

Evaluation of Selective and Non-Selective Alpha-Adrenergic Blockers in the Treatment of Distal Ureteral Stones

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ABSTRACT

OBJECTIVE: To evaluate the efficacy of selective and non-selective alpha-adrenergic blockers in enhancing lower ureteral stone passage and shortening stone passage time in comparison to the standard medical treatment of only high fluid intake and analgesic and anti-inflammatory drugs before rushing into invasive intervention.

PATIENTS AND METHODS: Our study consisted of 45 patients suffering from lower ureteral stones (not more than 10 mm in diameter) divided into 3 groups each consisting of 15 patients. The 3 groups were subjected to 3 different regimens of medical therapy for a maximum of 30 days.

Patients in Group 1 were given the standard treatment of high fluid intake, phytotherapy, and analgesic and anti-inflammatory drugs. In addition to the standard treatment, patients in Group 2 were given the non-selective α_1 -adrenergic receptor blocker Terazosin (2 mg) once daily before bed for 4 days and then 5 mg once daily before bed. Patients in Group 3 were given the selective α_{1a} -adrenergic receptor blocker Tamsulosin (0.4 mg) once daily in addition to the standard treatment.

All the patients were subjected to clinical assessment including history and examination. Laboratory investigations (complete urine analysis, urine culture and sensitivity if needed, serum creatinine) and imaging studies (plain X-ray, excretory urogram) were obtained for all patients.

RESULTS: There was a higher combined incidence of stone passage in Groups 2 and 3 (73.4%) than in Group 1 (53.3%) and a more rapid combined stone passage (14.4 days vs. 18.25 days). Patients in Group 3 demonstrated a higher incidence of stone passage (80%) than patients in Group 2 (66.7%) and more rapid stone passage (9.58 days vs. 19.20 days).

CONCLUSION: The use of alpha adrenergic blockers is recommended in patients with uncomplicated lower ureteral stones. Selective α_{1a} -adrenergic receptor blockers show better results because of their higher efficacy, minimum side effects, and excellent patient satisfaction. Further clinical research in this field is needed, and larger multicenter trials are awaited to formulate a standard regimen.

KEYWORDS: Lower ureteral stones; Alpha blockers; Medical treatment

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INTRODUCTION

Urinary stones have afflicted humankind since antiquity, with the earliest recorded examples detected in Egyptian mummies dated to 4800 BC. The specialty of urologic surgery was recognized even by Hippocrates who wrote in his famous oath for the physician, "I will not cut, even for the stones but leave such procedures to the practitioners of the craft" [1].

It has been well documented that calculi disease affects 12% of the world population. The disease frequency tends to increase in Western countries. Of all ureteral stones, 70% are found in the lower third of the ureter [2].

Until the 1980s, urinary stones were a major health problem, and a significant proportion of patients required extensive surgical procedures with a sizable minority losing a kidney. One study showed that about 20% of patients with recurrent stone disease who underwent surgery for obstruction and infection went on to develop mild renal insufficiency [2].

The advent of extracorporeal techniques for stone destruction and the refinements in endoscopic surgery have greatly decreased the morbidity associated with stone surgery. The optimal therapy for patients requiring removal of distal ureteral stones is controversial. Surgery, shockwave lithotripsy (SWL), ureteroscopy (URS), and medical treatment are effective treatments associated with high success rates and limited morbidity. However, one unfortunate result of this technologic success is that advances in medical management of stone disease and research in prevention have languished [3].

Despite the optimistic outlook for spontaneous passage of small stones, particularly those located in the distal ureter, the potential for unpredictable pain, time delay until successful passage, and variation in success rates associated with conservative management has prompted the search for pharmacologic agents that improve spontaneous passage rates. Because ureteral spasm and edema have been postulated to contribute to stone retention in the ureter, these effects have been targeted for therapeutic intervention. Corticosteroids, hormones, non-steroidal anti-inflammatory agents (NSAIDs), calcium channel blockers, and α_1 -adrenergic blockers have been evaluated for their efficacy in improving stone passage rates. Also, phytotherapy plays a role in the treatment [4-6].

MATERIALS AND METHODS

Patient description

Our study took place between June 2006 and July 2007 at the outpatient urology clinic at Beni-Swaif University and Cairo University and included men and women aged between 18 to 70 years. Patients presented with complaints of renal colic, and inclusion criteria included lower ureteral stones within the distal part of the ureter below the sacroiliac joint measuring ≤ 10 mm and detectable by radiological tests.

Patient evaluation

Clinical data were collected prospectively and included duration of pain; persistent fever, vomiting, or colic for more than 24 hours; previous stone disease or spontaneous stone passage; medication commonly used by the patient; previous ureteral surgery (URS or SWL); renal, hepatic, or cardiac diseases; and analgesic requirements and dosages.

Investigations including serum creatinine, urine analysis, plain abdominal x-ray, renal ultrasonography, and excretory urography were done.

The exclusion criteria included pregnancy; breast feeding; bilateral lower ureteral stones with anuria; severe hydronephrosis; severe persistent painful renal symptoms experienced for more than 24 hours; hepatic dysfunction; chronic renal failure (serum creatinine more than 1.6 mg/dl); and drug treatment with calcium antagonists, corticosteroids, other alpha-blocker drugs or nitrates.

Drug and doses

The study consisted of 45 patients divided into 3 equal groups as follows: Group 1 was given the standard treatment in the form of high fluid intake, phytotherapy, and analgesic and anti-inflammatory drugs for 28 days. In addition to the standard treatment, Group 2 was given the non-selective α_1 -adrenergic receptor blocker Terazosin (2 mg) once daily before bed for 4 days and then 5 mg once daily before bed for 28 days. Group 3 was given the selective α_{1a} -adrenergic receptor blocker Tamsulosin (0.4 mg) once daily for 28 days in addition to the standard treatment. Patients were randomized as follows: the first 15 patients were included in Group 1, the second 15 patients in Group 2, and the third 15 in Group 3.

Follow-up

All patients were examined weekly for 4 weeks by plain abdominal x-rays, renal ultrasonography, and physical examination for any signs or symptoms of fever. The treatment was not stopped unless one of the following criteria occurred: expulsion of the stone, stone documented to be passed after imaging was done, change to an interventional treatment option on patient demand, if the stone did not pass after 4 weeks of the conservative treatment, the development of a fever more than 38° C, severe hydronephrosis, or severe intractable recurrent renal pain (persistent more than 24 hours).

RESULTS

Overall, 13% of the patients gave history of previous spontaneous stone passage while 87% did not. There was no statistically significant difference between success of treatment and history of spontaneous stone passage among the 3 groups. Table 1 summarizes the characteristics of the 3 groups.

Concerning effectiveness of treatment, 8 (53.3%) patients in Group 1, 10 (67%) patients in Group 2, and 12 (80%) patients in Group 3 passed their stones within 1 month of treatment.

The mean duration for stone passage was 18.25 days for Group 1, 19 days for Group 2, and 9.6 days for Group 3. *P* value was 0.097 between Group 2 and Group 3 (Table 2).

In Group 1, 8 (53.3%) patients required daily analgesic medication, and a combined 7 (23.3%) of the 30 patients

receiving α -blockers [4 (26.7%) in Group 2, 3 (20%) in Group 3] required daily analgesic (*P* = 0.056).

The side-effects of α -blockers were postural hypotension, asthenia, dizziness, and retrograde ejaculation. No side-effects were seen in patients in Group 1, while 14 (46.7%) [11 (73%) in Group 2, 3 (20%) in Group 3] of patients on α -blockers suffered from side-effects (*P* = 0.001).

COMMENT

Minimally invasive therapies, such as SWL and URS, have been widely adopted during recent years for the treatment of ureteral stones. Their efficacy has been demonstrated by several studies, although they are not free of risk and inconveniences [7]. Moreover, even a simple watchful waiting approach can result in complications affecting renal function. According to the literature data, the expulsion rate of distal ureteral stones produced by a watchful waiting approach is 25% to 54%, the mean expulsion time is greater than 10 days, and it requires considerable analgesic use [8].

Because α_1 -receptors are predominant in the ureteral smooth muscle, it has been suggested that the blockade of such receptors by a specific antagonist will decrease ureteral peristaltic activity with a consequent loss of intraureteral pressure and an increase in fluid transport ability. Therefore, the use of α -blockers with the aim of facilitating lower ureteral stone expulsion has been advocated in this setting. Ukhal *et al.* [9] first reported effectiveness of α -blockers in accelerating

Table 1. Characteristics of the 3 groups

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	Standard	Terazosin	Tamsulosin	Total
History of previous stone disease (n (%))	2 (13%)	3 (20%)	1 (6.7%)	6 (13%)
Stone size				
Largest	7 mm	10 mm	10 mm	
Smallest	3 mm	4 mm	4 mm	
Mean	4.6 mm	6.6 mm	7 mm	
SD	1.6	1.8	1.98	
Stone passage (n (%))	8 (53.3%)	10 (66.7%)	12 (80%)	30 (66.7%)
Mean duration to stone passage (days)	18.25	19.20	9.58	15.10
Analgesics requirements (daily)	8 (53.3%)	4 (26.7%)	3 (20%)	15 (33.3%)
Side effects of treatment	0 (0%)	11 (73.3%)	3 (20%)	14 (31.3%)

lower ureteral stone passage in 1998. They found that the rate of spontaneous passage of distal ureteral stones during treatment with doxazosin was 71.1%. Furthermore, they emphasized that the treatment decreased the frequency of the renal colic.

More recently, it has been demonstrated by Sigala *et al.* [10] that specific adrenoceptors subtypes (α_{1a} and α_{1b}) are prevalent in the distal part of the ureter, and this finding supported the interesting results obtained by different groups with the use of Tamsulosin in the treatment of the distal ureteral calculi. Cervenakov *et al.* [11] performed a randomized study in 2002 and registered a significant advantage in stone expulsion rates when adding Tamsulosin to their standard therapy.

In our study, the results are more or less similar to those in the literature.

CONCLUSIONS

There are several options available in the management of lower ureteral stones. Treatment selection depends on stone size, location, and composition; efficacy of each modality; associated morbidity; available equipment; physical skills; patient health; and cost.

A conservative treatment should be considered as an option in the management of uncomplicated distal ureteral stones. Even if the best pharmacologic expulsive regimen remains to be established, the use of an alpha-adrenergic blocker is recommended. Tamsulosin shows better results because of its high efficacy, minimum side effects, and excellent patient satisfaction. Further clinical research in this field is needed, and larger multicenter trials are awaited.

Table 2. Duration to stone passage

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	n	Mean	SD	Standard error	95% confidence interval for mean		Minimum	Maximum
					Lower bound	Upper bound		
Standard	8	18.25	7.42	2.62	12.05	24.45	6	30
Terazosin	10	19.20	5.14	1.63	15.52	22.88	10	25
Tamsulosin	12	9.58	4.12	1.19	6.96	12.20	6	20
Total	30	15.10	7.004	1.28	12.48	17.72	6	30

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