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FEBUXSOSTAT AS A RENOPROTECTOR IN PATIENTS WITH CHRONIC RENAL INSUFFICIENCY

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Abstract

In the article presented the data about dependence of uricemia's level and the subjective assessment of the quality of life in patients with end stage renal disease (ESRD) and an increase ofresidual functional renal reserve in 90 patients under the influence of febuxsostat at a dose of 40 mg are given. It has been proved that by reducing the level of uric acid, the residual functional renal reserve increases and the quality of life of patients improves (according to the questionnaire). This is best reflected in predialysis patients with ESRD. The data obtained allow febuxsostat consider to be effective urates-reductive therapy.

Key words: chronic kidney disease, hyperuricemia, uric acid, febuxsostat.

Introduction. For a long time, hyperuricemia was not considered as a particularly significant pathology, since there was a small number of people with this problem and there was no reliable data of hyperuricemia effect on a human body. But the prevalence of this pathology is increasing from year to year and according to international screening studies, this condition is associated with disturbances of purine metabolism, which is observed in almost 20% of adults and 3% of the child population of the globe [4].

Today the following types of hyperuricemia are outlined: metabolic, renal and mixed.

By origin, this pathological process happens to be: primary, as a consequence of genetic anomalies of unknown reasons; and secondary, as a sign of any pathology.

Renal hyperuricemia is attributed to the deviation of the filtration tubular function.

Conditions of its occurrence are:

- participation of purine in metabolism;
- large formation of uric acid and its ruined withdrawal.

Trigger mechanisms, regardless of the conditions of the disease development, are considered defects of the tubular filtration function of the bodies concerned. The reasons for the acquired form are often atherosclerosis in the elderly and hardening of renal vessels; diabetes; hypertension; the result of long unreasonable treatment with some medications.

Also, the conditions of its formation can be blood diseases, accompanied by massive decay of nucleotides in the cell nucleus - these are disease of the lymphatic system of different kind, sarcoidosis, psoriasis and other pathological processes that can disturb renal excretion and other causes.

A classic manifestation of hyperuricemia is an increase of uric acid in blood. One can obtain a reliable result when conducting a biochemical blood test. The disease in most cases is not manifested by any specific symptomatology. But there are more well-known clinical manifestations, such as nephrolithiasis and gout. Until recently, this disease did not attract much attention, since there was its little prevalence in the population, but recent studies about this pathology influence on the course of cardiovascular and renal diseases, forced specialists to take a new look at the disease [3]. If the disease is in progression, the symptoms of hyperuricemia are accompanied by clinical manifestations of gout, and hyperuricemia's essential therapy will be considered.

Gout has changed considerably over the past decades, and gouty arthritis with a severe course, chronic tufus and refractory gout are prevailing among the hospitalized patients [5]. In this regard, it is important to determine the strategy of this disease optimal treatment. The solution to this task is contributed by the European League Against Rheumatism (EULAR) recommendations, which today are one of the main documents for the management of gout patients [5]. Recall selectively the main provisions regarding practice of nephrology:

1. Everyone who has gout and hyperuricemia should be systematically screened for concomitant illness and cardio-vascular diseases risk factors, renal insufficiency

2. The appointment of hypouricemic therapy (HUT) should be considered and discussed with each patient with a verified diagnosis of gout from the first episode. HUT is assigned for all patients with gout relapses, tofu, arthritis uratica and / or renal stones. HUT's initiation is recommended in the immediate future from the first diagnosis in the patients

under 40 years of age or with a very high level of uricemia (> 8.0 mg / dl, 480 mmol / l) and / or concomitant diseases (renal failure, hypertension, ischemic heart disease, heart failure).

3. For patients receiving HUT, the level of uricemia should be monitored and maintained to <6 mg / dL (360 mmol / L). The lower target (<5 mg / dL, 300 mmol / l) to facilitate rapid dissolution of crystals is recommended for patients with severe gout until complete dissolution of the crystals. The uric acid level <3 mg / dL (180 mmol / l) is not recommended in the long run.

From clinical practice it is known that recurrences of gout may be accompanied by urecemia's normal ranges and vice versa, a very high level of urecemia does not necessarily lead to the development of gout. In the disturbance of renal function, uricemia often increases, but it is unknown to what level.

The objective: to determine the effect of the lower levels of uric acid on the kidneys function and on the patients' quality of life.

Material and methods. There were 90 patients under observation. The following methods were used: clinical laboratory (biochemical blood test, determination of glomerular filtration rate (GFR), residual functional renal reserve (RFRR), instrumental (blood pressure measurement), statistical, and quality of life questionnaire.

Results and discussion. We performed a search analysis of uremic dependence on subjective estimation of life quality in patients with ESRD and increase of RFRR in these patients under the influence of febuxsostat at a dose of 40 mg.

The patients were divided into three groups according to febuksostat used with the aim to reduce the level of uric acid:

The Ist group included patients (n =30) with end stage renal disease (ESRD) who did not get renal replacement therapy (RRT);

The IInd group included 30 patients who got peritoneal dialysis (PD); and

the IIIrd group consisted of 30 hemodialysis-dependent (HD) patients

Febuxsostat ((2- (3-cyano-4-isobutoxyphenyl) -4-methylthiazole-5-carboxylic acid)) is a nonpurine, selective inhibitor of xanthine oxidoreductase isoforms. It is an alternative to a limited number of drugs for reducing levels of urates used in recent decades. Inhibition of xanthine oxidoreducease by febuxsostat is more potent and effective than allopurinol, as evidenced by the more frequent achievement of target serum urate levels, especially in patients with high concentrations of urates [6]. Unlike allopurinol, the pharmacokinetic properties of febuxsostat do not depend to a large extent on renal clearance, which is

important for CKD patients. It is also important that elderly patients do not require dose adjustment [4].

The studies conducted showed the following.

After the use of febuxsostat in the Ist group (before dialysis), the level of uric acid decreased, and the level of residual functional renal reserve increased (Table 1), which was also reflected in the questionnaires.

Table 1

Indicators of levels of uric acid and functional renal reserve in patients of group 1 under the influence of febuxsostat

Period	Uric acid	RFRR	Questionnaire
Pre-dose	291.5±16.7	-94.4±0.96	127.05±4.82
Post - dose	210.2±4.15	-84.8±1.9	123.4±4.99

One-factor dispersion analysis showed an inversely proportional relationship between uric acid level and residual functional renal reserve (Fig. 1, 2), as well as an assessment of the quality of life of this cohort of patients through a survey (Fig. 3)

Thus, the efficacy of febuxsostat use in the group of patients with end stage renal disease who did not use renal replacement therapy has been proved (Fig. 4)

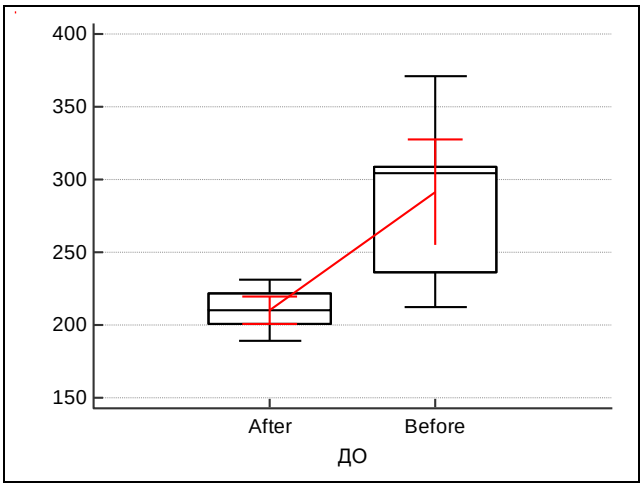

Fig. 1. The result of a one-factor dispersion analysis of blood uric acid indices before dialysis in graphic expression

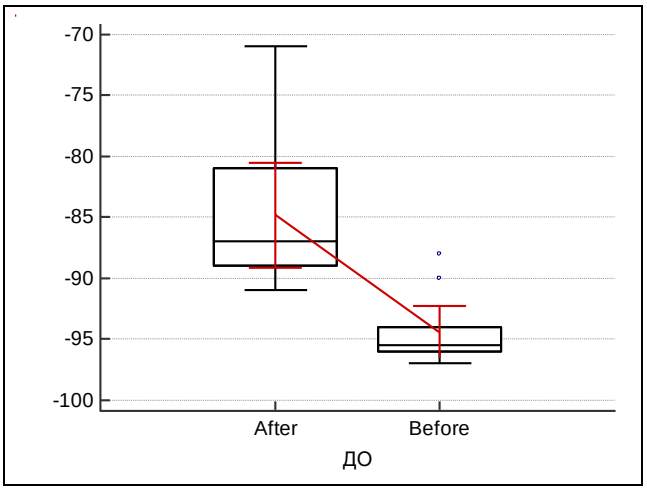

Fig. 2. The result of a one-factor dispersion analysis of functional renal reserve parameters before dialysis in graphic expression

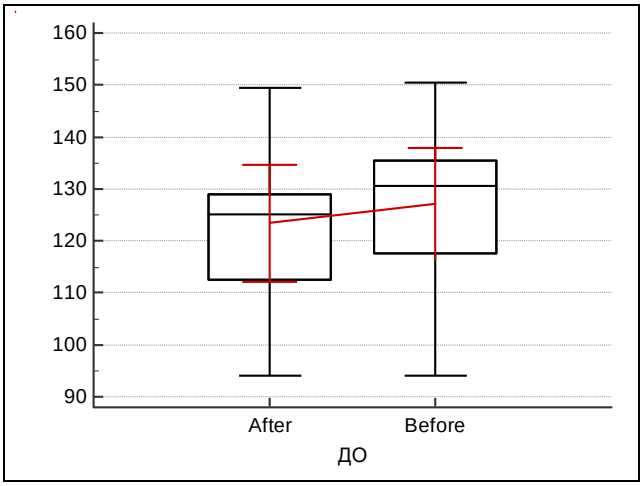

Fig. 3. The result of a one-factor dispersion analysis of the assessment of the patients' quality of life before dialysis in graphic expression.

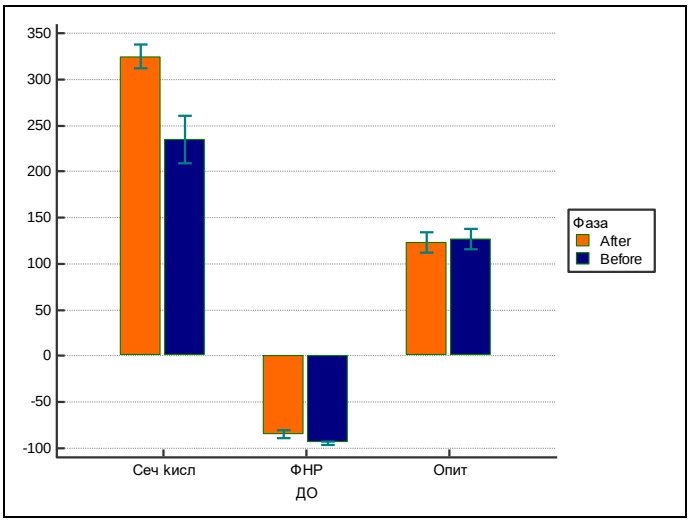

Fig. 4. Estimation of febuxostat application effectiveness before dialysis in graphic expression

After the use of febuxsostat in the 2nd (peritoneal dialysis patients), levels of uric acid decreased with an increase in RFRR level (Table 2), which was also reflected in the questionnaires.

Table 2

Indicators of levels of uric acid and functional renal reserve in patients of group 2 under the influence of febuxostat

Period	Uric acid	RFRR	Questionnaire
Pre-dose	497.0 ±18.77	-93.6±1.11	101.85±7.65
Post-dose	289.7±15.98	-92.1±15.98	99.7±6.92

The inverse proportional relationship between the level of uric acid and the residual functional renal reserve was established by one-factor dispersion analysis (Fig. 5, 6)

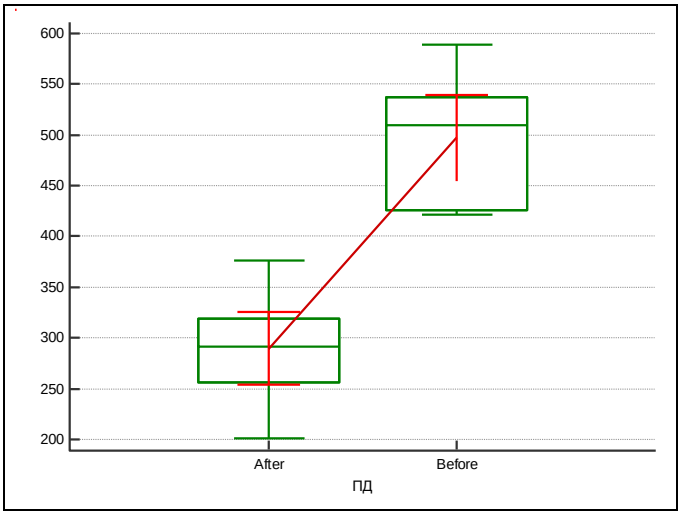

Fig. 5. The result of a one-factor dispersion analysis of blood uric acid indices in peritoneal dialysis in graphic expression

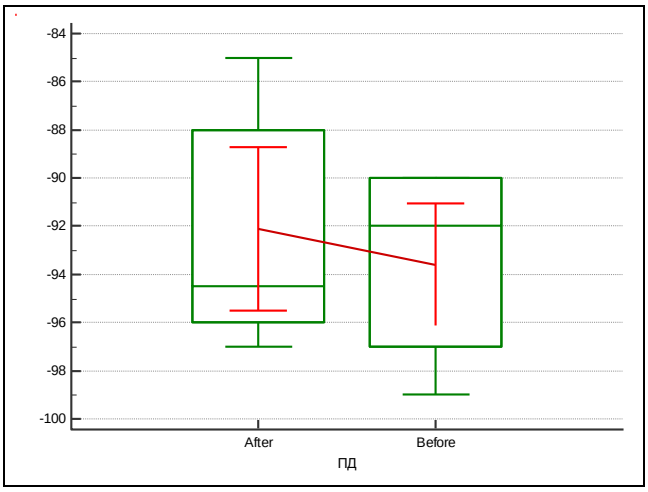

Fig. 6. The result of a one-factor dispersion analysis of functional renal reserve parameters in peritoneal dialysis in graphic expression

A survey conducted in this group patients showed an increase in the quality of life (Fig. 7).

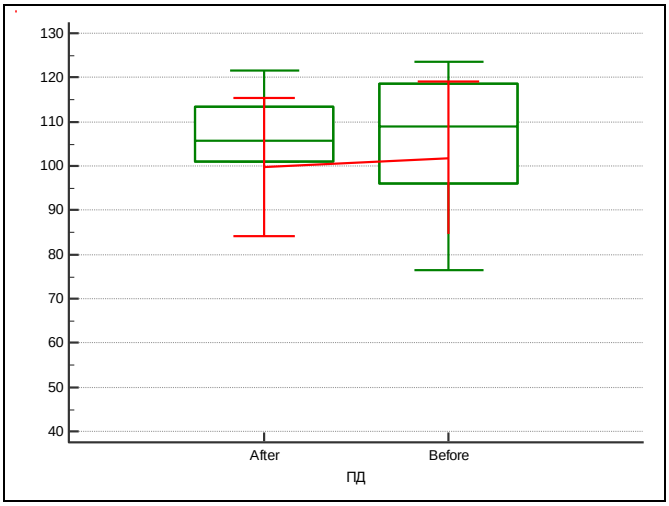

Fig. 7. The result of a one-factor dispersion analysis of the assessment of the quality of life of patients undergoing peritoneal dialysis in graphic expression

Thus, the use of febuxsostat in combination with peritoneal dialysis has led to an improvement in the patients' quality of life (Fig. 8).

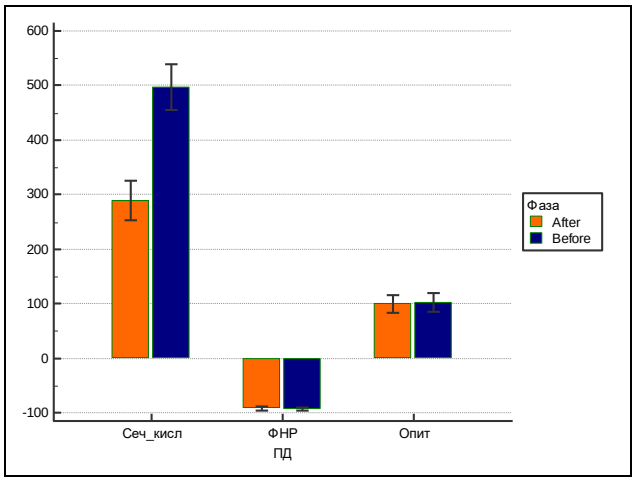

Fig. 8. Estimation of effectiveness of febuxsostat application in peritoneal dialysis patients in graphic expression

The 3rd group patients (dialysis-dependent) only the quality of life depending on the lower level of uric acid was determined, RFRR were not determined (Table 3).

Table 3

Indicators of uric acid level in the 3rd group patients under the influence of febuxsostat

Period	Uric acid	Questionnaire
Pre-dose	324.5 ±5.78	111.1±3.81
Post-dose	234.9±11.4	114.5±3.16

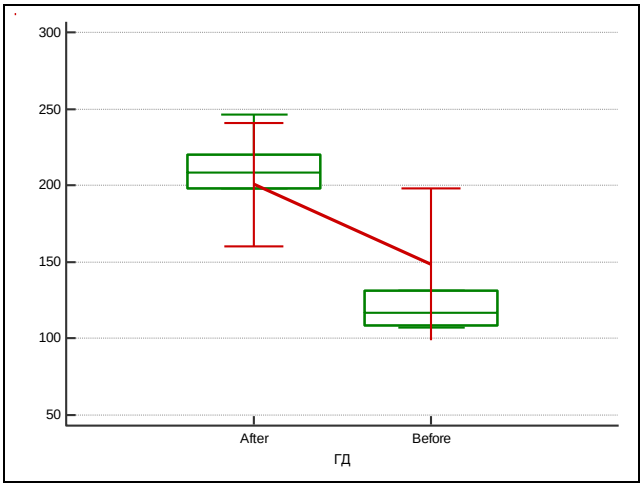

Fig. 9. The result of a one-factor dispersion analysis of blood uric acid indices in hemodialysis patients in graphic expression

Reducing of uric acid levels contributed to improvement of life quality (according to the questionnaire) in hemodialysis – dependent patients (Fig. 10)

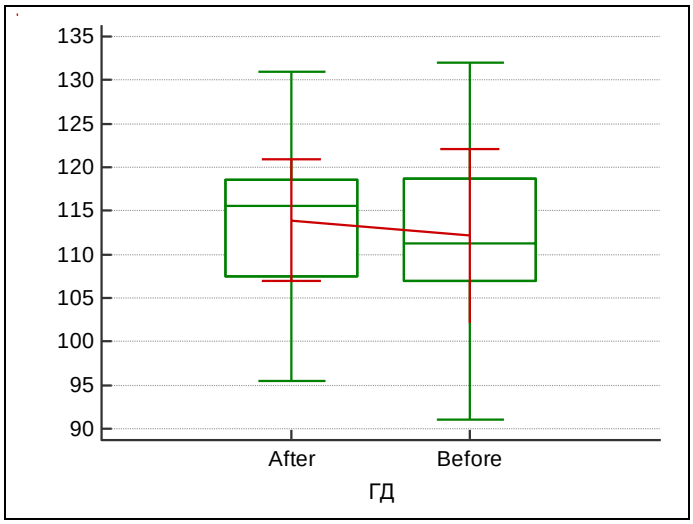

Fig. 10. The result of a one-factor dispersion analysis of assessing the quality of life of hemodialysis-dependent patients in graphic expression

The researches performed have shown that with decreasing levels of uric acid, RFRR increases and patients' quality of life improves (according to the questionnaire). It is best reflected in pre-dialysis ESRD patients.

Thus, the following conclusion can be made: since uric acid is a product of protein products metabolism, it may be that its low levels have a stimulating effect on kidneys functioning and increase GFR in order to increase the output of uric acid and, accordingly, normalize its level. The average level of uric acid reflects the dynamic changes in its concentration in the patient’s body, so at a single examination, you can get normal values of uric acid, which will not correspond to the real medical situation. Therefore, when the high values of the functional renal reserve are obtained, it may be worthwhile to focus more on the patient and trace the dynamics of uric acid and, if necessary, adjust them.

Higher indexes of functional renal reserve are closely related to higher patients’ quality of life, such as physical functioning, vital activity, and mental health. This is very important in terms of increasing life expectancy at the background of treatment, since it can provide patients with greater integration into the life of their families, society, longer to maintain professional activity.

The data obtained require further research to establish statistically significant trends and formulate recommendations for the practice of nephrology.

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