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# Personalized Litholytic Therapy With Blemaren: The Importance Of Density And Dimensional Characteristics Of Stones

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***Abstract***
*Litholytic therapy of urate stones is an important alternative to invasive methods of treating urolithiasis. The effectiveness of drugs such as Blemaren largely depends on the characteristics of the stones – their density and size. To evaluate the effect of the density and dimensional parameters of urate stones on the effectiveness of litholytic therapy with Blemaren. The study included 94 patients with urate stones who were prescribed Blemaren therapy. The density of the stones was estimated according to the MSCT data, and the size was estimated according to the maximum diameter. Follow-up examinations were performed after 4 and 8 weeks of therapy. The maximum efficacy (complete litholysis >85%) was achieved in patients with stones with a density of <400 HU and a size of <10 mm. With a density of >600 HU and a size of >15 mm, the efficiency was significantly reduced (<20%). Maintaining an optimal urine pH (6.2–6.8) significantly improved treatment outcomes. The density and size of the stone are key predictors of the success of Blemarene litholytic therapy. A personalized approach based on these parameters makes it possible to increase the effectiveness and rational use of medical resources.*
***Keywords***: *urate stones, litholytic therapy, blemaren, stone density, stone size, urolithiasis, urine pH.*

## INTRODUCTION

Urolithiasis (urolithiasis) is one of the most common urological diseases characterized by the formation of calculi in the organs of the urinary system. According to the World Health Organization, the prevalence of ICD in the world ranges from 1 to 20% and shows an increasing trend. This is due to changes in the diet of the population, increased consumption of animal proteins and sodium, the globalization of the Western lifestyle and the deterioration of drinking habits. In Russia, according to the Ministry of Health, ICD is one of the five leading causes of hospitalization in urological hospitals.Despite the active development of surgical and minimally invasive treatment methods (including remote lithotripsy, ureteroscopy, and percutaneous nephrolithotomy), drug-based litholytic therapy continues to retain its clinical significance, especially for soluble urate stones. One of the most commonly used drugs in this approach is Blemaren, a combination agent that promotes urine alkalinization, which increases the solubility of urates. However, despite the accumulated clinical experience of using Blemaren, the effectiveness of therapy remains ambiguous and varies from patient to patient. This is due to a number of factors, among which the physico-chemical characteristics of the stone, including its size and density, are of particular importance. Modern imaging techniques, primarily multispiral computed tomography (MSCT), make it possible to accurately measure these parameters. The density of the stone, expressed in Hounsfield units (HU), is an important prognostic factor: urate stones usually have a low density (<500 HU), while calcium oxalates and other insoluble concretions are much higher. Thus, the relevance of the study is determined by the need to individualize litholytic therapy, taking into account the objective characteristics of concretions, which is especially important for improving the effectiveness and reducing the duration of treatment. In the context of the growing burden on the healthcare system and the desire for minimally invasive, economically sound approaches to treatment, personalized selection of drug therapy tactics is becoming an important clinical task.Moreover, there is a lack of systematic data on how exactly the size and density of stones affect the outcome of litholytic therapy with Blemaren. Most of the published works focus either on the overall effect of the drug or on comparing it with surgical methods, without differentiating patients by the morphological features of the stones. This limits the doctor's ability to choose the optimal treatment strategy at the outpatient stage. Therefore, there is an urgent need to

conduct a clinical trial aimed at studying the effect of the size and density characteristics of concretions on the effectiveness of Blemaren therapy, which will justify more accurate criteria for selecting patients for conservative treatment and determine indications for switching to surgical methods in case of expected inefficiency.Drug-based litholytic therapy occupies an important place in the treatment of certain forms of urolithiasis, especially with urate and, less often, mixed stones. The main goal of this therapy is to create favorable conditions for dissolving existing stones and preventing the formation of new ones by changing the acid-base state of urine and correcting metabolic disorders. The solubility of urates in urine depends on its pH level. In an acidic reaction (pH < 5.5), uric acid salts are poorly soluble, which contributes to their precipitation. When urine is alkalized to pH values of 6.2–6.8, the solubility of urates increases significantly, creating conditions for their gradual litholysis. In this regard, the appointment of citrate mixtures, which have an alkalizing effect, is the main method of treating urate stones.One of the most commonly used drugs in clinical practice is Blemaren, a combination drug containing sodium citric acid, potassium citric acid and bicarbonate. It not only promotes the alkalinization of urine, but also has a citraturic effect, reducing the concentration of free calcium, which can also contribute to the prevention of calcium stones. Numerous clinical studies have demonstrated the high efficacy of Blemaren in dissolving urate calculi. According to the data of Russian and foreign authors, when observing the intake regime and controlling the pH of urine, the dissolution of stones occurs on average within 1-3 months in most patients. The drug has also shown positive results in preventing the recurrence of urolithiasis with prolonged use. In addition, Blemaren has a good safety profile, high patient commitment (including due to the presence of indicator strips for pH control) and can be used both in monotherapy and as part of complex treatment. However, despite the positive results, the variability of responses to treatment remains high, which requires further study of the predictors of effectiveness. These factors include dietary characteristics, hydration levels, metabolic disorders, and the morphology of the concretion itself, including its density, size, structure, and composition.Modern methods of radiation diagnostics, especially multispiral computed tomography (MSCT), make it possible to accurately assess the size, localization and density of urinary stones. The latter indicator, measured in Hounsfield units (HU), is an important prognostic criterion that allows us to assume the composition of the concretion before starting treatment. Urate stones, as a rule, are characterized by a low density (less than 500 HU), whereas oxalate stones are 800 HU and higher. However, there are mixed forms, the density of which can range from 500-800 HU, which makes the choice of treatment tactics more difficult. High-density stones often do not respond to medical dissolution and require instrumental intervention.Similarly, the size of the stone also has an impact on the outcome of treatment. Small stones (up to 10 mm) can be more quickly and completely dissolved, while large stones (>15 mm) require long-term therapy and often show partial litholysis or complete resistance to treatment. However, not only the absolute size is important, but also the shape, the presence of intracortical inclusions, as well as obstructive changes in the kidneys and ureters.

Nevertheless, in clinical practice there are no clear recommendations for the selection of patients for litholytic therapy with Blemaren, taking into account the density and size of stones. This leads to the fact that patients with initially unfavorable characteristics receive treatment that is obviously unlikely to have an effect, which may delay surgery and worsen the prognosis.One of the key factors determining the success of drug-based litholytic therapy for urolithiasis is the physico-chemical characteristics of the calculus. Among the most clinically significant indicators affecting the prognosis of treatment are the density of the stone and its size. An assessment of these parameters before starting therapy allows us to draw a preliminary conclusion about the potential effectiveness of treatment, choose the optimal tactics, and reduce the risks of unjustifiably prolonging therapy with obviously unfavorable concretion characteristics.The density of urinary stones, measured in Hounsfield units (HU) using multispiral computed tomography (MSCT), reflects the radiological "hardness" of the calculus and indirectly indicates its chemical composition. As a rule:

- Urate stones have a density of <500 HU
- Phosphate stones — about 400-600 HU
- Calcium oxalates — 800-1500 HU and above
- Cystine — <700 HU, but vary
- Mixed stones — from 500 to 1000 HU

Thus, the lower the density of the stone, the higher the probability of its dissolution during litholytic therapy. Recent studies have confirmed that in patients with concretions with a density of <500 HU, the probability of successful litholysis with Blemaren therapy is up to 85-90%, whereas with a density over 750 HU, the effect is practically nonexistent.It is important to note that a group of stones of the same composition (for example, urate stones) may exhibit different densities depending on the degree of mineralization, the presence of inclusions (for example, calcium) and the density of the crystal lattice, which requires an individual approach to treatment even when determining the intended composition of the stone.Stones 10-20 mm in size can be treated, but require a longer course (sometimes up to 4-6 months) and careful monitoring of effectiveness. At the same time, the clinical effect (reduction in size, fragmentation, spontaneous discharge) is recorded slowly.Large stones (>20 mm), especially coral-shaped ones or those occupying more than one cup, rarely completely dissolve with medication and in most cases require instrumental intervention.The combined assessment of the density and size of the stone makes it possible to more accurately predict the outcome of litholytic therapy. The most favorable conditions for dissolution are created when combined with:

- Small size (up to 10 mm)
- Low density (<500 HU)
- Absence of obstruction and concomitant infectious component

At the same time, even relatively large urate stones (up to 15-18 mm), with a density of <400 HU, with sufficient hydration and a strictly controlled pH level of urine, may be subject to partial or complete litholysis.At the same time, stones with high density (>700-800 HU), regardless of their size, are usually resistant to drug therapy. Attempts to dissolve such stones are often ineffective, lead to an unjustified delay in surgical intervention and can worsen the course of the disease (for example, with persistent obstruction or secondary pyelonephritis).

## MATERIALS AND METHODS

The study was conducted in the form of a retrospective and prospective cohort analysis. Patients with a confirmed diagnosis of urolithiasis were included, in whom, according to multispiral computed tomography (MSCT), urate nodules of various densities and sizes were detected. All patients received litholytic therapy with Blemaren for a period of 4 to 12 weeks.

The study included patients:

- Between the ages of 18 and 75;
- With single or multiple stones in the kidneys or ureter, established according to MSCT;
- With the estimated urate composition of the concretion (density according to MSCT < 750 HU);
- Stone size from 4 to 20 mm;
- Without pronounced urostatic obstruction;
- With an initial pH of urine <6.0;
- Those who received Blemaren according to the standard regimen for ≥4 weeks;
- In compliance with the pH control regime (self-monitoring at least once a day).

Exclusion criteria

- Stones with a density of >750 HU;
- Suspected mixed or calcium composition of the stone;
- Coral-shaped or multi-chambered stones;
- The presence of urinary tract infection in the active phase;
- Stage III–V chronic kidney disease (GFR <45 ml/min/1.73 m2);
- Severe ureteral obstruction or grade II–III hydronephrosis;
- The use of other urolytic drugs or interventions in parallel;
- Lack of reliable self-monitoring of pH or low adherence to therapy.

All patients received Blemaren at a dose of 2 to 3 tablets per day, depending on the pH level of urine. The target pH range was maintained in the range of 6.2–6.8, determined using indicator strips (included in the package of the drug). Dosage adjustment was carried out individually, depending on the dynamics of pH and clinical response.

In parallel, a diet with a restriction of animal protein and purines, an increase in daily diuresis to 2.0–2.5 liters, abstinence from alcohol and fasting meals, which contribute to acidification of urine, was recommended.

Methods for evaluating the effectiveness

of 1. Radiation diagnostics (MSCT)

- All patients underwent kidney CT before starting therapy and again after 4, 8 and 12 weeks.
- Measured:
- Stone density (in HU);
- Size (largest diameter, mm);
- The number and location of stones.

2. Laboratory tests

- General urinalysis;
- Urine pH (according to morning dose and self-monitoring data);
- Biochemical blood analysis (uric acid, creatinine, and electrolyte levels);
- Daily excretion of citrate and uric acid (as indicated).

3. Clinical control

- Assessment of the dynamics of symptoms (pain, dysuria, microhematuria);
- Adherence to therapy and diet;
- Side effects.

Evaluation of endpoints

Main endpoints:

- Complete litholysis of the stone (absence of visualized calculus on CT);
- Partial litholysis (size reduction by ≥50%);
- No effect (decrease <50% or lack of dynamics).

Additional indicators:

- Average time to achieve partial/complete litholysis;
- The result depends on the density of the stone (categories: <400, 400-600, >600 HU);
- The result depends on the size of the stone (categories: <10 mm, 11-15 mm, >15 mm).

**RESULTS**

The study included 94 patients with urate calculi who underwent Blemaren therapy under outpatient and inpatient supervision. The average age of the patients was 47.3 ± 9.6 years, of which 56 (59.6%) men and 38 (40.4%) women.

According to the location of stones:

- 62 patients (65.9%) in the kidney
- 18 patients (19.1%) in the proximal

ureter • 14 patients (14.9%) in the distal ureter

Among the included patients:

- Stones with a diameter of less than 10 mm in 36 people (38.3%)
- 11-15 mm in 37 people (39.4%)
- 15 mm in 21 patients (22.3%)

The stones were distributed according to density as follows:

- <400 HU in 28 patients (29.8%)
- 400-600 HU in 39 patients (41.5%)
- 600 HU (but <750) in 27 patients (28.7%)

The duration of therapy ranged from 4 to 12 weeks (on average, 7.6 ± 2.3 weeks), depending on the rate of effect and compliance with the regimen.

General results of litholytic therapy

Based on the results of treatment:

- Complete litholysis (complete disappearance of the stone on the control CT) was achieved in 44 patients (46.8%)
- Partial litholysis (reduction in size by ≥50%) — in 32 people (34.0%)

• No pronounced effect (<50% reduction or no changes) — in 18 patients (19.1%)

, the average time to achieve partial litholysis was 4.5 ± 1.7 weeks, and full — 7.3 ± 2.1 weeks.

The relationship between stone density and the outcome of therapy

Group I: density <400 HU (n=28)

• Complete litholysis in 24 patients (85.7%)
• Partial in 3 (10.7%)
• No effect in 1 (3.6%)

Group II: 400-600 HU (n=39)

• Complete litholysis in 17 (43.6%)
• Partial — in 17 (43.6%)
• No effect — in 5 (12.8%)

Group III: 601-750 HU (n=27)

• Complete litholysis in 3 patients (11.1%)
• Partial — in 12 (44.4%)
• No effect — in 12 (44.4%)

The relationship between the size of the stone and the result

Group A: <10 mm (n=36)

• Complete litholysis in 28 patients (77.8%)
• Partial in 7 (19.4%)
• No effect in 1 (2.8%)

Group B: 11-15 mm (n=37)

• Complete — in 13 (35.1%)
• Partial — in 19 (51.4%)
• Without effect — in 5 (13.5%)

Group C: >15 mm (n=21)

• Complete in 3 (14.3%)
• Partial in 6 (28.6%)
• No effect in 12 (57.1%)

The size dependence was also statistically significant: $p < 0.001$

Cumulative analysis: density + size

Maximum efficacy (total litholysis >85%) was achieved in a subgroup of patients with:

• Stone density <400 HU
• Size less than10 mm

The minimal effect (<20% of total litholysis) is in patients with:

• A density of 600-750 HU
• Size >15 mm

In the intermediate subgroups, the effectiveness varied:

Additional observations

• In patients who achieved stable pH maintenance in the range of 6.2–6.8, therapy was 2.4 times more effective than in patients with unstable pH ($p<0.01$).
• 7 patients (7.4%) had minor side effects (flatulence, abdominal discomfort, belching) that did not require drug withdrawal.
• In no case was there an increase in stone density or the appearance of new concretions during therapy.

Negative predictors of therapy

Multifactorial analysis revealed that independent negative predictors of litholysis success were:

• Stone density >600 HU (OR 4.3; 95% CI: 2.1–8.5)
• Size >15 mm (OR 3.7; 95% CI: 1.8–7.9)
• Urine pH <6.0 more than 30% of the therapy time (OR 2.9; 95% CI: 1.3–6.2)

The next section of the article will present a discussion of the data obtained, their comparison with the existing literature, as well as clinical recommendations for the personalized use of Blemaren based on the results obtained.

## DISCUSSION

1. The effectiveness of litholytic therapy with Blemaren significantly depends on the density and size of urate stones. Patients with stones with a density of less than 400 HU and a size of <10 mm demonstrate a high level of complete litholysis (more than 80%).
2. Stones with a density of more than 600 HU and a size of more than 15 mm have a low probability of successful dissolution, which requires consideration of alternative treatment methods.
3. Strict control and maintenance of urine pH in the range of 6.2–6.8 are key factors for the success of therapy and should be taken into account when prescribing and managing patients.
4. The development of personalized approaches to the choice of therapy, taking into account the density and dimensional characteristics of stones, allows optimizing clinical outcomes and reducing unnecessary time and resources.

## CONCLUSION

Personalized litholytic therapy with Blemaren is an effective and safe method of treating urate stones, especially considering their density and size. Reliable prediction of the result based on MSCT allows for a more rational approach to choosing patients for drug dissolution and timely referral of patients with a low probability of success to alternative treatment methods.
Further research and implementation of personalized therapy protocols will help improve the quality of medical care and reduce the incidence of complications associated with urolithiasis.

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