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The use of tamsulosin in the medical treatment of ureteral calculi: where do we stand?

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Abstract It has recently been demonstrated that specific adrenoceptors subtypes (α_{1A}/α_{1D}) are prevalent in the distal part of the ureter, a finding supporting the interesting results obtained by different groups with the use of tamsulosin in the treatment of distal ureteral calculi. We performed a prospective randomized study to evaluate the effects of the addition of tamsulosin on our standard pharmacological therapy for the treatment of selected ureteral stones. A total of 64 patients referred to our department for the management of symptomatic ureteral calculi were considered. Patients were randomly divided into two treatment groups: group A ($n=32$) who received diclofenac (100 mg/daily) plus aescin (80 mg/daily) and group B ($n=32$) who received the same therapy plus tamsulosin (0.4 mg/daily) for a maximum of 2 weeks. No significant differences were found between the groups for age, gender distribution and mean stone size measured in the single largest dimension at presentation. The stone expulsion rate was 60% (19/32 patients) for group A and 88% for (28/32) for group B with a mean expulsion time of 7.4 ± 2.2 (range 3.5–12) and 4.8 ± 2.7 days (range 1.8–10.5), respectively. Group B showed a significant advantage in terms of both expulsion rate ($P=0.01$) and expulsion time ($P=0.005$). Different analgesics from those used in the standard treatment regimen were required in ten patients in group A (31%) but only three patients in group B (9%). This

difference was significant ($P=0.003$). Hospitalization for recurrent colic was needed in 21% of patients in group A (7/32) and in 9% in group B (3/32) ($P=0.01$). Only two patients in each group (6%) experienced minor side effects associated with the expulsive therapy. Our data confirm the efficacy of tamsulosin in the treatment of distal ureteral stones up to 1 cm. This selective α -blocker should therefore be included in the pharmacological regimen of patients when a conservative approach is considered in the treatment of ureteral lithiasis.

Keywords Tamsulosin · Ureteral stones · Medical treatment

Introduction

α_1 -Adrenoceptor antagonists represent the major initial treatment for patients with LUTS suggestive of BPH. The use of a selective α_{1A}/α_{1D} -adrenoceptor antagonists, such as tamsulosin, has the advantage that it is not only effective, but also well tolerated and has a very fast onset of action [1].

Management of urinary stones still occupies an important place in everyday urological practice as 8–15% of the population in western countries suffer from this disease [2]. The stones are frequently located in the ureter, mostly in its distal part [3]. With the introduction and improvement of minimally invasive therapies, such as SWL and ureteroscopy, much has been written on the optimal active management of ureteral calculi. On the other hand, little emphasis has been placed on the role of conservative pharmacological therapy, which is generally indicated for small distal ureteral stones [4].

The physiology of the ureter and the changes that occur with ureteral obstruction have been well studied. The main factors associated with calculus retention include: ureteral muscle spasm, submucosal edema, pain and infection within the ureter. It seems logical that conservative therapy should address these factors. From

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the pioneering work of Borghi et al. [5], in which steroids and calcium-channel blockers were found to increase the rate of spontaneous stone passage, various medications have been used. Some groups have implemented an observational approach based only on the control of pain, while others treat the mentioned causes of stone retention pharmacologically in order to facilitate expulsion [6, 7].

A role for α -blocker agents has been advocated in this setting on the basis of evidence that α -1 receptors are predominant in the ureteral smooth muscle [8]. Therefore, it has been suggested that the blockade of α -adrenergic receptors by a specific antagonist will result in decreased ureteral peristaltic amplitude and frequency with a consequent loss of intraureteral pressure and an increase in fluid transport ability [9].

Ukhal et al. were the first to report positive results in accelerating lower tract ureter stone passage using an α -blocker [10]. More recently, it has been demonstrated that specific adrenoceptor subtypes (α_{1A}/α_{1D}) are prevalent in the distal part of the ureter [11], a finding which supports the interesting results obtained by different groups with the use of tamsulosin in the treatment of selected distal ureteral calculi [12–15].

We decided to perform a prospective randomized study to evaluate the effects of the addition of tamsulosin to our standard pharmacological therapy for the treatment of selected ureteral stones.

Materials and methods

Overall, 125 consecutive patients were referred to our department for the management of symptomatic calculi. Of these, 70 had unilateral distal ureteral calculi who were considered for this study. All stones were diagnosed with unenhanced CT scan. Exclusion criteria were urinary tract infection, severe hydronephrosis, diabetes, ulcer, hypotension or hypertension when in treatment with α -blockers or calcium-antagonists, pregnancy, multiple stones, history of spontaneous stone expulsion or ureteral stricture. Among the 70 patients who were screened, six were excluded because of diabetes (1), pharmacological treatment with calcium antagonists for hypertension (2), severe hydronephrosis (1), or who refused to participate in the protocol (2).

The remaining 64 patients were randomly divided into two treatment groups: A (32 patients) who received diclofenac (100 mg/daily) plus aescin (80 mg/daily) and B (32 patients) who received the same therapy plus tamsulosin (0.4 mg/daily) for a maximum of 2 weeks. All patients were instructed to drink 2 l of water daily. All received 20 mg omeprazole daily for the treatment period and 250 mg levofloxacin daily for the first week.

Randomization was done only with the patient's permission after they had read a summary describing the goals of conservative management and a description of the drugs they would be taking. Potential side effects and complications of the drugs were discussed.

The follow-up continued until the stones was passed or intervention occurred (SWL or ureteroscopy). The criteria for treatment discontinuation, as well as the need for hospitalization and/or endoscopic treatment, were uncontrollable pain, fever and/or severe hydronephrosis, or lack of success in expulsion after 2 weeks.

Since there was the risk that group B patients would be more likely to be managed as outpatients or without intervention, which could represent a bias in the study, two authors (R.D. and S.P.) decided on the need for hospitalization or intervention. They were blinded to the treatment since they did not directly participate in the randomization and initial management of the patients.

Statistical methods

The expulsion rate was the primary end-point of this study. Based on the results in the literature, it was determined that tamsulosin would be defined as effective should its use increase the expected expulsion rate by 30% or more. To detect a difference of this magnitude with a power of 80% and a significance level of 5%, about 30 patients per arm were required.

Treatment was assigned on a randomized basis according to a 1:1 ratio. Randomization, not blinded, was performed using a stratified permuted randomization algorithm. Stratification factors included age, sex and stone size. All randomly assigned patients were included in the efficacy and safety analysis. As secondary end-points, we evaluated expulsion time, need for analgesics, need for hospitalization, and side effects.

The Student's *t*-test was used to compare the means of normally distributed variables between the two treatment groups. Otherwise, the Mann-Whitney U-test was used. Nominal parameters were analyzed using Fisher's exact test. SPSS software was used to perform the analysis.

Results

No statistically significant differences were found between the groups for age, gender distribution or mean stone size measured in the single largest dimension at presentation (Table 1).

The stone expulsion rate was 60% (19/32 patients) for group A and 88% (28/32) for group B with a mean expulsion time of 7.4 ± 2.2 (range 3.5–12) and

Table 1 Patient and treatment data

<i>n</i>	Group A 32	Group B 32	<i>P</i>
Mean age	43	45	0.145
Sex ratio (male:female)	21:11	22:10	0.272
Mean size (range)	5.7 mm (3–10)	6.5 mm (4–10)	0.091

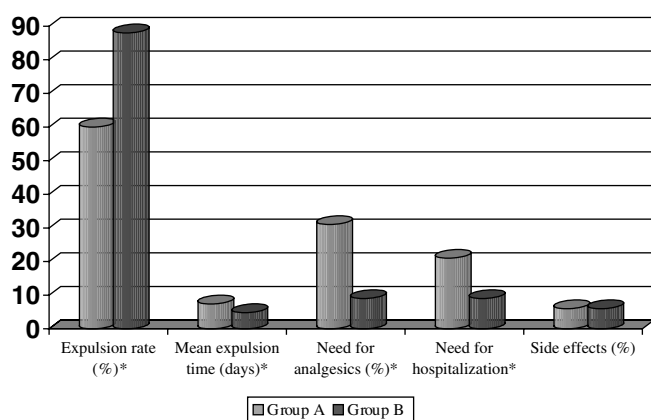


Fig. 1 Results comparing the two treatment schedules in the conservative treatment of . An asterisk indicates $P < 0.05$

4.8 ± 2.7 days (range 1.8–10.5), respectively (Fig. 1). Group B showed a statistical advantage in terms of both expulsion rate ($P = 0.01$) and expulsion time ($P = 0.005$). No significant difference in mean stone size was found between patients in either group (5.6 ± 1.2 and 6.1 ± 1.6 mm, respectively). Similarly no differences were observed in the distribution of expulsion by males or females.

Different analgesics from those used in the standard treatment regimen were required in ten patients in group A (31%) but three patients in group B (9%). This difference was statistically significant ($P = 0.003$). Hospitalization for recurrent colic was needed in 21% of patients in group A (7/32) and in 9% in group B (3/32) ($P = 0.01$). Only in the hospitalized patients in group A (50%, 5/10 patients) was there a need for an endoscopic maneuver to place a double J ureteral stent because of an uncontrollable pain. No patient in group B was submitted to the same procedure during the observation period.

Only two patients in each group (6%) experienced minor side effects associated with expulsive therapy. In group A, there was one case of malaise and one of diarrhea. In group B, there was one patient with transient hypotension and one with asthenia and dizziness. No stomach pain was recorded. Patients who were not stone free after the 4 weeks of follow-up (13 in group A and four in group B) were treated with ureteroscopy or SWL.

Discussion

A conservative approach to the patient with symptomatic distal ureteral stone should be focused on the patient's pain and known causes of stone retention. Hence, inability to control pain usually becomes the most common indication for an active treatment, and the cause of colicky pain is an increase in the intraureteral and intrarenal pressure secondary to the inability of

ureteral peristalsis to move the urine distally to the obstructing stone. The main factors associated with stone obstruction are ureteral muscle spasm, submucosal edema, pain and infection within the ureter. It seems logical that medical therapy address these factors. Various drug combinations have been described in the literature to assist the passage of ureteral stones, since several drugs can influence the contractile activity of the ureter.

Among the studied drugs, nifedipine has been shown to be effective in the relief of acute ureteral pain, as this calcium antagonist reduces the number of ureteral contractions [16]. Borghi et al. used an expulsive therapy consisting of methylprednisone and nifedipine in a randomized double-blind study, treating patients with stones of up to 1.5 cm in any tract of the ureter. They demonstrated the beneficial effect of nifedipine in reducing time to stone passage and improving expulsion rates [5]. Their results were confirmed by Porpiglia et al. who used nifedipine plus another corticosteroid agent, deflazacort [7]. Cooper et al. treated 70 patients with ureteral calculi and found that the addition of nifedipine, prednisone, acetaminophen and antibiotics to their standard medical therapy resulted in a much higher stone passage rate and fewer work days lost, emergency room visits and surgical interventions [6]. However, they underlined how difficult it was to quantify the contribution of each single drug to the outcome of treatment.

Several studies have focused on the role of the adrenergic system in ureteral physiology and a role for α -blocker agents has been advocated in this setting on the basis of evidence that α -1 receptors are predominant in the ureteral smooth muscle [8]. Therefore, it has been suggested that the blockade of α -adrenergic receptors by a specific antagonist results in decreased ureteral peristaltic activity with a consequent loss of intraureteral pressure and an increase in fluid transport ability [9]. Thus, some authors have proposed the use of α -blockers with the aim of facilitating lower ureteral stone expulsion. In particular, Ukhal et al. were the first to report positive results in accelerating lower tract ureter stone passage using an α -blocker [10].

More recently, it has been demonstrated that specific adrenoceptor subtypes (α_{1A}/α_{1D}) are prevalent in the distal part of the ureter [11], a finding which is supported by the interesting results obtained by different groups with the use of tamsulosin in the treatment of selected distal ureteral calculi [12–15].

Cervenakov et al. performed a randomized study and registered a significant advantage in stone expulsion rates when adding tamsulosin to their standard therapy, which was actually very complex, consisting of tramadol, diazepam, veram (non-steroid antireumatic) and yellon (antiexudativum) [12].

Promising results were also obtained by Dellabella et al. [13] who found a better efficacy with tamsulosin, which was compared to florglucine-trimetossibenzene, a spasmolytic drug very popular in Italy. These authors explained the positive effect of tamsulosin in that it

Table 2 Tamsulosin treated patients: comparing the results from randomized studies

Reference	Patients	Mean stone size in mm (range)	Pharmacological regimen (daily dose)	Observation time	Expulsion rate	Mean expulsion time (days)	Severe side effects (no. cases)
Cervenakov et al. [12]	51	5.8 (1–10)	Tamsulosin (0.4 mg) + tramadol (50 mg), Diazepam (5 mg), Veral (150 mg), Yellow (120 mg)	1 week	80.4%	3.1	–
Dellabella et al. [13]	30	6.7 (3.8–13)	Tamsulosin (0.4 mg) + Deflazacort (30 mg), Cotrimoxazole (640 mg), Diclofenac (75 mg on demand)	4 weeks	100%	2.7	0
Porpiglia et al. [14]	28	5.4 (3–10)	Tamsulosin (0.4 mg) + Deflazacort (30 mg), Diclofenac (75 mg on demand)	4 weeks	85%	7.7	2
Kupeli et al. [15]	15	4.7 (3–5)	Tamsulosin (0.4 mg) + Diclofenac (100 mg)	2 weeks	53%	–	1
Present study	32	6.5 (4–10)	Tamsulosin (0.4 mg) + Diclofenac (100 mg), Aescin (80 mg), Levofloxacin (250 mg)	2 weeks	88%	4.8	0

should induce an increase in the intraureteral pressure gradient around the stone as well as a decrease of frequency of phasic peristaltic contractions in the obstructed ureteral tract and, therefore, a reduction of the algogenic stimulus [13]. More recently, Porpiglia et al. performed a comparative study on the safety and effectiveness of nifedipine and deflazacort versus tamsulosin and deflazacort for the treatment of distal ureteral stones. With both regimens, the patients became stone free sooner and had less need of additional pain medication. They concluded that medical therapy, particularly with tamsulosin, could reduce expulsion times [14].

Finally, Kupeli et al. reported their experience on the addition of tamsulosin to medical therapy or to SWL for lower ureteral stones. They randomized 78 patients in four groups, all of whom were re-evaluated after 2 weeks. The difference between the stone-free rates for the tamsulosin versus control groups were statistically significant. The positive effect of the α -blocker was more evident for larger stones [15].

In the present study, patients were prospectively randomized to receive our standard therapy (diclofenac sodium + aescin + antibiotics) or standard therapy plus a selective α_{1A}/α_{1D} -adrenoceptor antagonist (tamsulosin). Therefore, our specific aim was to evaluate the potential role of tamsulosin in our standard medical approach for the conservative treatment of distal ureteral stones. As discussed above, various drug combinations have been described to assist stone passage. Moreover, the use of tamsulosin has already been advocated as an alternative to other spasmolytics. What we were interested in confirming in our daily clinical practice, was whether the use of tamsulosin can be considered worthwhile.

It is our belief that a conservative approach to ureteral stones up to 10 mm should not be carried out for longer than 2 weeks, in order to avoid renal function impairment, urosepsis and intractable pain. This period is shorter than the one proposed by Hubner et al. [17] and adopted by others. Placebo was not used in the control group because our main goal was to compare tamsulosin with our standard therapy. Moreover, it would have been difficult to offer a placebo when the passage of the stone is invariably associated with colicky pain that represents the main problem for the patient.

It would have been interesting to use analogue pain scores to compare differences in pain between treatment groups. However, what we believe to have a real *impact* in our real-life practice is the evaluation of expulsion rate and time, which represented our primary outcomes, as well as the need for hospitalization and for other analgesics. Obviously, all of these parameters are an indirect measurement of pain.

The use of an antibiotic was part of the protocol. It is widely recognized that infection within the ureter is a possible cause of calculus retention [6]. Therefore, it seemed opportune to include an antibiotic in the standard approach to the patient with symptomatic ureteral stone. The reason for the specific use of levofloxacin 250 mg is the fact that this drug can be administered

once daily, an aspect which can be important for the patient. We thought that a 1 week therapy could be an appropriate and reasonable measure in this setting. Similarly, in the study by Dellabella et al., patients received cotrimoxazol only for 8 days [13], whereas in the study by Cooper et al. they received trimethoprim sulfa for 7 days [6].

Diclofenac sodium is a nonsteroid anti-inflammatory drug (NSAID) possessing potent analgesic properties with fast onset and long duration. It has been advocated for use in painful conditions. Moreover, it has already been proposed that pain relief together with spasmolysis of the ureter, supporting stone passage, can be achieved by the application of NSAIDs like diclofenac [18]. Thus, one can hypothesize synergism between diclofenac and tamsulosin, or, in general, other agents acting on ureteral smooth muscle. Further clinical and experimental research is needed to confirm this.

Aescin, the major active principle from the horse chestnut tree, has shown satisfactory evidence for a clinically significant activity in postoperative oedema. Its therapeutic benefit is well supported by a number of investigations indicative of clear-cut anti-oedematous, anti-inflammatory properties and its excellent tolerability [20].

Patients in the tamsulosin group demonstrated a higher incidence of stone passage, more rapid stone passage and a reduction in complications deriving from stone passage. We observed only two cases of minor side effects in each group, confirming the safety and tolerability of the therapy. Although our side-effect profile for tamsulosin seems low compared with published data, you have to consider that our results are from only 2 weeks of treatment. None of the male patients reported any ejaculatory abnormality, probably because, again, of the short observation time and the decrease in coitus frequency owing to colicky pain. Our results were comparable to those of other groups (Table 2). The therapy proved to relieve ureteral pain, as shown by the significantly lower use of analgesics and need for hospitalization. Thus, these results indicate the possibility of home management and a loss of fewer working days. They also indicate an advantage in terms of costs, given that a conservative approach is associated to less expenses only if successful [20].

Conclusions

Patients in the tamsulosin group demonstrated a higher incidence of spontaneous stone passage, more rapid stone passage and a decreased need for analgesics and hospitalization. These data confirm the positive findings of other groups on the use of tamsulosin in the treatment of distal ureteral stones up to 1 cm. This selective

α -blocker should therefore be included in the different schedules used worldwide, when a conservative approach to this very common urological problem is considered. However, it would be interesting to evaluate other similar agents in this setting, making further clinical research in this field necessary.

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