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About author

Selitsky Stas, postgraduate student at the School of Computer Science and Technology;
e-mail: selitsky@yahoo.com; ORCID: 0000-0003-1758-0171

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CORRECTION OF ISCHEMIC REPERFUSION LIVER DAMAGE IN THE EXPERIMENT WITH THE USE OF ANTIOXIDANT DRUGS

Popov K. A., Bykov I. M., Tsymbalyuk I. Yu., M. I. Bykov

Kuban State Medical University, Krasnodar, Russian Federation

КОРРЕКЦИЯ ИШЕМИЧЕСКИ-РЕПЕРФУЗИОННОГО ПОРАЖЕНИЯ ПЕЧЕНИ В ЭКСПЕРИМЕНТЕ С ИСПОЛЬЗОВАНИЕМ АНТИОКСИДАНТНЫХ СРЕДСТВ

К. А. Попов, И. М. Быков, И. Ю. Цымбалюк, М. И. Быков

Кубанский государственный медицинский университет, Краснодар, Российская Федерация

The article assesses the effectiveness of correction of ischemic reperfusion damage to the liver of rats in an experiment. The study was conducted in 2 groups: the 1st group (n=15) of rats, which were intraperitoneally injected with 2 ml of physiological solution one day before the modeling of the pathological process and immediately before it; 2nd group (n=15) of rats were administered 2 ml of Remaxol and ascorbic acid 20 mg/ml with lipoic acid 3 mg/ml according to a similar scheme. Partial ischemia was simulated for 40 minutes, followed by a 3-hour reperfusion period. Lower markers of cytolic syndrome in rat blood plasma, higher antioxidant activity of blood plasma, and adequate prooxidant-antioxidant balance

in liver tissues accompanied antioxidant correction. In rats of the 1st group, the decrease in the level of glutathione in the postischemic tissue relative to the intact tissue was 44 %, and in rats of the 2nd group, it was 18 %. In the 2nd group, the intact parenchyma of the liver showed a lower concentration of glutathione but higher in the damaged lobes than in the 1st group rats. The study's results show the critical role of intact parenchyma of the liver without vascular exception in compensating for reperfusion changes in post-ischemic tissue. There are also opportunities to improve approaches to the correction of liver damage through combined antioxidant drugs or regimes of administration.

Keywords: ischemia, reperfusion, ischemia-reperfusion syndrome, antioxidants, oxidative stress, energotropic agents

В работе представлена оценка эффективности коррекции ишемически-реперфузионного повреждения печени крыс в эксперименте. Исследование проводилось в 2 группах: 1-я группа (n=15) крыс, которым за 1 сутки до моделирования патологического процесса и непосредственно перед ним внутрибрюшинно вводили по 2 мл физиологического раствора; крысам 2-й группы (n=15) по аналогичной схеме вводили по 2 мл ремаксола и аскорбиновую кислоту 20 мг/мл с липоевой кислотой 3 мг/мл. Моделировали частичную ишемию в течение 40 минут с последующим 3-часовым реперфузионным периодом. Антиоксидантная коррекция сопровождалась более низкими значениями маркеров цитолитического синдрома в плазме крови крыс, более высокой антиоксидантной активностью плазмы крови и сохранением адекватного прооксидантно-антиоксидантного баланса в ткани печени. У крыс 1-й группы снижение уровня глутатиона в постишемической ткани относительно интактной составляло 44 %, а у крыс 2-й группы – 18 %. Во 2-й группе наблюдалась более низкая концентрация глутатиона в интактной паренхиме печени, но более высокая в поврежденных долях, чем у крыс 1-й группы. Результаты исследования свидетельствуют о значимой роли интактной безваскулярной эксклюзии паренхимы печени в компенсации реперфузионных изменений в постишемической ткани, а также о перспективе совершенствования подходов к коррекции повреждений печени на основе использования комбинированных антиоксидантных препаратов или новых схем их введения.

Ключевые слова: ишемия, реперфузия, ишемически-реперфузионный синдром, антиоксиданты, окислительный стресс, энерготропные средства

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ABTS – 2,2′-azino-bis-(3-ethylbenzthiozolin-6-sulfonic acid)
ALT – alanine aminotransferase
AST – aspartate aminotransferase
FRAP – ferric reducing antioxidant power
LDH – lactate dehydrogenase
TAOA – total antioxidant activity
TBN – thiobarbituric number

Ischemic reperfusion syndrome is observed in a wide range of pathological processes and diseases accompanied by blood circulation disorders at the local or systemic level. The primary pathobiochemical mechanism of cell damage during ischemia and reperfusion is oxidative stress. The intensification of free radical processes begins even in the phase of the vascular elimination of the organ against the background of low oxygen stress in the tissue, hyperreduction of components of the electronic transport chain, and inhibition of aerobic breathing. A sharp increase in oxidative stress is observed during the transition to the seemingly salvific phase of reperfusion; However, the influx of large amounts of oxygen into the postischemic tissue is accompanied by an avalanche-like expansion of the formation of active oxygen forms and additional tissue damage [1, 2]. Traditionally, one of the most effective ways to prevent ischemic reperfusion damage is ischemic preconditioning, which is to perform multiple (usually two or three) episodes of short-term shutdown/activation of the blood flow in an organ that will be exposed to a longer-term harmful factor or other organ (remote conditioning) [3]. Imitation of the effects of ischemic preconditioning using chemical agents that act on individual pathogenetic links is called pharmacological preconditioning. It is well known that antioxidants (acetylcysteine, glutathione, ascorbic acid, α-tocopherol, β-carotene, zinc, selenium, etc.) can be used as pharmacological agents [4–6]. Remaxol refers to antioxidants of indirect action, which, also due to methionine, are hepatoprotective agents that can effectively reduce the level of hepatocyte cytolysis in chronic toxic and viral liver damage [7]. The effectiveness of Remaxol in preventing or correcting acute ischemic reperfusion liver damage is not high enough, which updates the search for more active agents or ways to increase Remaxol activity.

The study aimed to evaluate the combination of Remaxol and direct-action antioxidants to correct ischemic reperfusion liver damage in rats.

Material and Methods. To perform an experimental study, two groups of laboratory animals were formed, represented by white non-linear male rats weighing 220 to 250 grams each. The 1st (comparison) group was represented by 15 animals, which were intraperitoneal injected with 2 ml of saline one day before the modeling of the pathological process and immediately before the start. Rats of the 2nd (main) group (n=15) were administered twice in a similar manner with 2 ml of Remaxol (Polisan, Russia) with 20 mg/ml of ascorbic acid and 3 mg/ml of lipoic acid. The simulation of the pathological process, namely the ischemic reperfusion damage to the liver, consisted in performing a vascular exception by applying a clamp on the vascular leg that nourishes the left lateral and central lobe of the rat liver for 40 minutes. The

clamp is removed, and the reperfusion period is expected within 180 minutes. Thus, the partial vascular isolation of the liver is modeled. After the liver reperfusion of the rat was completed, blood was taken from the caudal floor into vials with sodium heparin, and the liver was accepted to study organ homogeneity. At the same time, liver lobes were taken separately, namely those subjected to modeling of ischemic damage and the intact ones. All manipulations were performed under general anesthesia with the Zoletil 100 (Virbac, France).

The laboratory stage of the experiment included the determination of such markers of the severity of the cytolytic syndrome as the activity of aminotransferases (ALT and AST) and LDH in the blood plasma of animals. The concentration of lactic acid (lactate) was also determined in blood plasma and liver tissue. Reagents manufactured by Randox (UK) and Super Z (China) automatic biochemical analyzer were used to determine the values mentioned above. Antioxidants to correct hepatic ischemic reperfusion require evaluation of oxidative homeostasis or antioxidant markers. For this purpose, the total antioxidant activity in blood plasma and liver homogenate by ferric reduction (FRAP), the radical sorption ability of ABTS+*, TBA reactive products, the content of which was expressed by a thiobarbituric number, reduced glutathione concentration, and total thiol groups (SH-) [8, 9].

Statistical analysis of the study results was carried out using the Stat Plus program (AnalystSoft Inc., USA). Taking into account the small size of the samples, the comparison of the indicators of the two groups of animals was carried out by calculating the nonparametric Mann – Whitney test. The differences between the groups were considered statistically significant by the level $p<0.05$.

Results and Discussion. Determination of the activity of aminotransferases and LDH in the blood plasma of laboratory animals demonstrated a relatively high protective efficacy of the proposed combination of Remaxol with ascorbic and lipoic acid (Table 1). The activity of ALT and AST in the blood plasma of rats of the main group was 2.5–3.0 times lower than in the blood of animals of the comparison group. The activity of LDH in the blood plasma of the 2nd group was also lower than that of the rats of the 1st group by 37 %. Assessment of changes in oxidative homeostasis in the blood confirmed the antioxidant activity of metabolic drugs used to correct ischemic reperfusion syndrome (Table 1). So, against the introduction of Remaxol with vitamin C and lipoic acid, a higher ferric-reducing activity of blood plasma was observed, exceeding the indicator of the comparison group by 32 %. The level of thiol groups in the blood plasma of animals of the 2nd group under similar conditions was 29 % higher than the value of the corresponding indicator of the 1st group. At the same time, the concentration of glutathione in erythrocyte suspension and the activity of radical plasma sorption in the blood did not reveal statistically significant differences in the core and comparative rats. The thiobarbituric number that characterizes lipid peroxidation product accumulation was significantly lower against the background of experimental correction of ischemic reperfusion liver damage. This indicator was 31 % lower in the erythrocyte suspension of rats of the 2nd group compared to the indicator of the 1stgroup.

The assessment of biochemical changes in the hepatic homogenate was based on relatively simple but informative methods, including determining the values in the modified organ parenchyma, twitching the vascular insulation for 40 minutes, and relatively intact parenchyma in the liver lobes. The blood supply was intact during the experiment. The analysis was therefore presented by comparing between groups and damaged and intact blades of rats of the same group (Table 2). The determination of the lactic acid concentration in the liver showed no differences both within the group and between groups. The absence of intergroup differences correlates well with ideas about the mechanism of Remaxol, ascorbic acid, and lipoic acid. Introducing these metabolic agents cannot affect the oxygenation of the ischemic tissue and the activity of anaerobic energy processes, which is reflected in an equally high lactate level. The absence of differences in the metabolite concentration in some regions of the parenchyma of the liver indicates a rapid redistribution in the body when blood flow is restored. In addition, the liver is the main «consumer» of lactate after ischemia, especially its intact part under the conditions of our experiment. A comparison of the concentration of intracellular regulator of redox homeostasis (tripeptide glutathione) showed differences in contrast to the lactate level, which can quickly diffuse outside the cell. Thus, a lower concentration of the reduced form of glutathione in the homogenate from the damaged liver lobes of rats of both groups was determined, corresponding to the concept of the development of oxidative stress during ischemic-reperfusion. At the same time, in rats of the 1st group, the decrease in the level of glutathione in the postischemic tissue compared with the intact tissue was 44 %, and in rats of the 2nd group – 18 %. It should also be noted that in animals of the 2nd group, a lower concentration of glutathione was observed in the intact liver parenchyma. Still, it was higher in the damaged lobes in comparison with similar parameters in rats of the 1st group.

Table 1

Changes in the biochemical parameters of blood in rats against the background of antioxidant correction of ischemic-reperfusion liver damage (Me (Q1/Q3))

Study parameters	Study groups	
	Group 1 (comparison)	Group 2 (experimental)
ALT, U/l	608 (554/675)	204 (158/238)*
AST, U/l	573 (540/621)	232 (189/255)*
LDH, U/l	824 (764/876)	523 (485/585)*
TAOA (FRAP), mM vit C	0.19 (0.16/0.21)	0.25 (0.23/0.28)*
TAOA (ABTS), mM vit C	0.32 (0.29/0.34)	0.34 (0.31/0.36)
Glutathione, μmol/ml	1.82 (1.68/1.94)	1.87 (1.73/2.01)
SH-groups, u.g.d.*100/g protein	0.14 (0.12/0.15)	0.18 (0.16/0.20)*
TBN, CU	1.56 (1.38/1.70)	1.08 (0.92/1.18)*

* Statistically significant differences between the indicators of the control and main groups ($p<0.05$).

It can be assumed that in the metabolic correction of ischemic reperfusion syndrome, intact liver lobes are more actively involved in compensating for damage to the postischemic parenchyma, which allows for mitigating the effects of the pathological process. The development of the reperfusion phase is accompanied by active leaching of products of altered metabolism, necrosis, and apoptosis of damaged liver cells, which contribute to the spread of the pathological process at the level of

the body. The development of multiple complications of organs after vascular exclusion of the liver is described. The main blow falls on the intact parenchyma of the liver, which has not undergone ischemia. Still, after restoring blood flow, it should ensure the neutralization of all toxins released into the systemic circulation. However, the high adaptive potential of the liver usually makes it possible to perform this task successfully. No morphological changes were previously found in the structure of the right hepatic lobe, which was not ischemically affected. The study was conducted on a 45-minute partial (70 %) hepatic ischemia model of the left side of the rabbit liver. Histological picture in such tissue corresponds to the liver of fraudulent rabbits with imitation of ischemic reperfusion [10]. However, this article provides laboratory evidence of the functional involvement of non-ischemic liver tissue in the recovery of the hepatic ischemic region during the reperfusion period. The approach, which includes the analysis of individual sections of the parenchyma of one organ, is quite simple and logical but not very common in experimental work [11].

Table 2

Changes in biochemical parameters in the liver of rats against the background of antioxidant correction of ischemic-reperfusion liver damage (Me (Q1/Q3))

Study parameters	Lobe of the liver	Study groups	
		Group 1 (comparison)	Group 2 (experimental)
Lactate, μmol/mg of protein	intact	2.8 (2.5/3.3)	3.5 (2.9/3.8)
	damaged	2.5 (2.3/3.0)	3.1 (2.8/3.5)
Glutathione, nmol/mg of protein	intact	5.9 (5.3/6.4)	4.9 (4.5/5.5)*
	damaged	3.3 (2.9/3.5)^	4.0 (3.6/4.6)*^
TBN, CU/mg of protein	intact	3.1 (2.6/3.3)	2.9 (2.6/3.2)
	damaged	3.8 (3.4/4.4)^	3.1 (2.8/3.5)*
TAOA (FRAP), mM vit C/mg of protein	intact	0.56 (0.52/0.63)	0.65 (0.60/0.72)
	damaged	0.60 (0.55/0.64)	0.63 (0.58/0.69)
TAOA (ABTS), mM vit C/mg of protein	intact	1.34 (1.19/1.52)	1.34 (1.22/1.48)
	damaged	0.63 (0.57/0.72)^	0.88 (0.83/1.02)*^

Note: * – statistically significant differences between the indicators of the control and main groups ($p<0.05$); ^ – statistically significant differences between the indicators determined in different lobes of the liver ($p<0.05$).

According to the determination of the thiobarbituric number after ischemic reperfusion in the tissue of the damaged parenchyma of the liver in rats of the 1st group, an increase in the content of lipid peroxidation products by 23 % was observed relative to the area of the parenchyma that was not subjected to vascular isolation (Table 2). In laboratory animals of the 2nd group, the level of TBN-reactive products in different lobes of the liver did not statistically significantly differ from each other and was within the values of the corresponding parameter of the intact parenchyma of rats of the 1st group. Changes in the level of ferric-reducing ability of liver homogenates from different lobes and different groups were not revealed; however, statistically significant differences were recorded when studying the level of sorption ability of the ABTS radical. This indicator in the homogenate of the postischemic liver tissue of rats in both groups was reduced relative to the values of the corresponding indicators obtained in the intact lobes of the organ. For animals of the 1st group, the decrease in the level of radical sorption was 53 %, and for animals of the 2nd group – 34 %. Thus, in blood plasma, a reduction in antioxidant activity was noted, determined by the ferric reducing method; in the liver, it was decided by evaluating radical sorption. In most cases, both analysis methods demonstrated similar results that correlate well with each other [12, 13]. Typically, ABTS neutralization analysis is more sensitive to relatively weak antioxidants due to the relative ease of interaction with radicals, which do not require high regenerative activity. The results of the determination of antioxidant activity are usually well correlated in studying one type of biofluid due to the contribution of a chemical compound [14]. The comparison of blood plasma and liver homogenate, which have a fundamentally different composition of antioxidants, shows contradictory results. Still, we think that this suggests the need for a differentiated approach to the analysis of a certain biofluid.

Conclusion. The data obtained showed high efficiency of antioxidant correction of ischemic reperfusion damage to the liver after partial vascular excision. As an antioxidant therapy, Remoxel was administered along with ascorbic and lipoic acid, which was accompanied by lower markers of cytolytic syndrome in rat blood plasma, higher antioxidant activity of blood plasma, and maintaining adequate prooxidant-balance of antioxidants in the liver. The study's results show the critical role of intact liver parenchyma, not exposed to vascular isolation, in compensating reperfusion changes in post-traumatic tissue. Possible measures to prevent or remedy damage caused by partial vascular isolation of the organ may aim at preserving the intact part of the organ. In contrast, local metabolism estimates in some parts of parenchyma can be used to increase the informational content of laboratory studies of ischemic reperfusion syndrome. A promising area for improving approaches to liver damage is also the use of combined antioxidant drugs or administration schemes, in particular, Remaxol with ascorbic and lipic acids.

Informed consent: The experimental study was conducted in full compliance with the Requirements of Proper Laboratory Practice (set out in the National Standard «Principles of Good Laboratory Practice» GOST R 53434–2009), in compliance with the International Principles of the European Convention for the Protection of Vertebrate Animals Used for Experiments and Other Scientific Purposes (Strasbourg, 1986), following International Recommendations for Conducting Biomedical Research Using Animals (1985), «General Ethical Principles of Animal Experiments» (Russia, 2011), rules of laboratory practice set out in the Russian Federation (Order of the Ministry of Health Care of Russia № 267 dated June 19th, 2003) and the positive conclusion of the Independent Ethics Committee at the Kuban State Medical University of the Ministry of Health Care of Russia at a meeting on January 29th, 2021, protocol № 96.

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About authors:

Popov Konstantin Andreevich, PhD, Associate Professor of the Department of Fundamental and Clinical Biochemistry;
tel.: 89288824941; e-mail: naftalin444@mail.ru

Bykov Ilia Mikhaylovich, MD, PhD, Professor, Head of Department of Fundamental and Clinical Biochemistry;
tel.: 89182125530; e-mail: ilya.bh@mail.ru

Tsymbalyuk Igor Yuryevich, Laboratory assistant of Department of Surgery № 2;
tel.: 89284300769; e-mail: igor_ts@inbox.ru

Bykov Mikhail Ilyitch, MD, PhD, Professor, Professor of the Department of Surgery № 1;
tel.: 89183596296; e-mail: bikov_mi@mail.ru