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Original Article

Assessment of the Nephroprotective Properties of the Erythropoietin Mimetic Peptide and Infliximab in Kidney Ischemia-Reperfusion Injury in Rats

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Abstract

Chronic kidney disease (CKD) or acute kidney injury (AKI) causes impaired kidney function, leading to cognitive impairment, neuropathy, and cerebrovascular disease. Due to kidney damage, toxins stay in the blood rather than leaving the body through the urine, and brain function is affected by kidney-brain interaction. The present study aimed to investigate the protective effects of erythropoietin mimetic peptide (pHBSP) and infliximab on ischemic renal reperfusion injury. The experiment was performed on 70 white male Wistar laboratory rats which received recombinant erythropoietin, pHBSP, and infliximab. Under anesthesia, traumatic vascular clamps were applied to the left renal pedicle for 40 min, and nephrectomy was performed on the right. Functional tests and laboratory tests were performed 5 min and 24 h after the reperfusion. Thereafter, 24 h after the surgery, the plasma creatinine and urea levels in the sham-operated animals were obtained at 45.9±0.8 mmol/L and 6.7±0.2 mmol/L, respectively. Plasma creatinine and urea levels in the control group animals were 102.63±3.6 mmol/L and 21.80±1.29 mmol/L, respectively. The administration of pHBSP and infliximab to the animals with ischemia-reperfusion kidney injury has a pronounced nephroprotective effect, as compared to erythropoietin. There was a significant decrease in blood levels of creatinine and urea, improvement of microcirculation in the kidney, normalization of glomerular filtration rate, and fractional sodium excretion. The results of the study demonstrated pointed to the prospects of pHBSP and infliximab administration in ischemia-reperfusion kidney injury and justified the feasibility of further research in this field.

Keywords: Erythropoietin mimetic peptide (pHBSP), Infliximab, Ischemia-reperfusion kidney injury, Rats, Microcirculation

1. Introduction

Ischemia/reperfusion injury (IRI) is caused by the limited blood supply to an organ, followed by blood flow and re-oxygenation. This complication can occur after stroke, sepsis, and organ transplantation, leading to the formation of inflammatory cascades. The IRI which is a clinical syndrome with rapid renal dysfunction contributes to a pathological condition called acute kidney injury (AKI) and increases mortality (1, 2). The pathophysiology of IRI in the kidney affects the activation of neutrophils, the release of reactive oxygen species, and other inflammatory mediators, including adhesion molecules and cytokines (3, 4). Doxycycline decreases levels of pro-inflammatory cytokines, decreased levels of tumor necrosis factor-alpha (TNF-α) using leptin, increased levels of nitrite through the inhibition of antioxidant activity are caused by fighting IRI (5-7).

The search for new drugs with cytoprotective activity based on antioxidant properties or having anti-inflammatory properties is an urgent task of modern pharmacology (8-12), and kidney surgery is one of the areas of their practical application. To date, morbidity in oncourology remains extremely high worldwide. According to the Russian Federal Service of State Statistics, from 2010-2018, there was an increase in the morbidity of kidney cancer from 18.7-24.3 thousand per year. This is partly a consequence of early diagnosis and restoration of the prophylactic medical examination service.

According to current trends, at the initial stages of the disease, it is considered optimal to perform organ-preserving surgery (kidney resection), most often performed under warm ischemia. Given this fact, doctors and scientists across the globe are striving to prevent the development of acute renal injury caused by the compression of renal vessels (13). The main pathogenetic link of acute renal injury is ischemia and reperfusion injury of the kidneys (14). Ischemia is a pathological state characterized by the reduced blood supply to an organ, leading to a decrease in oxygen and nutrients in tissues and organs, as well as a decrease in the excretion of metabolic products, followed by reperfusion with repeated oxygenation. Pharmacological preconditioning is one of the promising mechanisms for the prevention of ischemia and reperfusion injuries (15-17).

In several major studies, it was proved that erythropoietin has precondition properties (18, 19). The biological effects of erythropoietin are realized by binding to specific receptors that are expressed in the bone marrow, vascular endothelium, kidneys, nervous system, placenta, gastric mucosa, and skeletal muscles (20, 21). Two types of receptors have been recognized: homodimeric and heterodimeric. Binding to the homodimeric receptor inhibits apoptosis and activates erythropoiesis (22). The cytoprotective effects of erythropoietin are caused by the activation of heterodimeric receptors (23, 24). The realization of these effects is mediated by JAK-2, STAT5, PI3-K, and NFkB (25); nonetheless, the affinity of erythropoietin to the homodimeric receptor is significantly higher than that to the heterodimeric one (26). Therefore, systemic doses of erythropoietin need to be significantly higher than conventional therapeutic doses to realize the cytoprotective effect (27).

In practice, treatment with high doses of erythropoietin led to an increased risk of thrombotic events in the first year after transplantation (erythropoietin 24.4%, compared to placebo 6.4%) (28). To prevent these adverse effects, erythropoietin derivatives that merely activate the cytoprotective effect and do not affect erythropoiesis have been developed. Erythropoietin mimetic peptide (pHBSP) is a synthetic peptide that selectively binds to a heterodimeric receptor. It has already been demonstrated that pHBSP is not erythropoietic (29). In the present study, it was strived to assess the nephroprotective effects of pHBSP in ischemia-reperfusion kidney injury.

Pro-inflammatory cytokines, including TNF-α, play an equally important role in the pathophysiology of kidney ischemia-reperfusion injury (30). Free radicals cause the accumulation of white blood cells in the tissues. Activated neutrophils produce such enzymes as myeloperoxidase and release more free radicals (31). In pharmacology, some medicines, such as infliximab, have been recognized to suppress the activity of TNFα (32). Infliximab has a high affinity for the tumor necrosis factor-α; moreover, it decreases the concentration (binds and inhibits the synthesis) of interleukin (IL)-1, IL-6, IL-8, monocyte chemoattractant-1, nitric oxide, metalloproteinases (collagenase, stromelysin), as well as other inducers of inflammation and tissue destruction.

In light of the aforementioned issues, the present study aimed to assess the neuroprotective effects of pHBSP and infliximab on simulated ischemia-reperfusion kidney injury.

2. Material and Methods

The current study was conducted in the Clinical and Preclinical Studies Centre of Belgorod National Research University in accordance with the regulatory

legal acts and guidelines governing the conduct of experimental studies in the Russian Federation: Order of the Ministry of Health of the Russian Federation of 01.04.2016 N199n "On approval of the Rules of Good Laboratory Practice", GOST 33044-2014 "Principles of Good Laboratory Practice", GOST 33217-2014 "Guidelines for the maintenance and care of laboratory animals. Rules for the maintenance and care of laboratory predatory mammals", "Guidelines for pre-clinical trials of medicines" edited by Mironov A.N., 2012. Ethical principles of handling laboratory animals were in accordance with "Directive 2010/63/EU of the European Parliament and the Council of 22 September 2010 on the protection of animals used for scientific purposes".

The experiment was performed on 70 white male Wistar laboratory rats weighing 280g-320g. The animals were assigned to seven groups (n=10 in each group):

1. Sham-operated animals
2. Ischemia/reperfusion (I/R)-control
3. Ischemia/reperfusion+recombinant erythropoietin (EPO) (Epocrine®, FSUE "State Research Institute of Especially Purified Bioproducts" FMBA of Russia at the dose of 50 IU/kg intraperitoneally once 30 min before the ischemia simulation.
4. Ischemia/reperfusion+pHBSP at the dose of 5 µg/kg, intraperitoneally 30 min before the ischemia simulation
5. Ischemia/reperfusion+pHBSP at the dose of 25 µg/kg, intraperitoneally 30 min before the ischemia simulation
6. Ischemia/reperfusion +Infliximab (Remicade®, MSDIreland (Brinney) at the dose of 2 mg/kg intraperitoneally 1 h before the ischemia simulation
7. Ischemia/reperfusion+Infliximab (Remicade®, MSDIreland (Brinney) at the dose of 10 mg/kg intraperitoneally 1 h before the ischemia simulation

A midline laparotomy was performed under anesthesia (chloral hydrate, 300 mg/kg intraperitoneally) after preoperative showering. Following that, the loops of the intestine were mobilized and the kidneys with elements of the renal pedicle were isolated. Atraumatic vascular clamps were applied to the left renal pedicle for 40 min. The effectiveness of the ischemia was assessed by changing the kidney color, and the right nephrectomy was performed.

The level of microcirculation in the renal cortex was recorded using the MP100 hardware and software complex (BiopacSystem, Inc., USA) with the laser doppler flowmetry (LDF) module LDF100C and the TSD143 surface sensor, which was applied to the middle part of the kidney without affecting the hilum of the kidney. The estimation of microcirculation was performed 5 min after the removal of clamps from the vascular pedicle. The results were recorded and processed using the AcqKnowledge software (version 3.8.1). The values were expressed in perfusion units (PU). Subsequently, 4-5 ml of warm 0.9% sodium chloride solution was instilled into the abdominal cavity, and the wound was closed in layers.

Urine collection was carried out using special metabolic cages. The animal was placed in a cage for 24 h with free access to water. Thereafter, 24 h after reperfusion, the rats were re-anesthetized by intraperitoneal injection of chloral hydrate at the dose of 300 mg/kg of animal body weight. Following that, re-laparotomy was performed, microcirculation was estimated, and blood was sampled from the right ventricle for biochemical studies. Endogenous creatinine clearance (glomerular filtration rate) was calculated using the following formula:

$$GFR = \frac{\text{Urine creatinine (µmol/l) x Urine volume (ml)}}{\text{Serum creatinine (µmol/l) x Collection time (min)}}$$

The fractional excretion of sodium (FENa) was calculated as follows:

$$\frac{\text{Urine sodium(mmol/l) x Serum creatinine(µmol/l) x 100\%}}{\text{Serum sodium(mmol/l) x Urine creatinine(µmol/l)}}$$

3. Results and Discussion

Based on the results, 24 h after the surgery, the plasma creatinine and urea levels in the sham-operated animals were reported as 45.9±0.8 and 6.7±0.2 mmol/L, respectively. Plasma creatinine and urea levels in the control group animals were obtained at 102.63±3.6 and 21.80±1.29 mmol/L, respectively. In the group of animals that received erythropoietin, these indicators were lower: 61.01±2.88 mmol/l and 12.61±1.14 mmol/L, respectively (p<0.05).

The administration of pHBSP (25 µg/kg) led to a statistically significant decrease in the plasma level of creatinine (57.10±2.03 mmol/L) and urea (12.68±1.15 mmol/L) (P<0.05). The effect of pHBSP (5 µg/kg) was less pronounced: the values were 78.73±2.0 and 20.67±1.06 mmol/L, respectively (P<0.05). The administration of infliximab at the dose of 10 mg/kg was accompanied by a marked decrease in the parameters of nitrogen metabolism in blood plasma: creatinine (63.21±2.48 mmol/l) and urea (13.62±1.25 mmol/l), as compared to the animals in the control group (P<0.05). There were no significant differences in the levels of creatinine and urea when infliximab was administered at the dose of 2 mg/kg, in comparison with the control group (Figures 1 and 2).

The glomerular filtration rate was maximal in the group of sham-operated animals (0.75±0.02 ml/min), while it was minimal in the group of ischemia/reperfusion (0.09±0.01 ml/min).

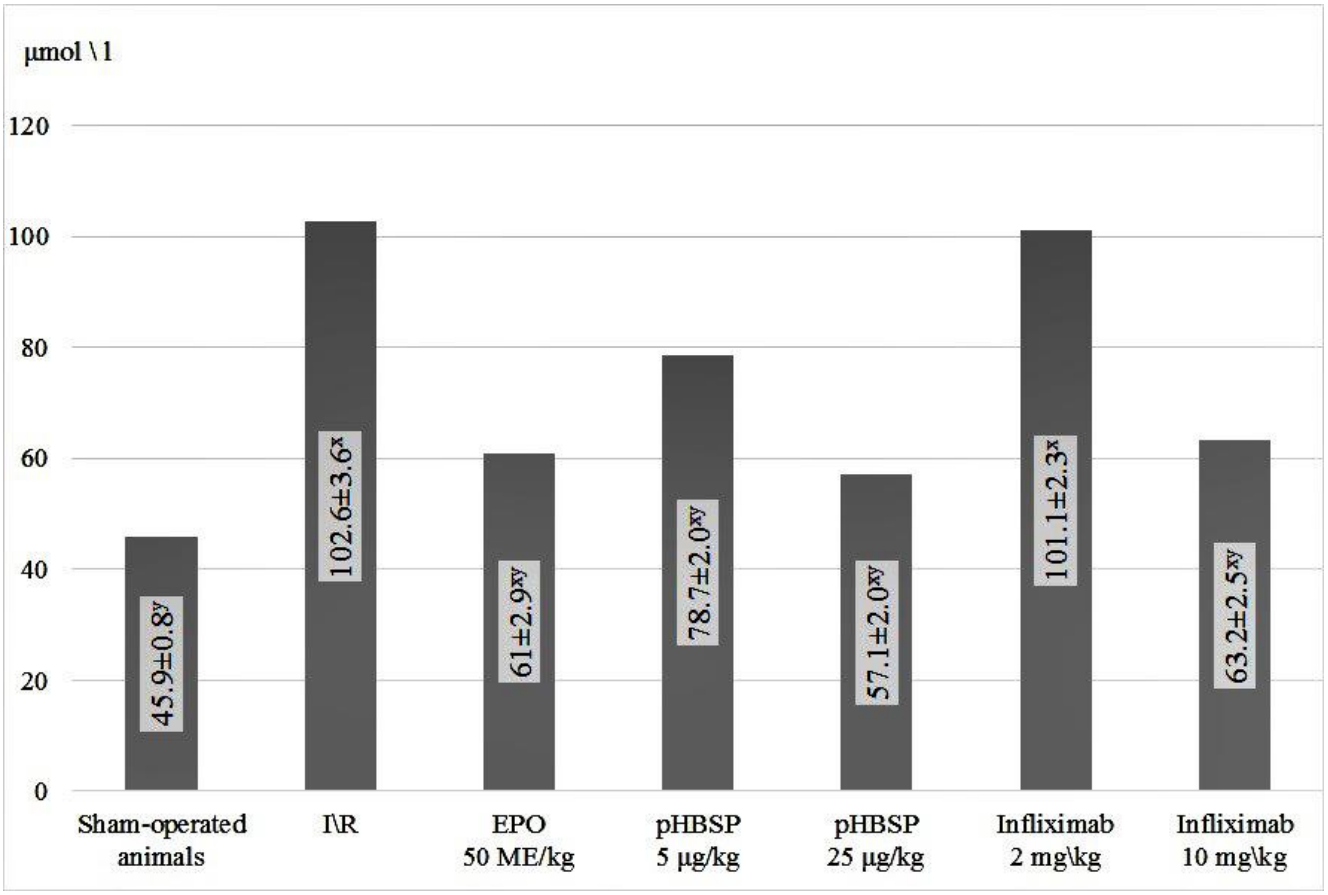

Figure 1. Values of serum creatinine concentration 24 h after the reperfusion in simulated ischemia-reperfusion injury of the kidney
Note: ^{x} – P<0.05, in comparison with the sham-operated animals. ^{y} – P<0.05, in comparison with the ischemia/reperfusion group

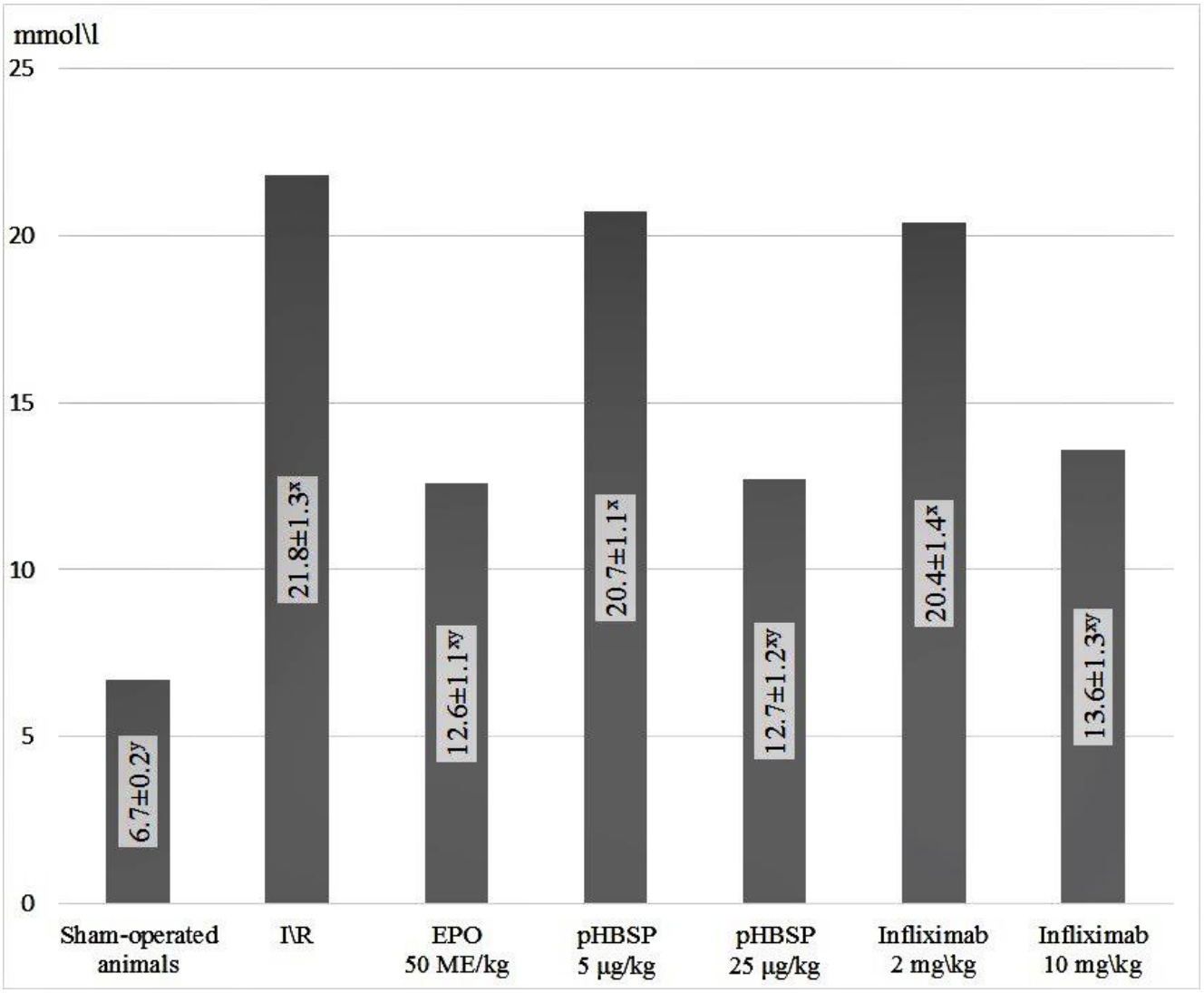

Figure 2. Values of serum urea concentration 24 h after the reperfusion in simulated ischemia-reperfusion injury of the kidney
Note: ^{x} – P<0.05, in comparison with the sham-operated animals. ^{y} – P<0.05, as compared to the ischemia/reperfusion group

In animals that received erythropoietin before ischemia, the glomerular filtration rate was 0.27±0.01 ml/min, which is comparable to the value in the pHBSP group (25 µg/kg) (0.29±0.01 ml/min). After the administration of pHBSP at the dose of 5 µg/kg, there was also an increase in the glomerular filtration rate to 0.27±0.01 ml/min, associated with an increase in the volume of diuresis. The glomerular filtration rate in the Infliximab group (10 mg/kg) was 0.22±0.01 ml/min. Infliximab at the dose of 2 mg/kg did not exert a pronounced effect on the glomerular filtration rate, which was 0.10±0.01 ml/min (Figure 3).

The assessment of the functional state of the renal tubules revealed a normal fractional sodium excretion index (FEna) in the group of sham-operated animals (0.37%±0.01%). The simulation of ischemia-reperfusion kidney injury led to an increase in FEna to 2.77%±0.1% which, along with a drop in glomerular filtration rate, points to the development of acute tubular necrosis. During the experiment, it was revealed

that the administration of pHBSP at the doses of 5 µg/kg and 25 µg/kg had a positive effect on renal tubules: the FENa indices were reported as 1.26±0.03% and 1.25±0.05%, respectively.

Against the background of the infliximab administration, a significant decrease was also noted in the FENa, in comparison with the ischemia/reperfusion group, and the doses 2 mg/kg and 10 mg/kg had a comparable effect: the FENa indices were obtained at 1.17±0.05% and 1.15±0.05%, respectively (Figure 4).

The assessment of the microcirculation pointed to the greatest effectiveness of pHBSP at the dose of 25 µg/kg: the value in both control points was as close as possible to the value of microcirculation in the kidneys of sham-operated animals. The administration of infliximab at the dose of 10 mg/kg also helped to keep the high level of microcirculation; nonetheless, the effect was slightly less than pHBSP at the dose of 25 µg/kg. The administration of pHBSP at the dose of 5 µg/kg increased the level of microcirculation by two times, as compared to only the ischemia/reperfusion group; however, it was significantly lower than pHBSP 25 µg/kg and infliximab 10 mg/kg. No significant difference was observed in the level of microcirculation between infliximab at the dose of 2 mg/kg and the pathology group (Table 1).

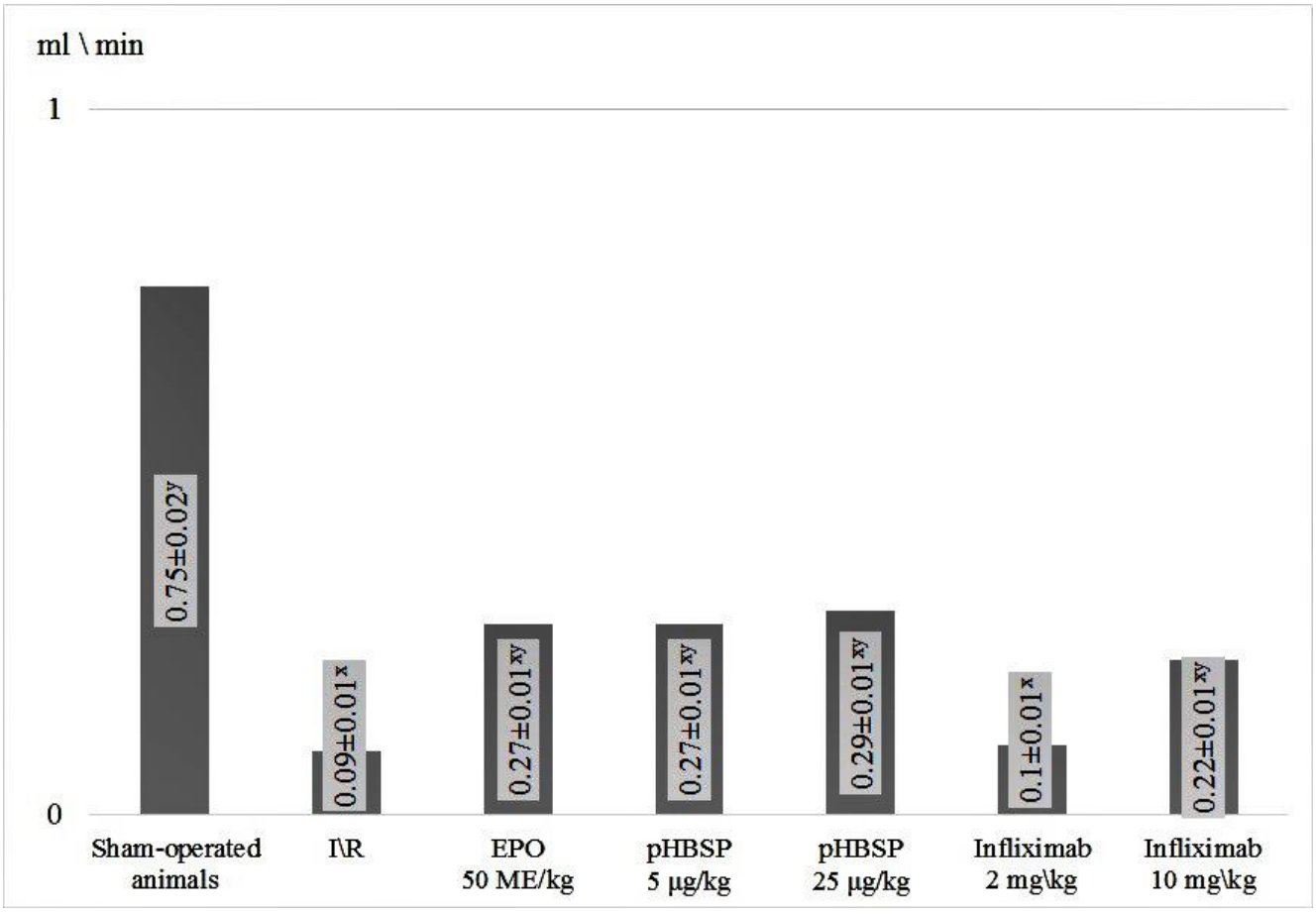

Figure 3. Glomerular filtration rate values 24 h after the reperfusion in simulated ischemia-reperfusion injury of the kidney
Note: ^{x} – P<0.05, in comparison with the sham-operated animals. ^{y} – P<0.05, in comparison with the ischemia/reperfusion group

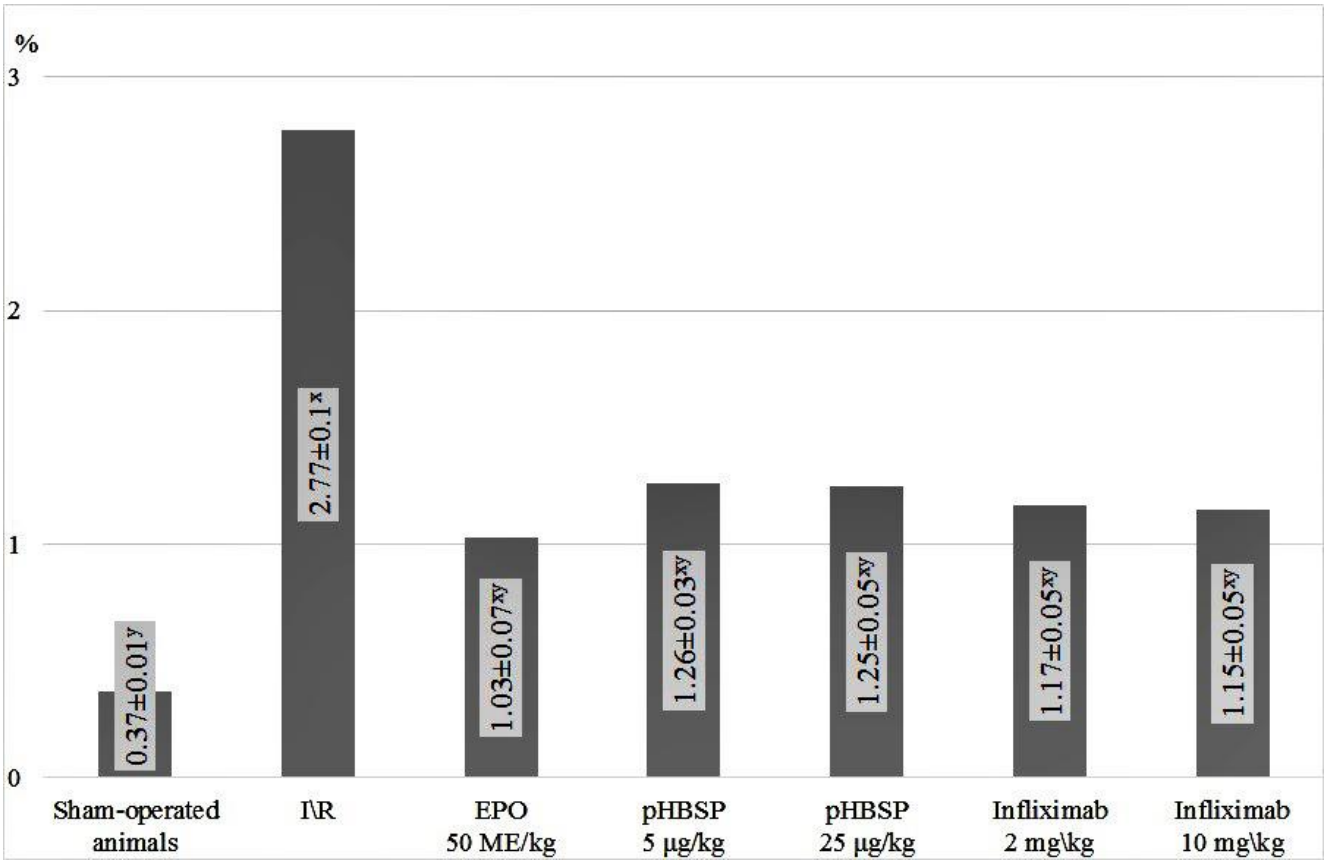

Figure 4. Values of fractional sodium excretion 24 hours after the reperfusion in simulated ischemia-reperfusion injury of the kidney
Note: ^{x} – P<0.05, in comparison with the sham-operated animals. ^{y} – P<0.05, in comparison with the ischemia/reperfusion group

Table 1. Effect of pHBSP and infliximab on renal microcirculation in simulated ischemia/reperfusion injury

Experimental groups	Before ischemia	5 minutes after	24 hours after
Sham-operated animals	898±44^{y}	900±42^{y}	881±38^{y}
I\R	904±45^{y}	219±12^{x}	430±20^{x}
EPO	899±37^{y}	637±27^{xy}	733±31^{xy}
pHBSP (5 µg/kg)	905±44^{y}	492±21^{xy}	607±28^{xy}
pHBSP (25 µg/kg)	895±15^{y}	693±28^{xy}	771±27^{xy}
Infliximab (2 mg/kg)	900±57^{y}	249±13^{x}	448±20^{x}
Infliximab (10 mg/kg)	903±72^{y}	674±28^{xy}	743±34^{xy}

EPO: Ischemia/reperfusion+recombinant erythropoietin, pHBSP: Erythropoietin mimetic peptide, I/R: Ischemia/reperfusion
Note: ^{x} – P<0.05, in comparison with the sham-operated animals. ^{y} – P<0.05, in comparison with the ischemia/reperfusion group

Currently, such kidney surgeries as transplantation and nephrectomy have firmly and permanently entered the practice of modern medicines. This highlights the necessity of preventing the development of the most dangerous complication of renal ischemia, acute renal injury. In the present study, it was proved that pHBSP and infliximab significantly contributed to the preservation of normal functional activity of the kidneys after simulated ischemia-reperfusion injury. The effect of pHBSP can be explained by its ability to selectively bind to the heterodimeric erythropoietin receptor, which leads to the activation of pleiotropic effects, including anti-ischemic, anti-apoptotic, and anti-inflammatory (19). This contributes to cytoprotective effects in the renal parenchyma, reducing the formation of humoral factors leading to glomerular and tubular dysfunction, as well as the activation of endothelial nitric oxide synthase (eNOS) (24).

It is also known that cell damage is aggravated by reperfusion: reactive oxygen species and pro-inflammatory cytokines, including TFN-α, triggering a pathological cascade of damage to the renal parenchyma (33). The nephroprotective effects of infliximab can be ascribed to its high affinity for TFN-α, as well as its ability to reduce the concentration (binds and inhibits the synthesis) of IL-1, IL-6, IL-8, monocyte chemoattractant-1, nitric oxide, metalloproteinases (collagenase, stromelysin) and other inducers of inflammation and tissue destruction (33). This, in turn, leads to the normalization of the functional activity of the kidneys in ischemia-reperfusion injury. Therefore, the obtained data suggested that pHBSP and infliximab may be useful for the prevention of acute renal injury in surgery with warm renal ischemia; nonetheless, further studies are needed to confirm these results.

In conclusion, following the administration of pHBSP at the doses of 5 μg/kg and 25 μg/kg 30 min before ischemia, a dose-dependent improvement was observed in the filtration function of the kidneys, in comparison to control animals (I/R) which manifested a decrease in the concentration of serum creatinine to 78.73±2.0 mmol/l and 57.10±2.03 mmol/l, while the glomerular filtration rate was 0.27±0.01 ml/min and 0.29±0.01 ml/min, respectively ($P<0.05$). There was also a 2.2-fold decrease in fractional sodium excretion, as compared to the ischemia/reperfusion group.

A comparable nephroprotective effect was provided by infliximab at the dose of 10 mg/kg when administered 1 h before ischemia: creatinine (63.21±2.48 mmol/L), urea (13.62±1.25 mmol/L), glomerular filtration rate (0.22±0.01 ml/min), and fractional sodium excretion(1.15%±0.05%). Infliximab at the dose of 2 mg/kg only affected the level of fractional sodium excretion (1.17±0.05%), apparently preventing pathological changes of different sections of nephron tubules.

A statistically significant ($P<0.05$) dose-dependent improvement was observed in microcirculation after pHBSP administration at the dose of 5 μg/kg and 25 μg/kg, as well as infliximab at the dose of 10 mg/kg.

Authors' Contribution

Study concept and design: A. S. N.
Acquisition of data: V. V. G.
Analysis and interpretation of data: M. V. P.
Drafting of the manuscript: A. V. G.
Critical revision of the manuscript for important intellectual content: Y. M. T.
Statistical analysis: I. S. R.
Administrative, technical, and material support: A. S. N.

Ethics

Ethical principles of handling laboratory animals were in accordance with "Directive 2010/63/EU of the European Parliament and the Council of 22 September 2010 on the protection of animals used for scientific purposes

Conflict of Interest

The authors declare that they have no conflict of interest.

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