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ORIGINAL ARTICLE

EVALUATION OF THE CORRECTIVE EFFECT OF THERAPEUTIC PLASMAPHERESIS ON THE STATE OF RENAL FUNCTION IN PATIENTS AFTER SURGICAL TREATMENT OF LOCALIZED KIDNEY CANCER

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ABSTRACT

Purpose of the study. To assess the state of renal function in the application of therapeutic plasmapheresis in order to correct the disorders accompanying the development of preclinical stage of AKI in patients after partial nephrectomy under conditions of warm ischemia.

Patients and methods. We examined 119 patients (average aged 57.6±7.8 years) from 2018 to 2019, who underwent open or laparoscopic kidney resection for cancer according to elective indications and with the usage of standard WIT technique within 15-21 minutes. Patients with a high risk of developing a clinical stage of AKI (n=21) were divided into 2 groups: in group I (n=10), patients continued to receive standard nephroprotective therapy, in group II (n=11), 24 hours after surgery, therapeutic plasmapheresis was performed according to the TPE (Therapeutic plasma exchange) protocol. During 7 days after the surgery patients in both groups were monitored daily for the rate of hourly diuresis, serum creatinine, and creatinine GFR. The presence of significant differences in the groups was evaluated using the STATISTICA 12.6 software package and the differences between the samples were considered significant at p<0.05.

Results. The development of the clinical stage of AKI in group I was detected in 80.0 % of cases, in group II in 9.0 % of patients (p=0.0019). The rate of diuresis in group II was significantly higher: by more than 2 times by day 3, by 90.0 % on day 4, by 81.4 % on day 5, by 36.8 % on day 6, and by 25.4 % on day 7 (p<0.05). The average increase in creatinine in group I was significantly higher: more than 5 times on day 5 and more than 4 times on day 6 and 7 of the study (p<0.05). GFR in group II was significantly higher on day 3 (65.3 %), day 5 (54 %), day 6 (39.2 %) and day 7 (50 %) (p<0.05).

Conclusion. Therapeutic plasmapheresis is highly effective in the correction of renal function disorders after kidney resection under WIT conditions and demonstrates an advantage in reducing the risk of developing a clinical stage of AKI in comparison with preventive measures that include standard nephroprotective infusion therapy.

Keywords:
renal cell carcinoma, acute kidney injury, biomarkers of kidney injury, therapeutic plasmapheresis, kidney function, partial nephrectomy.

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ОРИГИНАЛЬНАЯ СТАТЬЯ

ОЦЕНКА КОРРИГИРУЮЩЕГО ВЛИЯНИЯ ЛЕЧЕБНОГО ПЛАЗМАФЕРЕЗА НА СОСТОЯНИЕ ПОЧЕЧНОЙ ФУНКЦИИ У БОЛЬНЫХ ПОСЛЕ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ ЛОКАЛИЗОВАННОГО РАКА ПОЧКИ

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РЕЗЮМЕ

Цель исследования. Оценить состояние почечной функции на фоне лечебного плазмафереза, применяемого с целью коррекции нарушений, сопровождающих развитие преклинической стадии острого повреждения почек (ОПП) у больных после резекции почки в условиях тепловой ишемии (ТИП).

Пациенты и методы. Обследовано 119 больных (средний возраст 57,6±7,8 лет), которым с 2018 по 2019 гг. по элективным показаниям выполнена открытая или лапароскопическая резекция почки по поводу рака с применением стандартной методики ТИП длительностью 15-21 минут. Больные, имеющие высокий риск развития клинической стадии ОПП (n=21), были разделены на 2 группы: в группе I (n=10) больные продолжили получать стандартную нефропротективную терапию, в группе II (n=11) спустя 24 часа после операции проводили лечебный плазмаферез по протоколу TPE (Therapeutic plasma exchange). В течение 7-и суток после операции у больных обеих групп ежедневно осуществляли контроль скорости почасового диуреза, сывороточного креатинина, скорости клубочковой фильтрации (СКФ) по креатинину. Наличие достоверности различий в группах оценивали при помощи программного пакета STATISTICA 12.6, различия между выборками считали достоверными при p<0,05.

Результаты. Развитие клинической стадии ОПП в группе I выявили в 80,0 % случаев, во II группе в 9,0 % случаев (p=0,0019). Скорость диуреза во II группе была значимо выше: более чем в 2 раза к 3-им суткам, на 90,0 % на 4-е сутки, на 81,4 % на 5-е сутки, на 36,8 % на 6-е сутки и на 25,4 % на 7-е сутки (p<0,05). Средний прирост креатинина в I группе был значимо выше: более чем в 5 раз на 5-е сутки и более чем в 4 раза на 6-е и 7-е сутки исследования (p<0,05). СКФ во II группе была значимо выше на 3-и (на 65,3 %), 5-е (на 54 %), 6-е (на 39,2 %) и 7-е (на 50 %) сутки (p<0,05).

Заключение. Лечебный плазмаферез обладает высокой эффективностью в коррекции нарушений почечной функции после резекции почки в условиях ТИП и демонстрирует преимущество в снижении рисков развития клинической стадии ОПП в сравнении с профилактическими мероприятиями, включающими в себя проведение стандартной нефропротективной инфузионной терапии.

Ключевые слова:
почечно-клеточный рак, острое повреждение почек, биомаркеры почечного повреждения, лечебный плазмаферез, функция почки, резекция почки.

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RELEVANCE

Renal cell carcinoma is one of the most common oncological diseases, accounting for up to 4.0 % of all malignant neoplasms [1]. The frequency of detection of this pathology is constantly increasing, which is largely due to the technical improvement of modern imaging methods. In accordance with this, the main share of diagnosed nosological forms is represented by localized processes, the standard of treatment of which remains surgical operation: nephrectomy or kidney resection [2, 3].

If it is technically possible to implement it, according to international recommendations, the organ-preserving approach is the most preferable [4]. Resection of the kidney is most often performed using the method of total thermal ischemia (TTI), which consists in temporary clamping of the renal vein and artery. Long-term ischemic exposure in combination with a reperfusion damaging component exerted on a tumor – affected kidney increases the risk of developing a life-threatening condition in the early postoperative period-acute kidney injury (AKI), and subsequently chronic kidney disease [5].

Despite the presence of many well-known methods of anti-ischemic protection, including both surgical approaches (aimed at reducing the time of thermal ischemia, reducing the intensity of energy-dependent metabolic processes in the kidney through hypothermia, increasing the tolerance of the renal parenchyma to hypoxic conditions), and approaches based on the use of pharmacological agents (blood substitutes with oxygen transport function, drugs with anti-ischemic and anti-hypoxic effects), including the use of epidural novocaine blockades, the frequency of the development of the clinical stage of AKI after organ-preserving operations on the kidney remains high (from 5 to 15 % according to different authors) [6-10].

Based on the pathogenetic features of the development of AKI, the main links of which at the initial stages are the immune-mediated development of acute inflammation of the nephron tubules, the use of therapeutic plasmapheresis is pathogenetically justified, since the latter has significant reocorregating, immunocoregating and detoxifying properties [11-13].

Previously, we proposed a method for diagnosing AKI at the preclinical stage [14], which was later supplemented with recommendations for correcting this complication based on the use of therapeutic plasmapheresis [15]. The approach based on extracorporeal detoxification, aimed at correcting complications associated with ischemia-reperfusion syndrome, contributed to a significant reduction in the risk of AKI, which was demonstrated in a number of clinical observations. However, the obtained data should be justified using statistical methods of research with a more detailed assessment of the state of markers of impaired renal function (hourly diuresis rate, serum creatinine, glomerular filtration rate (GFR) for creatinine).

The purpose of the study: to evaluate the state of renal function in the context of therapeutic plasmapheresis, used to correct the disorders accompanying the development of preclinical stage of AKI in patients after kidney resection under conditions of thermal ischemia for cancer.

PATIENTS AND METHODS

A total of 119 patients with localized kidney cancer (72 men and 47 women) were examined, with an average age of 57.6±7.8 years. All patients in the conditions of the FSBI "NMRC of Oncology" of the Ministry of Health of the Russian Federation from 2018 to 2019, according to elective indications, underwent open or laparoscopic kidney resection, during which the standard total TTI technique was used. The criteria for the selection of patients were: normal preoperative creatinine values (in the examined patients they were 83.1±4.6 mmol/L), postoperative verification of localized forms (pT1a-bN0M0) of renal cell carcinoma and the duration of thermal ischemia from 15 to 21 minutes.

Patients with a high risk of developing AKI in the postoperative period were identified using the scale of diagnosis of the preclinical stage of AKI developed earlier [16]. To apply this scale, it is necessary to know the initial and postoperative values of a number of biomarkers of renal damage (cystatin C, L-FABP (Liver Fatty Acid Binding Protein) and NGAL (Neutrophil-Gelatin-Associated Lipokalin) of blood serum), which in patients included in the study were determined using ELISA using standard commercial

test kits: for cystatin C-BioVendor (Czech Republic), for NGAL – BCMDiagnostics (USA), for L – FABP-Hycult Biotechnology (Netherlands).

All patients at high risk of AKI were treated with nephroprotective infusion therapy 16 hours after surgery: albumin 20 % – 100 ml intravenously; sterofundin – 1000 ml + eufillin 2.4 % – 3 ml intravenously; saluretics were prescribed for diuresis of less than 70 ml / hour; oral patients received at least 1 liter of water [17]. Patients who had maintained a ten percent increase from the initial preoperative values of the NGAL and/or L-FABP biomarkers 24 hours after surgery were randomized into 2 groups (I and II). Patients of group I continued to receive conservative therapy, patients of group II were additionally treated with therapeutic plasmapheresis.

Therapeutic plasmapheresis was carried out according to the TPE protocol (Therapeutic plasma exchange) on the MCS+ "Haemonetics" device (USA) with a perfusion rate of 40-60 ml/min, V=4800 rpm; with plasma substitution by intravenous infusions of gelofuzine solutions, 5 % albumin, balanced crystalloid solutions in a total volume exceeding the amount of exfused plasma by 2 times in a ratio of 1 to 1 or 2 to 1, depending on the value of hematocrit and total blood protein levels in the predilution mode. The volume of plasma extraction was 800-1200 ml. Blood stabilization was carried out with 4 % sodium citrate in the ratio of anticoagulant/blood-1 to 12.

Patients of groups I and II were under dynamic observation during the first seven days after the operation. During this period, markers of renal damage (hourly diuresis rate, serum creatinine, and creatinine GFR) were monitored daily, and based on a comparison of their values in the study groups, the effectiveness of therapeutic plasmapheresis in correcting disorders associated with AKI was evaluated. The GFR for creatinine was calculated using the CKD-EPI formula [18]. The presence or absence of a clinical stage of AKI in all patients was confirmed in accordance with the generally accepted classification of KDIGO (Kidney Disease Improving Global Outcomes) 2012 [19].

The presence of significant differences in the groups was assessed using the software package STATISTICA 12.6 (2015). The nonparametric statistical Mann-Whitney U-test was used to compare two independent samples. To identify the significance of differences in the results of correction of homeostasis disorders associated with AKI in groups I and II, the exact Fischer test was used. The differences between the samples were considered significant at the level of statistical significance $p<0.05$.

RESEARCH RESULTS AND DISCUSSION

The use of a scale for the diagnosis of the preclinical stage of AKI with the calculation of the a-index made it possible to stratify all patients according to the degree of risk of acute kidney injury. According to the data obtained, in 31 (26 %) of the 119 patients, the value of the index a was 3 16 hours after surgery, that is, they had a high risk of developing the clinical stage of this complication, which was the reason for the start of nephroprotective therapy. Taking into account the principle of operation of the scale of diagnostics of the preclinical stage of AKI, which consists in calculating the sum of three indicators (X, Y, Z), two of which are measured in the pre- (Z) and intraoperative (Y) periods, further monitoring of patients should be carried out by measuring the indicator X, which characterizes the dynamic changes in the rate of diuresis and concentrations of biomarkers of AKI (cystatin C, L-FABP and NGAL of blood serum) in the postoperative period. Since the maximum value of each of the parameters can not exceed one, it is obvious that 16 hours after resection, the value of all indicators in each patient with a high risk of developing AKI was 1, and, consequently, all parameters of indicator X responded in 100 % of cases. Repeated measurement of the parameters of the X index in these patients 24 hours after surgical treatment revealed a significant decrease in them against the background of nephroprotective therapy. The data obtained are shown in the figure 1.

Therapeutic treatment, according to the obtained data, has significantly contributed to the restoration of the rate of diuresis of patients: the preservation of values of this parameter less than 70 ml/hour was observed only in 5 (16.1 %) patients. The number of patients in whom the increase in cystatin C values was 10 % or more compared to

the baseline values also significantly decreased: similar dynamics remained in 6 patients (19.3 %). At the same time, it should be noted that the proportion of patients in whom all the parameters of indicator X responded (that is, the rate of diuresis of these patients did not exceed 70 ml/hour, and the one-time increase in cystatin C, L-FABP and NGAL was equal to or greater than 10 %) remained high (67.8 %), most often due to the preservation of the increase in NGAL markers (in 51.6 % of cases) or L-FABP (in 58.1 % of cases). Thus, the above results indicate the need for and at the same time insufficient effectiveness of nephroprotective therapy in patients of this category.

In order to study the corrective effect of therapeutic plasmapheresis, patients at high risk of developing AKI, who 24 hours after surgery revealed the presence of an additional negative prognostic sign, such as the preservation or increase in the increase by 10 % from the preoperative values of the NGAL and/or L-FABP markers (n=21), were randomly divided into 2 groups. Group I consisted of 10 patients who continued to receive nephroprotective therapy, group II consisted of 11 patients whose treatment complex included plasmapheresis.

Since, according to studies, the concentration of serum creatinine increases in response to impaired renal function after 24-72 hours, further dynamic monitoring of the functional state of the kidneys of patients in groups I and II was carried out by determining the concentration of serum creatinine and GFR by creatinine, in addition, hourly diuresis was continued (in accordance with the clinical recommendations of KDIGO 2012) [19, 20]. The development of the clinical stage of AKI according to the results of monitoring in group I was detected in 8 patients (in 80 % of cases), which was confirmed by the presence of an increase in serum creatinine by 1.5 times or more from the initial values: in 6 patients (60 %) on day 3 and in 2 (20 %) patients on day 5 after resection. In group II, studies clinically confirmed the presence of AKI in only one (9 %) patient (p=0.0019, when compared with the results in group I using the exact Fischer test). The results of comparisons of dynamic changes in the functional markers under study are presented in more detail in the figures 2-4).

As shown in Figure 2, after therapeutic plasmapheresis in group II, the average values of the diuresis rate from the 3rd to the 7th day of the study did not have significant statistical differences in comparison with preoperative ones. At the same time, in the group of patients whose correction of renal function disorders was limited to nephroprotective therapy, a statistically significant decrease in the rate of diuresis compared to the initial values was observed by the 3rd day of the postoperative period (by 55.1 %). It is important to note that the average rate of diuresis from the 3rd to the 7th day of the study in group II was significantly higher: more than 2 times by the 3rd day (p<0.05), by 90.0 % on the 4th day (p<0.05), by 81.4 % on the 5th day (p<0.001), by 36.8 % on the 6th day (p<0.05) and by 25.4 % on the 7th day (p<0.05). Thus, the obtained results demonstrate a pronounced corrective effect of therapeutic plasmapheresis on the rate of diuresis in patients with a high risk of developing the clinical stage of AKI.

Based on the fact that AKI is usually diagnosed with an increase in the concentration of serum creatinine by 1.5 times from the initial values, it is more informative, from the point of view of this study, to present data comparing not the average values of

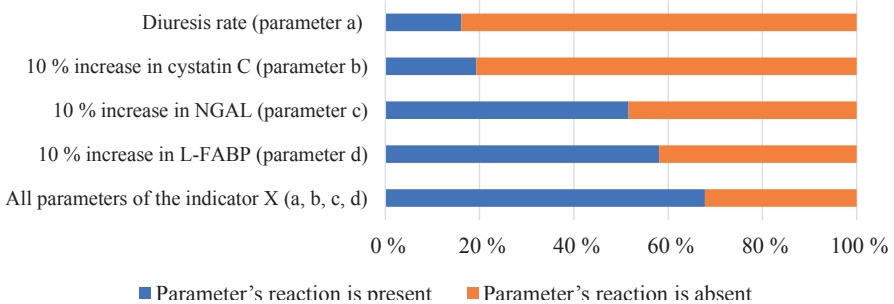

Fig. 1. The occurrence of indicators of the dynamics of the levels of three informative markers of AKI, taking into account the rate of diuresis (indicator X) in patients with a high risk of developing AKI (n=31) after the start of infusion therapy (24 hours after surgery), %.

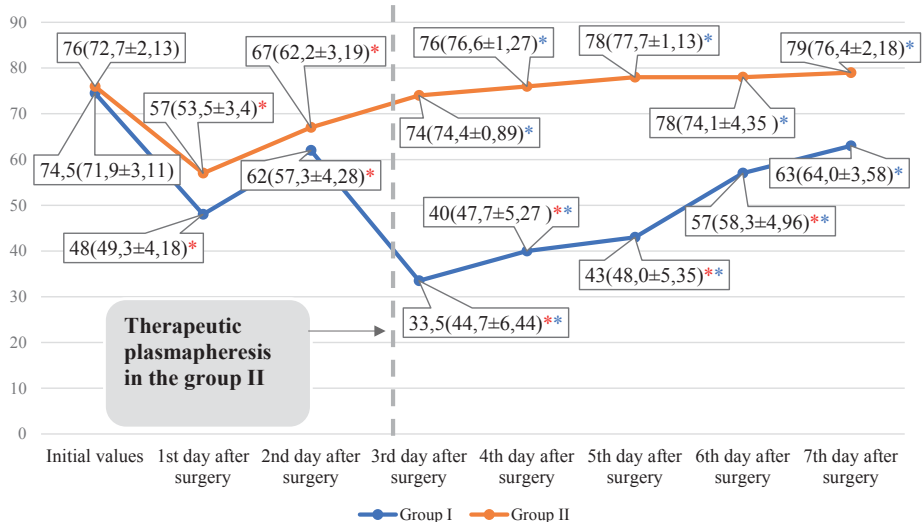

Fig. 2. Dynamics of diuresis rate in patients of group I and II in the perioperative period (Me (M±m)).

Note: * – reliability of differences with the initial values in the subgroup (p<0.05); * – reliability of differences between groups I and II (p<0.05).

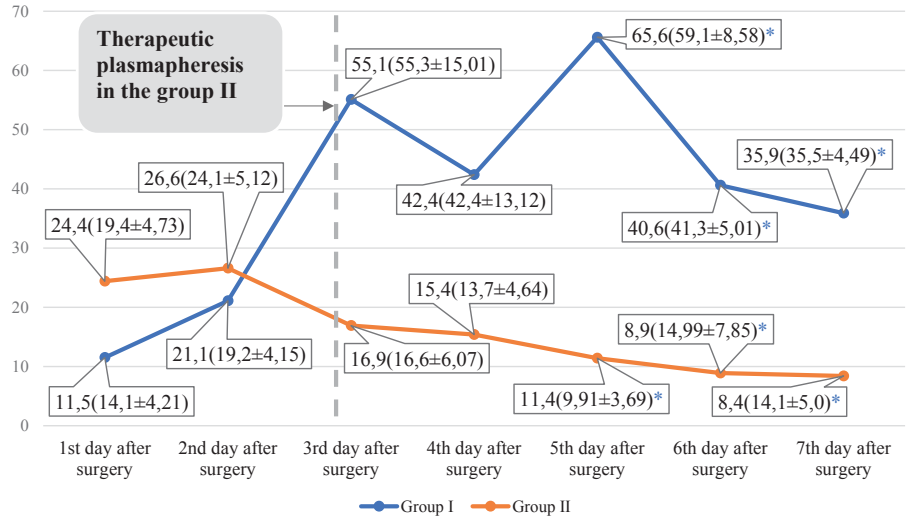

Fig. 3. Average increase in serum creatinine in patients of group I and II in the perioperative period compared to initial values (Me (M±m)).

Note: * – reliability of differences with the initial values in the subgroup (p<0.05); * – significance of differences between groups I and II (p<0.05).

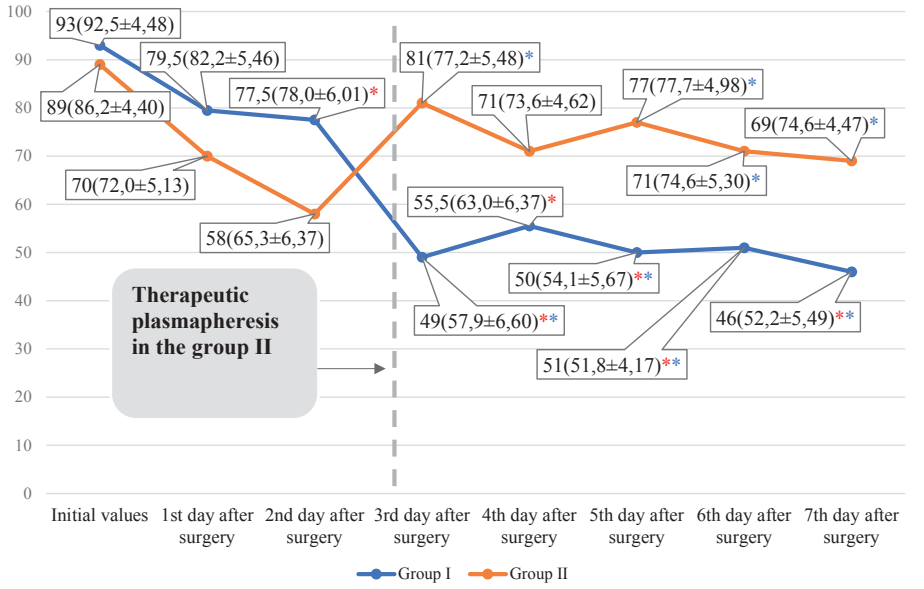

Fig. 4. Dynamics of GFR for creatinine in patients of group I and II in the perioperative period (Me (M±m)).

Note: * – reliability of differences with the initial values in the subgroup (p<0.05); * – reliability of differences between groups I and II (p<0.05).

serum creatinine, but the average values of its increase per day in relation to its initial values (Fig. 3).

To this end, we calculated the difference in creatinine values for each day of the postoperative period with the initial values in each patient and found the median from the resulting numerical series. The obtained results indicated significant differences in the average values of serum creatinine gain between the subgroups from the 5th to the 7th day of the study. The average increase in creatinine in group I was significantly higher (more than 5 times on day 5 and more than 4 times on day 6 and 7 of the study), which indicated that the majority of patients who received only nephroprotective therapy in comparison with patients who additionally received therapeutic plasmapheresis, more often observed an increase in serum creatinine, which, at the same time, was characterized by greater intensity. Dynamic changes in GFR also indicated statistically significant differences in the functional state of the kidneys in patients of groups I and II (Fig. 4).

When comparing the dynamic changes in GFR in the study subgroups, the latter were characterized by higher values in group II on the 3rd (by 65.3 %), 5th (by 54 %), 6th (by 39.2 %) and 7th (by 50 %) days after resection than in group I (at $p<0.05$ for all comparison cases). Analysis of the results of GFR calculation in group I revealed a significant decrease in the values of this indicator in comparison with the baseline on the 3rd day (by 47.3 %), on the 4th day (by 40.3 %), on the 5th day (by 46.2 %), on the 6th day (by 45.1 %) and on the 7th day (by 50.5 %) of the postoperative period. Consequently, the dynamics of GFR also confirmed the presence of higher functional results of correction of postoperative complications in the group of patients who underwent therapeutic plasmapheresis.

The main direction in the provision of therapeutic and preventive measures at the early stages of AKI development, both in domestic and foreign clinical recommendations, is the conservative correction of complications caused by renal dysfunction [19-24]. The use of combined infusion therapy, the purpose of which is to level protein-energy deficiency, uremic disorders, acid-base and water-electrolyte balance, is a pathogenetically justified, necessary, but insufficiently effective preventive measure, as evidenced by the high rates of morbidity and morbidity associated with AKI. The data presented in this study allow us to recommend the use of therapeutic plasmapheresis in combination with infusion therapy in clinical practice as the most effective approach to reduce the risks of developing and further progressing AKI in patients after kidney resection in conditions of thermal ischemia.

CONCLUSIONS

Based on the analysis of the dynamics of markers of renal functional impairment (serum creatinine, GFR, and diuresis rate), we can conclude that therapeutic plasmapheresis is highly effective in correcting ischemia-reperfusion syndrome induced by postoperative trauma.

The use of therapeutic plasmapheresis in combination with ifusion nephroprotective therapy, when identifying patients with preclinical stage of AKI, demonstrated an advantage in reducing the risks of progression and development of the clinical stage of this complication in comparison with preventive measures that include an exclusively therapeutic approach.

Authors contribution:

Dimitriadi S.N. – research concept and design, scientific and technical editing.

Ushakova N.D. – data analysis and interpretation, scientific and technical editing.

Velichko A.V. – data collection and statistical analysis, operation assistance, article preparation, text writing, bibliography design, illustration preparation.

Frantsiyants E.M. – scientific and technical editing, material processing.

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