

Assessment of the efficacy of α 1-blockers in managing patients with ureteral stones

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Abstract: The results of a study evaluating the effectiveness of α 1-blockers in the comprehensive treatment of ureteral stones are presented. A prospective, comparative, single-center study included 118 patients diagnosed with a single stone in various parts of the ureter. Following pain management, all patients underwent conservative treatment aimed at promoting spontaneous stone passage. The maximum duration of conservative therapy was 30 days, with weekly ultrasound monitoring conducted for all patients. In the control group, patients received only drotaverine 40 mg three times a day along with analgesics. In the main group, patients received drotaverine and analgesics, as well as the α 1-adrenergic blocker tamsulosin at a standard dose of 0.4 mg once daily. The likelihood of stone passage in the distal ureter was significantly higher ($p = 0.02$) in the group receiving α 1-blockers. Furthermore, patients in the main group experienced better pain control throughout the observation period, even if no stones passed. The probability of stone migration from the proximal to the distal ureter was 52% in the main group compared to 32% in the control group ($p = 0.17$). Adverse effects were similar in both groups, though dizziness, postural hypotension, and weakness were notably more frequent in the main group. Univariate and multivariate analysis using the proportional hazards model showed that the addition of α 1-blockers to the treatment regimen significantly increased the likelihood of stone passage from the distal ureter. It was also found that the type of therapy used directly impacted the risk of earlier stone passage. The inclusion of α 1-blockers in the treatment plan increased the chances of stone passage by a factor of 4.11.

Keywords: α 1-blockers, ureteral stones, drug treatment

Introduction

Despite advances in medical devices and surgical techniques for stone removal, conservative approaches aimed at promoting the spontaneous passage of stones and their fragments remain highly

relevant. Diuretics, antispasmodics, and increased fluid intake are most commonly used for this purpose [1, 2]. As our understanding of the molecular and biochemical aspects of ureteral smooth muscle physiology improves, alongside advances in pharmacology, there is growing interest in drug therapies that could significantly accelerate the process of spontaneous stone passage [3–5].

The physiological effects that occur when the ureter is exposed to pharmacological agents, particularly $\alpha 1$ -adrenergic receptor antagonists, suggest these drugs may be effectively integrated into conservative treatment strategies for urinary tract stones [6-8]. Additionally, the use of such agents could help reduce the frequency of recurrent pain episodes and alleviate the overall severity of pain during treatment..

The aim of the work to assess the effectiveness and safety of using $\alpha 1$ -blockers in the comprehensive treatment of ureteral stones.

The objectives of the study included assessing the effectiveness and timing of the use of $\alpha 1$ -blockers for ureteral calculi in comparison with standardly used antispasmodics; assessment of the probability of spontaneous passage of stones depending on their size and location during the use of $\alpha 1$ -blockers compared with standard antispasmodics: assessment of the probability of achieving migration of stones from the proximal to the distal ureter during the use of $\alpha 1$ -blockers compared with standard therapy; determining the severity of the influence on the possibility of stone passage of such predictors as the size of the stone, its location and the nature of therapy; assessment of the severity of pain during conservative therapy using $\alpha 1$ -blockers; assessment of the safety of prescribing $\alpha 1$ -blockers for the conservative treatment of ureteral stones.

Materials and methods. A comparative prospective single-center study was conducted with 118 patients who had a single ureteral stone located in different parts of the ureter. After initial pain relief, all patients underwent conservative treatment aimed at facilitating the spontaneous passage of stones, with a maximum treatment duration of 30 days. Weekly ultrasound monitoring was performed for all participants. Since the distribution of $\alpha 1$ -adrenergic receptors varies significantly between the lower third of the ureter and other parts of the ureter [9, 10], the study categorized stones as either proximal or distal based on their location relative to the terminal line of the renal pelvis. The upper and middle thirds of the ureter were classified as proximal, while only the lower third was considered distal.

The patients were divided into two groups based on their treatment regimen. The control group (n=58) received only standard therapy, which included antispasmodics and analgesics as needed. For antispasmodics, drotaverine (No-Spa), a commonly used drug in urological practice, was prescribed at 40 mg three times a day. Drotaverine works through the nonspecific inhibition of phosphodiesterase, an enzyme involved in smooth muscle function.

In the main group (n=60), in addition to standard medications, patients were prescribed the $\alpha 1$ -adrenergic blocker tamsulosin. Tamsulosin is a selective antagonist of the $\alpha 1A/D$ adrenergic receptor subtypes and has minimal effect on the $\alpha 1B$ subtype, which is found primarily in smooth muscle cells of blood vessels. This specificity contributes to tamsulosin's good tolerability and low incidence of adverse effects [11]. The standard dose was 0.4 mg once daily. If there was any change in the treatment approach, this was classified as a censored observation, including cases where the patient refused to take the $\alpha 1$ -blocker. The study excluded patients with the following conditions:

Obstruction of a single functioning kidney, ureteral anomalies, significant spinal pathology, previous upper urinary tract surgery, marked upper urinary tract dilation, intractable renal colic attacks, decompensated comorbidities, a glomerular filtration rate of <30 ml/min/1.73 m², a tendency to hypotension, a history of $\alpha 1$ -blocker intolerance. Pain severity during treatment was assessed using a numerical pain rating scale [12].

Results. The distribution of patients based on the location of stones in the ureter was similar in both treatment groups (Table 1). The majority of stones were localized in the distal part of the ureter, with 83 patients (79%) presenting with distal ureteral stones.

Table 1

Distribution of patients depending on the location of stones in the ureter

Localization of the stone	Main group n=60(%)	Control group n=58(%)
Lower third	42(70)	41(70,6)
Intramural department	10(16,7)	10(17,2)
Juxtavesical region	32(53,3)	31(53,4)
Proximal part	18(30)	17(29,3)
Middle third	6(10)	7(12,1)
Upper third	12(20)	10(17,2)

Both groups of patients were comparable in terms of key characteristics such as age, gender ratio, side of stone localization, and average stone size. Treatment outcomes were analyzed based on the initial stone localization. The results showed that the overall probability of stone passage was significantly higher in the main group (patients receiving an α 1-blocker) for stones localized in the distal ureter compared to the control group (patients receiving only standard therapy) — 85% vs. 66% ($p = 0.02$).

When assessing the severity of pain during treatment, patients in the control group experienced more frequent severe pain episodes. Specifically, 25% of patients in the control group reported repeated pain attacks at a "severe" level, compared to just 9% in the main group ($p = 0.03$). Additionally, a comparative analysis of pain intensity dynamics revealed that pain symptoms were much better managed in the main group, even if stones had not passed.

For patients with proximal ureteral stones, the probability of stone migration to the distal ureter was higher in the main group 52% vs. 32% ($p = 0.17$). The median time to stone passage was also faster in the main group, with a median of 6 days, while no such achievement was recorded in the control group.

Regarding pain intensity during the first 7 days of treatment, there was a significant difference between the two groups ($p = 0.046$). In the main group, pain was better controlled across all observation periods, including on the 21st and 28th days. The median pain intensity at these time points was 4 points in the main group versus 6 points in the control group ($p = 0.031$).

While the incidence of adverse effects was similar between the two groups, patients in the main group (receiving α 1-blockers) experienced dizziness, postural hypotension, and weakness significantly more frequently (Table 2).

Table 2

Frequency of occurrence of undesirable effects depending on the treatment regimen

Undesirable effect	Main group (%)	Control group (%)	<i>P</i>
Dizziness	9(15)	4(6,9)	0,031
Postural hypotension	4(6,7)	1(1,7)	0,024
Nausea	7(11,7)	8(13,8)	0,411

Headache	6(10)	5(8,6)	0,814
Rhinitis	2(3,3)	1(1,7)	0,46
Weakness	13(22,4)	7(12,1)	0,012

The results of the analysis of the risks of stone passage using the proportional hazards model are shown in Table. 3.

Table 3

Risk ratio (OR) for stone passage depending on the influence of various factors (univariate and multivariate analysis options)

Analyzed factor	OR	95% DI	P
<i>Univariate analysis</i>			
Patient gender	1,13	0,43-2,4	0,656
Localization side(right/left)	0,08	0,86-1,79	0,127
Treatment option (main regimen/control regimen)	4,11	2,03-5,61	<0,0001
Localization of the stone (distal/proximal)	9,67	7,45-11,82	<0,0001
Stone size (<7mm/≥7mm)	6,10	5,11-8,86	<0,0001
<i>Multivariate analysis</i>			
Therapy option	4,36	2,92-5-61	<0,0001
Stone size (<7mm/≥7mm)	8,89	6,34-10,01	<0,0001
Localization of the stone (distal/proximal)	10,03	7,34-12,23	<0,0001

Discussion. The treatment of ureteral stones aims to achieve two primary objectives: eliminating factors that hinder the stone's migration along the ureter and reducing the severity of pain during this migration. Factors that impede stone movement, and which are amenable to pharmacological intervention, include ureteral wall swelling, spasm, and urinary infection. The core principle of conservative treatment for ureteral stones is to create conditions that facilitate urine flow distal to the stone, thereby promoting its movement along the ureter [13].

To prevent the recurrence of painful attacks and alleviate discomfort during stone migration, it is essential to block excessive peristaltic activity of the ureter's smooth muscles and reduce the conduction of pain signals along afferent nerve fibers to pain centers in the spinal cord [14, 15].

α 1-adrenergic blockers are pharmacological agents that can address both of these treatment principles. Research has shown that the ureter wall contains a significant number of different subtypes of α 1-adrenergic receptors, with the highest density found in the distal portion of the ureter [9, 10]. Studies have demonstrated that α 1-blockers reduce the ureter's peristaltic activity, lower basal muscle tone, and decrease intraluminal pressure [16–18]. These effects help improve urine transport. When compared to other pharmacological classes, α 1-blockers have been found to have the most substantial impact on the ureter's motility and functionality [19]. The selection of tamsulosin for this study was based on its well-established tolerance profile and convenient dosage form.

The study clearly showed that adding an α 1-blocker to the treatment regimen significantly increased the likelihood of stone passage or migration along the ureter. Additionally, tamsulosin effectively controlled pain symptoms. It reduced both the intensity of pain and the frequency of severe pain attacks, especially in the first week of treatment, and continued to offer better pain management during the follow-up period.

However, the beneficial effect of $\alpha 1$ -blockers was most pronounced during the first two weeks. After that period, no further stone passages were observed, and the results were similar to those of conventional antispasmodic therapy alone.

Importantly, combining $\alpha 1$ -blockers with phosphodiesterase inhibitors did not lead to an increased incidence of adverse effects. While patients in the main group experienced some adverse effects related to $\alpha 1$ -adrenergic receptor blockade, such as postural hypotension and dizziness, these were relatively mild. Only one patient refused to continue treatment due to side effects.

Conclusion. Thus, the results of our study, including univariate and multivariate proportional hazards model analyses, demonstrated that the nature of the therapy used directly influenced the passage of stones from the distal ureter. The inclusion of an $\alpha 1$ -blocker in the treatment regimen increased the probability of stone passage by 4.11 times.

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