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THE METHOD OF CORRECTION OF HEMORRHAGIC SHOCK ACTION ON THE PRO- AND ANTIOXIDANT SYSTEM OF THE PERIULCERAL STOMACH TISSUES IN AN EXPERIMENT

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Annotation. *The article presents the results of an experimental study about modeling hemorrhagic shock in animals with chronic gastric ulcer and further evaluation of the pro- and antioxidant system in periulceral tissues. The effect of local injection of platelets-rich plasma was also explored. Experiments were performed on 77 white laboratory rats. The level of NADPH-oxidase and superoxide dismutase, as indicators of pro- and antioxidant systems, after local periulceral injection of saline or platelet-rich plasma was explored in comparison with such levels in animals with ulcers and hemorrhagic shock without treatment. The obtained data were processed using the statistical software package SPSS 20.0 for Windows. The obtained data show a modulation of the pro- and antioxidant defense system towards destructive changes, characterized by the activation of pro-oxidant and inhibition of antioxidant enzymes in the mucous membrane of the periulceral zone in shock condition. Local periulceral injecting of platelet-rich plasma allows to reduce oxidative stress, activate the system of antioxidant enzymes and potentially accelerate repair processes in the periulceral zone.*

Keywords: *ulcer, hemorrhagic shock, PRP, NADPH-oxidase, superoxide dismutase.*

Introduction

A chronic ulcer is the result of necrosis of the mucous membrane of the stomach or duodenum, primarily as a result of ischemia, with the cessation of the supply of nutrients and the formation of reactive oxygen species [11]. This, in turn, activates the processes of lipid peroxidation and free radical oxidation of proteins, which leads to the progression of destructive changes in tissues.

Platelets are one of the largest sources of growth factors in the body and actively influence tissue healing processes. Thus, platelets contain: platelet-derived epidermal growth factor (PD-EGF), platelet-derived growth factor (PDGF), bone morphogenetic protein (BMP), transforming growth factor (TGF), insulin-like growth factor (IGF), vascular endothelial growth factor (VEGF), endothelial cell growth factor (ECGF), basic fibroblast growth factor (bFGF) [5, 14, 18]. In addition, α-granules of platelets contain adhesive proteins (fibrinogen, fibronectin, vitronectin, thrombospondin-1), coagulation factors (factor V, factor XI, protein S, antithrombin), fibrinolytic factors (plasminogen, urokinase inhibitor, α-2 antiplasmin), proteases and antiproteases (TIMP-4, metalloproteinase-4, α-1 antitrypsin), basic proteins (platelet factor 4, β-thromboglobulin, endostatins), membrane glycoproteins (CD40-ligand, P-selectin). Also, dense granules of platelets contain biologically active molecules: serotonin, histamine, dopamine, ADP, ATP, Ca2+, catecholamines. These substances stimulate the proliferation of endothelial cells and the formation of capillaries, as well as the process of repairing damaged tissues in general. However, the effect of platelets on the activity of pro- and antioxidant tissue systems remains unknown.

The purpose of the study is to investigate changes in the pro- and antioxidant system of periulceral tissues in hemorrhagic shock conditions and their changes under the influence of local application of platelet-rich plasma.

Materials and methods

The experimental study was carried out in the vivarium of the National Pirogov Memorial Medical University, Vinnytsia with the permission of the bioethics committee, minutes of the meeting of the Bioethics Commission of the National Pirogov Memorial Medical University, Vinnytsia No. 5 dated September 1, 2022.

The experiment was conducted on 77 white laboratory rats. Seven intact rats were controls for evaluating biochemical processes in the mucous membrane of the stomach wall. The remaining 70 rats underwent modeling of the ulcer defect of the anterior stomach wall according to the method of Susumu Okabe (2005) - type I acetate ulcer [12].

On the third day of the experiment, when, according to the literature [12], stable acetate ulcers of the stomach wall are formed with the involvement of the muscle layer, hemorrhagic shock was simulated in 49 experimental animals. The remaining rats (n=21) were included in the comparison group - acetate ulcer without hemorrhagic shock and without stimulation of reparation.

In order to simulate hemorrhagic shock, blood was taken from the lateral vein of the tail. The obtained blood was used to prepare platelet-rich plasma (PRP) according to the standard method [14]. The volume of blood was determined individually and was equal to 1.5 % of the

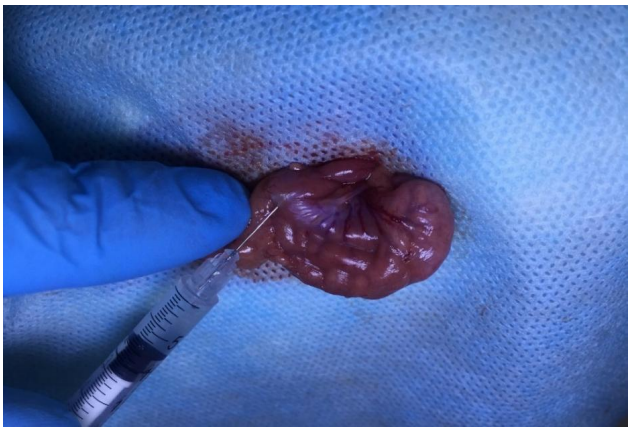

Fig. 1. Periulceral injection of PRP.

animal's weight, which corresponded to a blood loss of 20-25 % of the CBV.

On the fourth day of the experiment, 7 animals from the comparison group and from a large group (n=49) of rats with acetate ulcer and hemorrhagic shock were removed from the experiment to evaluate biochemical changes in periulceral tissues.

After that, the remaining animals with acetate ulcer and hemorrhagic shock (n=42) were randomly divided into three experimental groups.

The animals of the first experimental group (14 rats) were not subjected to any manipulations. The animals of the second experimental group (14 rats) were administered periulcerally with physiological solution. The animals of the third experimental group (14 rats) were injected periulcerally with PRP (Fig. 1).

The dynamics of biochemical indicators were evaluated on the seventh, eleventh and eighteenth days of the experiment, which corresponds to the third, tenth and fourteenth days after the introduction of PRP. For this purpose, 7 animals from each experimental group were removed from the experiment at each time point.

Biochemical research methods were performed in the research clinical and diagnostic laboratory of the Department of Biological and General Chemistry of the National Pirogov Memorial Medical University, Vinnytsia, certified by the Ministry of Health of Ukraine (certificate of the Ministry of Health of Ukraine on re-certification № 002/10 dated January 11, 2010; № 049/15 dated March 2. 2015).

To evaluate the biochemical indicators of the mucous membrane of the stomach wall around the ulcer defect, the stomach was removed, an autopsy was performed along the great curvature, and it was washed in a physiological solution of potassium chloride. The gastric mucosa was isolated, perfused with cold 1.15 % potassium chloride solution and homogenized at 3000 rpm (teflon-glass) in a medium of 1.15% potassium chloride (ratio 1:3). The homogenates were centrifuged for 30 min at 600 g, aliquots of the postnuclear supernatant were taken into Eppendorf microtubes and stored at a temperature of 15-25 °C until the research.

To assess the state of the pro- and antioxidant system of the gastric mucosa, the activity of NADPH oxidase and superoxide dismutase (SOD), respectively, was studied. NADPH oxidase activity was expressed in nmol/min per 1 mg of protein, superoxide dismutase activity was determined by the ability to inhibit quercetin oxidation, expressed in IU/mg of protein.

The obtained data were processed using a package of statistical programs SPSS 20.0 for Windows.

The research was carried out within the framework of the SRW "Development and implementation of innovative technologies in the treatment and prevention of violations of the integrity and patency of blood vessels in wartime conditions (0123U100204)".

Results. Discussion

The dynamics of changes in NADPH oxidase activity in the gastric mucosa in groups of animals is shown in Table 1.

In all studied groups and at all times of the study, indicators of NADPH oxidase activity were higher than indicators in the control group of animals (intact rats).

On the 4th day, all three main groups were characterized by significantly higher ($p<0.01$, χ^2 test with Yates correction) values of NADPH oxidase activity than in the comparison group. At the same time, the indicators of the main groups were not significantly different from each other ($p>0.05$, χ^2 test with Yates correction).

On the 11th day of the study, no significant difference in the values of the studied indicator was found between the comparison group and the third main group ($p>0.05$, χ^2 test with Yates correction), as well as between main groups 1 and 2 ($p>0.05$, χ^2 test with Yates correction). In a pairwise statistical comparison, the indicators in the comparison group and experimental group 3 were statistically significantly lower than the similar indicators of the main groups 1 and 2 ($p<0.01$, χ^2 test with Yates correction).

On the 18th day of the study, due to the decrease in NADPH oxidase activity values in all main groups, no statistically significant differences were found between the comparison group and main groups 1 and 2 ($p>0.05$, χ^2 test with Yates correction). At the same time, the values of

Table 1. Dynamics of changes in the activity of NADPH oxidase in the mucous membrane of the stomach in the studied groups of animals.

Groups	NADPH oxidase activity, nmol/min per 1 mg of protein		
	Day 4	Day 11	Day 18
Comparison group (AB)	1.287±0.043	1.313±0.014	1.319±0.026
Main 1 (AB+shock)	1.558±0.071	1.479±0.084	1.332±0.028
Main 2 (AB+shock+0.9 % NaCl)	1.569±0.067	1.471±0.048	1.309±0.028
Main 3 (AB+shock+PRP)	1.548±0.049	1.329±0.046	1.147±0.031

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enzyme activity in the main group 3 were significantly lower than the values in all other groups ($p<0.01$, χ^2 test with Yates correction) and approached the indicators of the control group.

When analyzing the dynamics of changes in NADPH oxidase activity in each group separately during the studied period, the following data were obtained. In the comparison group, although a progressive increase in numerical indicators of enzyme activity was observed during the experiment, this increase was not statistically significant ($p>0.05$, χ^2 test with Yates correction).

High indicators of NADPH-oxidase activity in the first main group on the 4th day of the study can be explained by the effect of hemorrhagic shock on the pro-antioxidant defense system with the activation of pro-oxidant enzymes. A further progressive and reliable ($p<0.01$, χ^2 criterion with Yates correction) decrease in the activity of the studied indicator indicates the activation of the body's compensatory capabilities and the gradual normalization of protective factors.

A similar trend was observed in the second main group. When comparing the dynamics of the investigated indicator in the main groups 1 and 2, it can be concluded that the very fact of local injection of physiological solution into the periulceral tissues does not affect the state of the pro-antioxidant protection system of the gastric mucosa in any way.

In the third main group, similarly to other experimental groups, the dynamics of NADPH oxidase activity was characterized by high values of the indicator on day 4 (the effect of hemorrhagic shock) and a progressive and reliable ($p<0.01$, χ^2 test with Yates correction) decrease of this indicator in the next 14 days. However, it should be noted that the decrease in enzyme activity occurred significantly ($p<0.01$, χ^2 test with Yates correction) faster than in other main groups. This is explained by the positive effect of PRP on the state of the pro-antioxidant defense system of the gastric mucosa.

The dynamics of changes in the activity of superoxide dismutase in the mucous membrane of the stomach in the studied groups of animals is shown in Table 2.

In the control group of animals, superoxide dismutase activity was 1.824±0.047 IU/mg of protein.

As can be seen from Table 2, in all studied groups and at all control time points, indicators of SOD activity were lower than in intact rats (control group).

On the 4th day, all three main groups were characterized by significantly lower ($p<0.01$, χ^2 test with Yates correction) values of SOD activity than in the comparison group. At the same time, there was no significant difference between the indicators of the main groups ($p>0.05$, χ^2 test with Yates correction).

On the 14th day, the studied indicator in the comparison group was not significantly different from the similar one in the third main group ($p>0.05$, χ^2 test with Yates correction). Also, a statistically significant difference according to this indicator was not proven ($p>0.05$, χ^2 test with Yates correction) for a pair of main groups 1 and 2. At the same time, in a pairwise statistical comparison, the indicators in the comparison group and main group 3 were statistically significantly higher than similar indicators in main groups 1 and 2 ($p<0.01$, χ^2 test with Yates correction).

Table 2. Dynamics of changes in the activity of superoxide dismutase in the mucous membrane of the stomach in the studied groups of animals.

Groups	Superoxide dismutase activity, IU/mg protein		
	Day 4	Day 11	Day 18
Comparison group (AB)	1.503±0.056	1.487±0.029	1.478±0.056
Main 1 (AB+shock)	1.238±0.050	1.347±0.059	1.517±0.079
Main 2 (AB+shock+0.9 % NaCl)	1.246±0.057	1.357±0.048	1.528±0.047
Main 3 (AB+shock+PRP)	1.229±0.048	1.508±0.019	1.749±0.078

On the 18th day of the study, due to the increase in SOD activity values in all experimental groups, no statistically significant differences were found between the comparison group and the main groups 1 and 2 ($p>0.05$, χ^2 test with Yates correction). At the same time, the enzyme activity values in the main group 3 were significantly higher than the values in all other groups ($p<0.01$, χ^2 test with Yates correction) and approached the values of the control group.

When analyzing the dynamics of changes in the activity of SOD in each group separately during the studied period, the following was demonstrated.

In the comparison group, a slight progressive decrease in the numerical indicators of enzyme activity was observed during the experiment, but statistically significant differences between this indicator at all control time points were not proven ($p>0.05$, χ^2 test with Yates correction).

Low indicators of SOD activity in experimental group 1 on the 4th day of the study can be explained by the effect of hemorrhagic shock on the pro-antioxidant defense system with inhibition of antioxidant enzymes. Further progressive and reliable ($p<0.01$, χ^2 criterion with Yates correction) increase in the activity of the studied indicator indicates the activation of the body's compensatory capabilities and the gradual normalization of protective factors.

An almost identical picture took place in experimental group 2. When comparing the dynamics of the studied indicator in experimental groups 1 and 2, it can be concluded that the local injection of physiological solution into the periulceral tissues does not affect the state of the pro-antioxidant protection system of the gastric mucosa in any way.

In experimental group 3, similarly to other experimental groups, the dynamics of SOD activity was characterized by low values of the indicator on day 4 (the effect of hemorrhagic shock) and a progressive and reliable ($p<0.01$, χ^2 test with Yates correction) increase of this indicator in the next 14

days. However, it should be noted that the increase in enzyme activity occurred significantly ($p<0.01$, χ^2 test with Yates correction) faster than in other experimental groups. This, in our opinion, is explained by the positive effect of PRP on the state of the pro-antioxidant defense system of the gastric mucosa.

Massive bleeding with the development of hemorrhagic shock due to a number of pathogenetic links causes a negative impact on absolutely all tissues and organs. One of the pathogenetic mechanisms involved in this process is oxidative stress, the meaning and mechanisms of which have been repeatedly highlighted in the scientific literature [7, 15].

Undoubtedly, manifestations of oxidative stress could not but affect the mucous membrane of the stomach during massive bleeding from a peptic ulcer. We could observe confirmation of this during the implementation of this study. Thus, in all experimental rats, after simulating gastric ulcer and hemorrhagic shock, indicators of NADPH oxidase activity were higher, and indicators of superoxide dismutase activity were lower, than similar indicators in intact animals.

Undoubtedly, the development of oxidative stress requires its correction. One of the possible ways of its correction, in our opinion, should have been the local introduction of plasma enriched with platelets.

The biological effects of PRP are provided through regenerative mechanisms, including inflammation, extracellular matrix synthesis, hemostasis, and angiogenesis [2].

Research in recent years shows a large amount of data on the successful use of platelet-rich plasma, not only in experimental, but also in clinical medicine [1, 4, 6, 8, 9, 16, 19, 20].

In the course of our study, it was demonstrated that stimulating therapy in the form of local periulceral injection of PRP reduces oxidative stress, activates the system of antioxidant enzymes, and accelerates repair processes in the periulceral zone.

This is not the first report on the antioxidant properties of platelet-rich plasma. Thus, its ability to influence oxidative stress in various tissues and in various pathological conditions was demonstrated in a number of scientific studies [3, 10, 13, 17].

Conclusion and prospects for further developments

1. The opposite dynamics of the activity indicators of NADPH oxidase and superoxide dismutase testifies to the correctness of the conducted research, since these enzymes are elements of opposite and opposite processes of oxidative stress and antioxidant protection.

2. In the mucous membrane of the periulceral zone, in comparison with the intact mucous membrane, there is a modulation of the pro-antioxidant protection system towards destructive changes, characterized by the activation of pro-oxidant and inhibition of antioxidant enzymes. This can explain the chronicity of the ulcer process in the stomach wall and the long-term non-healing of ulcer defects.

3. Simulation of hemorrhagic shock in rats with ulcer defects increased changes in the system of pro-antioxidant enzymes.

4. Stimulating therapy in the form of local periulceral injection of PRP allows to reduce oxidative stress, activate the system of antioxidant enzymes and potentially accelerate repair processes in the periulceral zone.

In the future, an experimental study of the effect of PRP on regenerative and biochemical changes in conditions of hemorrhagic shock in other organs is planned.

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СПОСІБ КОРЕКЦІЇ ВПЛИВУ ГЕМОРАГІЧНОГО ШОКУ НА ПРО- ТА АНТИОКСИДАНТНУ СИСТЕМУ ПЕРІУЛЬЦЕЛЯРНИХ ТКАНИН ШЛУНКУ В ЕКСПЕРИМЕНТІ

Петрушенко В. В., Собко В. С., Гребенюк Д. І., Стойка В. І.

Анотація. *У статті наведено результати експерименту з моделювання геморагічного шоку у тварин з хронічною виразкою шлунку та подальшим вивченням про- та антиоксидантної системи в періульцелярних тканинах. Вивчено також вплив на вказані системи локального введення плазми, збагаченої тромбоцитами. Досліди було проведено на 77 білих лабораторних щурах. Вивчали рівень NADPH-оксидази та супероксиддисмутази, як індикаторів про- та антиоксидантної систем, під впливом періульцелярного введення фізіологічного розчину або плазми, збагаченої тромбоцитами, у порівнянні з такими рівнями у тварин з виразкою та геморагічним шоком без лікування. Одержані дані піддавалися обробці за допомогою пакету статистичних програм SPSS 20.0 for Windows. Отримані нами дані свідчать про те, що у слизовій оболонці періульцелярної зони, у порівнянні з інтактною слизовою оболонкою, проходить модуляція системи про- та антиоксидантного захисту в бік деструктивних змін, що характеризується активуванням прооксидантних і пригніченням антиоксидантних ензимів. Стимулююча терапія у вигляді локального періульцелярного введення плазми, збагаченої тромбоцитами, дозволяє зменшити оксидативний стрес, активувати систему антиоксидатних ферментів і потенційно прискорити процеси репарації у періульцелярній зоні.*

Ключові слова: *виразка, геморагічний шок, PRP, NADPH-оксидаза, супероксиддисмутаза.*