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COMBINED HEPATOPROTECTIVE THERAPY FOR EXPERIMENTAL ALCOHOLIC LIVER DAMAGE

G. A. Ermakova, K. A. Popov, I. M. Bykov, I. Yu. Tsymbalyuk, A. G. Zavgorodnyaya, M. I. Bykov, A. S. Shevchenko

Kuban State Medical University, Krasnodar, Russian Federation

КОМБИНИРОВАННАЯ ГЕПАТОПРОТЕКТОРНАЯ ТЕРАПИЯ АЛКОГОЛЬНОГО ПОРАЖЕНИЯ ПЕЧЕНИ В ЭКСПЕРИМЕНТЕ

Г. А. Ермакова, К. А. Попов, И. М. Быков, И. Ю. Цымбалюк, А. Г. Завгородняя, М. И. Быков, А. С. Шевченко

Кубанский государственный медицинский университет, Краснодар, Российская Федерация

This paper offers a view at an experimental assessment of the effectiveness of combined hepatoprotective therapy employed for alcoholic liver damage treatment using sulfur-containing drugs. The study involved five groups of rats: Group 1 – intact rats; Group 2 – animals subjected to alcoholism for two months, with no correction carried out; Groups 3, 4 and 5 were rats that were given ademetionine (10 mg/100 g/day), lipoic acid (10 mg/100 g/day) and combined, respectively.

The studies showed that the AST and LDH activity in the animals' blood plasma in Group 5 was 16 % and 42 % below similar indicators of Group 2 only, yet also statistically reliably lower than the values of similar indicators in the animals in Groups 3 and 4. Combined use of ademetionine and lipoic acid came along with relatively low values of the total antioxidant activity, which was 32–40 % below that in control. Yet, it allowed the weakest levels of product accumulation to be arrived at through oxidative modifications of biomolecules.

The level of thiobarbituric acid reactive substances (TBA-reactive substances) measured in the blood of rats in Group 5 was 46 % lower than the corresponding marker value in Group 2 and 36–40 % lower than the values of similar indicators measured in the animals belonging to Group 3 and 4. The obtained data proved a higher efficiency of combined hepatoprotective therapy involving ademetionine and lipoic acid than monotherapy using respective drugs.

Keywords: ethanol, alcoholic hepatitis, antioxidants, hepatoprotectors, lipoic acid, ademetionine

Изучена эффективность комбинированной гепатопротекторной терапии алкогольного повреждения печени с использованием серосодержащих препаратов в эксперименте. Исследование было проведено на 5 группах крыс: 1 группа – интактные крысы; 2 группа – животные на фоне алкоголизации в течение 2 месяцев без коррекции; крысы в 3, 4 и 5 группах в условии алкоголизации получали адеметионин (10 мг/100 г/сутки), липоевую кислоту (10 мг/100 г/сутки) и комбинированную терапию соответственно.

Установлено, что активность АСТ и ЛДГ в плазме крови животных 5-й группы была на 16 % и 42 % ниже не только значений показателей 2-й группы, но также статистически значимо ниже значений аналогичных показателей крыс 3–4-й групп. Комбинированное использование адеметионина и липоевой кислоты сопровождалось сравнительно низкими значениями общей антиоксидантной активности, которая была ниже контроля на 32–40 %, однако позволяло добиться наиболее низкого уровня накопления продуктов окислительных модификаций биомолекул. Так, уровень ТБК-реактивных продуктов в крови крыс 5-й группы был на 46 % ниже значения соответствующего маркера крыс 2-й группы, а также на 36–40 % ниже значений аналогичных показателей животных 3-й и 4-й групп.

Таким образом, полученные данные показали более высокую эффективность комбинированной гепатопротекторной терапии с использованием адеметионина и липоевой кислоты в сравнении с монотерапией соответствующими препаратами.

Ключевые слова: этанол, алкогольный гепатит, антиоксиданты, гепатопротекторы, липоевая кислота, адеметионин

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ABTS – 2,2′-azino-bis-(3-ethylbenzthiosoline-6-sulfonic acid)
ALT – alanine aminotransferase
AST – aspartate aminotransferase
FRAP – ferric-reducing ability of plasma
LDH – lactate dehydrogenase
TAOA – total antioxidant activity
TBA – thiobarbituric acid

Alcohol abuse is a global issue that remains one of the most urgent medical & social problems faced by healthcare due to a high mortality rate affecting the capable population. As the Russian Statistics Agency reports in its Healthcare in Russia – 2023 accounts (published late December), the past decade witnessed an unprecedented fact – a growth in the number of cases where the alcohol dependence diagnosis was set. Reports are claiming that the number of patients with severe dependence (alcoholic psychosis) has gone up sharply in recent years [1]. Excessive alcohol consumption results in systemic intoxication and triggers a whole set of changes affecting nearly all of the body organs. At the same time, the liver is specifically susceptible, with acetaldehyde and acetic acid formed through alcohol dehydrogenase and the microsomal ethanol oxidizing system [2]. Given this, the functional status of the said organ has a significant role in the pathogenesis of acute and chronic alcoholism manifestations. 40 % to 80 % of all liver cirrhosis cases develop due to nothing else but damage caused by alcohol. In the pool of patients suffering from liver pathology, the lethality rate of liver cirrhosis originating from alcohol damage goes up as high as 44 % [3]. Research data proves that mechanisms like Kupfer cell activation, formation of free radicals and fungal and bacterial microbiome change significantly enhance ethanol's damaging effect on the liver. Liver damage progress results from lipids accumulating in its cells [4].

Many hepatoprotections have been proposed to prevent and treat liver damage. In contrast, the effectiveness of such protectors is often associated with the capacity to neutralize reactive oxygen species and stimulate the body's immune response under stress. One of the hepatoprotective agents proposed is lipoic acid, which features severe antioxidant properties due to 2 thiol groups and can get involved in the homeostasis redox regulation and the regulation of lipids and carbohydrates oxidation [5, 6].

Experimental and clinical studies suggest the potential use of lipoic acid in the treatment of fatty liver disease of non-alcoholic origin, as well as in the comprehensive detoxification scheme for alcohol intoxication [7]. There is evidence available that points to a positive effect that lipoic acid can work on the antioxidant activity of blood plasma in chronic alcohol intoxication.

However, the thioctic acid preparation had no significant effect on hepatocyte cytolysis, even under the same experimental conditions. Within the experiment, ademetionine, if compared with lipoic acid, revealed a more obvious hepatoprotective effect, yet a less pronounced antioxidant one.

Studies carried out in clinical settings and aimed at identifying the specific features of the effect that hepatoprotective agents with different mechanisms of action (remaxol, ademetionine, ursodeoxycholic acid) deliver to hepatocyte cytolysis and oxidative homeostasis in patients with alcoholic hepatitis, revealed no predominant effect of any of the hepatoprotective [8, 9]. This means that the experimental data concerning the effectiveness of S-containing drugs used in a comprehensive complex treatment mode to treat chronic alcohol intoxication are ambiguous. In contrast, data obtained through randomized clinical trials tend to offer even less reliable results.

There is particular interest to be taken in further assessment of the effect that hepatoprotective drugs have on pathobiochemical changes and in analyzing the potential link between the antioxidant effect and the cytoprotective action effectiveness. From this stance, a promising area would be the search for effective combined treatment modes employing hepatoprotective agents with different action mechanisms.

This study aimed to experimentally evaluate the effectiveness of combined hepatoprotective therapy for alcoholic liver damage while using sulfur-containing drugs.

Material and Methods. The study included five groups of 15 white non-linear male rats weighing 220–250 grams each. Group 1 animals (control) were kept in conditions similar to the other groups, yet without alcoholization and administration of drugs. Group 2 rats were given alcohol for two months instead of the standard drinking diet with no medications or biologically active additives.

Chronic alcohol intoxication was modeled for two months following the following scheme: Week 1 – the rats received 10 % ethyl alcohol; Week 2–20 % ethyl alcohol, and starting from Week 3 until the end of the experiment, the animals were given 30 % ethyl alcohol. Alcohol, in this case, ultimately replaced conventional water consumption [10]. The animals in Groups 3–5 were the main experimental groups, which, following a month of alcoholization, received the respective drugs injected in parallel with further use of ethyl alcohol. Group 3 rats were administered orally S-adenosyl methionine (10 mg/100 g/day).

Animals of Group 4 were orally given lipoic acid (10 mg/100 g/day). Group 5 rats received a combined type of correction using S-adenosyl methionine (100 mg/100 g/day) and lipoic acid (10 mg/100 g/day) simultaneously. The experiment involving laboratory animals was carried out strictly subject to the provisions of the European Convention for the Protection of Vertebrate Animals (Strasbourg, 1986) at the Kuban State Medical University and had received prior approval from the Independent Ethical Committee (protocol of meeting #111, 14/09/2022).

Two months later, the animals (with all the requirements for anesthesia observed; anesthesia with Tyrosol and Zolazepam) were removed from the experiment, with their blood and liver taken for laboratory studies. To describe the biochemical specifics of the cytolytic syndrome development in the blood plasma, measures were taken for the activity of aminotransferases (ALT and AST), the LDH activity, the concentration of total protein, and albumin and urea. The laboratory tests were done using an automatic biochemical analyzer and commercial reagent kits (Randox, UK).

The status of the prooxidant-antioxidant system was assessed according to a change in antioxidant activity, which, in turn, was identified by the ferric reducing FRAP method [11] employing the 2.2-dipyridyl (DIP) photometric reagent by adding it in equal amounts to a mixture of trivalent iron with an acetate buffer (pH=3.6). The resulting solution was expanded with the biological liquid further (after 30 minutes) to register the optical density at length waves of 520 nm.

Another value identified was the content of total thiol groups, which relied on using the Ellman reagent (dithiobisnitrobenzoic acid) in a phosphate buffer solution (pH=7.4). The analysis of ABTS radical absorption (2.2'-azino-bis-(3-ethylbenzthiosoline-6-sulfonic acid)) was carried out by the Re et al. method (1999) [12]. The content identification of the TBA-reactive substances (TBA-rs) rested on the technique [13], following which, after hour-long incubation of the erythrocyte suspension in saline solution, 20 % trichloroacetic acid and a TBA solution were added. Further on, after heating in a boiling water bath and centrifugation, measures were taken for the optical density of the filler liquid at wavelengths of 450 nm and 532 nm.

The obtained data was statistically processed with the StatPlus (AnalystSoft Inc., Walnut, USA). Given the small sample, the indicators for the animal groups were compared by calculating the nonparametric Kraskel – Wallis criterion, followed by a pairwise comparison employing the Mann – Whitney criterion. The differences among the groups were considered statistically significant at $p<0.05$.

Results and Discussion. The assessment of toxic liver damage against the backdrop of alcoholization of the animals implied the detection of hepatocyte cytolysis markers – ALT, AST, and LDH (Table 1). As a result, the above laboratory indices exceeded the control values many times after two months of consuming ethyl alcohol.

Table 1

Changes in the rats' blood biochemical values against the backdrop of hepatoprotective therapy for alcoholic liver damage (Me (Q1/Q3))

Groups	Indicators		
	ALT, u/l	*AST, u/l*	*LDH, u/l*
Group 1 (control)	23.3 (20.5/26.0)	44.5 (39.9/49.2)	114.0 (96.7/140.7)
Group 2 (comparison)	70.0 (58.9/82.9)*	112.9 (106.7/146.1)*	466.4 (425.0/528.7)*
Group 3 (Ademetionine)	30.3 (30.1/34.7)*^	111.5 (106.7/146.8)*	360.6 (352.6/392.4)*^
Group 4 (LA)	40.0 (38.9/41.4)*^	123.8 (115.0/135.0)*	393.2 (368.4/427.4)*
Group 5 (comb)	36.3 (33.3/36.7)*^	95.2 (92.4/111.3)*^	271.2 (269.6/390.7)*^

Note: * – statistically significant differences matched against the control group ($p<0.05$); ^ – statistically significant differences matched against the comparison group ($p<0.05$).

The experimental testing of metabolic hepatoprotective therapy involving sulfur-containing compounds, such as S-adenosyl methionine or lipoic acid, does not constitute anything new, so these groups can also be considered for comparison. A promising area in terms of boosting the treatment effectiveness, though, may be the combined use of several hepatoprotectors with different action principles. This described study has shown that combined administration of ademetionine and lipoic acid to rats, which were subjected to 2 months of alcoholism, helped arrive at a statistically significant decrease in the levels of the analyzed markers in blood plasma if matched against the comparison groups.

The ALT activity went down to the level typical for groups of rats undergoing monotherapy, or by 48 % compared to the corresponding value observed in Group 2 animals. The activity of AST and LDH in the blood plasma of Group 5 animals revealed the lowest values among all the experimental groups where the animals had alcoholic liver damage.

The blood plasma AST activity in Groups 3–4 was similar to the respective levels in the comparison group. In contrast, in the case of combined hepatoprotective therapy, the said value was reduced by 16 % compared to that in Group 2. The blood plasma LDH activity in Group 4 featured no statistically significant difference from the similar marker levels in Group 2. However, even though the conditions were the same, in the case of ademetionine administration, LDH levels went down by 23 %. In contrast, combined hepatoprotection came along a 42 % decrease in the levels of the analyzed marker.

All this points to a potential way to enhance the effectiveness of hepatoprotectors by combining several drugs possessing different action mechanisms. Within the described study, we employed ademetionine, which is involved in maintaining the liver's detoxifying function and which – as numerous experimental studies show – is reliably capable of protecting the liver parenchyma against unfavorable effects of various etiopathogenetic factors.

Lipoic acid, too, is often viewed as a potential hepatoprotector, even though data on its effectiveness in experimental and clinical studies have been ambiguous. This vitamin-like compound is undoubtedly able to support the antioxidant system. While that holds, however, the direct antioxidant action per se is usually insufficient to ensure effective cytoprotection in clinical settings, which means a need for designing and explaining more effective modes of metabolic treatment.

Given the leading role played by the hepatoprotectors in the cell oxidative homeostasis regulation, we evaluated the changes in markers of the blood plasma prooxidant-antioxidant balance, thus aiming to conduct a comparative analysis of their action (Table 2). This analysis makes it safe to say that the most pronounced metabolic support associated with an increase in total antioxidant activity was from lipoic acid used as monotherapy. However, this did not result in a significant decrease in the hepatocyte cytolysis levels discussed above. In contrast, the reduction in the TBA-rs levels accounted for no more than 15 % compared to comparison Group 2.

Ademetionine combined with lipoic acid was associated with relatively low total antioxidant activity, 32–40 % below the control. However, such a treatment scheme allowed arriving at the lowest levels of products accumulating due to oxidative modifications of biomolecules. For instance, the blood TBA-rs level in Group 5, for example, was 46 % lower than the value of the corresponding marker in Group 2 rats and 36–40 % lower than the values of similar indicators observed in the groups where the rats were given monotherapy.

Despite the significant antioxidant properties of the sulfur-containing drugs, none of the experimental groups

produced data pointing to a statistically significant growth in the levels of blood plasma thiol groups. In contrast, the overall antioxidant activity, although it showed positive trends against the treatment backdrop, remained much below the control values.

Table 2

Changes in the rats' blood oxidative homeostasis values against the backdrop of hepatoprotective therapy for alcoholic liver damage (Me (Q1/Q3))

Groups	Indicators			
	TBA-rs, rel. units	*SH-groups, opt. dens. un. *100/protein*	*AOA-FRAP, vit. C, mg*	*AOA-ABTS, vit. C, mg*
Group 1 (control)	0.58 (0.50/0.68)	0.36 (0.33/0.40)	0.53 (0.42/0.56)	0.53 (0.44/0.56)
Group 2 (comparison)	1.50* (1.36/1.65)	0.25* (0.21/0.30)	0.23* (0.19/0.28)	0.16* (0.09/0.19)
Group 3 (Ademetionine)	1.34* (1.20/1.62)	0.26* (0.23/0.27)	0.34*^ (0.29/0.35)	0.44*^ (0.35/0.47)
Group 4 (LA)	1.27*^ (0.95/1.41)	0.25* (0.23/0.29)	0.37*^ (0.32/0.42)	0.47 (0.42/0.51)
Group 5 (comb)	0.81*^ (0.69/0.94)	0.25* (0.24/0.31)	0.32*^ (0.28/0.42)	0.36*^ (0.32/0.39)

Note: * – statistically significant differences matched against the control group ($p<0.05$); ^ – statistically significant differences matched against the comparison group ($p<0.05$).

Notable is that despite the obvious antioxidant properties of the used drugs, none of the groups of animals receiving metabolic therapy against the backdrop of chronic alcohol intoxication could feature an increase in the level of blood plasma thiol groups. In contrast, the overall antioxidant activity remained significantly lower than the control indicators.

Despite the different etiological factors of liver damage, the intensified generation of free radicals and proinflammatory mediators is believed to be a common pathogenetic link here. This means compounds with antioxidant and anti-inflammatory properties should act as hepatoprotectors [14]. The best-known and reliably explained recommendations for toxic (acetaminophen, carbon tetrachloride) liver damage using N-acetylcysteine [15, 16].

Ethanol metabolism through alcohol dehydrogenase enzymes and microsomal cytochrome P450 leads to the development of acetaldehyde and reactive oxygen species, as well as reduces the glutathione level [17], so speaking of the analyzed experimental model, the high efficiency of sulfur-containing antioxidants was quite reasonable to expect. However, in this case, lipoic acid, with its most significant antioxidant potential, proved to have the least pronounced protective effect on the liver parenchyma.

Animals of Group 5, where the activity of cytolysis marker enzymes was relatively low, the blood plasma antioxidant activity remained significantly below control, which leaves the relationship between the antioxidant activity of the drug and the hepatoprotective effect open for discussion.

Conclusion. Based on the above, it is safe to say that the obtained data demonstrated the high effectiveness of hepatoprotective therapy relying on Ademetionine and lipoic acid. This effect manifested through a statistically significant decrease in the hepatocyte cytolysis level and improved oxidative homeostasis in the laboratory animals' blood against chronic alcohol intoxication.

In this study, the lowest AST and LDH activity values were detected while using a combination of the mentioned sulfur-containing drugs. However, the effectiveness evaluation for such combined hepatoprotective therapy will require further research. The data analysis carried out herein did not allow for drawing any reliable conclusions regarding the relationship between the antioxidant activity of drugs and the effectiveness of hepatoprotective therapy.

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Informed consent. This experimental study has been carried out in full compliance with the requirements of good laboratory practice (see the national standard of Principles of Good Laboratory Practice GOST R 53434-2009), as well as following the provisions of the European Convention for the Protection of Vertebrate Animals (Strasbourg, 1986), the International Guiding Principles for Biomedical Research Involving Animals (1985), the General Ethical Principles for Experiments with Animals (Russia, 2011), the Russian rules of laboratory practice (Order by the Ministry of Health of the Russian Federation, # 267 of 19/06/2003), and an approval issued by the Independent Ethics Committee of the Kuban State Medical University (meeting held on January 29, 2021, Minutes #96).

Disclosure: The authors herewith declare no conflict of interest.

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About authors:

Ermakova Galina Alekseevna, PhD, Associate Professor of the Department of Psychiatry of the Faculty of the Advanced Training and Retraining of Specialists;
tel.: +79189999195; e-mail: narko12@mail.ru; https://orcid.org/0000-0001-6473-3594

Popov Konstantin Andreevich, PhD, Associate Professor of the Department of Fundamental and Clinical Biochemistry;
tel.: +79288824941; e-mail: naftalin444@mail.ru; https://orcid.org/0000–0002–3649–1361

Bykov Il’ya Mikhaylovich, MD, PhD, Professor, Head of the Department;
tel.: +79182125530; e-mail: ilya.bh@mail.ru; https://orcid.org/0000-0002-1787-0040

Tsymbalyuk Igor’ Yur’evich, PhD, Assistant;
tel.: +79284300769; e-mail: igor_ts@inbox.ru; https://orcid.org/0000-0002-5711-6659

Zavgorodnyaya Anna Germanovna, postgraduate student;
tel.: +79182227525; e-mail: zavgorodnyaya.anna@bk.ru; https://orcid.org/0000-0002-3276-9733

Bykov Mikhail Il’ich, MD, PhD, Professor, Professor of the Department of Surgery № 1 Faculty of Continuing Professional Development and Retraining;
tel.: +79183596296; e-mail: bikov_mi@mail.ru; https://orcid.org/0000-0003-4537-2548

Shevchenko Aleksej Stanislavovich, postgraduate student of the Department of Fundamental and Clinical Biochemistry;
tel.: +79186754202; e-mail: forester5858@gmail.ru; https://orcid.org/0000-0002-2218-4205