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EXPERIMENTAL RATIONALE FOR THE USE OF FLUIDS WITH DIFFERENT REDOX POTENTIAL AS A BASIS FOR INFUSION THERAPY

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Abstract

Introduction: The hypothesis is that a change in the redox potential (Red-Ox) of infusion solutions can increase their pharmacological efficacy.

Objectives: To study the parameters of redox potential (ORP or Red-Ox) and pH of infusion solutions. To identify the general biological properties of ionized liquids with different ORP when administered by different methods to experimental animals and when applied to the wound surface. To study the effects of infusion therapy with solutions based on ionized fluids with various ORP in anaphylactic shock, bacterial sepsis, alcoholic hepatitis, dehydration, and skin injuries.

Materials and methods: Determination of practical osmolarity of ionized liquids with different ORP was carried out by the cryoscopic method with the use of the Beckmann thermometer. The study used experimental models of anaphylactic shock, bacterial sepsis, alcoholic hepatitis, dehydration and cutaneous injuries in rats. The study of the general biological properties of ionized liquids with different ORP was carried out in 4 groups of experiments. In the first group: experiments to investigate the effect of liquids with different ORP on the action of ophthalmic drugs and eye tissue – on 75 rabbits; in the 2-nd: experiments on the level of glucose in the blood; in the 3-rd: the study of reactions of the cardiovascular system to intravenous administration of ionized liquids with various ORP in the maximum permissible volumes; in the 4-th: the research of regenerative abilities of liquids with various ORP with a cutaneous injury.

Results: It was found that the ORP of infusion solutions is higher than the potential of liquid media by 100-400 mV. The cryoscopic method established the possibility of preparing isoosmolar infusion solutions with various Red-Ox potentials. In the models of anaphylactic shock and bacterial sepsis, the expediency of changing the Red-Ox potential of body fluids is shown. Addition of ionized liquids with different ORP to a 0.1% solution of adrenaline hydrochloride in a ratio of 1:1 leads to prolongation of the pharmacological effects of the drug. After instilling the ionized liquid with positive ORP in the conjunctiva a weak local anesthetic effect is observed. Electrocardiography of the experimental rabbits showed that a decrease in the Red-Ox potential of the isotonic sodium chloride solution increases its therapeutic range, reducing the load on the right atrium and ventricles. Regenerative efficiency in the treatment of wound surfaces was noted when using ionized liquid with ORP = minus 250 mV.

Conclusion: The use of ionized fluids with various ORP as the basis of infusion solutions for anaphylactic shock, bacterial sepsis, alcoholic hepatitis, and dehydration has shown high efficiency. At the same time, the issues of compatibility of ionized liquids with different ORP with various pharmacological preparations remain unresolved, the issues of pharmaceutical stability of liquids with negative Red-Ox potential, etc. are not solved either, which indicates the prospects of research in this direction.

Key words: infusion solutions; Red-Ox potential; oxidation-reduction potential; ionized liquids; infusion therapy; redox balance of the organism.

Introduction

In a General biological sense, the disease is a protective reaction of the organism, aimed at saving it from death. In response to the disease in the body can cause various pathophysiological condition, with many medical terminological interpretations. But in any pathological conditions, the body tends to maintain a certain level of its homeostasis, resulting from the

interaction of multiple layered systems [1]. Infusion therapy is the main tool to maintain homeostasis in severe pathological conditions [2]. With the development of the pathological state up to a certain severity, the doctors resort to the usage of infusion therapy and the more severe the condition, the more massive infusion support [3, 4]. Drugs for intravenous are used for restoring the circulating blood volume, rehydration of the tissues, maintenance of normoglycemia, correction of acid-base balance, to normalize the buffer systems of blood, and detoxification and dissidia [5, 6, 7]. Administering drugs via infusion allows the better control of their action and reduces the negative impact on the walls of blood vessels. A number of authors have noted the high effectiveness of application of infusion solutions in various shock states, sepsis, toxaemia, blood loss, dehydration, intoxication, peritonitis, etc [8]. Currently, infusion solutions must meet the mandatory requirements and properties: non-toxicity, fluidity, neutrality infusion medium, no mechanical impurities (transparency), sterility, apirogennost, relative stability and easy dosing. In addition infusion solutions, led by the bloodstream in large volumes, have special requirements, the main of which are soonest and isotonicity [9]. Currently under drip introductions of all known intravenous infusion solutions, patients frequently have sufficiently expressed negative reactions, in particular the violation of homeostasis [10]. This probably occurs due to mismatch of some parameters of infu-sion solutions and body fluids. Much attention in literature is paid to antioxidant defense and oxidative stress as a universal link of any pathological process [11]. Antioxidant protection has its own level in the regulation of homeostasis and constitutes a single system in a state of dynamic equilibrium and capable of self-regulation [12]. The result of paired functioning of the systems of generation of reactive oxygen species and antioxidative protection cell is established in the redox balance, or Red-Ox status [13]. The formation of the Red-Ox potential, reflecting the balance of Pro – and antioxidant systems of the body is influenced by the protein components of blood plasma, enzyme activity of catalase and many other components that are in their turn are the components of other systems [14]. Therefore, Red-Ox homeostasis acquires conceptual importance in a number of pathological conditions [15]. Not much developed is the issue of correcting Red-Ox system in the body for a number of technical difficulties [16]. Comparing the data of open literature sources and our own we have identified the main difficulties: the General instability of the reconstruction components of Red-Ox systems, short term storage solutions, no stable calibration solutions, low accuracy of measuring instruments when measuring negative values Red-Ox potential, high sensitivity of the measuring electrodes to the impurity, the absence of accurate information about the physiological values of the Red-Ox potential of liquids, tissues and cells of the body [17, 18]. Despite these difficulties there are fragmentary evidences that liquid environment of the body have a negative Red-Ox potential about minus 50 millivolts to 150 millivolts. The world Health Organization recommends drinking water with a Red-Ox potential not higher than + 50 mV [19]. According to our data, almost all infusion solutions have this indicator above 100 mV, which is not physiological and the introduction of such solutions Red-Ox balance shifts towards oxidation. A healthy body easily compensates for this shift at the expense of a complex of enzymes: superoxide dismutase, catalase, glutathione-dependent peroxidases, transferases, etc., as well as a number of metabolites cells: lipoic ascorbic, uric acid, tocopherols, carotenoids, flavonoids, polyphenols, carnosine, bilirubin, CoQ10 and other compounds, which are aimed at maintaining homeostasis [20, 21]. However, in severe conditions requiring massive infusion therapy solutions, system reduction level can not cope. This circumstance slows the recovery of such patients [22, 23, 24, 25, 26, 27]. In this regard, there remains the search for new liquids for intravenous administration, do not causing negative reactions of an organism [28, 29]. It is experimentally proved that the ionized fluid with a modified Redox-potential are effective in the treatment and prevention of anxiety and depressive states, schizophrenia, kidney disease, festering wounds, peritonitis, periodontitis, diseases of the gastro-intestinal tract and other diseases. The research results [30, 31] served as the basis for exploring the possibility of applying ionised fluids with different Red-Ox potential, often referred to as ORP (redox potential) as the basis of infusion solutions.

The research goal:

To justify the possibility of applying ionised fluids with different redox potential for improving the quality of infusion solutions.

Objectives:

1. To explore the parameters of the ORP and pH of infusion solutions, the most frequently used in medical institutions of the Voronezh region.
2. Establish the pH and ORP of body fluids.
3. To identify the general biological properties of ionized liquids with different ORP being administered in different ways and experimental animals up-on the applying to the wound surface.
4. To study the effects of the introduction of ionized liquids with differ-ent ORP in severe pathological conditions.
5. To justify the possibility of applying ionised fluids with different re-dox potential as the basis of infusion solutions.

Research methods:

The paper examines 925 samples of different solutions and liquids. The experiments were performed on 205 85 rabbits and rats. The study involved 82 volunteers. The content of laboratory animals meets the requirements (GOST R 50258-92). All materials used in the work procedures and protocols consistent with good laboratory practices according to guidance on experimental studies [32] and the Order of the health Ministry of Russia № 708H from 23.08.2010 "On approval of rules for laboratory practice" (GLP), compliance with International recommendations of the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes (ETS№ 124, Strasbourg, 22.06.1998). In the experiments we considered the requirements of the Commission on the issue of ethical treatment of animals of the Russian national Committee on bioethics science and ethics set out in the "International recommendations for conducting biomedical research using animals" (1989). The study was approved by the local independent ethics Committee at the Voronezh State Medical University (extract from minutes No. 6 dated 19.10.2013). Euthanasia of animals was carried out under the ether anesthesia mandatory in accordance with the methodological recommendations on the removal of animals from the experiment. All volunteers who participated in the research were taught the information about the study and signed the informed consent form in accordance with the Order of Ministry of health of the Russian Federation of 20 December 2012 № 1177н "On approval of the procedure of giving informed voluntary consent to medical intervention and refusal of medical intervention with respect to certain types of medical interventions, forms of informed voluntary consent to medical intervention and refusal of medical intervention".

During the research all the ethical standards, laid down in the Helsinki Declaration of 1964, the modified 41 world Assembly (Hong Kong 1989) and 52 of the General Assembly of the Academy (Edinburgh, Scotland (UK), October 2000), the Lisbon Declaration on the rights of the patient adopted by the 34 world medical Assembly, 1981, section V of the Code of medical ethics (07.06.1997) were complied. Developing a practical osmolarity of ionized liquids with different ORP conducted a cryoscopic method using Beckmann's thermometer. The study used an experimental model of severe pathological conditions.

Modeling of severe dehydration was carried out on 20 albino male rats weighing 200±20 g by keeping a fully dry diet by an animal for 10 days.

Modeling of acute alcohol poisoning was carried out on 30 rats of either sex weighing 250±20 g by intraperitoneal administration of 33% solution of ethyl alcohol (ethanol) at a dose of 0.8 LD50 [33]. Locomotor, exploratory and emotional activity were investigated using the methods of "an open field" [34].

Modeling of anaphylactic shock was conducted on 40 rabbits of Chinchilla breed of both sexes and weighing 2500-3500g after prior sensitization intramuscular introduction of horse serum at the rate of 1 ml/kg of animal weight injected into a regional vein of an ear of the rabbit resolution AG dose, rate of 1 ml/kg.

Modeling bacterial sepsis was conducted on 60 Chinchilla rabbits of both sexes, and average weight of 3000g by introducing into a regional vein of an ear of a culture of Staphylococcus aureus in 0.2% starvation agar to enhance the virulence properties of microorganisms. A suspension of staphylococci were injected at the rate of 0.1 ml per 1 kg of body weight.

The preparation of morphological drugs was carried out on the basis of the Central research laboratory of Vitebsk state medical University them. N. N. Burdenko. Fixation was performed in 10% neutral formalin solution, to which 1 part 40% formaldehyde solution diluted with 9 parts water. After rinsing the pieces were subjected to further compaction by dehydration in alcohols of in-creasing concentration. For review purposes the obtained sections were stained with hematoxylin-eosin.

Preparation of morphological preparations were carried out on the basis of the Central research laboratory of the Voronezh State Medical University. named after N. N. Burdenko. Fixation was performed in 10% neutral formalin solution, for which 1 part 40% formaldehyde solution was diluted with 9 parts water. After rinsing the pieces were subjected to further compaction by dehydration in alcohols of increasing concentration. For review purposes the obtained sections were stained with hematoxylin-eosin.

In vitro conducted the research of ionized liquids with different AFP from the standpoint of transfusion. We carried out several series of experiments where were studied: 1) 750 samples of ionised fluids with different re-dox potential in various conditions; 2) 70 samples of infusion solutions used in medical institutions of the Voronezh region; 3) 90 samples of body fluids; 4) 15 samples of different liquids to determine their osmolarity.

The study of the biological properties of ionized fluids with different re-dox potential. on rabbits, rats and volunteers in the 4 series. The 1st series: an experiment on the effect of liquids with various ORP on the action of ophthalmic drugs and eye tissues was performed on 75 adult Chinchilla rabbits of both sexes and weight of 2.9-3.4 kg. The 2nd series of

experiments included two groups: animals and volunteers. A study of the influence of ionized liquids with different ORP to the level of glucose in the blood laboratory was carried out on 30 rabbits of both sexes of chinchilla bread and 30 volunteers. The 3rd series: study of reactions of the cardiovascular system to intravenous administration of ionized liquids with different ORP maximum allowable amounts was carried out on 30 laboratory rabbits of both sexes Chinchilla. The 4th series: the study of the regenerative abilities of liquids with different ORP was conducted on 35 outbred white rats of both sexes and weighing 260-310 grams.

For the evaluation of the obtained results was used a number of methods. All the obtained results of the experiments data were analyzed using descriptive statistics. Used parameters: arithmetic mean (M), standard error of arithmetic mean (±m).

Statistical processing of obtained data was performed using the statistical packages of Microsoft Excel 2007 and "STATSGRAPHICS Plus 6.0" operating system Windows7.

Results

Storing ionized liquids with a positive ORP in a glass container dark, its ORP remained stable for 30 days, and the redox potential of the liquid stored in dark plastic containers was increased from the 1st day. Ionized liquid with a negative ORP keeps its negative oxidation-reduction potential within 5 hours. The heated, ionized liquids with a positive ORP of up to 400C and the liquid with a negative ORP of up to 300 ° C leads to an increase in the redox potential. The impact of negative temperatures leads to a significant increase in the redox potential of the investigated liquids, however, the indicators of the redox potential of a liquid with a negative ORP during thawing, acquire positive values. Diluting liquids with a positive ORP water, the redox potential decreases and dilution of the liquid with a negative ORP increases dramatically. By mixing ionized liquids with each other the change of ORP of a mixture is directly proportional to the ratio of breeding. Dilution in different ratios of liquids with a positive ORP of ethyl alcohol leads to a decrease of the ORP value, while the dilution liquid with a negative ORP in the same proportions, leads to a significant increase in the redox potential and with large dilutions of the parameters ORP acquire positive values.

In the study of the parameters of the ORP and pH of some parenteral solutions used in medical institutions of the Voronezh region determined that the values of these parameters are positive. In the study of the parameters of the ORP and pH of body fluids it was observed a decrease in ORP and increase in pH of amniotic fluid within 2 hours after their intake. Found that oral administration volunteers of liquids with a positive ORP does not change the value of SBP, DBP, heart rate, ORP and pH of urine, and the use of a liquid with a negative ORP inside decreases the redox potential of urine and increases its pH.

Assessing compliance of parameters of ionized liquids with different ORP requirements for infusion solutions there were determined theoretical and practical values of osmolarity of liquids with positive and negative ORP, which correspond to the values of the isotonic solutions. Thus, considering the data of Bresdin A. D. [2007] and Levchenko, Y. A. [2011], we can assume that intravenous administration of the investigated liquids will not lead to undesirable effects.

In the study of the influence of ionized fluids with different redox potential to the action of ophthalmic drugs it was found that IGP and IGO liquids do not have an effect on choline and adrenergic receptors, but by mixing the investigated liquids with 0.1% solution of epinephrine hydrochloride is observed prolongation of action of the drug. Liquid with a negative ORP reduces the effect of a 1% solution of pilocarpine hydrochloride and the water with positive ORP does not cause significant changes in the action of the drug. Dilution of 0.1% solution of atropine sulfate with ionized liquids with different ORP does not adversely impact on the effectiveness of the ophthalmic drug.

The study of the action of ionized liquids with different ORP to the level of glucose in the blood showed that the tested liquid did not significantly cause changes in the indicator, but the tendency is towards normalization, close to pathological.

Upon the intravenously administered isotonic sodium chloride solution (ORP = plus 315мВ) and ionized liquids with a positive ORP (ORP = plus 740мВ) to the maximum allowable extent there are signs of overload of the right atrium and ventricles. Intravenous administration of ionized liquid with a negative ORP (ORP = minus 550мВ) to the same extent the performance of the cardiovascular system are not modified.

The introduction of the maximum volume of liquid with a positive and a negative ORP leads to a slowing of respiration during the first hours after the injection. With the introduction of the maximum amount of liquids with a positive ORP tends to decrease heart rate. Introduction of the maximum amount of liquids with a positive ORP increases contractility of the heart.

The study of the action of ionized fluids with different redox potential in regenerative processes has established that the treatment of wound surfaces ionized fluid with a positive ORP efficiently 0.05% solution of chlorhexidine bigluconate. Processing of the wound surface fluid, ionized liquid with a negative redox potential with different ORP values after antiseptic liquid IGP regeneration of damaged tissues occurs much faster. The most effective is complex application of ionic liquids with a positive ORP and ionized liquid with a ORP of minus 250 mV (figure 1).

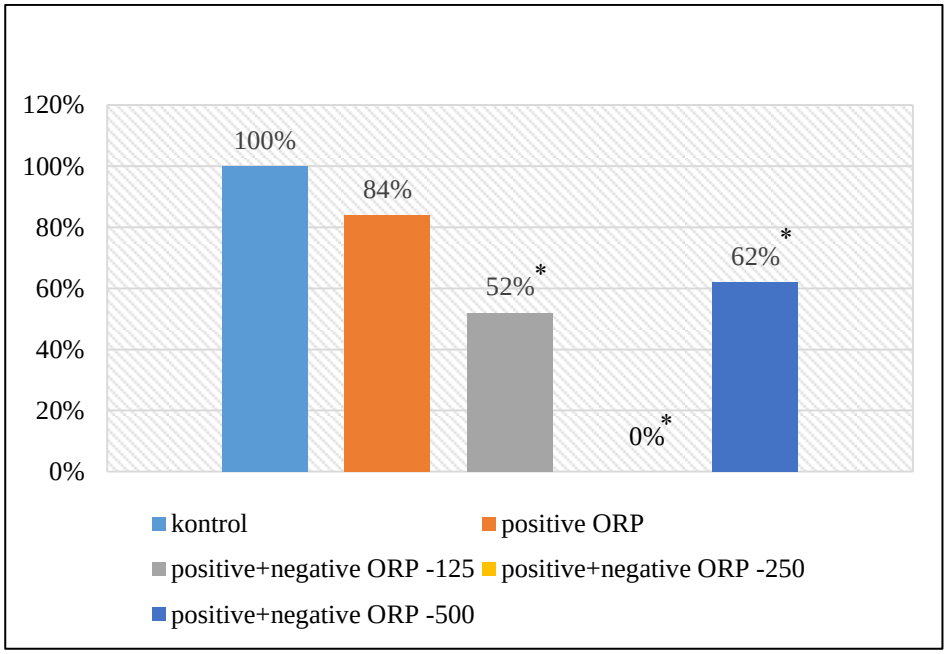

Fig. 1. The impact of liquids with different ORP for a change of the length of the wound on the 7th day.
Note * – differences statistically significant compared to the control group ($p<0.05$), n=7

In a study of rats the rehydration activity of ionized liquid with a negative ORP is studied. Full replacement of drinking water on the test liquid in animals with experimental dehydration have led to positive changes in all indicators of efficiency of process of rehydration. The analysis of the daily requirement for fluid of the animals upon rehydration, the changes in their body mass and volume of urination, it has been shown that ionized liquid with a negative ORP does not cause the accumulation of extracellular fluid and faster restores urine output (table 1).

Table 1

The influence of the ionized fluid with various ORP on the dynamics of changes in body weight and urine output of rats with rehydration therapy (M±m, n=10)

The date of measurement	The weight of animals, g		The volume of urine. ml	
	ionized liquid with a negative redox potential	K	ionized liquid with a negative redox potential	K
before the dehydration	203.9±8.1	203.9±8.1	16.0	16.0
10 days after the dehydration	136.7±10.1*	136.7±10.1*	0.8 *	0.8 *
1st day of rehydration	145.6±12.1 *#	164.1±12.7 *	6.0*#	3.7 *#
2nd day of rehydration	168.0±15.7 *#	180.5±17.9 #	8.0 *#	5.6 *#
3rd day of rehydration	173.1±15.8 *#	183.5±18.8 #	10.3 *#	7.8 *#
4th day of rehydration	176.7±15.8 *#	185.4±18.7 #	12.1 *#	8.6 *#
5th day of rehydration	179.6±16.1 *#	186.5±19 #	13.4 *#	9.0 *#
6th day of rehydration	191.0±17.6 #	197.3±19.4 #	14.8 #	10.3 *#
7th day of rehydration	190.5±17.4 #	205.8±20.7 #	15.1 #	10.8 *#
8th day of rehydration	196.6±18.4 #	202.8±19.8 #	15.8 #	11.3 *#
9th day of rehydration	199.1±18.4 #	207.7±20.7 #	15.1 #	12.0 *#
10th day of rehydration	204.1±17 #	211.6±20.1 #	15.9 #	13.6 *#

* – compared to the original value (before dehydration), ($p<0.05$)
\# – compared to the dehydrated ($p<0.05$)

The study of behavioral reactions of animals with the introduction of ionised fluids with various ORP on the background of experimental acute of alcohol poisoning by the test "an open field" was revealed the reduction of the effects of alcohol intoxication and improvement of the central nervous system.

It was installed a more pronounced effect of the liquid ionized liquid with a negative redox potential on the vertical motor activity and a significant increase in the level of emotional, horizontal locomotor activity and research activities with the introduction of the liquid, ionized fluid with a positive redox potential. Morphological analysis of the liver of animals treated with infusion fluids with different ORP showed a decrease of the damaging effects of ethanol (figure 2). In addition, we revealed the hepatoprotective action of ionized liquid with a negative ORP.

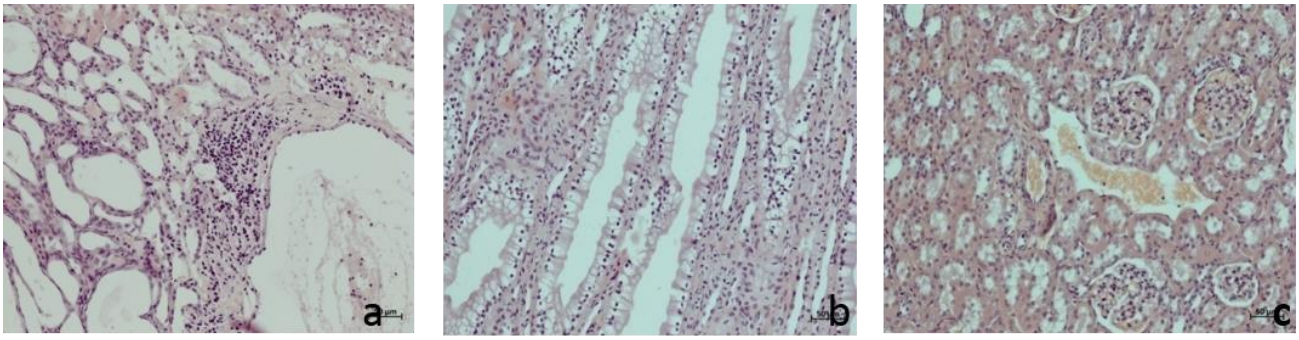

Fig. 2. The influence of ionized liquids on the morphological picture of liver of rats. The control group (**a**), a group of ionized liquid with a negative redox potential (**b**) and ionized fluid with a positive redox potential (**c**) on the 7th day after the acute alcohol poisoning. Colouring with hematoxylin-eosin, x100

The intravenous administration of fluid with a negative ORP to animals with experimental anaphylactic shock, a deterioration of all indicators and the percentage increase in animals mortality (table 2). The introduction of liquids with a positive ORP has the similar effects to those caused by the introduction of isotonic solution of sodium chloride. Therefore, ionized liquid with a negative redox potentialmay be used as the basis of infusion solutions in the treatment of anaphylactic shock. Analysis of morphological changes in tissues of brain, heart, kidneys and liver revealed that the introduction of fluid IIP has the least damaging effect.

Table 2

The effect of the liquid on the Distribution of animals in each study group according to severity of anaphylaxis and mortality (%).

Group	The degree of anaphylaxis. scores					Mortality	
	0	1	2	3	4	1st day	7th day
Control, %	12.5	37.5	0	12.5	37.5	25	12.5
Ionized fluid with a positive redox potential, %	12.5	25	25	12.5	25	25	0
Ionized liquid with a negative redox potential, %	0	33.3	11.1	11.1	44.4	44.4	0
Prednisolone, %	37.5	50	12.5	0	0	0	0

In a comprehensive assessment of the cardiovascular, respiratory system and of body temperature in animals with experimental staphylococcal sepsis, revealed a slower development of pathology when administered intravenously ionized liquids with a positive ORP. Intravenous application of a liquid with a negative ORP causes the deterioration of all indicators in comparison with the control group. The bacterial inoculation of the blood of animals revealed that the liquid IA active against saprophytes, but is not active against St. aureus. Ionized fluid with a positive redox potentialhas a bactericidal action against St. aureus (table 3).

Table 3

The impact of fluids of various ORP on the percentage of bacteria in the blood (n=20)

Groups	Bacteria that gave rise			
	St. aureus	Enterobacteria (E. coli ect.)	Saprophytes (large cocci)	Saprophytes (large sticks)
Control	100%	25%	25%	25%
Ionized liquid with a negative redox potential	75%	25%	-	-
Ionized fluid with a positive redox potential	-	50%	-	-

Morphological analysis of the liver and kidneys in laboratory animals with experimental staphylococcal sepsis showed that liquid with a positive ORP has a maximum of efficiency upon the intravenous administration of fluids with different redox potential within 5 days (Figures 3, 4).

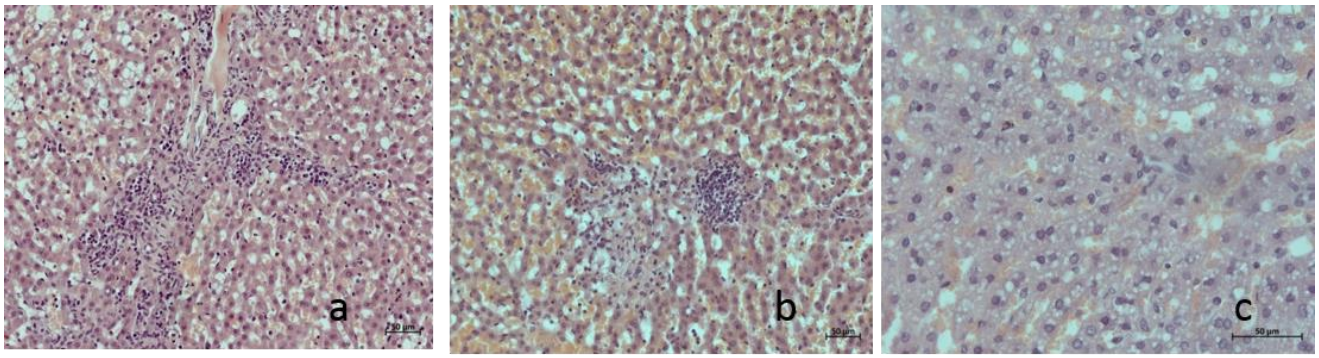

Fig. 3. The impact of liquids with different ORP on the condition of the tissues of the kidneys of rabbits upon the intravenous administration. **a** – control group (0.9% sodium chloride solution), **b** – liquid, ionized liquid with a negative redox potential and **c –** ionized fluid with a positive redox potential in terms of staphylococcal sepsis. Colouring with hematoxylin-eosin, x100

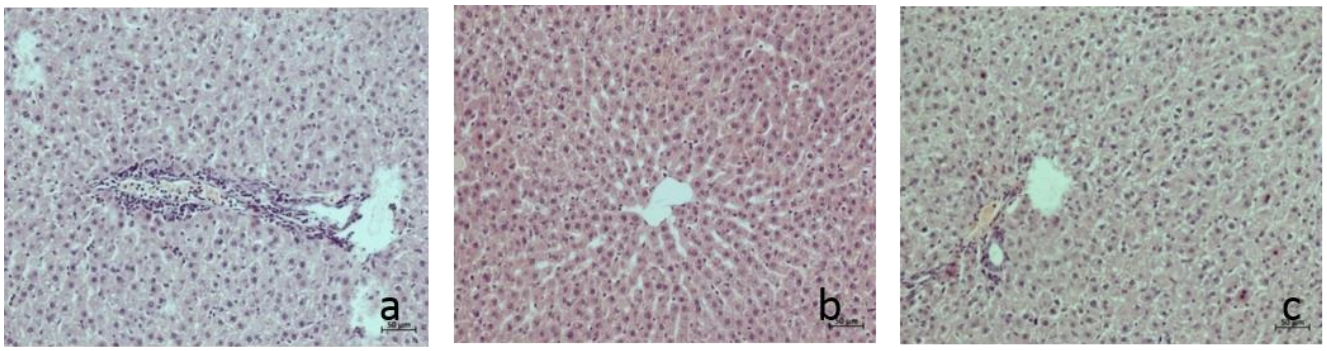

Fig. 4. The impact of liquids with different ORP on the condition of the liver tissue of rabbits being injected intravenously. **a** – control group (0.9% sodium chloride solution), **b** – liquid, ionized liquid with a negative redox potential and **c –** ionized fluid with a positive redox potential in terms of staphylococcal sepsis. Colouring with hematoxylin-eosin, x100

Conclusion.

As a result of pharmacological studies in ionized liquids with negative redox potential, identified antioxidant, rehydration, regenerating, immune, normovolemicescoy, cardioprotective, hepatoprotective and stimulating action, manifested externally and intravenously injected into the body with pathological indicators of the level of glucose in

the blood; when administered intravenously in the maximum allowable volume; when applied topically applied to the surgical wounds; when administered orally in a model of severe dehydration; intravenous use in the model of acute alcohol poisoning.

The ionized fluid with a positive redox potential was revealed the local anesthetic, antimicrobial, anti-inflammatory, antitoxic, anti-anxiety, anti-allergic and antibacterial action, which is manifested when applied topically in the treatment of surgical wounds and intravenous application in models of acute alcohol poisoning, anaphylactic shock and bacterial sepsis.

Conflicts of Interest: The authors have no conflict of interest to declare.

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