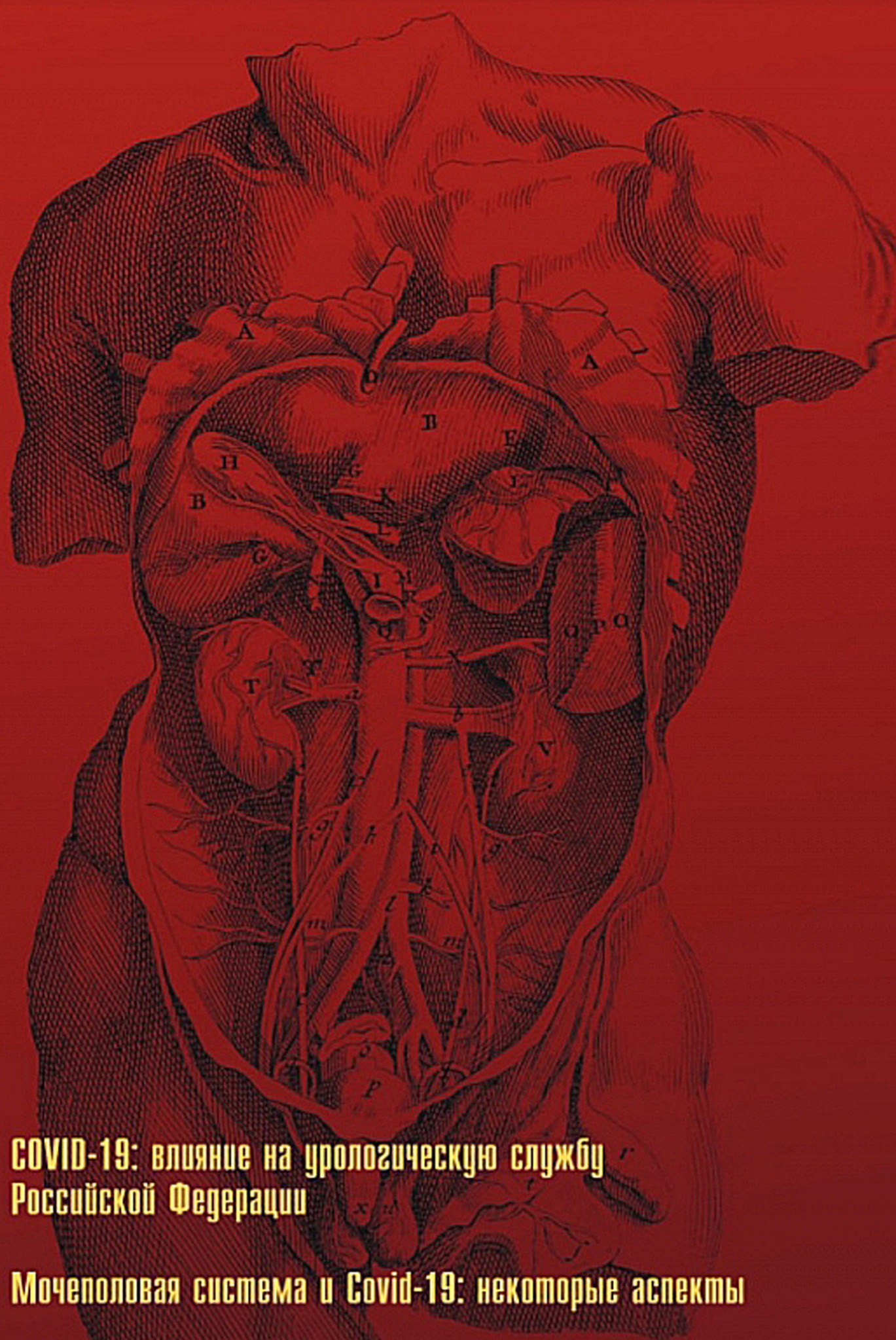




**COVID-19: влияние на урологическую службу
Российской Федерации**

Мочеполовая система и Covid-19: некоторые аспекты

**Перспективы лечения больных урогинекологического
профиля в условиях пандемии COVID-19 и
последующего снятия ограничительных мер**



Modern treatment of urinary stone disease: focus on improving outcomes

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Introduction. Modern sedentary lifestyle, high-calorie diet, and the presence of intercurrent diseases pose new challenges in the treatment of urolithiasis. The use of complex approach combining remote, contact lithotripsy and conservative therapy methods allows to achieve the best results and reduce the probability of residual stones.

The aim of this study was to evaluate the stone-free rate in patients after conservative therapy, remote and contact ureterolithotripsy.

Materials and Methods: From November 2019 to March 2020, 170 patients (82 men and 88 women) aged 23 to 84 years with kidney stones were treated at the D.D. Pletnev State Clinical Hospital. Depending on the size of the stone all patients were divided into three groups: the first group (n = 27) with stones up to 5 mm was subjected to conservative lithokinetic therapy, the second group (n = 74) with stones from 6 to 10 mm - to remote lithotripsy and the third (n = 69) with stones from 11 to 20 mm - to transurethral tulum lithotripsy. In all cases, the size of the stones was determined on the basis of computed tomography of the kidneys with determination of the stone density and its localisation. The main and control subgroups were divided into each group depending on the additional use of Renalof® complex supplement in the diet. The complex was administered in the therapeutic dose of 1 capsule 3 times a day for 1 month to the patients of the main group. The control group consisted of patients who were treated with standard uroanti-septic therapy for 1 month. We evaluated the frequency of stone absence after 1 month according to computer tomography data, assessed the degree of leukocyturia, urine pH.

Results: in all 3 groups of patients additional dietary Renalof® application resulted in statistically significant reduction of stone-free rate in the first subgroups compared to the control subgroups (81.8% vs. 43.7%, 75% vs. 54.3% and 84.8% vs. 58.3%, respectively). Additionally, there was a decrease in leucocyturia and normalisation of urine pH in the first subgroups compared to the second. There were no undesirable effects associated with the complex administration.

Conclusions: the authors demonstrated the advantage of using Renalof® complex in the complex treatment of urolithiasis.

Keywords: Renalof, phytotherapy, urolithiasis, laser lithotripsy.

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Modern treatment of urinary stone disease: focus on improving results

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Introduction. The modern sedentary lifestyle, high-calorie diet and comorbidities make new challenges in the renal stone disease management. The best policy to decrease residual stone rate is the combined use of shock wave lithotripsy (SWL), intracorporeal stone treatment and conservative therapy. **The aim** of the study was the evaluation of stone-free rate after conservative therapy, SWL and ureteroscopy lithotripsy. **Materials and methods:** Since November 2019 till March 2020 170 patients (82 males and 88 females, age 23-84y.o.) with renal stones were treated at the urological clinic in the Hospital named after D.D. Pletnev. First cohort (n = 27) with the less than 5mm stones were treated conservatively. The second cohort (n = 74) with the 6-10mm stones were managed with SWL and the third one (n = 69) with stone burdens from 11 to 20mm were treated ureteroscopically by means of thulium fibre laser. The diagnosis of stone has been confirmed at CT scan with evaluation of its density and location. The randomisation in the each group has been done in relation to the add-on therapy of the herbal dietary supplement Renalof®. The main group took additionally Renalof 1 capsule 3 times daily during 1 month. The control group received only routine antiinflammatory treatment 1 month too. The primary end-point was 1mo. stone-free rates, the secondary were - the level of leucocytes in urine and pH.

Results: the Renalof add-on application in all 3 cohorts resulted to the statistically significant decrease of stone residuals rate in main vs. control groups (81.8% vs. 43.7%, 75% vs. 54.3% and 84.8% vs. 58.3% respectively). Additionally there were decrease at the levels of WBC in urine and the normalisation of pH urine in the main vs. control groups. No drug-related adverse events were found.

Conclusion: the add-on application of Renalof® is justified in the complex management of urolithiasis.

Key words: Renalof, phytotherapy, renal stone disease, laser lithotripsy.

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INTRODUCTION

Urolithiasis is a nosology whose incidence is steadily increasing in developed countries. The reasons for the increase in the incidence of urolithiasis are sedentary lifestyle of patients, predominant consumption of high-calorie foods, concomitant endocrine diseases and gastrointestinal tract dysfunction, diseases of internal organs, which together lead to an increase in the incidence and prevalence of urolithiasis [1,2].

Over the last two decades, there has been a revolutionary change in the therapeutic approaches in the management of patients with urolithiasis. In addition to the increasing frequency of endourological treatment methods, the effectiveness of remote litho-tripsy is improving, and modern methods of lithokinetic therapy are being developed [3,4]. Every year, innovative technological solutions in this or that type of surgical treatment, as well as new drugs and complex biologically active supplements designed to increase the effectiveness of the treatment appear. At present, only a comprehensive, often individual approach to patient treatment is optimal, which consists not only of minimally invasive stone removal or fragmentation without significant traumatization of the renal parenchyma, but also includes anti-inflammatory treatment to eliminate local factors for stone recurrence (normalisation of urine pH, increased diuresis) and to ensure better quality of life of the patient [5-7].

Currently, conservative treatment is used in patients with small (up to 5 mm) kidney stones in the absence of urodynamic disturbances; this approach is associated with minimal chances for the development of obstructive complications of urolithiasis. The main fears of this category of patients are related to the fear of renal colic and possible ineffectiveness of the treatment [8-10].

Kidney stones up to 1 cm in most cases when indications for their surgical treatment are identified, they are treated with remote lithotripsy as the method of choice, which allows the vast majority of patients to achieve a positive effect. The main problems of this method of treatment are related to its possible ineffectiveness (lack of stone fragmentation) or failure to move already fragmented stone fragments [11-12].

Larger stones, with the exception of large (over 2 cm) and coral stones, are increasingly being treated with either flexible transurethral fibroureteropyeloscopy or minimally invasive percutaneous nephrolithotripsy options (mini- and percutaneous nephrolithotripsy).

micropercutaneous nephrolithotripsy) [13-15]. Combined operations performed from two accesses in the supine position are increasingly being described, which not only allow the patient to be completely free of stones, but also avoid inflammatory complications associated with the duration of the operation in conditions of increased intralocavitary pressure [15]. All the above-mentioned factors lead to the emergence of new non-drug methods, including dietary and lifestyle changes, which urologists could recommend to patients for a long period of time in order to increase diuresis after surgery for the evacuation of fragments of stone and early normalisation of urine composition [16].

Successful foreign experience in the use of Renalof® complex in the conservative therapy of urolithiasis, better fragment removal after remote and transurethral lithotripsy was one of the factors for its use after minimally invasive surgeries and metaphylaxis of stone formation [16-19].

Renalof® is a biologically active complex, which includes activated extract of the herb *Agropyron repens* and mannitol, which are widely known and used for metaphylaxis of urolithiasis, as well as in the complex therapy of chronic pyelonephritis [16].

The aim of the study was to determine the stone-free rate in patients after conservative therapy, remote and contact ureterolithotripsy, as well as to study the efficacy and safety of Renalof® complex in patients with urolithiasis.

MATERIALS AND METHODS

From November 2019 to March 2020, 170 patients (82 men and 88 women) aged 23 to 84 years with kidney stones were treated at the D.D. Pletnev State Clinical Hospital. In accordance with the goals and objectives of the study, the entire group of patients was divided into three groups. The inclusion criteria were: informed consent, absence of decompensated diabetes mellitus, confirmation of the stone diagnosis by CT scan, any localisation in the kidney except for the lower segment calyx, and follow-up examination after 1 month to assess the effectiveness of treatment. Exclusion criteria were patient's refusal to participate in the study, allergic reaction to the components of the complex, failure to attend the follow-up examination.

Depending on the use of Renalof® complex in the patients' diet, each group of patients was divided into two subgroups. The complex was administered 3 times a day, 1 capsule each, for 1 month.

After treatment has been administered or after the patient has been discharged from hospital following some form of surgical treatment.

The first group included 27 patients with kidney stones up to 5 mm who were treated with preservative lithokinetic therapy. 11 patients from this group additionally received Renalof® complex, 16 patients received standard therapy. As criteria of treatment efficacy, the frequency of stone absence, frequency of leukocyturia (leukocytes more than 10), urine pH before and after treatment, diuresis level according to urinary diaries, and quality of life according to the visual analogue scale were evaluated.

The second group of patients consisted of 74 patients after remote calico-(pyelo-)lithotripsy for kidney stones from 6 to 10 mm. 28 patients took Renalof® dietary supplements as part of dietary recommendations, 46 patients received standard anti-inflammatory therapy (kanefron 2 dragees 3 times a day or furagin 2 t 3 times a day). The same criteria were used in this group of patients as in the first group.

The third group of patients included 69 patients after transurethral fibrocalico(pyelo-)lithotripsy for stones ranging in size from 11 to 20 mm.

33 patients were additionally taking Renalof®, 36 patients - standard anti-inflammatory treatment. The peculiarity of this group of patients was the presence of an internal stent after surgery, so we did not use the degree of leukocyturia and urine pH as criteria of treatment efficacy in this group of patients [8].

The main group was recruited prospectively, and the control group - partially retrospectively with the inclusion of patients who repeatedly came to the clinic for removal of internal stents and control examinations on previously performed surgical interventions.

To assess the condition 1 month after surgery, a follow-up examination was performed, which included completion of the visual analogue scale (VAS), urinary diaries, control ultrasound of the urinary system, and control urinalysis.

and computed tomography of the kidneys without contrast. Information on the quality of life in patients after upper urinary tract surgery was obtained using a visual analogue scale filled out by patients, with "0" being absolutely unacceptable quality of life, and "100" being absolutely unacceptable quality of life, and "0" being unacceptable quality of life.

"100 is a great quality of life.

The primary endpoint of the study was to assess the stone-free rate 1 month after conservative or surgical treatment. Secondary endpoints were assessment of quality of life by VAS, leukocyturia, diuresis and urine pH.

The results were entered into Microsoft Excel® and subjected to standard statistical processing. The reliability of intergroup differences was determined using the Fisher test. Differences at $p < 0.05$ were considered statistically significant.

RESULTS

The first part of our study compared two groups of patients with kidney stones up to 5 mm who were treated with conservative therapy aimed at self-discharge.

The results of treatment of the patients in the first group are presented in Table 1.

Table 1 shows that in the first group, 9 patients in the first group and 7 patients in the second group had stones independently removed, and the differences were statistically significant. Leukocyturia was noted in 2 patients from the first group and in 9 patients from the second group, which was also statistically significant. Differences in quality of life and daily diuresis were not statistically significant, but in general the quality of life was higher in the first group and the daily diuresis slightly higher. Urine acidity was within the normal range in the first group, while the pH was statistically significantly lower in the second group.

The second part of our study included 74 patients with kidney stones up to 1 cm in size who underwent remote lithotripsy. Sixty-two patients had stones in the pelvis and 12 in the calyx (upper segment - 5, middle segment - 7). In the main

Table 1. Results of treatment of patients of the first group Table 1. Results of treatment of patients of the first group

Indicator Indicator	Main group (n = 11) Major group	Control group (n = 16) Control group
Departure of the stone	9 (81,8%)*	7 (43,7%)
Leukocyturia (L>10) Leukocyturia (L>10)	2 (18,2 %)	9 (56,3 %)*
Visual analogue scale Visual analogue scale	74±19	52±10
Daily diuresis, l Daily diuresis, l	3,3±0,4	2,8±0,4
pH of urine pH of urine	6,8±0,6*	5,2±0,7

* p (Fisher's test) < 0.05 * p (Fisher's test) < 0.05

28 patients were included in the group where Renalof® was additionally prescribed, and 46 patients were included in the control group. Patients with unfavourable anatomical factors (long and narrow cervical neck and lower segment calyx) were not included in the study.

The use of Renalof® complex in complex therapy after remote lithotripsy allowed statistically significant increase in the frequency of stone discharge from 54.3% to 75%, decrease in the frequency of leukocyturia by 25% compared to the control group of patients, increase in daily diuresis up to 3.2 litres in the main group from 2.8 litres in the control group (Table 2). In addition, urine pH during Renalof® use in the main group was statistically significantly higher than in the control group.

The third part of our study was devoted to the results of treatment of 69 patients who underwent transurethral contact pyelocalicolithotripsy. The difficulty of correct assessment of the results in this category of patients is due to the fact that after the operation the kidney was drained with an internal stent, so reliable assessment of leukocyturia and urine pH was not performed in this group. On the other hand, laser stone crushing was performed in these patients. We used tulium laser lithotripter U2 Fiberlase (LLC "IRE-Polus®"), the crushing was performed in fine-dusting mode, so the fragment sizes did not exceed 1 mm and the evaluation of lithokinetic effect of Renalof® complex in this clinical situation was difficult. Table 3 shows the results of treatment of this group of patients.

Renalof® complex was additionally prescribed to 33 patients, the results of treatment of 36 patients were used as a control group.

In the main group, complete stone fragment removal was detected in 28 (84.8%) patients and in 21 (58.3%) of the control group. This difference was statistically significant.

We did not observe any cases of cancellation of Renalof® complex due to the development of adverse events that could be associated with the administration of this complex. The analysis of complications of surgical treatment did not reveal significant intergroup differences.

OBSERVATION

Clinical experience of Renalof® use was evaluated in several studies. The first clinical study investigated the use of the complex in 78 patients with urolithiasis. The main group included 41 patients who were prescribed Renalof® complex as an auxiliary dietary recommendation [17]. The authors demonstrated the following positive qualities of the complex: the possibility of partial litholysis of oxalate stones, increase in urine pH due to increased excretion of citrates in the urine. The average stone sizes were 0.7 and 0.6 cm respectively. Patients from group 1 received Renalof 2 capsules 2 times a day. Blood and urine tests, renal ultrasound and radiological examination were monitored during the study. The course of treatment for all patients of both groups was 3 months. In the main group of patients already by the end of the 2nd week of Renalof® complex treatment there was an improvement of well-being in the form of reduction (in 27 patients) and absence of pains (in 14 patients). The dysuric phenomena were stopped on the 9th day of taking the preparation. In Group 1, reduction of the size of the stone was observed in 22 patients, which made up 53.6%. Stone fragments detachment was observed in 17 (41,4%) patients. In

In group 2, reduction of stone size was observed in 7 (18.4%) patients, independent stone discharge in the form of sand - in 9 (23.6%) patients. Improvement of laboratory parameters in the form of reduction of leukocyturia, erythrocyturia, bacteriuria, oxaluria was significantly more diagnosed in the main group.

Table 2. Results of treatment of patients of the second group

Table 2. Results of treatment of patients of the second group

Indicator Indicator	Main group (n = 28) Major group	Control group (n = 46) Control group
The discharge of stone fragments The discharge of stone fragments	21 (75%)*	25 (54,3%)
Leukocyturia (L>10) Leukocyturia (L>10)	7 (25 %)	23 (50 %)*
Visual analogue scale Visual analogue scale	76±21	53±12
Daily diuresis, l Daily diuresis, l	3,2±0,3	2,8±0,4
pH of urine pH of urine	6,7±0,5*	5,3±0,7

* p (Fisher's test) < 0.05 * p (Fisher's test) < 0.05

Table 3: Results of treatment of patients of the third group

3. Results of treatment of patients of the third group

Indicator Indicator	Main group (n = 33) Major group	Control group (n = 36) Control group
The discharge of stone fragments The discharge of stone fragments	28 (84,8%)*	21 (58,3%)
Visual analogue scale Visual analogue scale	64±21	41±14
Daily diuresis, l Daily diuresis, l	3,5±0,5	2,8±0,4

* p (Fisher's test) < 0.05 * p (Fisher's test) < 0.05

Another study related to the administration of Renalof® was also conducted in Kazakhstan and was aimed at studying the supportive role of Renalof® in patients after remote nephrolithotripsy. Renalof® was administered to 14 patients from the main group who underwent remote stone destruction as a dietary recommendation, 11 patients made up the control group. Renalof® resulted in a statistically significant increase in crushing efficiency after the first session from 51.6% to 79.6%, the efficiency of the second crushing was the same, the third crushing was not needed in any patient from the main group and was needed in 19.6% of patients from the control group. The authors noted a good effect of additional administration of Renalof® complex [7,16].

Another study conducted in Indonesia in 2011 analysed the results of 30 patients with kidney stones up to 20 mm (2 cm) in size. Renalof® was prescribed 1 capsule 3 times a day for 1 month. The authors noted an additional effect of Renalof® prescription in the form of normalisation of calcium and uric acid excretion in the urine [18].

Another study on the effect of Renalof® in patients with urolithiasis was published in Cuba in 2012. 110 patients were randomly selected to receive Renalof® (n = 52) and placebo (n = 58). The age of the patients included in the study ranged from 18 to 65 years. All patients had urolithiasis with stones up to 10 mm in size. Renalof® was administered 1 capsule 3 times a day for 3 months, with monthly clinical, radiological, tomographic and ultrasound control, with the help of which adverse reactions were recorded. The main criterion for assessing the effectiveness of treatment was the reduction in the size of the nodule or its complete elimination. The reduction in the number of stones was 7.7% in the group of patients taking Renalof® and 0% in the placebo group at the third month, while the elimination of stones was 86.5% in patients at the third month of treatment including Renalof® complex. The mean number of colic decreased after 3 months, only 0.4 ± 1.3 for the group of patients taking Renalof®. The authors concluded that Renalof® is effective in eliminating or reducing calcium stones in the kidneys and urinary tract without adverse reactions [19-22].

The complex action of Renalof® is due to the effects of its ingredients, especially the activated extract of *Agropyron Repens*, whose natural diuretic effect makes it ideal for the treatment of all urinary tract infections. Moreover, thanks to its diuretic effect, it can stimulate the removal of kidney stones. Additional therapeutic effects of *Pyreneae* are its anti-irritant and pro-

It has an anti-inflammatory effect, which reduces the likelihood of renal colic during standard lithokinetic therapy. Wheatgrass also has an antimicrobial effect, as it destroys pathogens and prevents their growth. Wheatgrass causes a good regeneration of the epithelium after stone excretion, which has an additional anti-inflammatory effect on the urinary system. Clinical studies have shown that Renalof® has a pronounced anti-inflammatory, antispasmodic and litholytic effect in patients with urolithiasis and provides painless excretion of small stones through the urinary system [16,17]. The data of the above-mentioned clinical observations show that a one-month course of Renalof® complex application leads to normalisation of clinical urinalysis indicators [16-19].

Our study represents the first domestic clinical experience with Renalof® complex in patients with urolithiasis. Taking into account previous publications, the study design was made in such a way as to clarify the effect of the complex, taking into account the clinical situations already studied for its use. To achieve the above objective, we divided the patients into 3 groups, which illustrate the vast majority of clinical situations in patients with urolithiasis. Stones up to 5 mm were treated with conservative lithokinetic therapy and Renalof® was additionally administered to the main group of patients, which resulted in statistically significant increase in the frequency of stone removal from 43.7% to 81.8% of cases, decrease in the frequency of leucocyturia from 56.3% to 18.2%, increase in urine pH from 5.2 to 6.8. Changes in diuresis and visual analogue scale, despite their better indicators in the main group, were statistically insignificant.

The second group of patients consisted of patients treated with remote lithotripsy. The following data were obtained. In the main group of 28 patients, better stone fragment removal rates and a decrease in leucocyturia were achieved. There were statistically insignificant differences in the indices of visual analogue scale and diuresis. As in the first group, the changes in urine pH were statistically significant. Thus, additional use of Renalof improved the effectiveness of remote lithotripsy and reduced the severity of inflammatory changes in the urine.

In the final part of our study we investigated the clinical efficacy of using the complex in patients after tulium laser lithotripsy. In this group of patients the main goal was not to investigate the frequency of microliths detachment, as their size after laser lithotripsy did not exceed 1 mm. Taking into account the location of the stent, we did not investigate



leucocyturia level and urine pH. Nevertheless, the frequency of microliths that were removed apart from the stent was statistically significantly higher in the main group than in the control group (84.8% vs. 58.3%). Diuresis and visual analogue scale index were also higher in the main group, however, taking into account the position of the internal stent, we did not consider these changes clinically significant.

Additional administration of Renalof® complex to patients who underwent endourological surgery for kidney stones improved their quality of life, slightly increased diuresis, and reduced leukocyturia. At the same time, there was a statistically significant increase in the frequency of kidney stone absence when Renalof® was administered compared to the control group.

Among other clinical advantages of Renalof® use we can mention its safety, as we have not observed any cases of undesirable events associated with the use of the complex, nor have we detected any abnormalities in laboratory parameters.

CONCLUSIONS

The use of Renalof® complex in patients with urolithiasis, including after remote lithotripsy and in the postoperative period after endoscopic surgeries on the upper urinary tract has the following clinical advantages:

- Improved self-discharge of stones;
- normalisation of urine acidity;
- increased diuresis in patients in the postoperative period;
- reduction of leukocyturia rates in patients in the postoperative period;
- faster excretion of residual fragments after endoscopic upper urinary tract surgery.

The results of the study allow the authors to recommend the use of Ren-lof® complex 1 capsule 3 times a day for 1 month. ■

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Authors' contributions:

Martov A.G. - concept and design of the study, analysis of modern literature and obtained data, processing of results and conclusions, 50%.
Ergakov D.V. - analyses of patient data, statistical analysis, writing and preparation for publication, 50%.

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