Article

The Effectiveness of Treatment Used for Chronic Periodontitis, Involving Antioxidant Drugs, in Patients With Comorbid Pathologies.

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Abstract:

Rationale.Despite the ongoing research and the respectively taken preventive measures, the prevalence of periodontal diseases reveals no tendency towards a decrease. When against a number of somatic diseases (peptic ulcer, diabetes mellitus, etc.), inflammatory and destructive issues affecting periodontium turn even more aggressive, whereas conventional treatment fails to ensure stable long-term remission. Antioxidant drugs, while activating the energy-synthesizing functions of mitochondria, correct disorders in the microcirculation system, as well as they improve the rheological properties of blood, and activate the immune system.**Aim of study.**The study was aimed at producing clinical and lab-data based substantiation of employing antioxidant drugs within comprehensive treatment offered to cases of periodontitis where patients feature a comorbid pathology.**Materials and methods**.The study methods included a clinical and laboratory examination and treatment of 232 patients aged 18-60 whose diagnoses were K25 and K26, and who suffered from chronic periodontitis. The entire pool of patients was broken randomly into groups depending on the treatment offered for chronic periodontitis. In Group I (117 patients), the treatment was carried out following the StAR Clinical Recommendations, whereas Group II (115 patients) had Mexidol antioxidant drug included into the treatment plan. Both groups were given first-

line pharmacotherapeutic support for peptic ulcer disease. The control group were 25 basically healthy individuals.During the study, the oral fluid cytokine content (IL-6, IL-10, IL-12, IL-18), the proliferative activity of gingival epithelial cells (I_{Ki-67}, Iapopt, Ibcl-2) were identified, as well as gingival epithelial cells immune-positive to NO-synthase, endothelin-1 and melatonin were detected both prior to and after treatment. The obtained materials were processed with the EXCEL and STATISTICA 6.0 statistical software packages.**Results.**The comprehensive treatment of periodontitis employed to deal with cases featuring comorbid pathology, where Mexidol was added to the standard mode, resulted in normalized proliferation and apoptosis in gingival epithelial cells, as well as in positive dynamics in the quantitative density of gingival epithelial cells immune-positive to nitric oxide synthase and melatonin; another beneficial effect observed was concentration of the studied cytokines in the oral fluid that persisted after 2 months. However, there was hyperplasia of gum cells immune-positive to endothelin-1 to be seen in both groups of patients suffering from moderate and severe periodontitis..**Conclusion**.Mexidol, introduced into the treatment, allowed bringing down the recurrence rate and maintain periodontitis remission in 90.4% of patients with comorbid pathology.

Keywords: periodontitis, comorbid pathology, antioxidant drugs.

Introduction.

Inflammatory periodontal diseases rate among the leading issues faced by dentistry nowadays. Periodontitis is one of the causes behind connective tissue destruction, bone resorption and the development of periodontal pockets, which often leads to pathological mobility and loss of teeth [1-5].

The wide prevalence of this pathology, its progressive course and the low effectiveness of treatment and preventive measures mean that inflammatory diseases of periodontal tissues are to be viewed as relevant and serious not from both the medical stance, yet also from the social one [6-10].

The diagnosis of periodontal diseases relies on data coming from clinical and X-ray examination, which allows identifying the severity of a disease that has developed already [11-15]. Potential prediction of the disease course would make grounds for getting an idea of the content and scope of treatment measures, and for preventing possible exacerbation of periodontitis. The search for extra diagnostic criteria that would help obtain information concerning the patient's status in terms of belonging to a particular risk group, the disease course and the treatment effectiveness is something reasonable and clinically justifiable [16-22].

97% of patients with periodontal diseases have pathology of internal organs detected in them, this pointing at common pathogenetic links between the health issues [23]. The traditional methods used to treat inflammatory periodontal diseases are aimed at eliminating the microbial factor and imply the control of plaque development, the use of local and general anti-microbial, anti-inflammatory drugs, as well as at improving surgical approaches to eliminating the infection and destruction focus in the periodontium. However, they are not always effective enough and often are not enough to prevent the pathology worsening. Antioxidants and antihypoxants, if used in the comprehensive treatment of inflammatory periodontal diseases combined with gastric ulcer (GU) and duodenal ulcer (DU), present a promising option [24,25].

Recent years have witnessed an antioxidant like Mexidol (3-hydroxy-6-methyl-2-ethylpyridine succinate) – a substance structurally similar to vitamin B6 group compounds –

used successfully in many areas of clinical medicine [26]. The benefits that Mexidol offers include antioxidant, antihypoxic, immunomodulatory and antimicrobial effects [27,28].

Aim of study.

The aim of the study implied clinical and laboratory explanation for the use of antioxidant drugs in comprehensive treatment offered for chronic generalized periodontitis (CGP) in patients with comorbid pathology.

Materials and methods.

In order to carry out the effectiveness assessment for Mexidol introduced into the treatment of periodontitis against GU and DU, the 232 patients were divided into 2 main groups. Group I included 117 patients who were given standard dental treatment subject to the Clinical guidelines for the diagnosis of *Periodontitis*. In Group II (115 patients), Mexidol was added to the treatment plan. The drug in question was used according to the scheme as follows: 2 ml of 5% solution, intramuscular, 1 time a day, as well as applications 2-3 times a day into the periodontal pocket (preparation: open 1 ampoule of the drug to soak the turunda with the solution and to be further placed in the periodontal pocket for 20 minutes). The recommended procedure was brushing the teeth with toothpaste from the *MEXIDOL dent* series (2 times a day for 3-5 minutes). The control group included 25 virtually healthy individuals.

The treatment of patients with peptic ulcer disease relied on the Russian Gastroenterological Association (RGA) clinical recommendations, and included a proton pump inhibitor – Omeprazole (20 mg 2 times a day), as well as two antibacterial drugs: Clarithromycin (500 mg 2 times a day), and Amoxicillin (1 g 2 times a day for 7 days), then – Omeprazole (40 mg/ day for 4-6 weeks).

The clinical diagnosis was given based on the classification of periodontal diseases (1983, rev. in 2001), as well as on ICD-C-3. The GU diagnosis relied on the classical criteria [29] and was set in view of clinical, endoscopic, functional and morphological data.

The inclusion criteria for the patients to join the study were as follows: both sexes; age – 18-60; diagnosed chronic generalized periodontitis against GU and DU in the acute phase; signed protocol of informed consent concerning the purpose and type of the activity to be carried out.

The exclusion criteria were: dental anomalies and deformities; dentition extended defects and pathological erasure; orthodontic appliances; Gu and DU complications (bleeding, perforation); long-term non-scarring gastric ulcer (12+ weeks) and duodenum ulcer (8+ weeks); concomitant diseases affecting the digestive system (chronic pancreatitis, chronic cholecystitis, chronic hepatitis in its acute phase); diabetes mellitus; severe concomitant health issues (myocardial infarction, acute cerebrovascular accident); tumors of any localization; complicated allergy history in relation to drugs to be used through the treatment; the patient's refusal to undergo examination.

To identify gum epithelial cells producing endothelin-1, melatonin and NO-synthase, as well as to study the proliferative activity of cells, an immunohistochemical study was performed using monoclonal mouse antibodies to NO-synthase (1:150, Novocastra), to endothelin-1 (Sigma, St. Louis, USA, titer 1:200), Ki-67 protein (1:100, Novocastra), Bcl-2 anti-apoptotic protein (1:100, Novocastra), rabbit antibodies to melatonin (1:100, CIDtech Res. Comp.). The proliferation index (Ki-67 nuclear label) and the apoptosis index were calculated as the rate (%) of positively colored nuclei of gingival mucosa epithelial cells based on the formula:

Ix (%) = N (x / N (i-heme) x 100, where N is the number of Moser-stained apoptotic nuclei or the number of Ki-67-positive nuclei per 1 sq.mm of the section area; N(i-heme) is the number of cell nuclei stained with hematoxylin on serial a slice at the examination area. Similarly to the apoptosis (Iapopt) and proliferation indices (I_{KI-67}), the Bcl-2 (which is an apoptosis suppressor) label index (Ibcl-2) was identified.

The indices were calculated in 10 view fields on three biopsy sections. The test area used to identify the indices included at least 2,000 cell nuclei. The concentration of IL-6, IL-10, IL-12 and IL-18 in the oral fluid was detected through a solid-phase enzyme immunoassay using a Uniplan enzyme immunoassay analyzer with the following kits: Interleukin-6 and Interleukin-10 (Cytokine, LLC, Russia), Interleukin-18 – IFA – BEST (Vector-Best, CJSC, Russia) and Interleukin-12+p40 (IBL, USA).

The statistical processing of the study results was performed with the EXCEL and STATISTICA 6.0 software package, where the average value and the error of the average were set employing the Student and Mann-Whitney reliability criteria. The study was approved by the Ethics Committee of the Saratov State Medical University.

Results

The effectiveness of the traditional treatment enhanced with Mexidol when dealing with patients suffering from periodontitis of various severity degrees has been proven through the positive dynamics of dental indices (Table 1).

Table 1. Dynamics of periodontium clinical indicators, examination carried out 2 months following treatment

Group of patients		SBI	PMA	OHI-s
Patients with mild CGP against GU	Prior to treatment, n=117	2.21±0.08	50.27±2.14	2.41±0.06
	Group I, n=62	0.62±0.07*	18.25±0.37*	1.38±0.07*
	Group II, n=55	0.30±0.05*#	5.88±0.32*#	1.06±0.06*#
Patients with moderate and severe CGP against GU	Prior to treatment, n=115	2.50±0.08	60.44±2.14	2.62±0.07
	Group I, n=55	0.76±0.08*	20.36±0.48*	1.56±0.08*
	Group II, n=60	0.35±0.07*#	12.24±0.45*#	1.25±0.08*#

Note: * the indicators are significantly different from the values registered prior to treatment; # - the indicators in Group II feature significant differences compared to the values in Group I ($p<0.05$).

According to all the respective index indicators (OHI-s, SBI, PMA), in Week 2 of the treatment and 2 months into the treatment following its start, the indicators in Group II patients were significantly lower than in Group I.

Remission of mild periodontitis in Group II was to be observed in all patients with an average of 9.75±0.26 days, respectively, which is in a shorter time if compared to Group I. Analyzing the postoperative period course following the surgical stage, we are safe to say that the

patients of Group II had pain and collateral tissue edema disappearing on Day 3.2 ± 0.3, whereas their counterparts of Group I featured similar phenomena on Day 4.7 ± 0.3. Healing at the surgical intervention spot in Group II was observed on average following 8.0±0.4 days, while in Group I – after 10.6±0.5 days ($p<0.05$).

An analysis of the regression of subjective and objective symptoms of periodontal diseases revealed that 2 months into the treatment, all the patients suffering from mild periodontitis had their remission remaining. Remission of moderate and severe periodontitis was identified in 95.7% of Group II patients and in 69% of the cases in Group I ($p<0.05$).

To obtain objective information concerning the periodontal tissues status after comprehensive treatment with Mexidol, the cell renewal dynamics was analyzed, as well as that of the status of neuroendocrine and cytokine regulation elements.

The results of morphometric analysis of gingival epithelial cells in Group II helped reveal improved proliferation and gingival epithelial apoptosis, along with positive dynamics in the quantitative density of epithelial cells immune-positive to nitric oxide synthase and melatonin, which could be accounted for by the anti-inflammatory and immunomodulatory effects of Mexidol. Furing that, hyperplasia of gum cells immune-positive to endothelin-1 persisted after treatment in both groups of patients with moderate and severe periodontitis(Table 2).

Table 2. The dynamics of cellular renewal in gingival epithelial cells, examination carried out 2 months following treatment

Group of patients		I $_{Ki-67}$ (%)	I apopt (%)	Ibcl-2 (%)
Virtually healthy individuals, n=25		13.5±0.7	0.52±0.04	2.9±0.3
Patients with mild CGP against GU	Group I, n=62	16.0±1.3	0.58±0.06	3.3±0.5
	Group II, n=55	14.0±0.8	0.47±0.06	3.8±0.5
Patients with moderate and severe CGP against GU	Group I, n=55	23.4±1.5*	0.67±0.05*	10.6±0.8*
	Group II, n=60	12.7±1.2#	0.50±0.04#	6.0±0.5*#

Note: the calculations are offered for 1 sq.mm of gum; *– the indicators reveal significant differences compared with the similar ones in the group including healthy individuals ($p<0.05$); # – indicators in Group II differ significantly from the values in Group I ($p<0.05$).

Analysis of cytokine balance indicators showed that 2 months following the treatment, Group II patients were observed to have improvement in IL-6, IL-10, IL-12 and IL-18 levels in oral fluid (Table 3).

Table 3. Quantitative description of gingival epithelial cells immune-positive to endothelin-1, melatonin and NO-synthase, patients examined 2 months following treatment

Group of patients	NO-synthase-immune-positive cells	Endothelin-1-immune-positive cells	Melatonin-immune-positive cells
Virtually healthy individuals, n=25	4.4±0.7	5.2±0.6	12.5±1.1

Patients with mild CGP against GU	Group I, n=62	5.7±0.6	6.0±0.7	13.2±1.0
	Group II, n=55	6.7±0.9	7.5±0.9	13.7±1.3
Patients with moderate and severe CGP against GU	Group I, n=55	10.3±0.9*	22.4±1.0*	8.2±0.7*
	Group II, n=60	5.5±0.7#	14.0±1.2*#	11.2±0.7#

Note: the calculations are offered for 1 sq.mm of gum; *– the indicators reveal significant differences compared with the similar ones in the group including healthy individuals ($p<0.05$); # – indicators in Group II differ significantly from the values in Group I ($p<0.05$).

Prospective follow-up in patients treated with Mexidol showed 100% of the patients having remission of mild periodontitis persisting after 6 months; for moderate and severe cases the same factor value was 90.4%. Talking of patients receiving conventional therapy, the rate of remission persisting for mild periodontitis cases was 95%, while for moderate and severe cases the rate in question was 58%(Table 4).

Table 4. Oral fluid cytokine content dynamics, patients examined 2 months following treatment

Group of patients		Indicator			
		IL-6, pg/ml	IL-10, pg/ml	IL-12, pg/ml	IL-18, pg/ml
Virtually healthy individuals, n=25		12.60±1.51	7.20±1.02	18.5±1.43	11.32±1.26
Patients with mild CGP against GU	Group I. n=62	16.82±1.57	6.40±0.94	23.5±2.59	12.40±1.43
	Group II. n=55	10.73±1.49	9.37±1.63	17.8±1.68	16.45±2.34
Patients with moderate and severe CGP against GU	Group I. n=55	48.6±4.37*	54.8±4.06*	22.72±2.6	38.3±2.53*
	Group II. n=60	15.4±2.05#	11.7±2.56#	20.82±1.0	14.6±1.64#

Note: * the indicators are significantly different from the values registered for healthy individuals; # - the indicators in Group II feature significant differences compared to the values in Group I ($p<0.05$).

Discussion.

The high clinical efficacy demonstrated by Mexidol introduced into treatment of periodontitis against peptic ulcer disease was associated with positive dynamics in the quantitative density of gingival epithelial cells immune-positive to nitric oxide synthase and melatonin, as well as with improved proliferation and apoptosis of gingival epithelial cells and cytokine content in oral fluid, and this outcome is generally in line with the data reported by other authors [30-32]. The results obtained allow claiming a restored balance between aggression factors and cytoprotective properties of periodontitis, which serves a favorable ground for remission in case of periodontitis.

Conclusion.

Using Mexidol allowed reducing preoperative preparation time down to 9-10 days, as well as arrive at stable remission for cases of moderate and severe periodontitis in 90.4% of the patients featuring comorbid pathology, within 6 months of follow-up.

Conflicts of interest. The author have no conflicts of interest to declare.

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