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Assessment Of Drug Nephrocisin's Hypoazotemic Efficiency At Various Stages Of Chronic Kidney Disease In Clinical Conditions

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ABSTRACT
Chronic renal failure is a disease resulting in severe uremic intoxication. In this research, the hypoazotemic efficacy of the domestically produced flavanoid nephrocyzine in patients with chronic kidney disease has been studied. The results show that in the group of patients who took the drug nephrocizine, in contrast to the control group, there was a significant decrease in the levels of urea, creatinine and increase in the glomerular filtration rate.
Key words: chronic kidney disease, glomerular filtration rates, flavanoids, nephrocyzine.

Keywords: service quality, behavioral intention, emotional satisfaction, childcare center

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INTRODUCTION
The number of patients with chronic renal failure (CRF) is growing steadily around the world. Over the past decade, the number of patients with chronic renal failure in Russia was 100-600 cases per 1 million population, in the USA - 600-700 cases, 50-100 people per 1 million people suffer from this disease every year [1; 2]. Since the data on the CRF prevalence are based on research data or data provided by hemodialysis centers, the actual CRF prevalence and incidence may be much higher [9; 10; 11].
The increase in the CRF prevalence is explained not only by an increase in the number of patients with primary renal pathology, but also by diabetes mellitus, obesity, aging (long life expectancy) and damage to individual renal vessels [4; 5; 6]. Currently, arterial hypertension and hyperglycemia play an important role in kidney damage, and risk factors for the renal pathology development include smoking, hyperlipidemia, obesity and metabolic syndrome [4; 12; 13]. Kidney disease is more severe when multiple risk factors are present. Over the past 15-20 years, the number of patients receiving renal replacement therapy has increased more than 4 - 5 times [7; 8].
In the early stages of the renal failure forming, there are no renal disfunction symptoms. A further decrease in the loss of functioning nephrons (up to 30% of the norm) leads to a more pronounced impairment of renal function - an increase in the concentration of nitrogen metabolites (urea, creatinine), electrolyte imbalance, anemia, and so on.
From the literature can see that in cases of hyperazotemia, bioflavonoids made from plant materials are effective drugs, of which flavonoids are the drugs of choice for complex use in the renal failure treatment (the most widely used) [6; 7]. Hypoazotemic activity was revealed in the research of the flavonoid nephrocizine's pharmacological properties isolated from the surface parts of the native plant Ferula varia in the Republic of Uzbekistan. It is known that flavonoids have capillary-strengthening, angioprotective, moderately hypotensive, diuretic, antiulcer, hepatoprotective and some other properties (V.A. Baraboy, 1976, V.G. Minaeva, 1978). The most valuable flavonoids' property is their excretion of urea and other nitrogenous products from the blood, which is extremely important in chronic kidney diseases of various etiologies (V.E. Sokolova et al., 1975). Nephrocizine, a drug belonging to the group of flavonoids, was developed as a substance at the Institute of Plant Chemistry of the Republic of Uzbekistan (reg No. 2 of 12.06.2009). Thus, we considered it necessary to monitor the effect of nephrocizine on renal function parameters and evaluate its hypoazotemic efficacy for the complex treatment of CKD patients in the pre-dialysis period.

AIM OF RESEARCH
To study the effect on renal function indices and to evaluate the hypoazotemic efficacy of the drug nephrocizine in patients with stage III-IV chronic kidney disease.

MATERIALS AND METHODS
For the research, 123 patients with CKD were selected, which developed because of nephropathy of various origins (GFR 15-59 ml/ min/m^2), who were treated at the Department of Nephrology of the Tashkent Medical Academy. The CKD diagnosis and stages were formulated according to the recommendations of the US National Kidney Foundation (CKD K / DOQI, 2002).
From an etiological point of view, most patients, namely 106, were diagnosed with chronic glomerulonephritis, and 12 - with chronic pyelonephritis. The nosology of pyelonephritis also includes secondary pyelonephritis caused by urolithiasis and polycystic kidney disease. Several other diseases were also included (2 patients with chronic tubulointerstitial nephritis, 3 patients with lupus nephritis and systemic lupus erythematosus) (Figure 1). However, the group of diseases with the following criteria was not included in the research: diabetes mellitus and other CKD of endocrine genesis, kidney tumors, acquired or congenital diseases of the

cardiovascular system, nephropathies caused by acute infectious diseases.

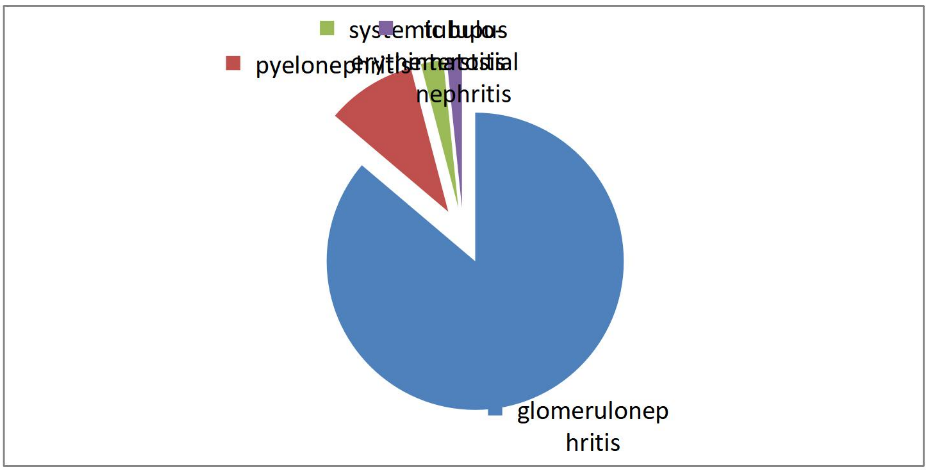


Fig 1. DISTRIBUTION OF PATIENTS BY NOSOLOGY

The age of the patients ranged from 19 to 50 years (mean 38.63 ± 1.09). Of these, 67 were men and 56 were women. The disease duration ranged from 5 to 10 years, with an average of 7.8 ± 2.3 years. All patients were randomly divided into 4 groups: 1A, 1B (GFR 30 - 59 ml/min) and 2A, 2B (GFR 15 - 29 ml/min): group 1A - 32 patients with stage III of CKD received traditional treatment according to the recommendations of international standards; group 1B - 31 patients with stage III of CKD, in addition to traditional treatment in accordance with international treatment standards, received nephrocizine at a dose of 300 mg/day (50 mg in 1 tablet, 2 tablets 3 times a day, for 3 months), group 2A - 30 patients with stage IV of CKD received traditional treatment in accordance with international treatment standards; Group 2B - 30 patients with stage IV of CKD were prescribed nephrocizine at a dose of 300 mg/day (50 mg per 1 tablet of the drug, 2 tablets 3 times a day for 3 months), in addition to traditional treatment, as recommended by international treatment standards. No side effects were observed in patients with stage III of CKD who received nephrocizine. In the group of patients with stage IV of CKD, undesirable effects were noted: 3 patients had tachycardia, 4 had severe nausea, and 5 had headaches. These changes are associated with an increase in complaints of uremic intoxication because of BCS exacerbation not associated with treatment.

The study has been performed over 3 months. At the time of inclusion in the study, all patients had a documented diagnosis of stage III or IV of CKD based on the eGFR determined from the serum creatinine concentration using the CKD-EPI formulas (2009) in the modification of 2011 (an on-line calculator was used at the website http://nefrosovet.ru/). At the beginning of treatment, after 10 days, after 1 and 3 months, all patients were examined on the level of urea and creatinine, as well as GFR. The results were statistically analyzed.

RESULTS AND DISCUSSION

The renal function state: in groups 1A and 1B, the urea level averaged 11.4 ± 0.28 before treatment; the level of creatinine increased on average by 191.1 ± 6.47, GFR decreased to 39.2 ± 9.2 ml/min.

On the 10th day of treatment in patients of group 1A, the urea level averaged 10.6 ± 0.30; creatinine decreased by an average of 180.2 ± 8.73, GFR increased to 40.9 ± 1.27 ml / min. One month after the start of therapy, the urea level in group 1A was 10.1 ± 0.24; creatinine decreased to 171.3 ± 7.74, GFR was 42.1 ± 1.26, and after three months the urea parameters increased to 16.6 ± 0.41; creatinine increased to 198.9 ± 8.98, GFR decreased to 37.2 ± 1.30 ml/min.

In patients in group 1B, urea on the 10th day of treatment averaged 10.5 ± 0.25; creatinine decreased to an average of 179.6 ± 6.88, while GFR increased to 41.2 ± 1.14. After a month, the urea values were 9.8 ± 0.20; creatinine decreased to 167.2 ± 5.83, GFR increased to 44.3 ± 1.23, three months after the start of treatment, the urea level was 9.4 ± 0.135; creatinine decreased to 154.7 ± 4.93, and GFR increased to 47.3 ± 1.68 ml/min.

Table 1

Renal function status in patients with stage III of CKD

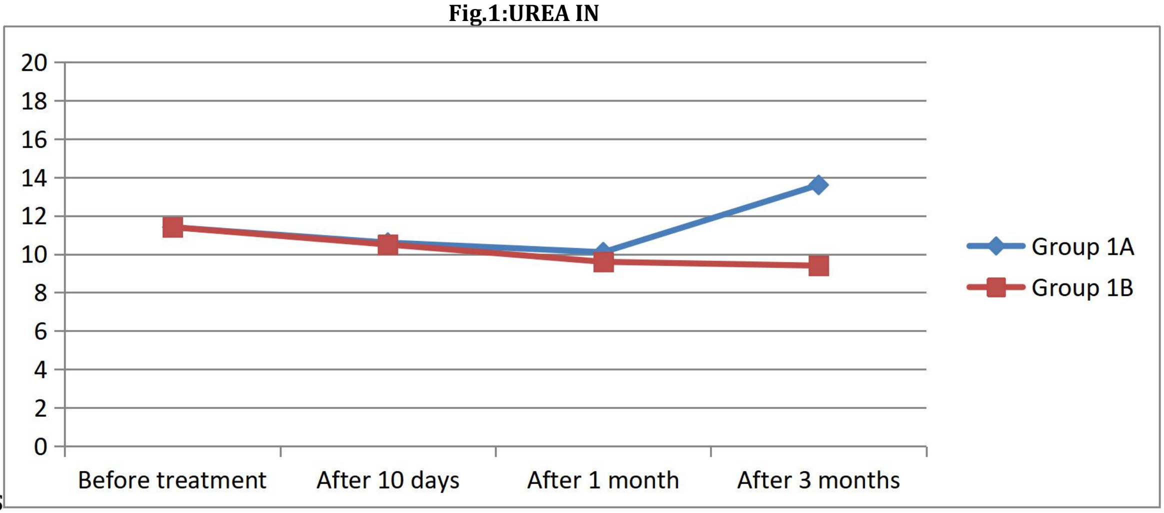
Parameters	Control group (n=20)	Before treatment	Group 1A (n-31)			Group 1B (n-32)		
			After 10 days	After 1 month	After 3 month	After 10 days	After 1 month	After 3 month
urea mmol/l	6,8±0,13	11,4±0,288***	10,6±0,30***	10,1±0,24***^^^	13,6±0,411***^^^	10,5±0,25***^	9,8±0,20***^^^	9,4±0,135***^^^

Creatinine µmol/l	71,6±1,53	191,1±6,47***	180,2±8,73***	171,3±7,74***	198,9±8,98***^^^	179,6±6,88***	167,2±5,83***	154,7±4,93***
GFR, ml/min	104±4,82	39,2±0,92***	40,9±1,27***	42,1±1,26***	37,2±1,30***^^^	41,2±1,14***	44,3±1,23***^^	47,3±1,68***^^^

Note: * - significant differences relative to the control group (*** - P <0.001); ^ - differences were significant relative to the parameters of the group before treatment (^ - P <0.05, ^^ - P <0.01, ^^^ - P <0.001).

If we consider each indicator in the renal function assessment, on the tenth day of treatment, there was a slight decrease in the urea level in both groups (A and B). One month after treatment, despite a positive shift, the urea and creatinine levels were almost the same in both groups. However, after 3 months there was a significant decrease in the level of urea in group 1 B, who received nephrocizine, compared with group 1A, a positive shift was evident.

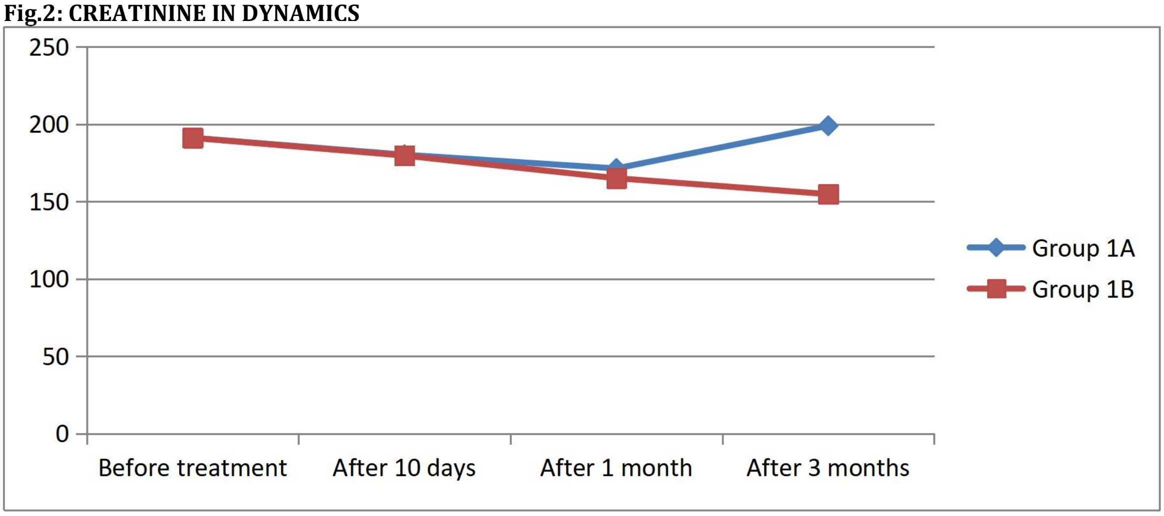
Fig.1:UREA IN



DYNAMICS

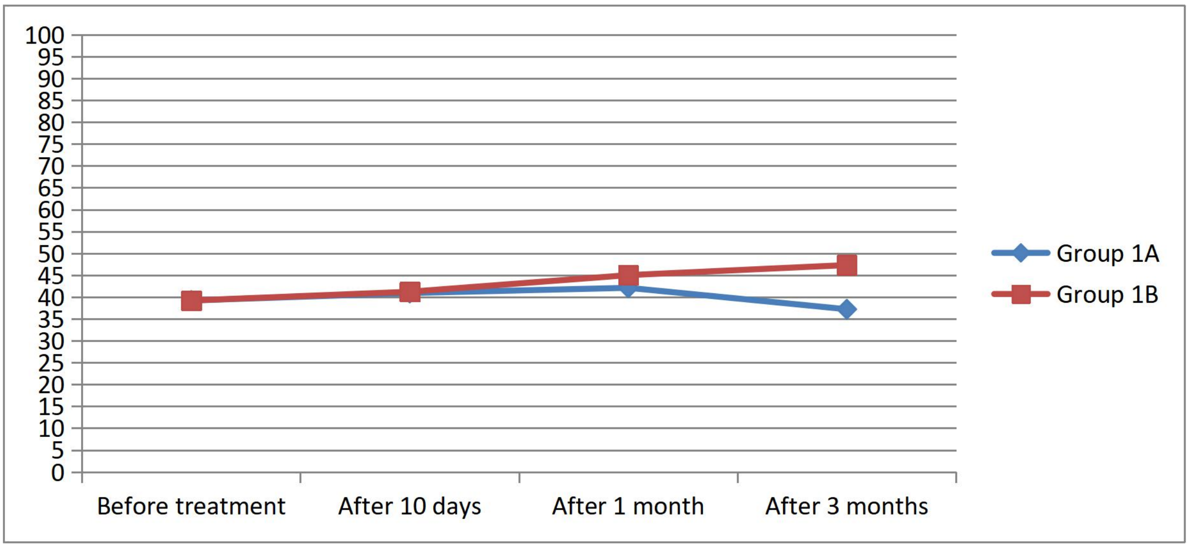
On the tenth day of treatment, creatinine levels decreased evenly in both groups (A and B), however, after a month, group 1B began to lead. After 3 months from the start of therapy, there was a positive shift: the creatinine level in group 1B, receiving nephrocizine, was significantly lower than in group 1A.

Fig.2: CREATININE IN DYNAMICS



If we pay attention to GFR, which is the main indicator in the assessment of renal function, then the positive changes in renal function a month after therapy were at the same level in both groups. However, after 3 months, the positive shift was more pronounced in group 1B, which received nephrocyzine, compared with group 1A. In group 1 A, who did not receive nephrocizine, GFR was lower than at the beginning of treatment, indicating progression of CKD. Therefore, the effectiveness of treatment in group 1B was significantly higher. This situation can also be seen in the diagram below:

Fig.3: GLOMERULAR FILTRATION RATE IN DYNAMICS



In the second group, the renal function indicators before treatment on average were: urea level - 16.9 ± 0.52; creatinine averaged 347.2 ± 12.37, GFR decreased to 21.8 ± 0.59 ml/min.

On the tenth day of treatment in group 2A, urea parameters increased on average to 17.8 ± 0.79; creatinine decreased on average to 345.7 ± 19.31, and GFR slightly increased to 22.1 ± 0.80 ml/min. A month later, in group 2A, the urea level averaged 15.8 ± 0.54; creatinine decreased on average to 338.9 ± 15.75, and GFR increased to 22.9 ± 0.69 ml/min. Three months later, the urea parameters increased to 19.83 ± 0.561; creatinine increased to 379.8 ± 14.24, and GFR decreased to 17.5 ± 0.31 ml/min. In group 2 B, on the tenth day of treatment, the urea parameters increased to 17.9 ± 0.42; creatinine decreased to 344.2 ± 10.38, GFR was 22.6 ± 0.72 ml/min. After a month since the start of therapy, the urea values were 15.0 ± 0.52; creatinine decreased to the level of 336.7 ± 11.23, GFR increased to 23.1 ± 0.56, and after three months - urea was 13.5 ± 0.293; creatinine decreased to 326.6 ± 10.67, and GFR reached 24.6 ± 0.42 ml/min.

Table 2.: Renal function status in patients with stage IV CKD

Parameters	Control group (n=20)	Before treatment	Group 2A (n-30)			Group 2B (n-30)		
			After 10 days	After 1 month	After 3 months	After 10 days	After 1 month	After 3 months
urea mmol/l	6,8±0,13	16,9±0,52 ***	17,8±0,79** *	15,8±0,54** *	19,83±0,56* **^^^	17,9±0,42** *	15,0±0,52** *^	13,5±0,29** *^^^
Creatinine	71,6±1,53	347,2±12, 37***	345,7±18,82 ***	338,9±15,75 ***	379,8±14,2 4***	344,2±10,38 ***	336,7±11,2* **	326,6±10,6 7***
μmol/l	104±4,82	21,8±0,59 ***	22,1±0,80** *	22,9±0,69** *	17,5±0,31** *^^^	22,6±0,72** *	23,1±0,56** *	24,6±0,42** *^^^

Note: * - significant differences relative to the control group (*** - P <0.001); ^ - differences were significant relative to the parameters of the group before treatment (^ - P <0.05, ^^ - P <0.01, ^^^ - P <0.001).

If we look at the indicators that assess renal function, then on the tenth day of treatment in both groups of creatinine and CFT, there was practically no dynamics (A and B). This indicates that as CKD worsens, it becomes more difficult to influence the processes. However, with treatment, there was a significant increase in urea in both groups. This is due to the release of large amounts of urea and other residual nitrogen products into the peripheral blood at the beginning of the treatment process. Although the positive shift in renal function after one month of treatment was almost the same in both groups, the positive shift was more pronounced in group 2B treated with nephrocizine, compared with group 2A after 3 months.

Fig 4. UREA IN DYNAMICS

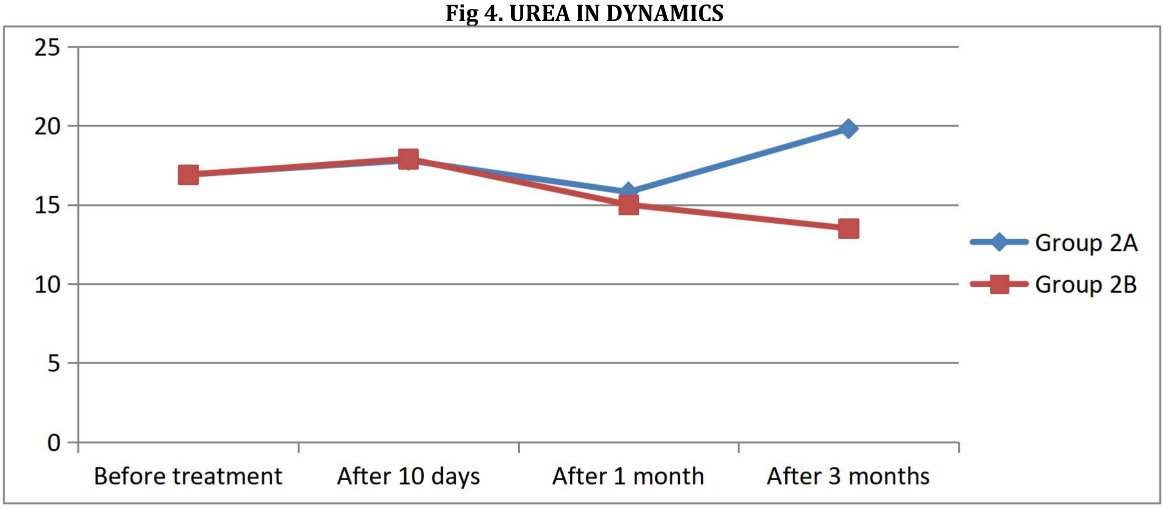
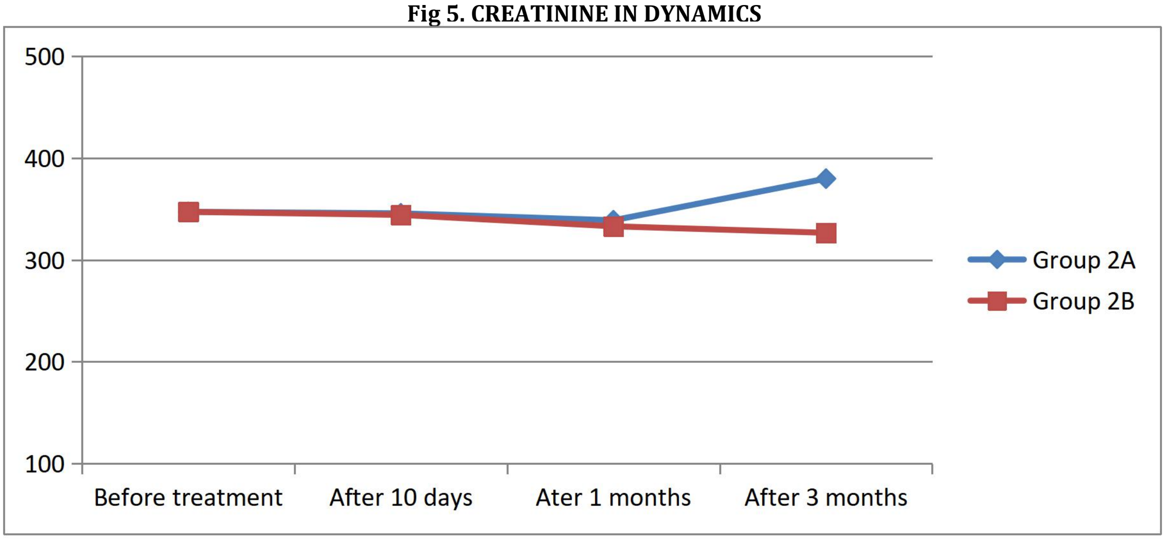
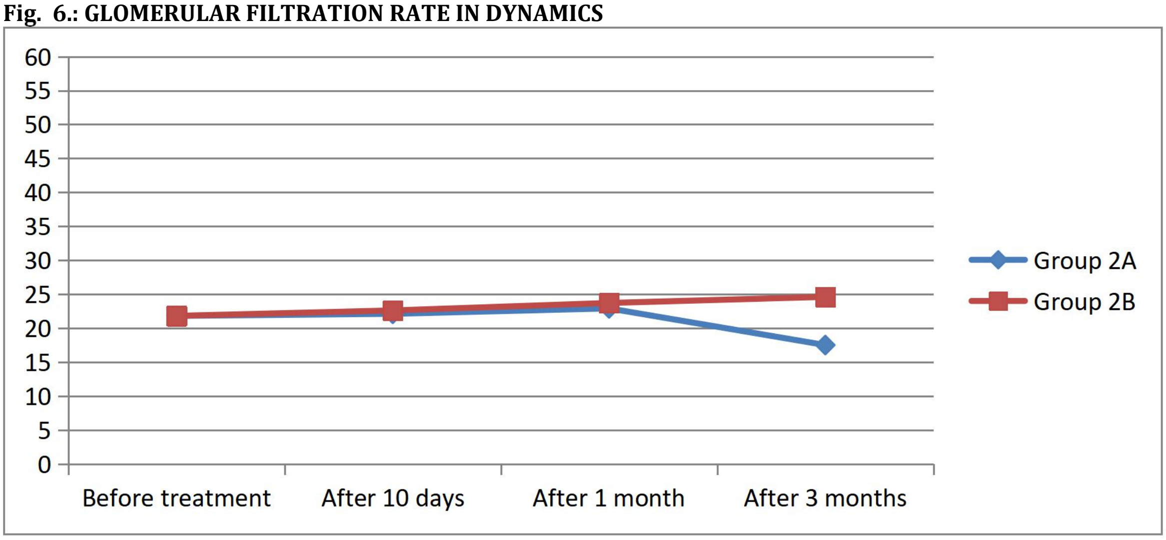


Fig 5. CREATININE IN DYNAMICS



GFR, which was the most important criterion or indicator in assessing renal function, also did not change significantly in the first month of treatment. A positive change was observed only in group 2B, which received nephrocizine, compared with group 2A by the third month. That is, in group 2B, who received nephrocizine, the treatment effectiveness was higher than in group 2A.

Fig. 6.: GLOMERULAR FILTRATION RATE IN DYNAMICS



When comparing CKD stage III and IV groups, the nephrocizine effect on the relatively early CKD stages is observed. In groups B with a positive effect, the difference in creatinine and GFR at the beginning and at the end of treatment was 25.2 µm/l - in group 1 B, 20.6 µm/l - in group 2 B, 8.1 ml / min - in group 1 B, in group 2 B it was equal to 2.8 ml/min.

With deepening of the process, the effectiveness of both traditional treatment methods and hypoazotemic drugs decreases. The reason is that as CKD progresses, the number of nephrons, the morphofunctional unit of the kidney, decreases [5]. Like all hypoazotemic drugs, the nephron is a source of nephrocizine. Thus, during our research, the effectiveness of hypoazotemic drugs treatment in the relatively early stages of patients with preliminary CKD dialysis is high. Even though a little less than a quarter of the XXI century has passed, the problems of the course and treatment of chronic kidney diseases have not been properly resolved [3; 4]. This is due to the multifactorial nature of the disease, that is, both gross and irreversible disorders of many pathogenetic processes, such as a violation of protein metabolism, water-electrolyte, mineral metabolism, acid-base imbalance, serious qualitative and quantitative changes in the composition of the blood. The main factor that worsens, speeds up, and leads to death, is uremic intoxication [3; 5; 6]. Thus, during the research, we found that the treatment of CKD patients with nephrocizine, a hypoazotemic drug that belongs to the group of bioflavonoids, in the pre-dialysis period, as a result of reducing uremic intoxication, is the most optimal way to treat the disease.

CONCLUSIONS

1. In all patients with CKD in the pre-dialysis period, renal disfunction is noted, which is reflected in an urea and creatinine level increase, as well as a decrease in GFR.
2. In the pre-dialysis stages of CKD, improvement in renal function and a certain positive shift in treatment are achieved with the use of nephrophysin.
3. The hypoazotemic effect of nephrocizine at stage III is more effective than at stage IV of CKD.
4. The drug nephrocizine reduces uremic intoxication and slows down the CKD progress.

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