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ORIGNAL PAPER

Does tamsulosin change the management of proximally located ureteral stones?

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Abstract The objective of this study is to assess the efficacy of an alpha-1 adrenergic receptor blocking agent on the spontaneous passage of proximal ureteral calculi ≤10 mm. 92 patients having single radio-opaque proximal ureteral stone ≤10 mm were randomized into two groups. Group 1 patients ($n = 50$) were followed with classical conservative approach and patients in Group 2 ($n = 42$) additionally received tamsulosin, 0.4 mg/day during 4 weeks follow-up. The stone passage rates, stone expulsion time, VAS score, change in colic episodes, and hospital readmission rates for colicky pain were compared. The patients were furthermore stratified according to stone diameters <5 and 5–10 mm. The data of these subgroups were also compared. Stone expulsion rates showed statistically significant difference between tamsulosin receivers and non-receivers (35.7 vs 30%, $p = 0.04$). Time to stone expulsion period was also shortened in those receiving tamsulosin (8.4 ± 3.3 vs 11.6 ± 4.1 days, $p = 0.015$). Likewise, the mean VAS score and renal colic episodes during follow-up period were significantly diminished in Group 2 patients (4.5 ± 2.3 vs 8.8 ± 2.9, $p < 0.01$ and 66.6 vs 36%, $p = 0.001$, respectively). Among the stones <5 mm, tamsulosin receiving patients had higher spontaneous passage rate (71.4 vs 50%, $p < 0.001$). The prominent effect of tamsulosin on the 5–10 mm stones was the relocation of the stones to a more distal part of ureter (39.3 vs 18.7%, $p = 0.001$). Administration of tamsulosin in the medical management of proximal ureteral calculi can facilitate the spontaneous passage rate in the stone <5 mm and the relocation of the stones between 5 and 10 mm to more distal part of the ureter.

Keywords Alpha-1 blockers · Medical expulsion treatment · Proximal ureter · Stone

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Introduction

With a constantly increasing incidence, urinary stone disease has an estimated lifetime risk of 5% in Europe and 12% in the USA, affecting 13% of men and 7% of women. Since 50% of patients will have a recurrence of renal colic within 5 years of their first episode, as a chronic disease, urolithiasis has substantial economic consequences and is of great public health importance [1].

The overall likelihood of the spontaneous passage of proximally located ureteral stones is relatively lower than distally located ones and conservative approach in appropriate cases is cost-effective when compared with minimally invasive surgical methods [2, 3]. However, during conservative follow-up period, patients may experience some certain well-known problems such as repeated renal colic attacks, urinary infection, and hydronephrosis, all of which may require prompt readmission and management, usually in emergency departments. Traditionally,

antispasmodic agent is the one of the most commonly used medication to shorten the time for stone passage and reduce the colic pain attacks, thereby reducing the need for surgical intervention.

In recent years, several studies have focused on accelerating the spontaneous expulsion of ureteral stones by evaluating the possible effects of certain medical agents. Among these drugs, analgesic agents, anti-inflammatory drugs, calcium antagonists (nifedipine), and alpha-1 blockers constitute the most commonly used ones [4]. Of these agents, alpha-1 blockers have been found effective in the medical expulsive management of such stones by increasing the likelihood of spontaneous stone passage in a relatively shorter time period while decreasing the need for analgesics as well as the need for hospitalization. As a result, following clinical use in an effective manner (medical expulsive treatment [MET]), alpha-1 blockers did significantly change the clinical course as well as the management protocols that have been proposed and applied in distally located ureteral calculi [5–8].

Taking the clinically proven effects of alpha-1 blockers on distal ureteral stones into account, in this present study, we aimed to evaluate the possible effect of an alpha 1 antagonist (tamsulosin) therapy on the management and the course of the disease in patients with upper ureteral stones.

Materials and methods

Between December 2004 and November 2008 patients with radio-opaque proximal ureteral stones with a diameter $\leq$10 mm were included into the study programme. Proximal ureter was defined as the ureteral segment between uretero-pelvic junction and upper margin of sacro-iliac joint. Exclusion criteria included patients having severe hydronephrosis, a solitary kidney, an extra stone in the upper urinary system, a previous surgical history, or diseases such as diabetes, hypertension, and pregnancy and those whose renal reserve was reduced by more than 50%. Radiologic evaluation of the urinary system included plain X-ray (KUB film), abdominopelvic sonography, and non-contrast spiral computerized tomography. Intravenous urography was performed if needed.

In addition to conservative approach, 92 patients were randomized independently into two groups as follows. While the patients in Group 1 ($n = 50$) were followed with classical conservative approach (adequate hydration, increased physical activity and routine pain management with hyoscine-*N*-butylbromide 10 mg three times daily); patients in Group 2 ($n = 42$) did additionally receive an alpha-1 adrenergic receptor blocking agent (tamsulosin, 0.4 mg/day) during the same 4-week follow-up period. Patients passing the stone during this period stopped receiving medication after appropriate radiological confirmation. In addition to plain film (KUB), a non-contrast spiral CT was performed if there was suspicion of spontaneous passage of the stone. In patients failing to pass the stones or in whom the clinical course of the disease required stone removal (colicky pain, development of hydronephrosis and infection, hematuria) shock wave lithotripsy (SWL) and ureteroscopy were considered as further treatment modalities to make the patients free of stones. During these stone removal procedures no significant patient- or stone-related factors could be identified that explained the failure.

During close follow-up period, all patients in both groups were comparatively evaluated with respect to the stone passage rates, mean stone expulsion time, the mean VAS score, change in colic episodes, and hospital re-admission rates for colicky pain attacks. Pain perception of the patients at every painful attack was noted by physician using the visual analog scale (VAS) [9].

Additionally, the stones in both groups were categorized in terms of size where a distinction was made between stones <5 mm and the stones 5–10 mm. Data obtained from these subgroups were also compared with respect to the above-mentioned parameters.

Statistical analysis was carried out with Students' *t*-test for parametric data and Chi-square (with Yates' correction) test and Fisher's exact test for non-parametric values.

Results

A total of 92 patients (Group 1: 50; Group 2: 42) were included in this study. There were 54 men and 38 women (M/F = 1.42) with a mean age value of 34.2 $\pm$ 12.6 years (from 19 to 51 years). No statistically significant difference was shown with respect to patient age, sex, or stone size among the two groups (Table 1). None of the patients left the study due to the side effects of the medication(s).

Evaluation of the stone expulsion rates in both groups showed a statistically significant difference between patients receiving tamsulosin (35.7%) and patients without this medication (30%) ($p = 0.04$). Time to stone expulsion was also shortened in those receiving tamsulosin when compared with Group 1 patients (8.4 $\pm$ 3.3 and 11.6 $\pm$ 4.1 days, respectively) ($p = 0.015$). With respect to the mean VAS scores both groups did show a statistically significant difference (Table 1, $p < 0.01$).While mean VAS score value was 8.8 $\pm$ 2.9 in Group 1, this value was 4.5 $\pm$ 2.3 in patients receiving tamsulosin (Table 1, $p < 0.01$). When the incidence of renal colic episodes during this period was compared, patients in Group 2 had fewer renal colic episodes than their counterparts ($p = 0.001$). Consequently, evaluation of the hospital readmission rates for severe painful colic attacks (readmissions/

Table 1 Demographic features of the patients and the evaluation of clinical course of ureteral stones in both groups

	Group 1 (50)	Group 2 (42)	*p* value
Age (years)	33.5 ± 10.1 (22–51)	34.9 ± 11.8 (24–51)	0.24
Male/Female	30/20 (60% male, 40% female)	24/18 (57% male, 43% female)	0.37
Stone size (mm)	6.6 ± 2.7 (3–10)	6.4 ± 2.1 (3–9)	0.19
Expulsion rate (%)	30% [15/50]	35.7% [15/42]	0.04
Expulsion time (day) (number of patients)	11.6 ± 4.1 (6–20 days) (n = 14)	8.4 ± 3.3 (4–15 days) (n = 15)	0.015
VAS score (mean)	8.8 ± 2.9	4.5 ± 2.3	<0.01
Decrease in colic episodes	36.0% (18/50)	66.6% (28/44)	0.001
Re-admission rate	52% (26/50)	33.3% (14/42)	<0.001
Distal relocation	24.0% (12/50)	35.7% (15/42)	0.018

Table 2 Spontaneous passage and distal relocation of the stone according to stone size

	<5 mm (n = 32)			5–10 mm (n = 60)		
	Tamsulosin (n = 14)	No tamsulosin (n = 18)	*p* value	Tamsulosin (n = 28)	No tamsulosin (n = 32)	*p* value
Stone free	10 (71.4%)	9 (50%)	<0.001	5 (17.8%)	6 (18.7%)	0.346
Distal relocation	4 (28.5%)	6 (33.3%)	0.08	11 (39.3%)	6 (18.7%)	<0.001
No-change	–	3 (16.7%)		12 (42.9%)	20 (62.5%)	<0.001

total number of patients) revealed a 33.3% readmission in upper ureteral calculi under tamsulosin medication; this value was 52% for calculi followed under sole conservative measures ($p < 0.001$).

Lastly, stone passage as well as relocation rates were evaluated with respect to stone size (<5 mm and 5–10 mm). As demonstrated in Table 2, in addition to causing a higher spontaneous passage rate in patients having stones < 5 mm, the more important and prominent effect of tamsulosin on stones 5–10 mm was the relocation of the stones to a more distal part of the involved ureter.(39.3 vs 18.7%, respectively) ($p < 0.001$).

Of the 70 and 64% of stones that did not pass in Groups 1 and 2, respectively, ureteroscopic stone removal was carried out for those that were relocated during follow-up period. Relocation was recorded in 24% of the patients in Group 1 and in 35.7% in group 2. Stones that remained in the original position were treated with SWL.

Discussion

As a major health problem, urolithiasis constitutes the third most common disease of the urinary tract, affecting 2–3% of the population, with a high recurrence rate of almost 50% [1]. Of these cases, symptomatic ureteral calculi represent the most common reason for stone management by urologists in emergency departments [10]. At initial presentation, the vast majority of ureteral stones are located in the lower third of the ureter (70%), and spontaneous passage is an important consideration for ureteral calculi with a diameter <5 mm [11].

Regarding the likelihood of spontaneous passage of conservatively treated ureteral calculi, the results of a meta-analysis demonstrated that stones <5 mm and 5–10 mm had 68 and 47% of spontaneous passage, respectively, during follow-up (95% CI and 46–85%) [12]. In the literature, the data also showed both the expulsion rate and time to expulsion depend heavily on size and location of the ureteral stone(s) [13–15]. Thus, a considerable amount of ureteral calculi may pass spontaneously during MET.

Several drugs-such as alpha-1 blockers, calcium channel blockers, prostaglandins synthesis inhibitors, glyceryl trinitrate, and steroids-have been used to facilitate spontaneous passage [16–19]. Of these agents, alpha-1 blockers were one of the most commonly studied. The density of alpha-1 adrenergic receptors in ureteral smooth muscle cells is significantly greater than other adrenergic receptors, and alpha-1 blockers have been used to inhibit basal ureteral wall tone, decrease ureteral peristaltic frequency, and reduce ureteral spasm [20]. In this regard, several studies have demonstrated that distal ureteral stone can be treated efficiently with different types of alpha-1 blockers with a low incidence of side effects [5, 6, 17]. The effect of alpha-1 blockers on the spontaneous passage of distal ureteral calculi has been well studied when compared with proximal

counterparts and finally, EAU guidelines suggested the clinical use of alpha-1 blockers as a part of medical therapy for distal ureteral stones [2].

Regarding the presence of alpha-1-adrenergic receptors in the ureteral wall, although many studies concentrated on the distal part of the ureter, some authors showed that alpha-1 subtypes of this receptor were also present in the proximal part of the ureteral wall [20, 21]. Additional support for the presence of these receptors in this part of the ureter has been offered by Davenport et al. [22] who clearly demonstrated the decrease in ureteral luminal pressure through the entire ureter following the application of tamsulosin in a clinical study. Therefore, although spontaneous passage rate is higher in the distal part of the ureter, expulsion of the ureteral calculi <10 mm can also be expected for proximal ureteral stones. According to our literature review, there is no clinical study specifically indicating the effect of alpha-1 blockers on a proximal ureteral stone. In a retrospective study, Watts and co-workers evaluated the effect of tamsulosin on stone passage rates in all part of ureter. They found that patients with ureteral stones given tamsulosin had a higher success in stone passage irrespective of location [23]. In the present study, we found a higher stone-free rate in patients who had a <5 mm stone and were receiving tamsulosin and also those patients passed their stones more quickly than their counterparts. However, the expulsion rate was almost the same for tamsulosin-recipient and non-recipient patients in those with a 5–10 mm stone.

A decreased time to passage of stones in the distal part of the ureter has been well documented in several studies [5, 7, 8]. Likewise, such a relation was seen in the proximally located ureteral stone of a size <5 mm in our study, too. Last but not least, the alpha-1 blocker application did significantly reduce the need for a minimally invasive procedure, including SWL and endourological intervention, in these patients by increasing the stone passage rates for stones smaller than 5 mm.

Additional benefits of the alpha-1 blockers as a part of MET are fewer pain episodes, lower VAS scores, and a decreased need of analgesics [14, 24–26]. In this study, the patients taking tamsulosin showed fewer colicky episodes and lower VAS scores than their counterparts, regardless of the stone size. Consequently addition of tamsulosin to the conservative treatment of patients with proximal ureteral stones allowed to have a more comfortable social life (rapid return to daily activities and work, fewer emergency department visits, and fewer surgical procedures) [24]. All these positive effects, in turn, seem to have a great impact on the social as well as daily life of the patients, making their referral for stone and colic pain management more rare than before.

Up to now, no study discussed the distal relocation of the proximal ureteral stones under MET therapy. In this study, the relocation of the stones in a considerable percent has been noted as an additional benefit of tamsulosin on the clinical course of ureteral calculi located in the upper ureter. While the patients having stones <5 mm passed the stones more effectively in relatively shorter periods of time, the patients with 5–10 mm stone had tendency to pass their stones downward to the distal part of the ureter. Thus, apart from facilitating the spontaneous passage of the relatively smaller calculi, one prominent additional beneficial effect of these agents on larger stones would be the relocation of the calculi to a more distal part of the involved ureter, enabling the urologist to remove the calculi using ureteroscopy in a safer and more practical manner. Although the number of the patients evaluated in our trial could be a major limitation of the study, we believe that our data will give further insight for the clinicians to assess the efficacy of such medications in the conservative management of proximal ureteral calculi.

Conclusions

In light of our findings, patients with relatively small (<5 mm) ureteral stones treated with alpha-1 blockers may have a greater likelihood of spontaneous stone passage during conservative follow-up period. On the other hand, as a further beneficial effect; tamsulosin caused relocation of relatively large stones (5–10 mm) to the distal ureter. This may be an advantage for the urologists in practice in terms of a practical and safer management.

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