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Evaluation of the effectiveness of α1-blockers in the treatment of patients with ureteral stones

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Abstract: The results of a study assessing the effectiveness of the use of α1-blockers in the complex treatment of ureteral calculi are presented.
A comparative prospective single-center study was conducted, which included 118 patients with single diagnosed stones in various parts of the ureter. After pain relief, all patients underwent conservative therapy aimed at spontaneous passage of stones. The maximum duration of conservative treatment was 30 days. All patients underwent weekly ultrasound monitoring.
Patients in the control group received only drotaverine 40 mg 3 times a day and analgesics.
In the main group, along with drotaverine and analgesics, the α1-adrenergic blocker tamsulosin was prescribed in a standard dosage of 0.4 mg once a day. The overall probability of passage of stones localized in the distal part of the ureter was significantly ($p = 0.02$) higher in the group of patients receiving α1-blockers. For patients in the main group, the treatment regimen allowed them to better control pain during all periods of observation, even if no stones passed. The overall probability of migration of stones from the proximal to the distal ureter in patients of the main group was 52 versus 32% in the control group ($p = 0.17$). The incidence of adverse effects was comparable in both groups. In the main group of patients, dizziness, postural hypotension and weakness were significantly more common.
Univariate and multivariate analysis of the proportional hazards model demonstrated that the inclusion of α1-blockers in therapy led to an increased likelihood of stone passage from the distal ureter. It was shown that the nature of the therapy used directly influenced the risk of earlier stone passage. Inclusion in the treatment regimen
α1-blockers increased the likelihood of stone passage by 4.11 times

Key words: α1-blockers, ureteral stones, drug treatment.

Introduction. Despite the development and improvement of medical instruments and methods of surgical stone removal, the use of conservative measures to promote the spontaneous passage of stones and their fragments does not lose its relevance. Most often, diuretics and antispasmodics are used for this purpose, as well as increased water load [1, 2]. With the accumulation of knowledge about the molecular-biochemical features of the physiology of ureteral smooth muscle cells and the development of pharmacology, interest in drug therapy is growing.
means that could significantly speed up the process of spontaneous stone passage [3–5]. Physiological changes that occur when the ureter is exposed to pharmacological agents - α1-

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adrenergic receptor antagonists, suggest the possibility of using these drugs in a complex of conservative therapy for urinary tract stones [6-8]. Moreover, the use of these drugs can reduce the frequency of repeated pain attacks and, in general, the severity of pain symptoms during treatment.

The aim of the work was an assessment of the effectiveness and safety of the use of α1-blockers in the complex treatment of ureteral stones.

The objectives of the study included assessing the effectiveness and timing of the use of α1-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 α1-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 α1-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 α1-blockers; assessment of the safety of prescribing α1-blockers for the conservative treatment of ureteral stones.

Materials and methods. A comparative prospective single-center study was conducted involving 118 patients with single stones in various parts of the ureter.

After pain relief, all patients underwent conservative therapy aimed at spontaneous passage of stones. The maximum duration of conservative treatment was 30 days. All patients underwent weekly ultrasound monitoring. Since the distribution density of α1-adrenergic receptors, according to studies [9,10], varies markedly in the lower third of the ureter and its remaining parts, we distinguished the proximal and distal localization of stones, which was determined in relation to the terminal line of the pelvis. Thus, we classified the upper and middle thirds of the ureter as proximal localization, and only the lower third as distal. Depending on the conservative treatment regimen used, patients were divided into two groups. Patients in the control group (n=58) were prescribed only standard therapy - antispasmodics and analgesics (as indicated). As an antispasmodic, we used drotaverine (no-shpa), widely used in urological practice, 40 mg 3 times a day, the action of which is associated with nonspecific inhibition of phosphodiesterase, a key enzyme in the functioning of smooth muscle cells. In the main group (n=60), along with standard medications, patients received the α1-adrenergic blocker tamsulosin. This drug, being a selective antagonist of the α1A/D subtypes of adrenergic receptors, has virtually no effect on the α1B subtype of receptors, which are localized primarily in the smooth muscle cells of blood vessels. This explains the good tolerability of tamsulosin by patients and the low incidence of adverse effects [11]. Tamsulosin was prescribed at a standard dose of 0.4 mg once daily. If it was necessary to change the initial treatment tactics, we classified this fact as censored observations. In addition, censored observations included the fact that the patient refused to take an α1-blocker.

The study did not include patients with obstruction of a single functioning kidney; anomaly of the ureter; pronounced pathological changes in the spine; those operated on the upper urinary tract; pronounced dilatation of the upper urinary tract; intractable attack of renal colic; concomitant diseases in the stage of decompensation; a pronounced degree of decrease in

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glomerular filtration rate (<30 ml/min/1.73 m2); tendency to hypotension; intolerance to α1-blockers according to medical history.

To assess the severity of pain during treatment, a numerical pain rating scale was used [12].

Results. The distribution of patients depending on the location of stones in the ureter in both treatment groups was similar (Table 1). Most often, stones were localized in the distal part of the ureter - 83 (79%) patients.

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 similar in terms of the main characteristics: age, gender ratio, side of the stone localization and its average size. Treatment results were assessed depending on the initial level of stone localization.

The obtained curves suggest that the overall probability of passage of stones localized in the distal part of the ureter was significantly higher in the main group of patients receiving an α1-blocker compared to the control group of patients receiving only standard therapy (85 vs. 66%; p = 0.02).

When comparing the severity of pain during therapy, it was noted that repeated attacks corresponding to the “severe” level occurred much more often in patients in the control group (25 vs. 9%; p = 0.03).

A comparative analysis of the dynamics of pain intensity when using two treatment options demonstrated that in patients of the main group, pain symptoms were much better controlled, even if the passage of stones was not noted.

The results of treatment of patients with stones of proximal localization demonstrated the following patterns. The overall probability of migration of stones to the distal ureter in the main group was higher - 52 versus 32% (p = 0.17). The median probability of stone passage in patients of the main group was 6 days, while in the control group no achievements in this indicator were noted.

The intensity of pain during the first 7 days of treatment, depending on the therapy used, differed significantly (p = 0.046).

A comparative analysis of the severity of pain over time demonstrated that in patients the main group, pain was better controlled during all observation periods, including the 21st and 28th days. The median pain intensity during that period of time (Fig. 6) was 4 points in the main group and 6 in the control group (p = 0.031).

Overall, the incidence of adverse effects was comparable in both groups.

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Significantly more often in the main group of patients receiving α1-blockers, dizziness, postural hypotension and weakness occurred (Table 2).

Table 2. Frequency of occurrence of undesirable effects depending on the treatment regimen.

Undesirable effect	Main group (%)	Control group (%)	P
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
Univariate analysis			
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
Multivariate analysis			
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. Treatment of ureteral stones has two goals: to eliminate the influence of those factors that interfere with the migration of the stone along the ureter, and to reduce the severity of pain during migration. Factors that can impede the migration of stones, but at the same time are available for drug intervention, include swelling of the ureteral wall, its spasm and urinary infection. The main principle of conservative therapy for ureteral stones should be to create conditions for the passage of urine flow distal to the stone, which in turn will facilitate its movement along the ureter [13].

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Prevention of the development of repeated painful attacks and reduction of general discomfort during stone migration is achieved by blocking excessive peristaltic activity of the smooth muscles of the ureter and reducing the conduction of pain impulses along afferent fibers to the centers of pain sensitivity localized in the spinal cord [14, 15].

A pharmacological agent whose effects make it possible to combine both of these principles of treatment are α1-adrenergic blockers. It has been established in detail that a significant number of different subtypes of α1-adrenergic receptors are present in the wall of the ureter, with their highest density observed in the distal part of the ureter [9, 10]. Numerous experiments have shown that the use of α1-adrenergic receptor antagonists causes a decrease in peristaltic activity of the ureter, a decrease in basal tone and a decrease in intraluminal pressure [16–18]. All these aspects should help improve urine transport. When comparing the effect of pharmacological agents of different classes of substances, it was demonstrated that α1-blockers have the greatest effect on the described properties of the ureter [19]. The choice of tamsulosin was due to the fact that this pharmacological agent is well tolerated by patients, and its dosage form is convenient to use.

The study clearly showed that the inclusion of an α1-blocker in the treatment regimen significantly increased the likelihood of stone passage or migration along the ureter. The use of an α1-blocker also provided good control of pain symptoms. The administration of tamsulosin contributed to a lower intensity of pain attacks and the frequency of repeated intense attacks of pain both during the 1st week and during longer follow-up of patients.

The effect of prescribing α1-blockers was noted only during the first two weeks. Upon further observation, no stone passages were noted, which did not differ from the use of only conventional antispasmodics.

Prescribing patients treatment with α1-blockers together with phosphodiesterase blockers did not lead to a significant number of adverse effects. Significantly more often they experienced only adverse effects associated with blocking α1-adrenergic receptors localized in the vascular wall: postural hypotension, dizziness. And only one patient refused to take the drug.

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 α1-blocker in the treatment regimen increased the probability of stone passage by 4.11 times.

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