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# The effect of the phytocomplex Renotinx® on postoperative period after external shock wave lithotripsy in patients with urolithiasis

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**INTRODUCTION:** Phytopreparations are one of the leading medicines used as preoperative preparation and postoperative management in patients with urolithiasis.

**THE AIM** of the study was to evaluate the nephroprotective effect of Renotinx® in patients with urolithiasis after extracorporeal shock wave lithotripsy (ESWL).

**MATERIALS AND METHODS:** The study included 86 patients (43 in the main and the comparison group) with urolithiasis with localization of the stone in the renal pelvis without disturbing the outflow of urine. All patients underwent extracorporeal shock wave lithotripsy (ESWL). After ESWL patients in both groups received spasmodic, anti-inflammatory, antibacterial therapy. Patients of the main group additionally received Renotinx® 2 capsules 3 times a day for 14 days before and 14 days after surgery.

**RESULTS:** During the observation a more effective discharge of calculus fragments was noted in patients of the main group while taking the phytocomplex Renotinx®, as well as less pronounced damage and faster recovery of the renal parenchyma after ESWL according to the level of enzimuria.

**CONCLUSION:** The results of the study indicate the feasibility of prescribing the phytocomplex Renotinx® for nephroprotective and lithokinetic therapy in patients after ESWL.

**Keywords:** urolithiasis; herbal medicine; Renotinx®; enzymuria; nephroprotective therapy.

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## Влияние фитокомплекса Ренотинекс® на течение послеоперационного периода после дистанционной ударно-волновой литотрипсии у больных мочекаменной болезнью

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**Введение.** Фитопрепараты — это одни из ведущих лекарственных средств, применяемые в качестве предоперационной подготовки и послеоперационного ведения у пациентов с мочекаменной болезнью.

**Целью** исследования стала оценка нефропротективного действия препарата Ренотинекс® у больных уролитиазом после дистанционной ударно-волновой литотрипсии.

**Материалы и методы.** В исследование были включены 86 пациентов (по 43 в основную и группу сравнения) с мочекаменной болезнью с локализацией камня в лоханке почки без нарушения оттока мочи. Всем пациентам выполняли дистанционную ударно-волновую литотрипсию. После нее пациенты обеих групп получали спазмолитическую, противовоспалительную, антибактериальную терапию. Пациенты основной группы дополнительно получали Ренотинекс® по 2 капсулы 3 раза в сутки в течение 14 дней до и 14 дней после операции.

**Результаты.** В ходе наблюдения было отмечено более эффективное отхождение фрагментов конкремента у пациентов основной группы на фоне приема фитокомплекса Ренотинекс®, а также менее выраженное повреждение и более быстрое восстановление почечной паренхимы после дистанционной ударно-волновой литотрипсии по данным уровня энзимурии.

**Выводы.** Результаты проведенного исследования указывают на целесообразность назначения фитокомплекса Ренотинекс® для нефропротективной и литокинетической терапии у пациентов после ДУВЛ

**Ключевые слова:** мочекаменная болезнь; фитотерапия; Ренотинекс®; энзимурия; нефропротективная терапия.

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## INTRODUCTION

The urgency of urolithiasis (UL) is currently not decreasing [1, 2]. Treatment of patients with UL remains one of the most complicated tasks in modern urology [2, 3]. Extracorporeal shock wave lithotripsy (ESWL) is significant among minimally invasive surgical methods of treatment for UL [4, 5]. However, during lithotripsy, even using the most sparing technique, the shock wave inevitably damages the renal parenchyma. In this regard, the use of nephroprotective agents becomes necessary, such as phytopreparations. Herbal preparations based on terpenes are the most studied nephroprotective agents [6, 7]. One of them is Renotinx<sup>®</sup> phytocomplex, which contains six types of terpenes (pinene, camphene, borneol, anethole, fenchon, and cineole). Studies have tried to prove the anti-inflammatory effect of terpenes. The latter is associated with both suppression of the release of arachidonic acid, which is a substrate for the formation of various inflammatory mediators, and a decrease in macrophage activation. The combination of camphene and borneol inhibits the enzyme acetylcholinesterase, exerting a cholinergic effect, in particular, on M3-cholinergic receptors in the smooth muscles of the urinary tract, thereby increasing motility and improving the flow of urine and calculi. The antiseptic effect of terpenes and their ability to dilate blood vessels, improving the trophism of organs and tissues, are also known [6, 7].

*This study aimed mainly to assess the efficacy and safety of Renotinx<sup>®</sup> phytocomplex in the treatment of patients with UL. The primary aim of the study was to evaluate the nephroprotective effect of Renotinx<sup>®</sup> in ESWL in patients with UL. Secondary aims were to assess the lithokinetic properties of Renotinx<sup>®</sup> phytocomplex in this category of patients and to evaluate tolerability of the drug based on the analysis of adverse events and changes in laboratory parameters of clinical and biochemical blood tests and general urine analysis.*

## MATERIALS AND METHODS

This single-center prospective randomized study included 86 patients with UL aged 22–65 years, hospitalized for ESWL.

The inclusion criteria were as follows:

- Presence of a calculus with diameter of 0.5–2 cm with localization in the renal pelvis without impairment of the urine outflow.
- Signed informed consent to participate in the study.

The exclusion criteria were as follows:

- Nephrolithiasis with calculi of >2 cm in diameter, requiring another type of surgical treatment.
- All other urological diseases in the acute stage.
- Severe dysfunctions of the liver and/or kidneys and/or other vital organs, accompanied by decompensation of their functions.

- Inability to answer adequately the investigator's questions, fill out the necessary documents, and use the drugs under study
- Participation in the study of any other drug and/or method of treatment.

All patients who met the inclusion criteria and were enrolled in the study were randomized into two groups, namely, the comparison group (group 1) ( $n = 43$ ) and the main group (group 2) ( $n = 43$ ). The average age of patients in the main group was  $40.7 \pm 4.8$  years and that in the comparison group was  $42.8 \pm 5.4$  years.

In this study, 16 patients of the main group and 12 patients of the comparison group were monitored earlier due to UL. Moreover, six patients in the main group and five patients in the comparison group had previously received drug treatment for UL. Phytopreparations and antispasmodics were most often used. Renotinx<sup>®</sup> has not been prescribed to any patient before. In patients with bilateral nephrolithiasis, the condition of the calculus was assessed only on the side of the lithotripsy performed.

After study enrolment, patients of the main group received Renotinx<sup>®</sup> two capsules three times a day for 28 days. On the day of ESWL, therapy that included drotaverine 40 mg three times a day for 5 days, ciprofloxacin 500 mg two times a day for 10 days, and increased fluid intake (1.5–2 liters per day) was prescribed to the patients of both groups.

The study protocol included four visits. During visit 1, the patient signed a written consent to participate in the study. History taking, collection of complaints, and physical examination were performed, with registration of concomitant diseases and drugs taken by the patient, as well as previous drug and non-drug treatment of nephrolithiasis. Ultrasound (US) examination of the kidneys, plain and excretory urography, and multispiral computed tomography (MSCT) of the kidneys were performed. Biological material was collected for a clinical blood test, general urine test, and biochemical blood test. Along with the general set of examinations, the urine levels of alkaline phosphatase (ALP), lactate dehydrogenase (LDH), gamma glutamyltransferase (GGT), and leucine aminopeptidase (LAP) were determined. The activities of ALP, GGT, and LDH in the urine were studied using unified kinetic methods for determining the blood serum levels of these enzymes. LAP in urine was determined with ready-made reagent kits from Spinreact (Spain) [8]. After the necessary examinations, Renotinx<sup>®</sup> was prescribed to the main group according to the above scheme.

During visit 2, that is, on day 14 after enrolment in the study, adverse events that occurred during treatment were recorded, and disease symptoms were assessed. This was followed by an ESWL session (3000 impulses).

At visit 3, 7 days after ESWL (day 21 after enrolment in the study), the frequency of discharge of calculus fragments was assessed, and renal US examination, plain and excretory urography, clinical and biochemical blood tests, and general urinalysis were performed.

During visit 4, 14 days after ESWL (day 28 after enrolment in the study), disease symptoms were recorded, the frequency of discharge of calculus fragments was assessed, and renal US, plain and excretory urography, clinical and biochemical blood tests, and general urine analysis were performed.

In addition, the level of enzymuria was assessed in all patients on the next day after ESWL.

The patient could be excluded from the study for reasons of occurrence of serious adverse effects leading to temporary disability; violation of the protocol by the patient or investigator; at the discretion of the researcher, if he believes that the continuation of the study is harmful to the patient's health; or at the request of the patient himself.

Various methods of statistical processing were used, depending on the type of random variables and research task [9]. To assess the shape of the distribution of attributes, kurtosis and asymmetry were used, which characterize the shape of the distribution curve. The distribution was considered normal when the values of these indicators ranged from  $-2$  to  $2$ . The equality of sample variances was assessed by the  $F$ -test. Paired Student's  $t$ -test was used to compare the related samples. If distributions do not correspond to the normal, as well as in the case of inequality of variances, the nonparametric Mann-Whitney  $U$ -test (for independent samples) and Wilcoxon  $T$ -test (for linked samples) were used. The nonparametric  $\chi^2$  test was used to compare qualitative attributes. At low frequencies ( $<10$ ), the Yates correction for continuity was used for this criterion. Dunnett's  $Q$ -test was used to compare the study groups. In the case of distributions that do not correspond to the normal, as well as in the case of inequality of variances, the nonparametric Dunn  $Q$ -test was used for multiple comparisons. The critical level of statistical significance when testing the null hypothesis was  $0.05$ . In all cases, two-sided variants of the criteria were applied. Data processing was performed using Statistica v. 6.0 and Excel 2003.

## RESULTS

Indicators of general and biochemical blood tests and general urine analysis (protein level, specific gravity, bacteria content, and pH) in the study groups with follow-up control were within the reference values and did not differ significantly.

Several days after ESWL sessions, all patients noted an admixture of blood in the urine, which ceased spontaneously. In seven patients of the main group and six patients of the comparison group upon inclusion in the study, the general urine analysis showed signs of inflammation, which were also arrested in all cases during the follow-up.

US examination, X-ray imaging, and MSCT of the kidneys upon enrolment revealed pelvic calculi up to 2 cm

in size in both groups. The mean density and size of the calculi in the main and comparison groups did not differ significantly ( $1018 \pm 76.16$  and  $1005 \pm 66.2$  HU;  $1.6 \pm 2.5$  and  $1.8 \pm 1.8$  cm, respectively ( $p > 0.1$ ). When assessing the severity of clinical symptoms on day 1 after surgery, the frequency of attacks of renal colic in the main group was less than that in the control group, which can be due to the nephroprotective and antispasmodic effect of preoperative therapy with Renotinx® phytocomplex. The frequency of complete discharge of fragments of the destroyed stone was also higher in the main group (28.6%) than in the comparison group (19.4%).

In the analysis of the severity of enzymuria, an increase in the excretion of ALP, LDH, and GGT was noted. ALP and GGT are found in the epithelium of the proximal nephron, and their increased level in the urine indicates damage to the renal tissue. An increase in LDH level can serve as an indicator of ischemia of the renal parenchyma [10]. Kidney ischemia is accompanied by the accumulation of  $\text{Ca}^{2+}$  in the mitochondria with a sharp inhibition of their energy production and, in combination with stimulation of proteases, leads to destructive changes in the cell [10]. In addition, the accumulating reactive oxygen species and other oxidants interact with the plasma membrane lipids, which are accompanied by its structural changes, and lead to impaired permeability. Therefore, the determination of LDH activity in the urine can be used as a test reflecting the level of ischemic exposure [10].

On day 1 after ESWL, all patients had a significant increase in the level of urine enzymes, which indicated damage to the tubular nephron and, as a consequence, an increase in the permeability of the renal membranes and renal parenchyma ischemia. However, in the main group during therapy with Renotinx® phytocomplex, these changes were less pronounced due to the nephroprotective effect of terpenes. In the comparison group, on day 7 after ESWL, during conventional antispasmodic therapy, levels of the enzyme decreased. By day 28 after ESWL, enzymuria reached its initial level (Table 1).

In the main group of patients, who received Renotinx® phytocomplex in combination with conventional therapy, the level of enzymuria decreased significantly to the initial values on day 7 after ESWL. Within 28 days after ESWL, the levels of urine enzymes remained at a low level in all patients of the main group, which was regarded as a complete restoration of the functional state of the kidney.

The tolerability of treatment with Renotinx® phytocomplex was satisfactory. During the study, no allergic reactions were noted in any of the patients. Moreover, there was no deterioration in the general condition of the patient, and emergence of new complaints or pathological deviations of laboratory parameters during the study was not recorded.

**Table.** Dynamics of enzymuria indices in patients of the main group and the comparison group ( $n = 86$ )**Таблица.** Динамика показателей энзимурии у пациентов основной группы и группы сравнения ( $n = 86$ )

| Indicator | Main group ( $n = 43$ ) |                  |                  |                   | Comparison group ( $n = 43$ ) |                  |                  |                   |
|-----------|-------------------------|------------------|------------------|-------------------|-------------------------------|------------------|------------------|-------------------|
|           | Before treatment        | Day 1 after ESWL | Day 7 after ESWL | Day 14 after ESWL | Before treatment              | Day 1 after ESWL | Day 7 after ESWL | Day 14 after ESWL |
| GGT, U/L  | 7.28 ± 0.42             | 9.3 ± 0.51       | 5.8 ± 0.8        | 5.7 ± 0.5         | 7.28 ± 0.28                   | 12 ± 0.32*       | 7.32 ± 0.36      | 7 ± 0.38          |
| ALP, U/L  | 10.9 ± 0.46             | 14.2 ± 2.42*     | 11 ± 0.83        | 10.3 ± 0.54       | 11 ± 0.52                     | 24 ± 1.73*       | 13 ± 1.02        | 11.2 ± 1.05       |
| LDH, U/L  | 8.3 ± 0.43              | 9.5 ± 1.2        | 6.4 ± 0.24       | 6.3 ± 0.43        | 8.3 ± 0.38                    | 11.5 ± 0.89*     | 8.4 ± 0.54       | 8 ± 0.45          |
| LAP, U/L  | 10.23 ± 1.1             | 12.14 ± 0.98     | 8 ± 0.45         | 10.2 ± 0.35       | 10.2 ± 0.35                   | 13.5 ± 0.78*     | 11 ± 0.7         | 10 ± 0.8          |

\* $p < 0.05$  compared with baseline. *Note.* ALP, alkaline phosphatase; GGT, gamma glutamyltransferase; ESWL, extracorporeal shock wave lithotripsy; LDH, lactate dehydrogenase; LAP, leucine aminopeptidase.

## CONCLUSION

The study results suggested that Renotinx® phytocomplex can be used as nephroprotective and lithokinetic therapy in patients undergoing ESWL. Renotinx® is characterized by a high safety profile, which is very important when prescribing therapy in patients with increased membrane permeability after ESWL. Thus, we consider it promising to study further the therapeutic effect of terpenes that are part of Renotinx® phytocomplex.

Based on the results obtained, the following conclusions were made:

1. In patients with nephrolithiasis, the activity level of urine enzymes increased after ESWL, which is regarded as damage to the nephron cytomembrane.

2. Prescription of Renotinx® phytocomplex to patients with nephrolithiasis 14 days before ESWL and after ESWL contributes to the reduction of enzymuria level and improvement of the functional state of the kidneys, which is due to its nephroprotective effect.

3. The use of Renotinx® phytocomplex improves the course of the period after ESWL, contributing to a more efficient discharge of calculus fragments.

## ADDITIONAL INFORMATION

**Conflict of interest.** The authors declare no conflict of interest.

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