteroid and antibiotic therapy increased juxtavesical stone expulsion and an almost complete disappearance of pain symptomatology in up to 80% of cases [9–16]. Recent studies have shown contradictory results. Most of the positive results were observed in Asian patients [17–21], meanwhile negative results occurred in European patients [22, 23]. With this in mind, the objective of the present study was to determine tamsulosin efficacy when compared with conventional treatment in distal ureteral stone expulsion in Mexican patients.

Materials and methods

A double-blind clinical trial was carried out from June 2006 to December 2007 on patients who came to the emergency room of the Hospital Regional Universitario of the Health Department of Colima, Mexico, presenting with reno-ureteral pain. Patients of both sexes were older than

18 years and presented with reno-ureteral stones between 5 and 10 cm, determined by plain abdominal film and kidney ultrasound. Patients presenting with hydronephrosis, acute or chronic renal insufficiency, multiple ureteral lithiasis, a history of surgery or endourologic procedures, large and impacted ureteral calculi, pregnancy, lactation, distal ureteral lithiasis in a single kidney, patients taking alpha- or beta-blockers, nitrates or calcium antagonists and patients who worked as airline pilots were all excluded from the study.

Patients were treated for pain and once it had subsided they were asked to participate in the study. Risks and benefits involved in the study were explained in detail and the participating patients signed letters of informed consent. These patients were then randomly assigned to the two treatment groups (Fig. 1). Group A received conventional treatment + 0.4 mg of TAM daily for 4 weeks and Group B received conventional treatment + placebo (starch tablets) daily for 4 weeks. All patients were instructed to drink at least 2 liters of water per day and to carry out their normal activities. Patients of both groups were checked every 14 days to evaluate treatment adherence and clinical progression through plain abdominal film and abdominal ultrasonogram (Fig. 1). The variables evaluated were: size and localization of stones in relation to patient's right or left side, stone expulsion time, and secondary reactions to medication. Treatment failure was considered when there was no spontaneous stone expulsion during the length of time of the study and those patients then underwent endoscopic or surgical procedures.

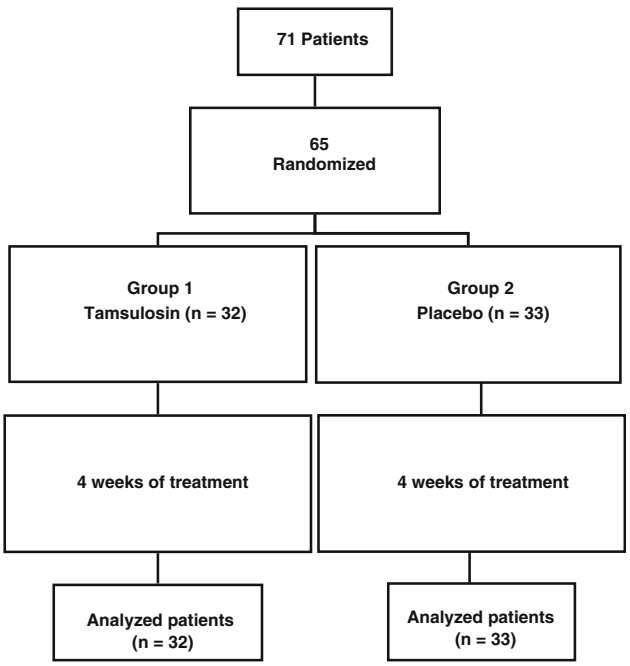

Fig. 1 Study patient flow diagram

Patients who did not participate in the study for the full amount of time for reasons unrelated to treatment (secondary reactions) or because of treatment failure were eliminated from the analysis. This study was approved by the Local Ethics Committee of the Teaching and Research Department of the Hospital Regional of Colima.

The following formula from the EPI INFO 6-04b statistical package was used to calculate sample size:

$$n = \frac{(Z\alpha + Z\beta)^2\, \overline{p}(1-\overline{p})(r+1)}{(d)^2 r}$$

$Z\alpha = 95\% = 1.96$
$Z\beta = 80\% = 0.84$
$d = 0.35$
$r =$ relation between number of individuals in both treatment groups $= 1$
$p1 =$ proportion of non-responsive individuals in the experimental treatment group $= 1 - 0.85 = 0.15$
$p2 =$ proportion of non-responsive individuals in the control group $= 1 - 0.50 = 0.50$.

According to this formula, sample size was 32 per group. However, loss percentage was considered at 20–25% and the final result was ~70 patients.

Statistical analysis

Percentage, mean, and standard deviation were used. Percentage comparison was made with the Chi-square test or Fisher exact test and mean comparison with the Student's *t* test. All tests had a 95% confidence interval (CI) and there was statistical significance when $P < 0.05$.

Results

Of the total of 71 patients, 65 (91.6%) completed the study (Fig. 1) and were distributed in the following manner: Group A = 32 patients (15 men and 17 women) and Group B = 33 patients (21 men and 12 women). The similar demographic characteristics between the two groups are shown in Table 1.

There was no significant difference in stone expulsion percentage between groups: 69% in Group A ($n = 22$) versus 70% in Group B ($n = 23$), $P = 0.9$.

There was also no significant difference in the comparison of mean expulsion time in days between groups: Group A 22 ± 6.77 days (11–30 days interval) versus Group B 23 ± 6.36 days (11–30 days interval), $P = 0.3$.

Adverse reactions presented in 12.5% ($n = 4$) of Group A patients (dizziness $n = 2$ and retrograde ejaculation

Table 1 Group A and B clinical and demographic characteristics

Variables	Group A ($n = 32$)	Group B ($n = 33$)	P
Age in years (mean ± SD)	38.5 ± 11.3	38.2 ± 12.4	0.6*
Size calculation in mm (mean ± SD)	5.3 ± 0.55	5.2 ± 0.39	0.1*
Stones ≤ 5 mm, *n* (%)	21 (66%)	27 (82%)	0.3
Stones of 6 mm, *n* (%)	10 (31%)	6 (18%)	0.2
Stones of 7 mm, *n* (%)	1 (3%)	0 (0)	–
Stone localization, *n* (%)			
Right side	12 (38%)	16 (48%)	0.4
Left side	20 (62%)	17 (52%)	0.3

P Chi-square test; * Student's *t* test

$n = 2$). Symptomatology was mild in all cases and patients were able to continue treatment. The 20 patients from both groups who were not able to spontaneously expel their stones received the following treatment: seven Group A patients underwent ureterolithotomy ($n = 7$) and double-J ureteral catheter was placed in the remaining three ($n = 3$); six Group B patients underwent ureterolithotomy ($n = 6$) and ureteral catheter was placed in the remaining four ($n = 4$).

Comparison of clinical and demographic characteristics was carried out on patients who expelled their stones and no differences were found between the two treatment groups (Table 2).

Discussion

The objective of kidney stone treatment is to alleviate pain and to expel stones (either spontaneously or by induction). Analgesics, anti-inflammatory drugs, smooth muscle relaxants such as nitrates and calcium-channel blockers are used for this purpose [8, 9, 11].

Tamsulosin (TAM), the α-1 adrenergic blocker that is used in prostatic hyperplasia treatment, has been shown to promote distal reno-ureteral stone expulsion and to reduce colic pain [14]. However, efficacy varies according to the population studied. Good efficacy was observed in Turkish [21], Arab [18, 20], Japanese [19] and Thai patients [17]. On the other hand, in Swiss patients [23] and in patients from a United States hospital emergency department [24], tamsulosin did not improve stone expulsion. An Italian study reported the need for a second cycle of 10 days of TAM in first cycle nonresponders in order to be effective [22]. In the present study, approximately 70% of patients treated with TAM expelled their stones. However, the percentage in the control group was similar, indicating that more than 50% of the population studied presented with spontaneous expulsion. These results are similar to those reported by Resim et al. [25] and Hermanns et al. [23], in which TAM expulsion percentage was 86% and also there was no significant difference with the control group. There is no exact explanation for the difference among populations. There could be a genetic influence, given that certain genetic polymorphisms are predominant in one population and rare in another. For example, the Bsml polymorphism of the vitamin D gene receptor in patients with rheumatoid arthritis, considered to be a risk factor for vertebral fractures, has 0.6% prevalence in Asians and 20% prevalence in white Europeans [26, 27]. In addition, studies demonstrating TAM efficacy describe mean expulsion time of almost 3 days [14]. In our study, the mean was over 20 days and there was no significant difference with the control group. There is also no precise explanation for this finding either. The abovementioned hypothesis could also be considered to play a role. In routine clinical conditions patients are observed for 4 weeks in order to allow for the spontaneous passing of stones, as was done in the present study.

Since there are no reports in the literature available to us evaluating stone expulsion percentage between men and women, the present study stratified patients according to sex for the purpose of evaluating whether or not there was an expulsion percentage difference between sexes. No significant difference was found between men and women in either group.

With regard to mean stone size no significant difference was observed between the two groups. It was also seen that

Table 2 Clinical and demographic characteristics of patients who expelled stones

Variables	Group A ($n = 22$)	Group B ($n = 23$)	P
Sex			
Female (%)	13 (59)	10 (43.4)	0.2
Male (%)	9 (41)	13 (56.6)	0.2
Age			
<37 years (%)	12 (54.5)	14 (60)	0.4
≥38 years (%)	10 (45.5)	9 (40)	0.4
Stone size			
<15 mm^2 (%)	19 (86.3)	22 (95.6)	0.2
≥18 mm^2 (%)	3 (13.7)	1 (4.4)	0.2

P Chi-square test

stones were expelled in both groups in the same proportion, regardless of size. There was no apparent relation between stone size and expulsion time, suggesting that other factors such as shape, anatomic alterations, ureteral spasm, edema and infection should be contemplated [28]. On the other hand, because the fundamental objective of the present study was to observe stone expulsion, unfortunately no pain follow-up was carried out. In addition, patients were included in the study after pain was controlled. This is a subject that should be considered for future study on the Mexican population.

The most frequent secondary effects of TAM that have been reported are headache, abnormal ejaculation, dizziness and diarrhea [16]. In the present study, four patients presented with mild, transitory adverse effects. Open surgery or ureteral catheter placement was carried out in 20 patients—10 in each group—in the present study. This number is lower than that described by other authors who report that approximately 50% of patients with stones larger than 5 mm are likely to need one of these procedures [29]. Ureterolithotomy was employed in the present study because it is an affordable and technically viable procedure in the authors' hospital, and most likely this situation is common in developing countries.

It is important to carry out studies on different populations in order to obtain specific results. In this regard it has been reported that despite evidence that alpha-blockade may be beneficial to patients arriving at the emergency department with ureteral stones, this approach is still used inconsistently by emergency physicians [30]. Autorino et al. [31] make the reasonable suggestion that if TAM is going to be truly useful, significant benefit should be seen within the first 2 weeks of administration.

The present study concludes that tamsulosin as monotherapy did not demonstrate greater efficacy than conventional treatment for distal ureteral stone expulsion in Mexican patients. Perhaps a combination therapy [31] or a second cycle of TAM [22] would provide more successful results in this population.

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