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INFLUENCE OF REDUCED GLUTATHIONE ON THE INTENSITY OF OXIDATIVE STRESS IN PATIENTS WITH ULCER OF STOMACH AND DUODENAL WITH FIXED METAL DENTURES

Abstract. *The efficiency of restored glutathione (hepaval) in the therapy of the patients with gastric and duodenal ulcer with fixed metal dentures has been studied. It was established that the use of hepaval is significantly more effective compared to the use of vitamin E on the stable inhibition of the lipid peroxidation and oxidative modification of proteins. Combined enteral use with local applications on the oral mucosa of restored glutathione showed higher efficiency on the rebalancing of oxidant-antioxidant system at the both levels: systemic and local, as a result of elimination of negative prooxidant effect of fixed metal dentures in patients with gastric and duodenal ulcer compared to enteral use of restored glutathione.*

Key words: *gastric ulcer, fixed metal dentures, restored glutathione.*

Introduction. Relevance of the study is caused by the high incidence of combination of dental disease and acid diseases (AD) of gastric (GU) and duodenal ulcers (DU), leading to tooth loss [2,5]. This process is caused by anatomical and physiological proximity of oral cavity and digestive tract (DT), community of innervation and humoral regulation, that create preconditions for the involvement of periodontal tissues in pathological process at AD [2,5,6]. Pathology of periodontal tissues is diagnosed in 92% of patients with GU and DU, and is mostly represented by generalized periodontitis, which can cause tooth loss [2].

Particularly, activation of lipid peroxidation (LPO) and of oxidative modification of proteins (OMP) in gastroesophageal acid reflux, inflammation of periodontal tissues, is associated with pathogenic influence of hydrochloric acid, proteolytic enzymes, microorganisms of plaque. This activation is manifested by the development of inflammation, tissue hypoxia, apoptosis acceleration and intensified desquamation of the epithelium of the mucous membranes both of the digestive tract and the mouth, significant imbalance of generation of elements of

connective tissue, which fix the tooth, which in turn accelerates the loss of teeth [2,3,4]. Probably, the situation is complicated by the use of fixed metal containing dentures (FMD), as they provoke LPO and OMP and promote the intensifying of all known ways of progression of pathological states.

The development of ulcer and inflammatory disease of periodontium is a result of an imbalance between defense mechanisms and factors of aggression with a predominance of the latter [2,5]. Among the protective factors of periodontium and mucous membrane of gastroduodenal area the state of antioxidant system (AOS) is essential [1,6].

There are significant intensity of oxidative stress and significant imbalance AOS at the presence of FMD in patients with GU and DU. Thus, it would be logical to study the efficacy of antioxidants in order to test the working hypothesis about their positive influence on reducing of intensity of LPO and OMP.

Objective: to find out the efficacy of reduced glutathione (GW) in combined therapy of GU and DU in acute phase in the presence of fixed metal dentures by study of intensity of LPO and OMP in the blood and oral fluid.

Materials and methods. 45 patients with GU and DU in the acute phase of FMD were examined. For determination of efficiency of therapy 3 groups of patients were formed. The patients were randomly assigned by the age, sex, stage of ulcer and its current phase. The first group of patients (control 1-14 people) in addition to the traditional therapy of the underlying disease received 100 mg of vitamin E once a day for 30 days. The second group of patients (study 2-16 people) in addition to the traditional therapy of the underlying disease received restored glutathione (hepaval) enterally in a dose of 250 mg once a day for 30 days. The third group of patients (study 3 - 15 people) in addition to the traditional therapy of the underlying disease received 250 mg of RG (hepaval) enterally 1 time a day, and 250 mg RG locally as application to gums 1 per day (at night) for 30 days.

Content of molecular products of LPO – isolated double bonds (IDB) in compounds, diene conjugates (DC) – In the blood was studied by I.A. Volchehorsky et al., content of malonic aldehyde (MA) in oral fluid was studied by U.A. Vladymyrov, A.I. Archakov. Intensity of OMP in blood serum was determined by the method of Dubinina O.Ye. et al. in modification of the I.F. Meshchysen. The activity of catalase was studied by M.A. Koroliuk et al. The enzyme activity was calculated per 1 g of Hb. Statistical analysis of data was performed using modern methods of variation statistics.

Results and discussion. Before therapy there is considerable intensity of oxidative stress in patients with GU and DU with FMD (Table. 1), which is significantly higher compared to those in patients with ulcer with intact tooth row ($p < 0.05$) and fixed metal-ceramic dentures ($p < 0.05$).

At the proposed therapy in patients with ulcer there is a significant decrease in the intensity of LPO (Table. 1). As a result of antioxidant action RG there is a more significant decrease in content of LPO products in the blood serum of patients of 2 and 3 groups already on the 30th day of therapy ($p < 0.05$): content of MA in the blood serum in 2 group decreased on 27.9% compared to initial values ($p < 0.05$), and

the same content in 3 group decreased more significantly: on 30.7% ($p < 0.05$). Instead effect of vitamin E in the control group on parameters of intensity of LPO by the content MA in the blood serum reveals just a downward trend ($p > 0.05$). In one month after therapy MA content in the blood serum in patients of 2 and 3 groups are significantly lower (in 38.9% and 40.0% respectively ($p < 0.05$)) compared to the content on the 30th day of therapy and compared to the content in patients of the control group ($p < 0.05$).

As to the influence of just enteral and enteral with local impact of RG, the analysis of the content of MA in the blood serum after therapy, and at all times of observations indicates the absence of significant changes ($p > 0.05$) (Table. 1). It should also be noted that the achieved stabilization of parameters in patients of 2 and 3 groups is stable and it can be observed even in 6 months after therapy ($p < 0.05$).

Contents of intermediates of LPO in the blood change more significantly under the influence of the therapy (Table. 1). Thus, content of IDB in the blood in patients of 1 group decreased in 1.4 times ($p < 0.05$), in patients of 2 group – in 2.0 times ($p < 0.05$), in patients of 3 group – in 2.1 times ($p < 0.05$), with the existence of statistically significant intergroup differences only compared to group 1 ($p < 0.05$). The decrease in the content of DC in blood during therapy is the less: in patients of 1 group - on 11.4% ($p < 0.05$), 2 group - on 39.1% ($p < 0.05$), 3 group - on 39.8% ($p < 0.05$) with the existence of statistically significant intergroup difference only compared to the parameters of 1 group ($p < 0.05$). Thus, the efficacy of the proposed therapy with the inclusion of RG is higher compared to the use of natural antioxidants (vit. E) due to the intensity of effect on LPO.

The study of the effectiveness of combined therapy that includes RG showed a significant effect on the intensity of oxidative modification of proteins (Table 1). Thus, content of R-AKDNP in the blood of patients in all groups decreased significantly compared with 1, 2, 3 groups, in 1.3 times ($p < 0.05$), in 1.6 times ($p < 0.05$) and in 1.7 times ($p < 0.05$) respectively with the reliable intergroup differences

Table 1

Parameters of intensity of lipid peroxidation and oxidative modification of proteins in blood of patients with GU and DU FMD during therapy (M±m)

Time of observation	Parameters, measurement unit	Groups of examined patients		
		Group 1 (n=14)	Group 2 (n=16)	Group 3 (n=15)
HI	MA, μmol/l	2.53±0.07		
	IDB, E220/ ml.bl.	2.62±0.03		
	DC, E232/ ml.bl.	1.46±0.02		
	R-AKDNPH	1.37±0.02		
	N-AKDNPH	14.13±0.15		
Before therapy	MA, μmol/l	4.52±0.13 *	4.48±0.12 *	4.50±0.14 *
	IDB, E220/ml.bl.	6.48±0.06 *	6.49±0.07 *	6.48±0.06 *
	DC, E232/ ml.bl.	2.70±0.06 *	2.74±0.05 *	2.69±0.06 *
	R-AKDNPH	2.68±0.03 *	2.70±0.02 *	2.69±0.03 *
	N-AKDNPH	21.51±0.45 *	22.18±0.39 *	21.29±0.43 *
After therapy	MA, μmol/l	4.03±0.12 *	3.23±0.18 */**/#	3.12±0.21 */**/#
	IDB, E220/ ml.bl.	4.50±0.14 */**	3.18±0.13 **/ #	3.07±0.14 **/ #
	DC, E232/ ml.bl.	2.39±0.07 */**	1.67±0.05 **/ #	1.62±0.02 **/ #
	R-AKDNPH	2.11±0.06 */**	1.72±0.04 */**/ #	1.57±0.03 */**/ #/ ##
	N-AKDNPH	19.21±0.54 */**	16.10±0.37 */**	15.32±0.32 */**/ #
In 1 month after therapy	MA, μmol/l	3.93±0.41 *	2.75±0.15 **/ #	2.67±0.13 **/ #
	IDB, E220/ ml.bl.	4.12±0.17 */**	3.08±0.11 */**/ #	2.85±0.02 **/ #/ ##
	DC, E232/ ml.bl.	1.96±0.13 */**	1.59±0.07 **/ #	1.48±0.06 **/ #
	R-AKDNPH	1.93±0.09 */**	1.50±0.02 */**/ #	1.39±0.01 **/ #/ ##
	N-AKDNPH	18.53±0.48 **	15.45±0.12 */**/ #	14.67±0.11 **/ #/ ##

Notes. 1. * - the difference is statistically significant compared to the parameters in healthy individuals ($P < 0.05$); ** - the difference is statistically significant compared to the parameters before treatment ($P < 0.05$);

- the difference is statistically significant compared to the parameters in group 1 patients after therapy ($P < 0.05$);

- the difference is statistically significant compared to the parameters in group 2 patients after therapy ($P < 0.05$).

2. Measurement units of content in of R-AKDNPH and N-AKDNPH blood - opt.un.g / l of protein.

between all groups ($p < 0.05$). The content of N-AKDNPH during therapy also decreased significantly: in 1, 2, 3 groups, in 10.7% ($p < 0.05$), in 27.5% ($p < 0.05$) and in 28.1% ($p < 0.05$) respectively with the reliable intergroup differences between all groups ($p < 0.05$). The mentioned indicates not only higher efficiency of RG compared to vitamin E, but also significantly higher efficiency of combined enteral and local use of RG on intensity of systemic oxidative stress in relation to impact on

OMP. Moreover, the decrease in intensity of OMP is stable only in patients of 2 and 3 groups throughout all the observation period.

While study of the contents of studied parameters in oral fluid the significant decrease in the intensity of LPO in the oral mucosa at the proposed therapy is was found out (Table 2). The result of antioxidant action of RG is higher statistically significant decrease in content of LPO products in the oral fluid, especially in patients of 3 group already after 30 days of

therapy (p<0.05). Thus, the content of MA in group 1 patients is not statistically significant. In group 2 MA content decreased on 27.5% compared to initial values (p<0.05) and similar parameters in the 3rd group decrease even more, on 45.2% (p<0.05), with the intergroup differences when compared among all groups (p

<0.05).

In 30 days after treatment MA contents in oral fluid in patients 2 and 3 groups are significantly lower (on 32.9% and 46.2% (p<0.05)), compared to the parameters before therapy, and compared to the parameters in the control group of patients (1) (p<0.05).

Table 2
Parameters of intensity of lipid peroxidation and antioxidant system state in the oral fluid of patients with GU and DU with FMD during therapy (M±m)

Time of observation	Parameters, measurement unit	Groups of examined patients		
		Group 1 (n=14)	Group 2 (n=16)	Group (n=15)
HI	MA, μmol/l	1.50±0.23		
	DC, μmol/l	12.21±1.15		
	Catalase, mmol/min·l	2.72±0.19		
Before therapy	MA, μmol/l	4.23±0.21 *	4.25±0.17 *	4.23±0.19 *
	DC, μmol/l	39.42±1.63 *	39.79±1.57 *	40.08±1.66 *
	Catalase, mmol/min·l	1.46±0.07 *	1.44±0.09 *	1.43±0.08 *
After therapy	MA, μmol/l	4.15±0.24 *	3.08±0.13 */**/ #	2.32±0.12 */**/#/ ##
	DC, μmol/l	32.50±2.14 */**	25.18±2.19 */**/ #	14.22±1.14 **/ #/ ##
	Catalase, mmol /min·l	1.89±0.04 */**	2.37±0.03 **/ #	2.62±0.02 **/ #/ ##
	MA, μmol/l	3.97±0.35 *	2.85±0.15 */**/#	2.27±0.13 */**/ #/ ##
	DC, μmol/l	31.86±2.42 */**	18.53±1.17 */**/#	12.85±1.08 **/ #/ ##
	Catalase, mmol /min·l	1.96±0.15 */**	2.49±0.05 **/ #	2.68±0.04 **/ #/ ##

Notes. * - the difference is statistically significant compared to the parameters in healthy individuals (P <0.05); ** - the difference is statistically significant compared to the parameters before treatment (P <0.05); # - the difference is statistically significant compared to the parameters in group 1 patients after therapy (P <0.05); ## - the difference is statistically significant compared to the parameters in group 2 patients after therapy (P <0.05).

As to the influence of just enteral and enteral with local impact of RG, the analysis of the content of MA in oral fluid after therapy, and at all times of observations indicates the presence of significant changes (p<0.05) (Table. 1). Increase in the content of intermediates of LPO (DC) in oral fluid during therapy is higher than in the content of the final products (MA).

Thus, there is a decrease in DC content in 1.2

times in patients of Group 1 (p<0.05), in 1.6 times - in group 2(p<0.05), in 1.8 times - in group 3 (p<0.05) with the statistically significant intergroup difference not only compared to group 1 (p<0.05), but when comparing parameters between 2 and 3 groups (p<0.05). Thus, the efficacy of the proposed therapy with the inclusion of RG is higher not only in comparison with the use of natural antioxidants

(vit. E) by the intensity of influence on parameters of lipid peroxidation, but also at the combined use of RG enterally and locally by application to the oral mucosa in comparison with the only enteral use. The confirmation is considerable increase in the activity of the factors of LPO, particularly to treat oppressed catalase in oral fluid of patients with ulcer under the influence of combined therapy with RG (Table 2). During therapy the activity of catalase in patients of 1 group increases in 1.3 times ($p < 0.05$), 2 group - in 1.6 times ($p < 0.05$), 3 group - in 1.8 times ($p < 0.05$), that is the maximum of groups. Probably, these results may indicate the patients obtained the double dose of RG, as applied locally, RG eventually absorbed into the systemic blood flow and produced its systemic antioxidant effect, but the significant difference between parameters in groups 2 and 3 while studying of markers of OMP and LPO in systemic blood flow has been found out.

Conclusion. 1. Use of the reduced glutathione (hepaval) in the combined therapy of patients with GU and DU with the FMD is significantly more effective than the use of natural antioxidants (vitamin E) by a stable inhibition of processes activated by lipid peroxidation and oxidative modification of proteins.

2. Combined enteral and local use of glutathione reduced as applications on the oral mucosa showed higher efficiency compared to enteral use of glutathione as to restore of the balance of oxidant-antioxidant system both at the systemic and at the local levels, due to the elimination of negative prooxidant effect of fixed metal dentures in patients with gastric ulcer and duodenum ulcer.

Prospects for further research. Further studies may be devoted to evaluation of possible effect of reduced glutathione on parameters of antioxidant and detoxification systems of patients with gastric ulcer and duodenal ulcer that use fixed metal dentures.

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