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CLINICAL EFFICACY OF USE OF PHYTOPREPARATION "NOKAMEN" IN THE COMPLEX TREATMENT OF PATIENTS WITH UROLITHIASIS

According to data of different authors, patients with urolithiasis make a large part of (30 to 45%) patients in urology hospitals, and their amount continues to grow [1,2,3]. In Ukraine, over the past decade, the incidence of urolithiasis has been increased from 305.6 cases per 100 000 of adults in 1989 to 535.8 cases in 2009 [4,5].

The introduction of lithotripsy into the urological practice has fundamentally changed the approaches for urolithiasis therapy, and opened new prospects to decrease morbidity and disability, allowing to refuse a surgery and an anesthesia [6,7].

The ultimate success of lithotripsy is determined by auxiliary therapeutic measures aimed at acceleration of the discharge of fragments, as well as the prevention of stone formation, that allows to avoid re-lithotripsy and other endoscopic procedures.

The herbal complex Nokamen manufactured by the pharmaceutical company "Ananta Medicare", United Kingdom, is registered and approved for use as a food supplement in Ukraine. Nokamen is an uroprotector with an accent on litholytic effect. The Nokamen's composition contains the following active ingredients: Crataeva nurvala bark - 100 mg, Saxifraga ligulata rhizomes - 60 mg, Butea frondosa flowers - 40 mg, Dolichos biflorus seeds - 40 mg sodium bicarbonate - 20 mg, Boerhavia diffusa roots - 70 mg, Asphaltum - 70 mg, Tribulus terrestris fruits - 100 mg, Rosmarinus officinalis extract - 20 mg, Rubia cardifolia extract - 20 mg.

The purpose of study is the determination of the possibility of use of Nokamen phytopreparation in the complex treatment of patients with nephrolithiasis treated with remote lithotripsy. In the period from November 2014 to February 2015 were examined and treated 42 patients with calculi in the kidneys and ureters. Nokamen was indicated in 2 tablets, 2 times a day after meal. The course of treatment made 45 days.

Research tasks:

1. To assess the Nokamen's effectiveness for the prevention of infectious and inflammatory complications after remote lithotripsy.
2. To assess the Nokamen's effect on the time limits of the discharge of calculi after lithotripsy.
3. To study the possibility of Nokamen's effect on microcirculation of renal parenchyma to reduce trauma risks in remote lithotripsy.

Complex examination of patients with nephrolithiasis was carried out with the use of modern methods of diagnosis:

1. Plain and excretory urography (to confirm the presence of calculi and determine the functional state of the kidneys).
2. Renal ultrasound with Doppler sonography (to determine the blood flow state in the parenchyma) before and at different stages after lithotripsy.
3. General analysis of blood and urine (detection of hidden leukocyturia).
4. Bacteriological urine examination.
5. Biochemical blood tests.

The comparative analysis of the results of the treatment of the patients with nephrolithiasis was carried out in two groups of patients. First, the control group, consisted of 20 patients with localized calculi in the renal pelvis of the ureter, was treated with remote lithotripsy followed by conventional post-operative conservative therapy. The second group was the main group consisted of 22 patients with comparable localization and clinical disease. But unlike the first group of patients, after lithotripsy therapy these patients were administered with Nokamen only in the dose of 2 tablets 2 times a day after meal. Dynamic observation was carried out for 45 days. The main group consisted

of 9 men (41%) and 13 women (59%). The average age of patients was 42 years (16 to 71 years). According to calculi localization the patients were classified as follows (Table 1.)

Table 1. Classification of patients of the main group in accordance with localization of concrements:

Localization of concrements	Amount of patients	
	Persons	%
Pelvis and calyx	11	50
Ureter	9	41
Ureteropelvic junction	2	9
TOTAL	22	100%

The sizes of calculi in the kidneys fluctuate between 6 and 24 mm, ureters - between 6 and 9 mm. According to the data of excretory urography and ultrasound a moderate ureteropyelectasis was revealed in all patients with ureteral calculi, and in 2 patients with calculi in the UPJ.

Out of the total amount of patients of the main group (22) complaints on renal colic were observed in 18 (81.8%), leukocyturia of different severity was revealed in 19 patients (86.4%). According to the urine culture results bacteriuria from 10^3 to 10^5 cfu/ml, was revealed in 11 (50%) of 22 patients in the main group. The characteristic of obtained microflora was presented in Table 2.

Table 2. The characteristic of obtained microflora in the patients of the main group before start the treatment.

Microflora	Amount of patients	
	Persons	%
Ecoli	5	45,4
Pseudomonas aerug.	1	9,1
Proteus mirabilis	2	18,2
Providencia rettgeri	1	9,1
Enterococcus	2	18,2
TOTAL	11	100%

Remote lithotripsy was carried out according to the indications for all 22 patients in compliance with necessary conditions for the operation. The only one lithotripsy session has been enough for the fragmentation of calculi in the prevailing number of patients (21 pers.). 3 lithotripsy procedures were performed for only one patient with localization of 25 mm stone in the pelvis.

The assessment criterions of the treatment efficiency were: frequency of renal colic occurrence, the time of clearance of urinary tract from all fragments after lithotripsy, the dynamics of changes in urine results (leucocyturia, bacteriuria), the dynamics of changes in Doppler parameters and tolerability. Doppler ultrasound was carried out before lithotripsy and right after lithotripsy, and then in 7 days, in 2 weeks and in 7 weeks after starting the treatment. X-ray was performed when indicated.

The analysis of clinical observation has shown that from the 22 patients treated with Nokamen on the background of lithotripsy, in the postoperative period a renal colic occurred only in 2 patients, and it makes 9% from the total number of the patients of the main group. In this case, these 2 patients had calculi of significant sizes (> 20 mm), and after lithotripsy the steinstrasse occurred and it was the indication for additional therapy. In the control group of patients treated without Nokamen, the renal colic was observed in 57%. The results show pronounced antispasmodic properties of Nokamen preparation.

The positive dynamics of urinalysis has been recorded. Before starting the treatment, leukocyturia of different severity (from 4500 to 28000 in 1ml on Nechiporenko) occurred in 19 (86.4%) of 22 patients of the main group. In a week after starting the treatment with Nokamen the leukocyturia's severity was significantly reduced (up to 8000 in 1 mL) in most patients. The results of urine were

normalized in 7 of 19 patients with leukocyturia, thereby the total amount of patients with leukocyturia has been reduced down to 54.5% (12 patients). These results confirm the anti-inflammatory properties of the Nokamen. The follow-up (2 weeks) for patients treated with Nokamen, allowed to confirm the effectiveness of the drug regarding the infectious-inflammatory process. Thus, the number of patients with leukocyturia was reduced down to 8 (36.4%) in three weeks. The patients, who had a stable leukocyturia, were treated with antibiotic therapy according to the sensitivity of the urine microflora. 4 weeks later in the group of patients treated with Nokamen, 4 patients still had leukocyturia (18%) and for these patients the antibiotic therapy was continued with medications in combination with Nokamen. After 7 weeks of treatment the number of patients with bacteriuria was reduced. If there are 11 patients with bacteriuria in the main group before starting the treatment, then in a month after the treatment, bacteriuria 10 CFU / ml was revealed in 3 (13.6%) patients only. There were not revealed any changes of electrolytic composition of blood serum (Na +, K +, Ca ++, Mg ++) in 7, 14 and 45 days.

The time of discharge of calculi has been significantly reduced in the patients after remote lithotripsy during the treatment of Nokamen. The urinary tracts were cleaned from fragments by the end of the first week survey. The lithotripsy, followed by traditional drug therapy, was carried out in the group of patients with the similar localization of the calculus, and the urinary tracts were completely cleaned from the fragments in two - three weeks. The re-lithotripsy sessions should be carried out for two of these patients. Thus, Nokamen promotes more rapid discharge of calculi from the urinary tract after lithotripsy.

Ultrasonography with dopplerography was performed in the postoperative period after remote lithotripsy in the control group (without Nokamen) and in the main group (with Nokamen) in terms, such as: before lithotripsy, right after lithotripsy, in 2 days, 7 days, 2 weeks, 4 weeks after starting the treatment of Nokamen . The blood flow condition was evaluated by the pulsatility index (P_1) at the level of the renal artery and segmental vessels.

The analysis of the dynamics of Doppler ultrasonography indicators in the patients of the control group showed a significant increase of the pulsatility and resistivity indices: right after lithotripsy and during the early postoperative period. They became normal only in 7 days (Table. 3).

In patients after lithotripsy the disorder of renal blood flow occurs due to shock wave, and the severity and the damage mode depends on the initial state and the urodynamics behavior [3].

Due to the fact that in patients with pyeloectasia the pulsatility and resistivity indices had high values: $P_1 = 1,23 \pm 0,06$ ($P < 0,05$) and $CI = 0,72 \pm 0,03$ ($P < 0,05$), we divided the main group into two subgroups. The first one consisted of 11 patients with calculi in pelvis and calyx without ectasia, the second one - 11 patients with ureteropyeloectasia.

Table 3. The dynamics of dopplerography indices in patients of the control group (without Nokamen)

Index	Before lithotripsy	Indices after lithotripsy		
		Right after	In 2 days	In 7 days
P_1	$1,1 \pm 0,02$	$1,3 \pm 0,04$ $P < 0,01$	$1,14 \pm 0,013$ $P < 0,01$	$1,04 \pm 0,036$ $P < 0,05$
CI	$0,66 \pm 0,01$	$0,75 \pm 0,023$ $P < 0,01$	$0,68 \pm 0,02$ $P < 0,05$	$0,63 \pm 0,02$ $P < 0,05$

P – in comparison with indices before lithotripsy.

Table 4. The dynamics of dopplerography indices after lithotripsy with Nokamen treatment.

Index	Before lithotripsy	Indices after lithotripsy				
		Right after	In 2 days	In 7 days	In 2 weeks	In 7 weeks
P_1	$1,03 \pm 0,08$	$1,3 \pm 0,04$ $P < 0,005$	$0,94 \pm 0,05$ $P < 0,01$	$0,96 \pm 0,09$ $P < 0,01$	$0,95 \pm 0,06$ $P < 0,01$	$0,96 \pm 0,03$ $P < 0,01$

CI	0,63 ± 0,02	0,75 ± 0,023 P <0,01	0,6 ± 0,016 P <0,01	0,61 ± 0,03 P <0,01	0,6 ± 0,02 P <0,01	0,55 ± 0,05 P <0,01
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P – in comparison with indices before lithotripsy.

In order to define the effect of the Nokamen preparation on the state of renal blood flow after lithotripsy, we have carried out the comparative analysis of pulsatility and resistivity indices in the equal groups of patients (in 11 patients), while maintaining the urine outflow. Table 3 shows the patients' indices after lithotripsy without using Nokamen, and Table 4 - indices after lithotripsy in patients treated with Nokamen.

It was found that in the group of patients who underwent lithotripsy without using Nokamen, the restoration of renal hemodynamics occurred only on the 7th day after lithotripsy. Normalization of hemodynamics after lithotripsy in patients treated with Nokamen, was more rapid, and in 2 days after lithotripsy the pulsatility and resistivity indices corresponded to indices before the intervention. These indices were not varied for the entire observation period, regardless of the number of lithotripsy sessions (Table. 4).

The received data allow to draw a conclusion that the prescription of Nokamen for the patients with urolithiasis before lithotripsy allows to restore a renal blood flow more rapidly, to reduce the trauma of parenchyma as a result of the shock wave impact to a minimum level and to reduce the period between sessions down to 2 days, if necessary.

As mentioned above, during the disorder of urine outflow from the upper urinary tract, the disorder of renal blood flow at the level of vessels of renal hilum was observed. And this disorder consisted in a significant increase of pulsatility index: $1,5 \pm 0,4$ ($p > 0.001$). The last one remained significantly increased, and it testified to the decrease of blood velocity in the parenchyma.

In a week P_1 and CI indices in the Nokamen's group were $0,96 \pm 0,1$ ($P > 0.01$) and $0,6 \pm 0,03$ ($P > 0.01$) respectively. It testifies to the normalization of blood velocity. The study of hemodynamics in patients with urolithiasis has revealed a significant increase of P_1 and CI indices when ureteropyeloectasia. It is connected with the increase of intrapelvis pressure, leading to disorder of blood flow in the parenchyma.

For a more detailed study of the change of blood velocity P_1 and CI indices were determined at the segmental level of the vascular bed. Analysis of the results showed that in the group of patients who did not receive Nokamen, P_1 and CI indicators were increased up to $1,43 \pm 0,07$ and $0,76 \pm 0,01$, respectively. At that time the patients treated with Nokamen, hemodynamic changes were expressed slightly - 1.11 ± 0.06 and 0.64 ± 0.02 , respectively.

Thus, the efficacy of Nokamen in improvement of blood flow not only at the level of the renal arteries, but also at the level of microcirculation was confirmed.

Conclusions

These results confirm the effectiveness of the herbal remedy Nokamen in patients with urolithiasis in combination with the remote lithotripsy:

1. Nokamen is effective in the prevention and treatment of infectious and inflammatory complications, reducing the severity of leukocyturia and bacteriuria.
2. The terms of the discharge of fragments from the urinary system after lithotripsy are reduced in two times. Nokamen reduces the frequency of renal colic and the risk of formation of steinstrasse after remote lithotripsy.
3. Nokamen improves renal blood flow and reduces the risk of traumatic parenchymal damage due to shock wave during lithotripsy.
4. Nokamen should be prescribed one week before the planned lithotripsy followed by the administration in the postoperative period to prevent possible vascular and Infectious complications.