Research Article

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The Effect of the Enteral Correction Program on Oxidative Stress Parameters in Patients with Poisoning with Psychopharmacological Agents or Corrosive Substances

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RATIONALE Acute exogenous poisonings represent a serious medical problem due to the prevalence, severity of the course and high lethality. In their pathogenesis, an important place is given to oxidative stress (OS). Among modern methods of treatment of acute poisoning, the attention is drawn to approaches aimed at normalizing homeostatic indicators by cleansing the enteric environment, restoration of its barrier function.

PURPOSE OF THE STUDY Assess the impact of the enteral correction program (ECP) on the parameters of lipid peroxidation (LPO) and antioxidant systems in acute exogenous poisoning.

MATERIAL AND METHODS 119 patients who underwent treatment at the N.V. Sklifosovsky Research Institute for Emergency Medicine, of which 45 were with severe acute poisoning with psychopharmacological agents (PPPA) and 74 with poisoning with corrosive substances (PCS). The two study groups consisted of 40 patients with PCS and 23 patients with PPPA, whose standard therapy was supplemented with ECP. The ECP included making intestinal lavage on admission, the introduction of glucosed saline enteral solution in the following days; and for patients with PCS the treatment also included enteral nutrition and Pectovit. The comparison groups included 56 people (34 with PCS and 22 with PPPA) comparable to the patients of the study groups by sex, age, the type and severity of poisoning poisoning treated with standard therapy

The severity of OS was assessed by the KMDA/TAA index which was calculated by means of measuring the concentration of malonic dialdehyde (as an LPO parameter) and total antioxidant activity in the blood plasma of the patients. Serum levels of nitric oxide stable metabolites were also measured.

The analysis of the results was performed with the regard to patient's age.

RESULTS In patients of working age, regardless of the toxicant type, LPO activation occurred, which was expressed with an increased KMDA/TAA by 1.4–1.8 times compared to the norm. Using ECP at the study stages contributed to maintaining this balance level between pro- and antioxidants. In patients of comparison groups there was an increase in the LPO system imbalance, while KMDA/TAA exceeded the norm by 2.2–2.4 times that was statistically significantly different from the parameters in the study groups.

Older patients showed decreased levels of LPO products, the total antioxidant activity compared to the normal for the age, and, as a result, a decrease in KMDA/TAA by 1.3–1.5 times in PCS and by 2–2.4 times in PPPA. This is due to the low adaptive potential of this category of patients. In this age group, ECP contributed to a moderate activation of LPO, which provided the trend towards normalization of OS parameters.

CONCLUSIONS The use of the enterable correction program has a positive impact on the dynamics of oxidative stress parameters, ensuring the maintenance of oxidative processes at the level required for an adequate protective reaction of the body to chemical injury.

Keywords: enterable correction program, acute poisoning, oxidative stress, nitric oxide

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AOS – antioxidant system
AP – acute poisoning
CS – corrosive substances
ECP – enteral correction program
ES – enteral solution
GIT – gastrointestinal tract
IL – intestinal lavage
$K_{MDA/TAA}$ – coefficient for assessing the severity of oxidative stress
LPO – lipid peroxidation
MDA – malondialdehyde
OS – oxidative stress
PCS – poisoning with corrosive substances
PPPA – poisoning with psychopharmacological agents
ROS – reactive oxygen species
TAA – total antioxidant activity of serum

According to modern concepts, an uncontrolled activation of free radical oxidative processes and insufficiency of the antioxidant system are regarded as the main pathogenetic factor of many diseases and pathological conditions accompanied by impaired barrier functions of cell membranes. A developing imbalance in the prooxidant/antioxidant system is called oxidative stress (OS) [1, 2]. In acute exogenous poisoning (EP) in the early period of the disease, OS occurs as a result of exposure to the toxicant itself, and the protective reaction of the body; and in the somatogenic stage, it occurs in connection with the development of endotoxicosis [3, 4]. Expressed manifestations of the imbalance in pro- and antioxidant processes in AP contribute to complications and increase the risk of poor outcome in a disease [4, 5], One of the factors supporting endogenous intoxication in AP, is a pathologically increased intestinal resorption with the entry of endogenous compounds into the internal environment [6-8]. In this regard, medical technologies aimed at cleansing enteral environment, functional recovery of the impaired gastrointestinal intestinal tract (GIT), can be considered as promising in the treatment for AP [7, 8],

The purpose of the study was to evaluate the effect of the enteral correction program on the lipid peroxidation (LPO) and antioxidant system (AOS) parameters in acute exogenous poisoning.

MATERIAL AND METHODS

We followed-up 119 patients aged 27-85 years, admitted for treatment in the Department of Acute Poisoning and Somatopsychiatric Disorders of the N.V. Sklifosovsky Research Institute for Emergency Medicine of Moscow Healthcare Department. Seventy four of them (44 men and 30 women) had the poisoning caused by the intake of corrosive substances (CS). The severity of poisoning with CS (PCS) was assessed upon hospital admission in terms of length and depth of the chemical burn to the gastrointestinal tract according to

the classification proposed by S.V. Volkova et al., supplemented by T.P. Pinchuk et al. [9, 10]. At endoscopic examination, all patients were diagnosed with a chemical burn of the mucosa of oropharynx, esophagus (2nd-3rd degree) and stomach (2nd-4th degree).

Forty five patients (27 women and 18 men) had severe acute poisoning with psychopharmacological agents (PPPA). The severity of poisoning was assessed by the Glasgow Coma Scale (obtundation, stupor, coma) taking into account the baseline level of the consciousness disorder, and according to classification by E.A. Luzhnikov [4].

In 40 patients with PCS and 23 patients with PPPA (study groups), the complex of therapeutic measures included an enteral correction program (ECP). In the first hours of chemical injury, they underwent intestinal lavage (IL) using enteral solution (ES) in a volume of 4.5 to 15 liters. For this purpose, they were given to drink 200 ml every 5 minutes of ES, which temperature was 18-22o C. In cases where patients were unable to take the solution independently due to the severity of the condition (impaired consciousness, impaired swallowing function), ES was administered through a nasogastric tube. ES contains: sodium phosphate, sodium chloride, sodium acetate, potassium chloride, citric acid, disodium salt of ethylenediaminetetraacetic acid (Na2EDTA chelate), as well as calcium chloride, magnesium sulfate and purified drinking water. Osmolarity of the solution is 290-310 mOsm/L (depends on the volume of water used to dissolve salts), pH≈5.8 [3, 7]. The IL procedure lasted for a mean of 3 hours. Patients tolerated it satisfactorily, and no adverse reactions or complications were seen. On subsequent days, as nutritional support, patients were given a glucose-activated enteral solution orally in portions of 200 ml in a total volume of 4-5 liters per day and balanced nutrition formulae. In addition, from the 2nd day of their hospital stay, the patients of the study group with PCS took Pectovit 5.5 g 3 times a day for 5 days.

The comparison group consisted of 56 patients (34 with PCS and 22 with PPPA) who received standard therapy. Patients of the study and comparison groups were comparable by gender, age, type and severity of poisoning.

The study was approved by the Committee on Biomedical Ethics (extract from Protocol No. 5-16 of 21.11.2016).

To assess the severity of OS, the content of LPO and AOS products in blood were measured. The content of LPO products was studied by the level of malondialdehyde (MDA) in blood serum according to the method by V. B. Gavrilov [11]. The AOS state was assessed by measuring photometrically the total antioxidant activity (TAA) of blood serum using an AU 2700 biochemical analyzer (Becman Coulter, USA) with reagents from Randox (Great Britain).

The oxidative stress index ($K_{MDA/TAA}$) for each patient was calculated as a ratio of the measured values reduced to their normal values. The OS parameters in the blood of patients of all groups were measured on day 1, day 3, and day 5. Due to the fact that we previously identified differences in the OS severity between the working age group (up to 60 years) and older group (over 60 years of age) [12], the studied parameters were considered separately in two age subgroups.

The endogenous vascular regulation impairments were assessed by the blood serum level of nitric oxide (NO), which was measured by the serum content of NO stable metabolites: the sum of nitrite (NO_2⊠) and nitrate (NO_3⊠) anions (NO_x). NO_x assessment was made by the method according to which cadmium reduces nitrate to nitrite in the presence of zinc [13].

The obtained results were statistically processed using Statistica 10.0 software. The normality of the data distribution was assessed using the Shapiro–Wilk test at n of no more than 50. For nonparametric data, the median (Me), the 25th and 75th percentiles were determined. Independent groups were compared using the Mann-Whitney U–test, and linked samples were compared using the Wilcoxon test.

RESULTS AND DISCUSSION

On hospital admission the patients of working age with PCS (Table 1), both in the study group and in the comparison group, showed statistically significant increases in MDA by 41% and 60%, respectively, and TAA by 10% and 24%, respectively. Meantime, the OS index on day 1 in patients of both groups was increased by mean of 1.5 times from the normal value. On day 3 of the study, an increased MDA level persisted and a tendency to TAA decrease relatively to the baseline value was seen in both groups, while the value of the LPO/AOS imbalance increased by 20% in the study group, and by 30% in the comparison group, versus day 1. By day 5, the patients of the study group had experienced a decrease in the MDA level to the baseline values,

and the TAA value remained below normal; the imbalance coefficient decreased. In the comparison group, further LPO activation was observed, which was expressed in an increase in the MDA value by 20% from the baseline, while TAA remained at the same level, which indicated an increase in OS. KMDA/TAA increased by 2.4 times relative to the normal, which reached a statistically significant difference in that parameter in the study subgroup.

Table 1

Dynamics of parameters of lipid peroxidation and antioxidant protection of blood in patients with acute poisoning with corrosive substances

Parameters	Study stages						
	Normal	1st day		3rd day		5th day	
		Study group	Comparison group	Study group	Comparison group	Study group	Comparison group
	Persons under 60 years of age						
MDA, mcmole/L	2.27 (2.11–2.47)	3.202* (2.603; 3.776)	3.607* (2.929; 4.322)	3.407*, 2 (3.284; 3.724)	3.748* (3.520; 4.042)	3.206*, 2 (2.649; 3.572)	3.896* (3.422; 4.122)
TAA, mcmole/L	1.61 (1.56–1.68)	1.77 (1.53; 2.02)	1.99 (1.75; 3.51)	1.551 (1.38; 1.73)	1.60 (1.52; 1.64)	1.591 (1.42; 1.74)	1.69 (1.62; 1.75)
KMDA/TAA	0.96 (0.91; 1.11)	1.38 (1.29; 1.55)	1.60 (1.35; 2.16)	1.83* (1.48; 1.93)	2.09* (1.38; 2.23)	1.77*, 2 (1.52; 1.91)	2.33*(1.87; 2.97)
NOx, mcmole/L	18.61 (17.70–23.62)	18.9 (16.3; 27.3)	17.85 (7.95; 21.67)	15.5 (14.3; 29.7)	16.4 (14.2; 21.7)	18.9* (14.9; 29.6)	22.2 (20.7; 27.0)
	Persons aged 60 years and older						
MDA, mcmole/L	4.59 (4.02; 6.01)	3.360 (3.198; 4.021)	3.154* (2.974; 3.479)	3.674*, 1, 2 (3.523; 3.838)	3.346* (3.10; 3.69)	3.7211, 2 (3.206; 4.187)	3.103 (2.910; 3.358)*
TAA, mcmole/L	1.55 (1.49; 1.64)	1.67 (1.30; 2.36)	1.55 (1.36; 1.64)	1.38 (1.25; 1.42)	1.381 (1.33; 1.59)	1.33*, 1 (1.23; 1.43)	1.42 (1.19; 1.49)
KMDA/TAA	2.26 (1.96; 2.76)	1.55 (1.44; 1.76)	1.71 (1.63; 1.98)	2.0 (1.83; 2.20)	2.06 (1.72; 2.51)	2.22 (1.84; 2.72)	2.00 (1.98; 2.24)
NOx, mcmole/L	22.85 (18.55; 30.4)	24.8 (17.2; 40.9)	22.9 (15.3; 24.9)	14.60*, 1, 2 (13.9; 21.2)	26.551 (21.0; 28.9)	19.82 (18.7; 20.4)	23.2 (21.9; 32.3)

Notes: * statistically significant difference from the norm ($p<0.05$, according to the Mann-Whitney test), 1 statistically significant difference from the baseline value ($p<0.05$, according to the Wilcoxon test), 2 statistically significant difference from the comparison group parameter (p $K_{MDA/TAA}$, coefficient for assessing the severity of oxidative stress; MDA, malondialdehyde; TAA, total antioxidant activity of serum; NO_x, nitric oxide

In the study group and the comparison group of the older patients (Table 1), the baseline MDA and TAA parameters had similar values. MDA was reduced by 30%, TAA was almost close to normal, and KMDA/TAA was 1.4 times lower than normal. By day 3, the imbalance index increased in both groups, approaching the norm. On day 5, a further increase in MDA was observed in the study group, which contributed to restoring the balance between pro- and antioxidant parameters. In the comparison group, all measured parameters and the imbalance coefficient remained reduced.

When studying the dynamics of LPO/AOS in patients with PPPA under 60 years of age (Table 2), there was an increase in MDA both in patients of the study group and in the comparison group: by 37% and 30%, respectively. Meanwhile, both groups showed a statistically significant decrease in TAA compared to normal values by 12% and 16%, respectively. The oxidative stress index KMDA/TAA was increased by 1.4 and 1.6 times in the study and comparison groups, respectively. By day 3, all patients had shown an increase in MDA and a decrease in TAA. However, the index of LPO/AOS imbalance increased by 23% compared to the baseline values in the patients of the study group, and by 37% in the comparison group. At day 5, the MDA value did not significantly change in patients of both groups. However, the TAA value in patients of the study group increased; and in patients who received a standard therapy, there was a tendency to further decrease in TAA, which was 1.3 times statistically significantly lower than normal. As a result, KMDA/TAA in patients of the study group exceeded the norm by 1.6 times, while that parameter in the comparison group remained at the same level, differing from the norm by 2.1 times.

Table 2

Dynamics of parameters of lipid peroxidation and antioxidant protection of blood in patients with acute poisoning with psychopharmacological agents

Parameters	Normal	1st day		3rd day		5th day	
		Study group	Comparison group	Study group	Comparison group	Study group	Comparison group
	Persons under 60 years of age						
MDA, mcmole/L	2.27 (2.11–2.47)	3.11 (2.73; 3.22)	2.96 (2.82; 3.16)	3.251, 2 (2.42; 3.63)	3.711 (3.29; 4.03)	3.28 (2.89; 4.07)	3.61 (3.22; 4.08)
TAA, mcmole/L	1.61 (1.56–1.68)	1.41* (1.09; 1.48)	1.36* (1.35; 1.41)	1.20*;1 (1.17; 1.28)	1.24*, 1 (1.08; 1.41)	1.512 (1.25; 2.14)	1.20*, 1 (1.19; 1.42)
KMDA/OAA	0.96 (0.91; 1.11)	1.62 (1.35; 1.73)	1.34 (1.18; 1.42)	1.84 (1.47; 2.19)	2.15 (1.53; 2.68)	1.86 (1.79; 1.91)	2.11 (1.66; 2.42)
NOx, mmol/L	18.61 (17.70–23.62)	13.16* (10.13; 14.07)	16.3 (11.53; 22.20)	10.94*, 2 (7.35; 13.17)	23.33 (11.15; 34.10)	14.17 (8.75; 19.21)	18.07 (11.79; 22.66)
	Persons aged 60 years and older						
MDA, mcmole/L	4.59 (4.02; 6.01)	3.65*;2 (3.23; 3.89)	3.00* (2.76; 3.24)	3.49* (3.24; 3.96)	3.10* (2.89; 4.11)	4.02 (3.76; 5.62)	3.47* (3.15; 4.74)
TAA, mcmole/L	1.55 (1.49; 1.64)	1.21* (1.03; 1.42)	1.24* (1.16; 1.27)	1.01*, 1 (0.95; 1.07)	1.14* (0.97; 1.48)	1.30*, 2 (1.29; 1.44)	1.07*, 1 (1.00; 1.13)
KMDA/TAA	2.26 (1.96; 2.76)	1.157 (0.82; 1.38)	0.94 (0.82; 1.24)	1.26 (1.07; 1.58)	1.104 (0.75; 1.23)	1.02 (0.93; 1.46;	1.16 (1.28; 1.17)
NOx, mcmole/L	22.85 (18.55; 30.4)	10.18* (8.61; 23.85)	15.5* (9.44; 16.92)	12.49* (7.35; 13.58)	11.59* (7.67; 27.00)	15.7*;1 (12.93; 21.23)	19.09 (10.84; 24.95)

Notes: * statistically significant difference from the norm ($p<0.05$, according to the Mann-Whitney test), 1 statistically significant difference from the initial value ($p<0.05$, according to the Wilcoxon test), 2 statistically significant difference from the comparison group parameter (p KMDA/TAA, coefficient for assessing the severity of oxidative stress; MDA, malondialdehyde; TAA, total antioxidant activity of serum; NOx, nitric oxide

In the group of elderly and senile age patients with PPPA (Table 2) the baseline MDA levels were reduced relative to normal in the study and comparison groups by 20.5% and 35%, and TAA was statistically significantly lower than normal values by 22% and 20%, respectively. The imbalance index on day 1 in patients of both groups was reduced, to a greater extent in patients who underwent a standard set of treatment. Further, the MDA in the study group slightly decreased compared to the baseline value, while in the comparison group there was a tendency to its increase. Meantime, the level of TAA decreased synchronously in both groups. At this stage of the study, the OS index in the study group was slightly higher than in the comparison group. By day 5, patients in the study group showed an increase in the values of MDA and TAA compared to the baseline values of these parameters, while patients in the comparison group showed an increase in the level of MDA and a decrease in TAA compared to the baseline values. $K_{МДА/ОАА}$ at that stage of the study remained reduced from the normal in patients of both groups.

Free radical reactions, being the most labile link in the adaptive restructuring of the body during extreme exposures, perform an important regulatory function and, with adequate stimulation, increase the body's resistance [2, 3]. At the same time, an excessive production of reactive oxygen species (ROS), insufficient effectiveness of antioxidant protection, and reduced production of AOS components reflect a breakdown in the body's adaptive capabilities.

Currently, free radicals are often considered as intracellular messengers necessary for the body functioning in normal and pathological conditions. Studies have shown that the increase of the ROS level in the fight against infection is a part of the cellular immune response when ROS and reactive forms of nitrogen act together with reactive forms of halogen to fight microorganisms [2, 14]. Thus, both extremely increased and extremely decreased POL and AOS are unfavorable factors. ECP has a positive effect on the dynamics of LPO and AOS parameters in patients with PPPA. In addition, the data obtained indicate a specific course of acute PPPA in elderly and senile individuals. In patients of this category, there are reduced values of both MDA and TAA parameters and the KMDA/TAA index in general. Based on the fact that reactive oxygen species are unavoidably involved in vital processes, this situation indicates a low adaptive potential accompanied by a decrease in the body's natural detoxification processes and inadequate adaptive reactions in this category of patients. When analyzing the obtained parameters, redox processes were seen to get activated in patients with PCS.

It should be noted that PCS deserve special attention, since this group is characterized by a severe course and frequent development of complications when the mortality rate can reach up to 30% [4]. The clinical presentation of PCS includes damaged mucous membrane of the digestive tract and respiratory tract of various extent and severity and is complicated by impairments in homeostasis parameters, including the blood acid-base state [4, 9]. Moreover, the nature of the LPO and AOS processes becomes disturbed. Increased LPO in the mitochondria and liposome membranes is the most common cause of their damage in AP [4]. These derrangements lead to an increased permeability of cell membranes for ions, which can result in osmotic effects and membrane breaks with the release of enzymes, in particular cytochrome C, into the intercellular space. Further lipid oxidation leads to a complete destruction of membranes, cell death, and expansion of necrosis zones [4, 5].

The results obtained indicate that ECP supports the activity of free radical processes aimed, among other things, at eliminating the products of burn tissue destruction and promotes the activation of antioxidant protection in patients with PCS, especially in people of working age.

The relative decrease in the values of LPO and AOS parameters in people over 60 years of age on day 1 and day 3 observed in PCS, as well as in PPPA, should be regarded as a decrease in their compensatory capabilities of the body. In general, the results of the study showed that old-aged patients with PCS who received ECP demonstrated a restored balance in the pro–oxidant-antioxidant system by day 5.

Endogenous nitric oxide (NO) is a universal regulator of cellular metabolism and intercellular interactions. The NO system is considered unique, since its action is not associated with receptors; and NO itself can penetrate into cells of various tissues and pose an effect on many processes. The NO effect on individual processes in different tissues is ambiguous and multidirectional. The effects of its action depend on the concentration in cells, the presence of oxygen, oxidative stress metabolites, and antioxidants, which can change its amount, signaling function, and physiological activity [15]. Without normal cellular NO metabolism, it is impossible to maintain an optimal state of human health. No in a free state is a short-lived molecule whose half-life ranges from 0.5 to 30 seconds, after which it is rapidly destroyed. With its excessive amount in the cell, the nitric oxide can bind to proteins and peptides, that is, be deposited and stored for a longer time. It is assumed that the NO deposition in a protein-bound form plays an important role in the formation of the body's resistance to injury primarily inflicted by free radicals caused by both its deficiency and hyperproduction [16].

In our study, we found that in PPPA, the NO level was statistically significantly reduced at baseline in both groups, regardless of age, and this trend persisted up to 5 days (Table 2).

When assessing the dynamics of the blood NOx content in working-age patients with PCS, we observed the following changes. Initially, the NOx level in both groups did not significantly differ from the norm. By the 3rd day, the values decreased, and on day 5, they returned to normal. In the comparison group, the median NOx value was statistically insignificantly higher.

In the subgroup of old-aged patients with PCS, the NOx parameter underwent more considerable changes. The baseline normal values of this parameter had significantly decreased (by 40%) by day 3 in the study group, and increased by 16% in the comparison group. On day 5, there was a tendency to normalization of the NOx level in both groups, however, a statistically significant difference between them still persisted.

Our results are consistent with the literature data, which show that when the NO level decreases in tissues, the adaptive capabilities of the body decrease and pathological changes in metabolism are observed, complicating the course of the disease [17, 18].

The reduction of NOx level on the 3rd day of the study and the increase in KOS can be explained by the fact that nitric oxide can interact with superoxide (O2–) turning it into a very toxic substance, peroxynitrite (OPOO–), which is the most powerful oxidant that destroys the cell membrane by damaging the DNA molecules, modifies proteins and lipids of the vascular endothelium cell membranes, increases platelet aggregation, and participates in other pathophysiological reactions. This leads to a derangement of the metabolic processes and conductivity of signaling pathways. A so-called oxidative-nitrate stress is created in cells, which induces their death [1, 2]. Normalization of NOx and OS levels by day 5, which is more pronounced in the study group, indicates the efficacy of ECP.

Thus, the use of the enteral correction program has a positive effect on the dynamics of oxidative stress parameters, ensuring the maintenance of oxidative processes at the level necessary for an adequate protective response of the body to chemical trauma.

CONCLUSIONS

1. In patients of working age, regardless of the type of toxicant, the activation of free radical processes is observed, which has been expressed by an increase in the coefficient of KMDA/TAA by 1.4-1.8 times compared to the norm. The use of the enteral correction program at the study stages contributes to maintaining this level of balance between pro- and antioxidants, while in patients of the comparison groups there is an increase in the imbalance in the LPO/AOS system, as a result of which the KMDA/TAA exceeded the norm by 2.2–2.4 times, statistically significantly different from the values in the study groups.

2. In older patients, regardless of the type of toxicant, the inhibition of oxidative processes was revealed, which was manifested by a decrease in KMDA/TAA by 1.3–1.5 times compared to the normal for that age on poisoning with corrosive substances and by 2.0–2.4 times in poisoning with psychopharmacological agents. This indicates a reduced adaptive potential of this group of individuals. The use of an enteral correction program in older individuals promotes a moderate activation of lipid peroxidation, which leads to the normalization of the oxidative stress index by day 5 in cases of poisoning with corrosive substances and its relative stabilization in cases of poisoning with psychopharmacological agents.

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