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Investigations

Regularities of the Oxidative Stress Processes in Case of Bleedings from Acute and Chronic Ulcers of the Stomach and Duodenum

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Abstract: The main aim of the study was to determine ways of improving the results of treating patients with ulcer bleeding of various nature and severity. It was provided by the system study of free radical processes and evaluation of the effectiveness of timely antioxidant therapy. Material and methods. The study included 153 patients aged 18-94 years with acute and chronic gastric and duodenal ulcers complicated by gastroduodenal bleeding. Patients were divided into two groups: group I (experimental group) included 62 patients who received antioxidative therapy with reamberin as a part of the basic therapy; and group II (control group) included 91 patients who received standard therapy. Various parameters of Free Radical Processes (FRP) were studied in dynamics in all patients. Results. We revealed the significance of oxidative stress on the first day of hospitalization in patients with gastrointestinal ulcerous bleeding of various character and severity. It was discovered mostly in severe patients with acute Gastroduodenal Ulcerous Bleeding (GDUB). In case of mild gastrointestinal ulcerous bleeding, oxidative stress disorders affected an oxygen stage of oxidative stress and represented themselves adaptive compensatory mechanisms. As the severity of the disease increased, intensification of an oxidant stress was manifested by a decrease in oxygen activity and an increase in lipid imbalance. Imbalance in free radical processes continued for a long time until discharge of patients from the hospital. The data obtained claimed to be the basis for recommendation to include antioxidant energy-conserving therapy in the complex of therapeutic measures in the earliest possible terms. We found out an efficacy of using succinic acid therapy with reamberin in patients with gastrointestinal bleeding. Positive effect of succinic acid on the markers of oxidative stress was confirmed by improvement in the disease pattern and success of the treatment.

Keywords: Free Radical Processes, Gastrointestinal Bleeding, Oxidative Stress, Acute Ulcerous Bleeding, Antioxidants

Introduction

Gastrointestinal Bleeding (GIB) is a dangerous complication of gastric or duodenal ulcers, associated with high mortality rates. Its treatment continues to be one of the most urgent problems of the urgent surgery, accounting for up to 60-80% of all haemorrhagic complications of digestive tract diseases (Pai and Fox, 2017; Garber and Jang, 2016; Tielleman *et al*., 2015; Abougergi *et al*., 2015; Korolev, 2011). Until recently, it has been generally acknowledged that peptic ulcerous disease predominates in the structure of GIB causes. However, nowadays bleeding from acute ulcers (diagnosed in 50-70% of cases) comes to the forefront rather than bleeding associated with chronic acid-peptic ulcers (Nable and Graham, 2016; Monteiro *et al*., 2016;

Sung *et al*., 2010). The main causes of acute ulcers are decompensation of concomitant pathology and multiple organ failure, exogenous and endogenous intoxications, combined injuries, increased volume of surgical interventions, intake of various drugs, alcohol. At the same time, the mortality rate in GIB in

In this regard, the correct choice of treatment tactics must take into account GIB triggering causes. The tactics of treating patients with bleeding from hyperacid ulcers with high acid production is based on the prevention of bleeding recurrence and antisecretory therapy. Treatment of comorbid, symptomatic ulcers should be based on the correction of microcirculatory disorders, as well as oxidative and metabolic disorders. In this respect, preparations with antioxidant and antihypoxic properties attract attention of the scientists. On the one hand, these preparations may help to reduce concentration of active free radicals and on the other hand, they contribute to the normalization of ATP synthesis, by means of providing mechanisms of organ homeostasis.

The aim of the study was to determine ways to improve the results of treating patients with ulcerous bleeding of various nature and severity by means of system study of Free Radical Processes (FRP) and evaluation of the effectiveness of timely antioxidant therapy.

Materials and Methods

The study included 153 patients (89 (58.2%) males and 64 (41.8%) females) aged from 18 to 94 years (58.82±18.08 years, mean age = 61 years) with acute and chronic gastroduodenal ulcers complicated by gastroduodenal bleeding, examined and treated in the surgical and resuscitation departments of the Multidisciplinary Hospital No. 15 named after O.M. Filatov of the Moscow city. 81 patients (52.9%) were admitted to the specialized surgical departments, 31 patients (20.3%) were admitted in ICU and 41 (26.8%) patients were treated in the other departments (general medicine, neurology, cardiology, etc.), where GIB developed. According to fibrogastroduodenoscopy, 106 (69.3%) patients were diagnosed with bleeding from acute ulcers, while in 47 (30.7%) patients ulcers appeared as chronic ones (Fig. 1).

case of such ulcers in the intensive care units reaches 80% (AUGB, 2012; Rotondano, 2014; Rey *et al*., 2015). This fact is explained by the comorbidity of acute ulcers associated with cellular apoptosis in terms of an organ hypoxia, ischemia and the development of oxidative stress (Silina *et al*., 2011).

Most often, Gastroduodenal Ulcerous Bleeding (GDUB) episodes developed against the background of cardiovascular comorbidity and uncontrolled intake of medications (NSAIDs, anticoagulants) (n = 71; 46.4%) against the backdrop of MODS syndrome (n = 45; 29.4%), distress (n = 17; 11.1%). GIB against the background of another exacerbation of peptic ulcer was diagnosed in 20 people (13.1%). Concomitant pathology was detected in 128 (83.7%) patients, including 93 (87.7%) patients with acute pathology and 35 (74.5%) with chronic ulcers. Pathology of cardiovascular system and CNS prevailed. In 95 (74.2%) patients, there were ≥2 pathologies. At the time of inclusion in the study, duration of GDUB ranged from 1.5 to 96 h (an average of 28.4±25.8/2.1, Me = 24 h). 51 (48.1%) patients with acute ulcers and 13 (27.7%) patients with chronic ulcers were admitted in the first 24 hours after the onset of gastroduodenal ulcer, 42 (39.6%) of patients with acute and 27 (57.4%) with chronic ulcer - in the period of 24-48 h. 13.1% of patients were admitted over 48 h - 13 (12.3%) with acute and 7 (14.9%) with chronic ulcers.

All the patients on admission underwent clinical and laboratory evaluation of the degree of severity of blood loss according to A.I. Gorbashko (1974). 35 (22.9%) patients had mild blood loss, 45 (29.4%) patients – moderate blood loss and 73 (47.7%) patients – severe blood loss. Clinical severity of the patient's condition was assessed by the integrated *Multiple Organ Dysfunction Score* (MODS *1985*) scale. There were 111 (72.5%) patients hospitalized in the state of moderate severity (less than 8 points according to the MODS scale) and 42 patients in severe state (≥8 points) - (27.5%). Endoscopic criteria for the risk of bleeding recurrence were determined by Forrest (1974). There were 110 (71.9%) patients with a high risk of recurrence (FI A, B: n = 52, 34.0% and FII A, B: n = 58; 37.9%) and 43 patients with a low risk (28.1%) (FIIC).

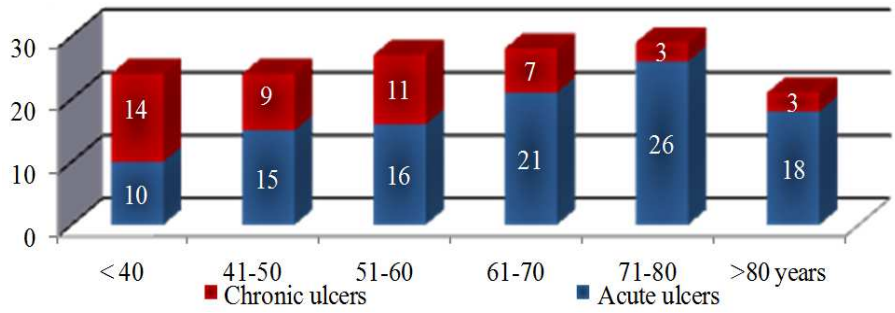


Fig. 1: Distribution of patients by the age and character of gastroduodenal ulcerous bleeding

In order to assess secretory function of the stomach, endoscopic (topographic) rapid pH-metry was used in 98 (64.1%) patients. Hypo- and normal acidity was registered in 52 (53.1%) patients, hyperacidity - in 46 (46.9%) patients. In order to assess the effect of antisecretory drugs and adjust adequate doses of the drugs after stabilizing the patient's condition, daily monitoring of gastric secretion (daily pH-metry) was performed.

Patients were divided into two groups:

1) group I (basic) included 62 (40.5%) patients aged from 20 to 94 years (58.98±18.09/2.29, Me = 58 years), including 33 (53.2%) men (52.36±17.02/2.96, Me = 52 years) and 29 (46.8%) women (66.52±16.47/3.05 Me = 64 years) who received an antioxidative therapy with reamberin in the dose of 500 mL per day i.v. drip from day 1 to day 8 as a part of the basic therapy
2) Group II (comparison group) included 91 (59.5%) people aged from 17 to 89 years (58.71±18.17/1.90 Me = 62 years), including 56 (61.5%) men (55.89±16.64/2.22, Me = 57.5 years) and 35 (38.5%) women (63.23±19.81/3.34, Me = 70 years) who received the therapy that met the standards of medical care for this category of patients in a hospital. All the patients were prescribed with proton pump inhibitors - esomeprazole in the dose of 80 mg i.v., then 8 mg/h for the first 3 days, after which the dose was changed to 40 mg b.i.d. After stabilization of the condition, omeprozole was prescribed in the dose of 20 mg b.i.d. for 14 days. The studied groups of patients were comparable ($p>0.05$) (Table 1)

In 82 (53.6%) patients, bleeding was stopped endoscopically (group I – 38 patients (61.3%), group II – 44 patients (48.4%). Due to the ineffectiveness of the endoscopic hemostasis and a high threat of recurrence of bleeding in emergency, 21 patients (13.7%) underwent surgical operation (group I – 6 (28.6%) individuals) and group II – 15 (16.5%) individuals. Surgical tactics and the volume of operative and conservative interventions in both groups of patients were identical ($p>0.05$).

The comprehensive assessment of the patient's condition was carried out in dynamics (at admission, on days 3, 7 and 14) and included assessment of the severity of the condition according to the MODS scale, monitoring of clinical and biochemical blood analysis, EGDS and studies of free radical processes in blood plasma.

The following markers were used to study the FRP. Chemiluminescent (CL) parameters of Generation of Reactive Oxygen Species by Blood Leukocytes (GROSBL) were studied on the adapted chemiluminescence meter of LKB "Wollac" (Sweden) at the standard temperature of 36.9°C. The level of basal (spontaneous) index Intensity of Chemiluminescence (ICLb), characterizing spontaneous CL of leukocytes at rest, outside of phagocytosis and initial state of metabolic processes were determined. After the addition of the activator (0.1 mL of zymosan 1% solution) the stimulated (s) Intensity of Chemiluminescence (ICLs) was investigated the presence of Reactive Oxygen Species (ROS) in the system was measured. The intensity of leukocytes CL was calculated according to the following formula: ICL = maximal CL$\times 10^6$/amount of granulocytes and monocytes in the studied volume of leukomass. The procedure for studying the Antiperoxide Activity of secondary Plasma (APA) is based on the measurement and comparison of indices of hydrogen peroxide-induced CL and spontaneous CL (Ind/SpCL). The calculated ratio is inversely proportional to plasma's APA. The smaller this ratio is, the greater APA is and vice versa. Malone Dialdehyde (MDA), a secondary product of lipid peroxidation, was determined by Douest JC method, the essence of which was the interaction of Thiobarbituric Acid (TBA) with secondary plasma. An optical density was measured on spectrophotometer. MDA concentration of plasma was calculated by the formula: $C = D \times 10p/1.56$, where *D is the optical density, p is the dilution rate, 1.56 is the correction factor, expressing the final result in μmol/L.* The investigated parameters of free radical processes were compared with those of 34 healthy people.

Statistical processing of the study results was carried out by using STATISTICA 6.0 and SPSS 20.0 programs. Descriptive statistics of continuous quantitative data are presented as the mean value (M), standard deviation and also as the median (Me), lower (Q25) and upper (Q75) quartiles in case of distribution different from the normal one.

Normality of the distribution was estimated by the Kolmogorov-Smirnov method. Analytical statistics were performed by using the Student's t-test for quantitative data with normal distribution. The Mann-Whitney test (U) was used in order to compare two independent nonparametric samples and the Kruskal-Wallis test - for multiple comparison. The Wilcoxon test was used in order to compare two dependent non-parametric samples, while the Friedman test was used for multiple comparison. Qualitative variables were compared by using the x^2 test (contingency tables). Correlation analysis was performed by the Pearson method. Differences were considered significant at $p<0.05$. Prognostic models were performed by using the ROC analysis.

Table 1: Distribution of patients of both groups by sex, age, severity of the condition, severity of hemorrhage, etiology and concomitant pathology

	Group I (n = 62)	Group II (n = 91)	R	Total (n = 153)
Distribution of patients by gender				
Men	33 (53.2%)	56 (61.5%)	0.308	89 (58.2%)
Women	29 (46.8%)	35 (38.5%)		64 (41.8%)
Distribution of patients by age				
≤30	5 (8.1%)	9 (9.9%)	0.962	14 (9.2%)
31-40	4 (6.5%)	6 (6.6%)		10 (6.5%)
41-50	10 (16.1%)	14 (15.4%)		24 (15.7%)
51-60	15 (24.2%)	12 (13.2%)		27 (17.6%)
61-70	8 (12.9%)	20 (22.0%)		28 (18.3%)
71-80	8 (12.9%)	21 (23.1%)		29 (19.0%)
> 80	12 (19.4%)	9 (9.9%)		21 (13.7%)
Mean age	58.98±18.09	58.71±18.17		58.82±18.08
Distribution of patients according to the severity of the condition (according to the MODS scale) upon admission				
<8 points (n;%)	46 (74.2%)	65 (71.4%)	0.750	111 (72.5%)
≥8 points (n;%)	16 (25.8%)	26 (28.6%)		42 (27.5%)
Distribution of patients by the degree of severity of blood loss on admission				
Mild	16 (25.8%)	19 (20.9%)	0.667	35 (22.9%)
Medium	17 (27.4%)	28 (30.8%)		45 (29.4%)
Severe	29 (46.8%)	44 (48.4%)		73 (47.7%)
Distribution of patients according to etiology of gastrointestinal ulcerous bleeding				
Acute ulcers	44 (71.0%)	62 (68.1%)	0.710	106 (69.3%)
Chronic ulcers	18 (29.0%)	29 (31.9%)		47 (30.7%)
Distribution of patients according to duration of gastrointestinal ulcerous bleeding				
<24 hours	26 (41.9%)	38 (41.8%)	0.885	64 (41.8%)
24-48 hours	27 (43.5%)	42 (46.2%)		69 (45.1%)
> 48 hours	9 (14.5%)	11 (12.1%)		20 (13.1%)
Distribution of patients by etiology of ulceration and gastrointestinal bleeding				
Distress	9 (14.5%)	8 (8.8%)	0.718	17 (11.1%)
Intake of medicines				
(NSAIDs/anticoagulants)	25 (40.3%)	46 (50.5%)		71 (46.4%)
MODS	18 (29.0%)	27 (29.7%)		45 (29.4%)
Exacerbations of ulcerous disease	10 (16.1%)	10 (11.0%)		20 (13.1%)
Patient distribution by the frequency of concomitant pathology				
Ischemic heart disease	28 (45.2%)	45 (49.5%)	0.603	73 (47.7%)
Arterial hypertension	38 (61.3%)	64 (70.3%)	0.246	102 (66.7%)
Diabetes	7 (11.3%)	17 (18.7%)	0.219	24 (15.7%)
Cerebrovascular disease	14 (22.6%)	24 (26.4%)	0.595	38 (24.8%)

Results

Markers of Oxidative Stress in Patients with Ulcerative Gastrointestinal Bleeding of Varying Severity

In the course of the study, it was found that in patients with gastric and duodenal ulcer complicated by hemorrhage, there were violations of FRP. A significant imbalance of FRP in oxygen and peroxide-lipid components in patients with GDUB was registered already from day 1: LBCLb on the average was lower by 1.68 times ($p = 0.011$), LBCLb was 2.20 times higher ($p<0.001$), MDA was 1.29 times higher ($p = 0.019$) in comparison with the same indicators of healthy people. At the same time, the level of the protective APA was stable, which indicated high adaptive reserves in a number of patients.

The level of CP imbalance depended on many factors, including the severity of the condition, the severity of bleeding and the level of acid-producing function of the stomach.

Direct relationship between the degree of imbalance of free radical process and the severity of posthemorrhagic anemia was found, it reached the maximum levels in case of severe blood loss. With a small blood loss, only oxygen markers of free radical processes were changed. Intergroup differences were

related to peroxide-lipid markers only. APA index was the most striking in this respect. It characterized the level of protective-adaptive antioxidant mechanisms. It was associated with 1.07-fold increase in patients with non-severe blood loss and significantly decreased (by 1.14-fold) in case of a severe blood loss relative to the normal range. Imbalance in free radical processes increased in proportion to the clinical severity of the patient's condition (≥8 points according to the MODS scale). Correlation analysis revealed a significant relationship between the severity of the GDUB (according to the MODS scale and A. Gorbashko) with such markers of oxidant stress as APA ($r = 0.195$, $p = 0.041$ and $r = 0.214$, $p<0.01$) and MDA ($r = 0.321$; $p<0.001$ and $r = 0.245$, $p<0.01$), respectively. In severe GDUB patients, there was an imbalance of peroxide-lipid component, while in case of less severe patients there was an imbalance in the oxygen component of free radical processes (Table 2).

Prognostic Value of Free Radical Processes in Patients with Different Hospital Outcome of Ulcerative Gastrointestinal Bleeding

In 28 cases (18.3%), gastroduodenal ulcerous bleeding ended in a fatal outcome. Already upon the admission, an imbalance of free radical processes in these patients was shifted to the peroxide-lipid side (MDA >2.03, APA<1.29 ($p<0.05$)). The correlation analysis revealed a significant relationship between the outcome of the disease and ICLs values ($r = -0.336$, $p<0.05$) and MDA ($r = 0.404$, $p<0.001$). Thus, parameters of free radical processes can be used as an auxiliary diagnostic test in order to assess the severity and early prognosis of the course of the disease.

Table 2: Indicators of free radical processes in case of hospitalization of patients with gastroduodenal ulcerous bleeding of varying severity and outcome in comparison to the same indicators of healthy people

	ICLb (mV/c×10^6 L)	ICLs (mV/c×10^6 L)	Ind/SpCL(1/APA)	MDA(μmol/L)
Normal range	Me = 62.50	Me = 465.50	Me = 2.74	Me = 2.73
(n = 34)	41.61/80.30	307.55/564.43	2.01/3.15	2.52/3.68
GDUB	37.12	1025.00	2.82	3.53
(n = 153)	19.12/70.24	570.70/1622.00	2.16/3.73	2.46/5.13
P	*0.011	*0.001	0.122	*0.019
Parameters of free radical processes in patients with gastroduodenal ulcerous bleeding of varying severity (according to the MODS scale)				
GDUB<8 points	34.10	1096.00	2.80	3.21
(n = 111)	16.52/67.99	605.25/1723.50	2.17/3.70	2.45/4.98
	*(p = 0.01)	*(p<0.001)	(p = 0.104)	*(p<0.001)
GDUB ≥8 points	45.38	872.80	3.01	3.87
(n = 42)	23.55/75.29	472.91/1441.90	1.96/4.33	2.63/6.11
	*(p = 0.04)	*(p<0.001)	*(p<0.001)	*(p<0.001)
p	0.100	0.106	# 0.015	# 0.033
Indicators of free radical processes in patients with gastroduodenal ulcerous bleeding of varying severity (according to A. Gorbashko)				
Light and mild	38.35	941.30	2.56	3.15
(n = 80)	19.68/70.24	592,80/1625,00	2.18/3.47	2.41/4.93
	*(p = 0.013)	*(p<0.001)	(p = 0.329)	(p = 0.093)
Severe	37.32	1119.50	3.12	3.59
(n = 73)	19.53/75.74	509.85/1534.50	2.26/4.14	2.54/5.34
	*(p = 0.038)	*(p<0.001)	*(p = 0.013)	*(p = 0.009)
p	0.789	0.487	# 0.039	# 0.049
Parameters of free radical processes in patients with different outcome of gastroduodenal ulcerous bleeding				
Favorable outcome	36.92	1049.00	2.80	3.02
(n = 125)	21.07/70.44	580.70/1579.5	2.23/3.67	2.37/4.21
	*(p = 0.009)	*(p<0.001)	(p = 0.244)	(p = 0.196)
Lethal outcome	45.38	1021.00	3.60	6.14
(n = 28)	15.64/83.82	415.27/1545.50	2.18/6.21	4.54/7.47
	(p = 0.059)	*(p<0.001)	*(p = 0.004)	*(p<0.001)
p	0.932	0.978	# 0.045	#<0.001

Statistical results: first line (Me) - median; second line - (Quartiles 25/75%) - lower and upper quartile; third line is the difference from the normal range

* - statistically significant difference at $p<0.05$ compared to the normal range

- statistically significant difference at $p<0.05$ in the index for different severity of the condition

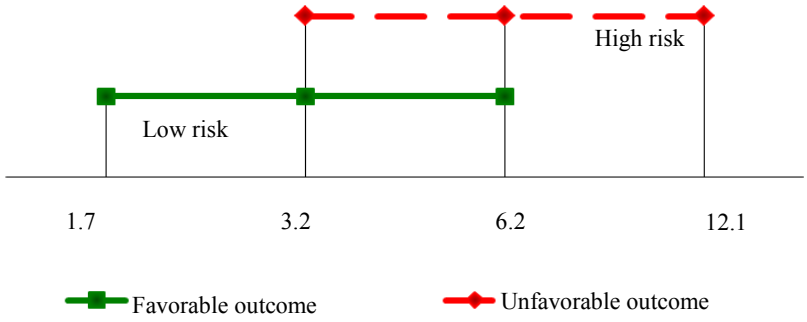


Fig. 2: 95-percentile ranges of MDA span in GDUB patients in the groups of favorable and unfavorable outcomes of the disease

Analysis of 95-percentile span of MDA titer in patients with favorable and unfavorable outcome showed the possibility of early prognosis of the lethal outcome. MDA level <3.2 μmol L^{-1} corresponded to the low risk; 3.3-6.2 μmol L^{-1} – to the average risk; >6.2 μmol L^{-1} – to the high risk (Fig. 2). Diagnostic Sensitivity (*DS*) of the method was 67.2%, specificity (*DS*) - 98.1%, accuracy (*DA*) - 79.1%; Positive Predictive Value (*PPV*) - 93.1% and Negative Predictive Value (*NPV*) - 76.2%. The same levels of MDA allowed to predict postoperative lethality, the risk of which at MDA>6.2 μmol L^{-1} was 77%, at MDA level 3.3-6.2-55% and at MDA level<3.2 μmol L^{-1} - 0%. The correlation analysis showed a direct correlation between the postoperative outcome of the disease and MDA level ($r = 0.319$, $p<0.05$). ROC-analysis (*Receiver Operator Characteristic*) of the curves confirmed the effectiveness and reliability of this test (Fig. 3).

The maximal disturbances of free radical processes were found in patients with SPON and bleeding from acute ulcers. In the latter, ICLs was increased 2.35 times and the MDA - 1.36 times, ICLb was decreased 1.75 times and APA - 1.07 times ($p<0.05$). At the same time, the level of MDA in the patients with acute gastroduodenal ulcerous bleeding from acute ulcers in the first hours of bleeding was 28% higher than in the GDUB patients with typical clinical picture of peptic ulcerous disease. The 2-fold increase in ICLs in case of chronic ulcer and the absence of changes in peroxide-lipid link of free radical processes confirmed a high protective-adaptive response.

Free Radical Processes in Patients with Various Secretory Activity of the Stomach and with Different Methods of Hemostasis

Changes in the level of FRP differed depending on the secretory activity of the stomach. The greatest free radical imbalance was revealed in case of a decrease in the secretory function before hypoacidity (ICLb<72%, MDA>26%, APA<22%) compared to the patients with hyperacidity (Fig. 4). Correlation analysis revealed a correlation between the degree of activity of gastric secretion and APA parameters ($r = 0.222$, $p<0.05$) and MDA ($r = 0.542$, $p<0.001$).

The data obtained testify to various pathophysiological mechanisms of ulceration: A high adaptive reserve in patients with hyperacid ulcers and an important role of oxidative stress in the pathogenesis of acute and hypoacid ulcers.

The study of the dynamics of free radical processes in the patients who received standard treatment with the use of proton pump inhibitors revealed a persistent significant free radical imbalance throughout the period of inpatient stay. The greatest dysregulation was recorded after surgical interventions, with its augmentation by day 14. After endoscopic hemostasis, free radical imbalance was less pronounced and normalized by day 14 (Fig. 5).

Dynamics of free Radical Processes in Patients with Ulcerative Gastroduodenal Bleeding of Various Nature and Severity During Standard Therapy and Additional Administration of Antioxidants

The revealed changes in free radical processes objectify the advisability of prescribing Antioxidant (AO) drugs to all GDUB patients. This is especially true for the patients with acute ulcers on the background of vascular comorbidity. The conducted studies have confirmed an initial hypothesis that the appointment of antioxidant therapy leads to the positive changes in the dynamics of free radical processes. Thus, the regression of ICLs in patients who received the AO therapy (which is noticeable already on day 3 of the study) indicates remitting of active forms of oxygen. The growth or stabilization of APA (on days 7-14) in these patients and the decrease in MDA (on days 3-7-14) indicate stimulation of protective factors and regression of necrobiotic processes (Fig. 6).

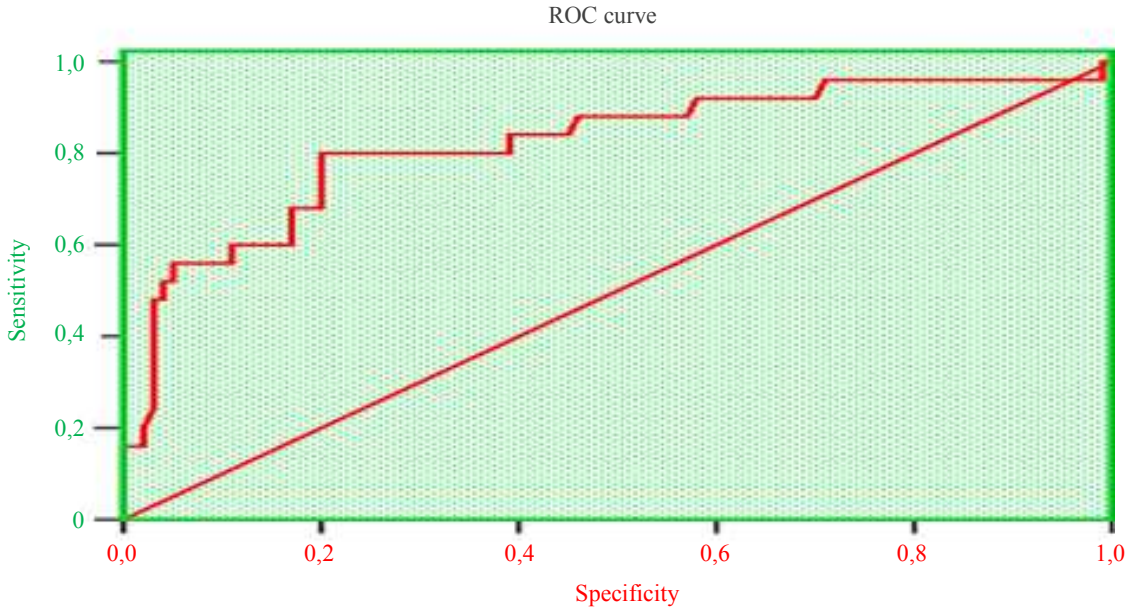


Fig. 3: ROC-curves for predicting the outcome of the disease in GDUB patients. Area under the curve - 0.849; CI – bottom border is 0.734; top border - 0.964; p<0.001)

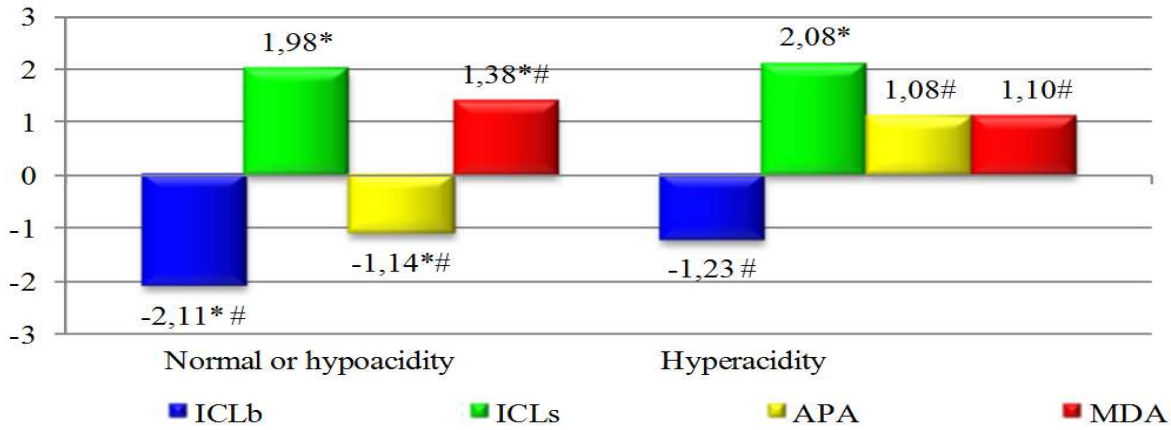
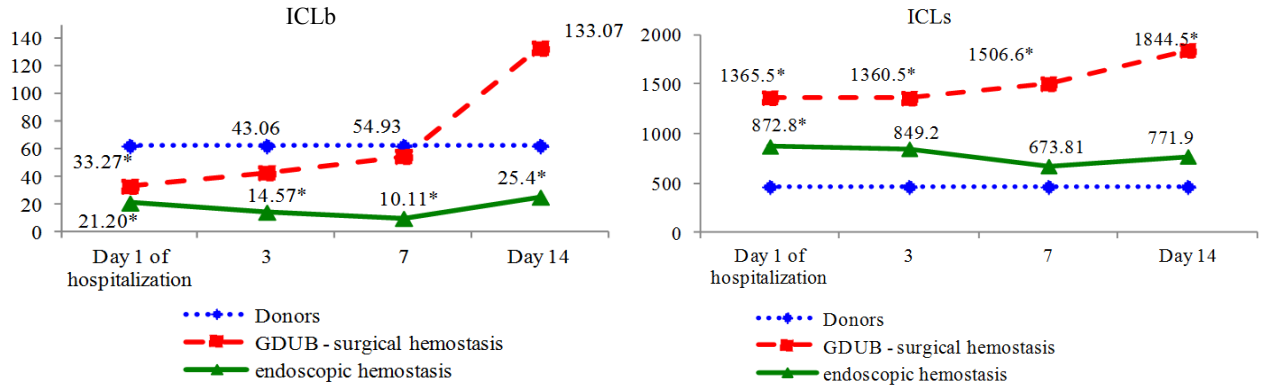


Fig. 4: Imbalance of free radical processes in GDUB patients with different secretory activity (# -true intergroup difference for p<0.05; * - difference of the parameter from the normal range for p<0.05; Mann-Whitney criterion)



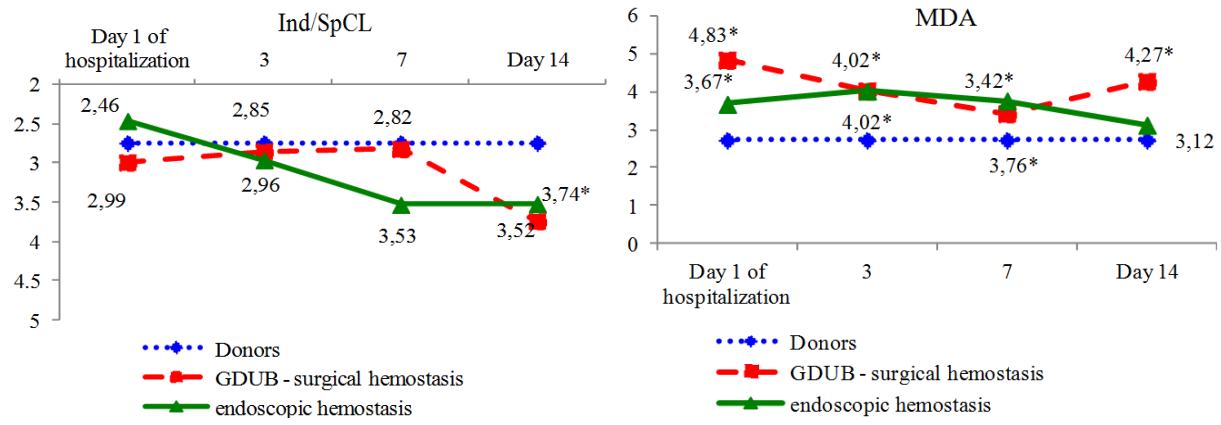


Fig. 5: Dynamics of markers of oxidative stress in patients with gastroduodenal ulcerous bleeding after endoscopic and surgical hemostasis *(* -p<0.05 - difference from the normal range)*

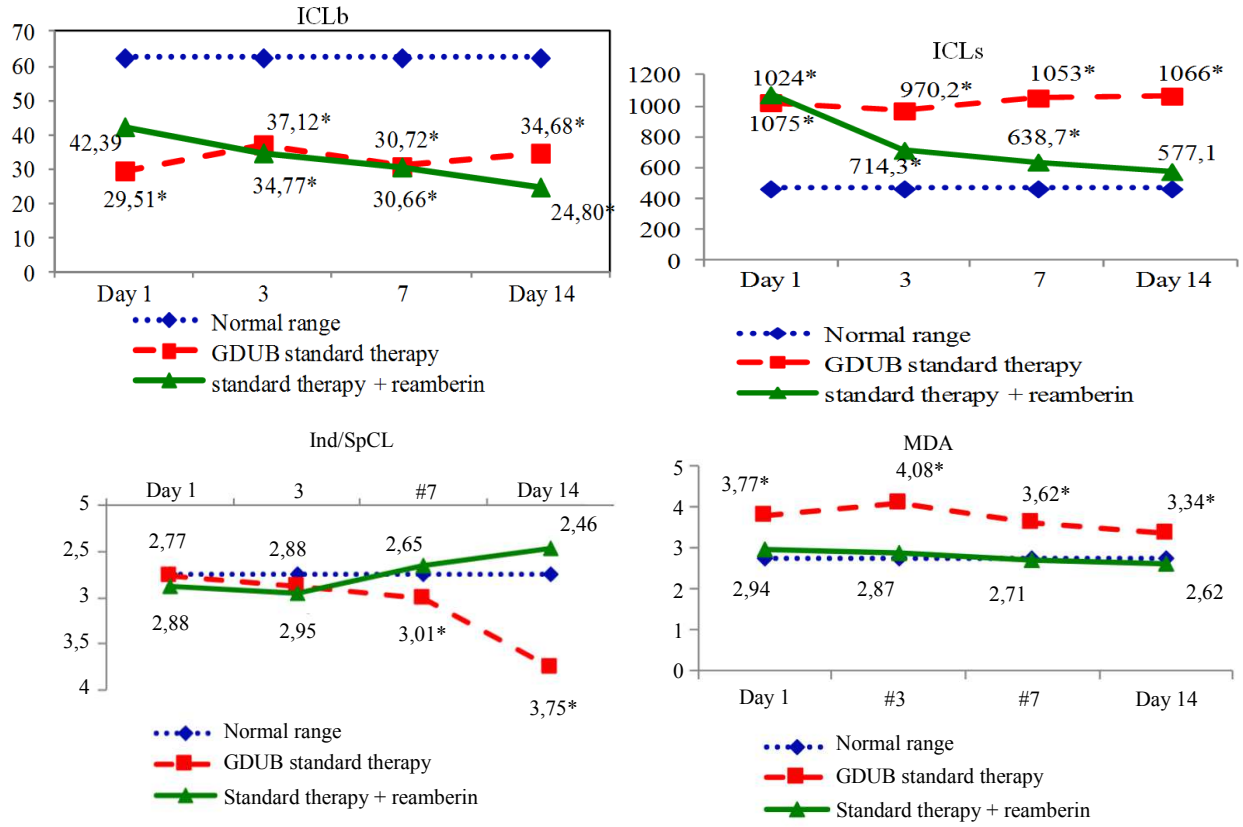


Fig. 6: Dynamics of the parameters of free radical processes in GDUB patients who received and did not receive antioxidant therapy as a part of the standard therapy (* -p<0.05 - significant difference from the normal range, # - p<0.05 - significant intergroup difference in the indicator at the certain time point of the study)

Analysis of the dynamics of FRP in patients with different levels of gastric secretion revealed that disbalance of free radicals at normo- and hypoacid pH was more pronounced throughout the observation period. The appointment of the AO therapy as a part of the standard treatment of the GDUB patients from the first day results in the stabilization of free radical processes in patients with increased and, especially, with reduced secretory activity of the stomach. This scientific fact indicates the preservation of cell viability and allows us to recommend an early inclusion of antioxidant therapy in the treatment regimen of GDUB patients regardless of the secretory activity of the stomach (Fig. 7).

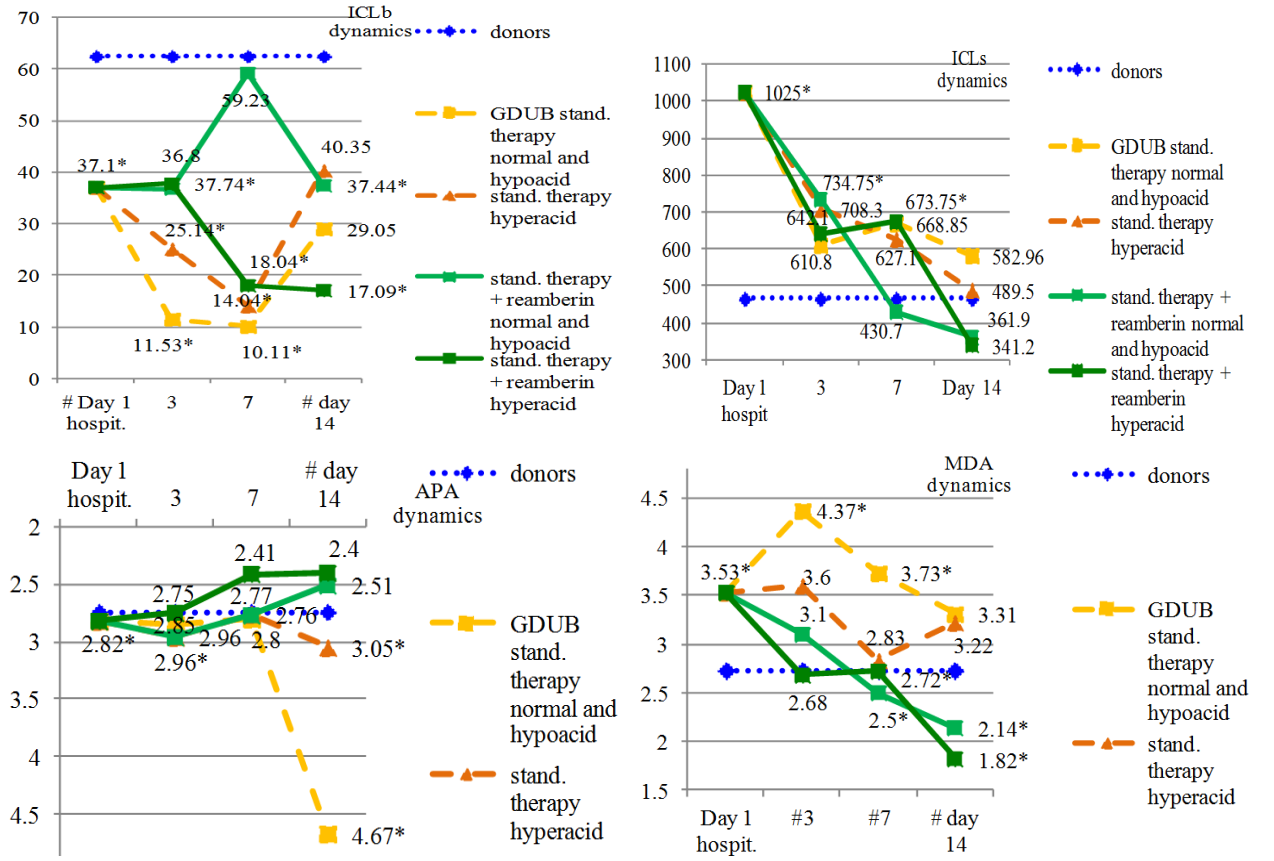


Fig. 7: Dynamics of parameters of free radical processes in GDUB patients with different secretory activity of the stomach receiving and not receiving antioxidant therapy *(* -p<0.05 - significant difference in comparison with the norm; # - p<0.05 - significant intergroup difference in the indicator at the certain time point of the study)*

In cases where ulcers according to the esophagogastroduodenoscopy looked like chronic ones and patients had a history of ulcer or a clinical picture typical for the acid-peptic disease, an imbalance of free radical processes was moderate and ICLb, ICLs and MDA parameters returned to the normal range on days 7-14 of the study. In the patients with bleeding from acute ulcers, an imbalance of free radical processes was more pronounced and by day 14 only ICLb normalized, while ICLs was 3.7 times higher, APA was 1.5 times lower, MDA was 1.34 times higher at day 14 of the study. Assignment of AO therapy to patients with gastroduodenal ulcerous bleeding from chronic ulcers led to normalization of both oxygen and peroxide-lipid parameters already by day 3 of the study and in patients with gastroduodenal ulcerous bleeding from acute ulcers – by days 3-14 (Fig. 8).

Clinical and Laboratory Evaluation of the Effectiveness of the Antioxidant Therapy in Patients with Ulcerative Gastroduodenal Hemorrhage

The comparative analysis of the degree of severity of the condition according to the MODS scale within the same group of patients with different secretory activity of the stomach showed a significant efficacy of the performed therapy at various observation times in the group of standard antisecretory therapy. In the group of patients who received additional antioxidant therapy, arameters of the severity of the state according to the MODS scale improved with respect to the comparison group ($p<0.001$). When conducting a comparative analysis at the same time points, a positive significant difference was observed, beginning from day 3 of the therapy up to day 14 of follow-up, also indicating a positive effect of antioxidant therapy on the severity of the condition ($p<0.05$) (Fig. 9).

The conducted correlation analysis between the initial MODS parameters and the dynamics of the change in MODS scale revealed a strong positive correlation ($r = 898$, $p<0.001$). This confirmed once again positive impact of the AO therapy on the rate of recovery from severe clinical situations of GDUB patients.

The dynamics of laboratory indicators revealed the prolonged depression of total protein, SaO_2%, RBCs and hemoglobin, as well as leukocytosis and elevated lactate level in dynamics. Administration of the AO therapy positively influenced the above-noted lab markers.

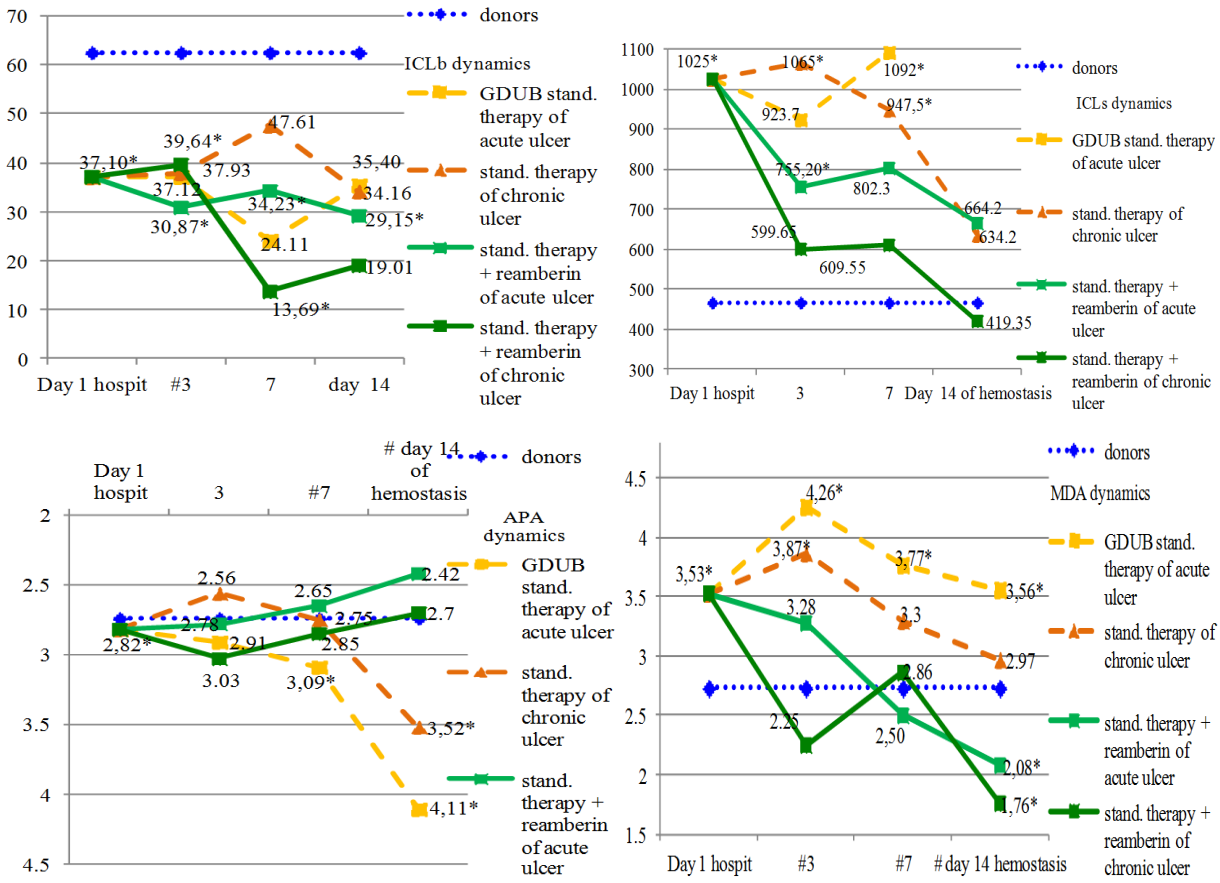


Fig. 8: Dynamics of ICLb, ICLs, APA and MDA parameters in patients with various types of gastroduodenal ulcerous bleeding who received and did not receive antioxidant therapy *(* -p<0.05 - significant difference in comparison to the normal range, # - p<0.05 - significant intergroup difference of the indicator at the certain time point of the study)*

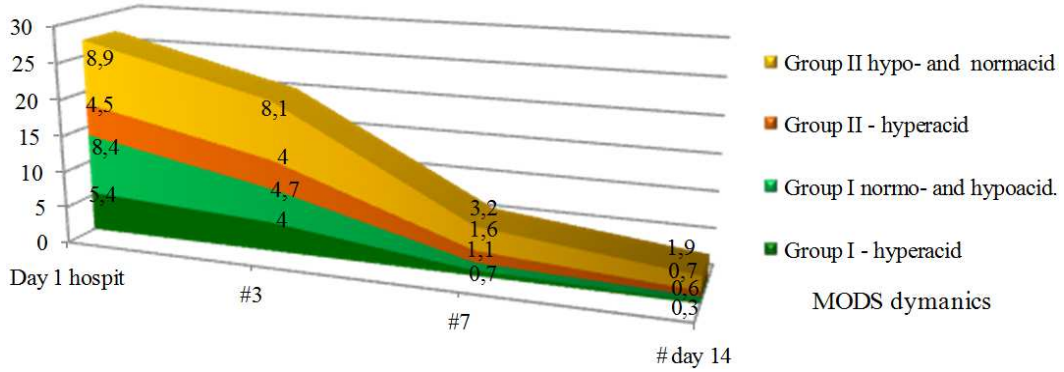


Fig. 9: Dynamics of the severity of the condition of GDUB patients who received and did not receive antioxidant therapy according to the MODS scale (points) depending on the secretory activity of the stomach *(# -p<0.05-significant intergroup difference of the parameter at the certain time point of the study)*

On the background of the AO therapy blood lactate decreased more quickly and qualitatively, indicating an expediency of its conduct. The correlation analysis showed a significant direct correlation between the level of blood lactate and such markers of oxidative stress as APA and MDA (r = 0.242, p = 0.030).

Addition of the AO therapy to the scheme of the standard treatment of the GDUB patients promoted improvement of the clinical picture of the disease, reduction of the periods of scarring and epithelialization of acute ulcers 1.32 times, chronic ulcers - 1.22 times (p<0.01), duration of the ICU stay - 1.31 times (p<0.01).

The periods of scarring and epithelization on the average were 13.6±4.51 days in the comparison group and 10.3±1.82 days in the main group ($p<0.01$). The duration of stay in the ICU in the comparison group was 5 days on average (Me) (Q25 = 2; Q75 = 11; 9.11±10.17 days) and in the main group - 3 days (Q25 = 2; Q75 = 6; 6.39±8.45 days (that was 2 days less; $p<0.05$).

In the standard therapy group, the recurrence rate of GIB was 17.6% (n = 16), including the only case in 15.4% patients (n = 14) [6 (9.7%) from acute ulcers; 8 (27.6%) from chronic ulcers] and 2 cases (3.2%) - repeatedly (only in patients with acute ulcers). In patients of the AO group, recurrence of GIB was observed 1.39 times less frequently, in 12.9% (n = 8) [6 (13.6%) - acute; 2 (11.2%) - chronic ulcers].

Operative treatment was performed in 21 (13.7%) patients (6 (9.7%) of the test group and in 15 (16.5%) patients in the comparison group). It was GIB relapse to be the reason for the surgical operation in the main group. In the comparison group, 13 patients underwent surgery, 1 patient was treated due to inefficiency of endoscopic hemostasis and 1 person was at risk of recurrence.

Postoperative complications were observed in 7.8% (n = 12) of cases, including 3 (4.8%) cases in the AO therapy group (2 (4.5%) with acute and 1 with chronic ulcer) and 9 (9.9%) cases in the standard therapy group (acute ulcers - 2 (3.2%) cases, chronic ulcers - 7 (24.1%) cases. Thus, introduction of the AO therapy in the complex treatment of GDUB patients showed an advantage, reducing all of the above-noted complications by a factor of 1.7 ($p<0.05$). We registered significant reduction in various surgical problems (bleeding relapse, complications of the early postoperative period) in the GDUB patients receiving AO by an average of 1.86 times (absolute risk reduction (ARR) - 6.5%; relative risk reduction (RRR) - 21.2%) ($p = 0.003$). Calculation of the effectiveness of the AO therapy in patients with acute rhabdomyolysis from acute ulcers: ARR - 4.2%; RRR - 120%; from chronic ulcers – ARR – 29.5%; RRR – 42.9%.

The results obtained in the course of the study showed a significant decrease in mortality rate in the GDUB patients who received the AO therapy 2.04 times ($p<0.001$) *(CAP - 11.8%, OR - 51.1%)*. In the standard therapy group, mortality rate was 23.1% (n = 21), including 15 (24.2%) patients with acute ulcers and 6 (20.7%) patients with chronic ulcers. Causes of the fatal outcome included severe posthemorrhagic anemia (n = 1), acute impairment of cerebral circulation (n = 4), polyorganic insufficiency syndrome (n = 6), acute cardiovascular insufficiency (n = 5), pneumonia (n = 2), acute myocardial infarction (n = 1), pulmonary embolism (n = 1), pancreatic necrosis (n = 1). In the main group, 7 (11.3%) patients died, including 6 (13.6%) with acute ulcers and 1 (5.5%) with chronic ulcer. The fatal outcome was caused by an acute cardiovascular failure (n = 4), posthemorrhagic anemia (n = 2), stroke (n = 1). The data obtained allow us to state that inclusion of drugs with antioxidant properties is an important component of pathogenetic treatment and complex conservative therapy and various types of surgical intervention in patients with bleeding of varying severity from acute and chronic ulcers and with different levels of gastric secretion.

Outcomes

1. Acute ulcerative gastroduodenal hemorrhages are accompanied by FRP imbalance: ICLb is 1.75 times lower, ICLs is 2.35 times higher, APA is 1.07 times lower and MDA is 1.36 times higher compared to the normal range. Oxidative stress is amplified and shifted to the peroxide-lipid side of disregulation in proportion to the duration and severity of bleeding
2. The greatest FRP imbalance was detected in case of unfavorable outcome of GDUB. Dysregulation of all FRP markers in deceased patients on day 1 of hospitalization with an increase in MDA 2.23 times was found; in absolute figures it was equal to MDA level >6.2 μmol L^{-1}; the 1.31-fold decrease in APA values, the 1.37-fold decrease in ICLb and the 2.19-fold increase in ICLs, significantly different from the level of FRP markers with a favorable outcome, were found already on day 1 of the disease
3. Disbalance of oxygen and peroxide-lipid FRP stages is most pronounced in patients with gastrointestinal bleeding from acute hypoacid ulcers from the stomach and duodenum, which is expressed in a significant increase in ICLs 1.98 times and MDA - 1.38 times, as well as the 2.11-fold decrease in ICLb and the 1.14-fold decrease in APA values. The course of FRP in patients with gastrointestinal bleeding from chronic ulcers on the background of hyperacidity is characterized by a favorable adaptive response, which is expressed in lower MDA intensification (by 39%) and stable APA
4. After open surgical interventions and anesthesia, patients with GDUB revealed more significant FRP disregulation compared to endoscopic hemostasis; it was preserved and even tended to activate at time of the discharge (by 14 days), while an imbalance in FRP after endoscopic methods of bleeding cessation in these terms tended to normalize; MDA value was 1.37 times lower
5. The use of antioxidants in complex therapy of patients with GDUB allows to normalize the imbalance of FRP. A significant intergroup difference was registered by MDA indicators on days 3-7-14 (less in the group of antioxidant therapy by 1.42, 1.33 and 1.28 times, respectively); by APA - on days 7-14 (increased adaptive-protective activity by 1.14 and 1.52 times, respectively)

6. Early inclusion of the antioxidant therapy in the complex treatment of GDUB patients contributes to reduction in the epithelization of acute ulcers 1.32 times on the average, the 1.22-fold decrease in the scarring of chronic ulcers, the 1.86-fold decrease in the incidence of complications; the 1.12-fold reduction in the duration of stay in the hospital and the 1.31-fold decrease in the duration of stay in intensive care units, as well as reduction in the absolute risk of lethal outcomes by 11.8%

Discussion

The analysis of free radical processes in patients with gastrointestinal ulcerous bleeding revealed the significance of oxidative stress, which is most pronounced in somatically severe patients with acute ulcers. In case of mild form of GDUB, disorders of free radical processes affect only an oxygen stage of oxidative stress and represent an adaptive compensatory mechanism. Intensification of free radical processes as it grows consists of a decrease in the activity of the oxygen imbalance and a significant increase in the lipid imbalance. The level of anti-peroxide activity can be recommended as an early prognostic marker of the course and outcome of the disease. Imbalance of free radical processes continues for a long time until discharge of patients from the hospital. The data obtained serve as a basis for recommending the earliest possible inclusion of antioxidant energy-correcting drugs in the complex of therapeutic measures of the GDUB patients.

The effectiveness of the use of energy-correcting antioxidant therapy has been confirmed by the example of correction of oxidative stress in patients with gastroduodenal ulcerous bleeding of various genesis and severity. The positive effect of succinic acid on the markers of oxidative stress was accompanied by the improvement in the clinical picture of the disease and results of the treatment.

Conclusion

The conducted study has a certain degree of innovation. For the first time we have obtained the reliable data on correlation of markers of different FRP stages with severity of hemorrhage, condition and etiology of GDUB. The possibility of using the malondialdehyde marker as an early diagnostic parameter for assessing the severity of the course, prognosis and effectiveness of GDUB treatment of various etiologies was demonstrated. Based on the results of the treatment and data on the dynamics of FRP course, the purpose and positive effect of antioxidant therapy in GDUB patients with different secretory activity of the stomach, studied by means of pH-metric, was revealed.

Thus, our Work has Promising and Reliable Practical Recommendations

1. Oxidative stress markers allow predicting the course of the disease and choosing an appropriate method for timely surgical or conservative treatment, therefore it is advisable to study the parameters of an oxidative stress in GDUB patients of different etiology and severity starting from the first day of hospitalization
2. The degree of dysregulation of the course of FRP in patients with GDUB (revealed during admission) can serve as an additional objective criterion in choosing a surgical or endoscopic method of hemostasis
3. An early increase in MDA level above 6.2 μmol L^{-1} in GDUB patients indicates that there is a high risk of an adverse outcome, including those resulting from a high incidence of postoperative complications, which may be regarded by the medical council as an argument against possible surgical intervention. MDA level below 3.2 μmol L^{-1} determines the high effectiveness of the treatment
4. Reduced secretory function of the stomach, revealed by intragastric pH-metry during an urgent esophagogastroduodenoscopy, can help in determining ischemic nature of the bleeding ulcer
5. In GDUB patients of any severity, especially with reduced secretory activity of the stomach and in the presence of vascular comorbidity, we advise an early start of antioxidant correction of FRP dysregulation; duration of the therapy should be at least 7-8 days and it should be controlled by oxidative stress parameters

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Author's Contributions

All authors participated in all experiments, coordinated the data-analysis and contributed to the writing of the manuscript.

Ethics

Authors declare no conflicts of interest.

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