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STATE OF THE HEMOSTASIS SYSTEM IN PATIENTS WITH CHRONIC GENERALIZED PERIODONTITIS IN ALTERNATIVE METHODS OF TREATMENT

Abstract: The aim of the research was to study the indicators of the hemostasis state in the blood and oral fluid in chronic generalized periodontitis (CGP) of moderate severity before and after the standard treatment and with the use of the neurotropic drug «Cortexin». The study included 60 patients aged 25-60 years, divided into 4 groups of 15 persons with moderate CGP and 15 healthy individuals aged 18-24 years forming the control group. The analysis shows the insufficient effectiveness of standard treatment in chronic generalized periodontitis of moderate severity, and the inclusion of «Cortexin» in therapy leads to an improvement or normalization in the hemostasis system in young and middle-aged people.

Keywords: periodontitis, oral fluid, hemostasis, fibrinolysis, 'Cortexin'.

Introduction. Inflammatory periodontal diseases are quite common pathologies, in particular chronic generalized periodontitis - one of the most complex pathologies of the maxillofacial region, with physical, psychological suffering, leading to early tooth loss, reduced functional capabilities of the denture system, foci formation of chronic infection, leading to the development of somatic pathology and sensitization of the body [2. 4. 10. 11. 15-17]. Various scientific researches present that the life quality in chronic generalized periodontitis is characterized as low [16, 18-20].

Hemostasis system changes in chronic generalized periodontitis are widely discussed in studies [3, 8, 9, 12-14]. We need a multilateral study of the mechanisms of disease development in order to study and understand etiopathogenesis, as well as prevent exacerbation of the course of the disease and its complications due to the prevalence of chronic generalized periodontitis and the insufficient effectiveness of treatment.

The aim of the research is to identify the dynamic features of the hemostasis system condition in blood and oral fluid in the complex treatment of chronic generalized periodontitis by using the neurotropic drug Cortexin.

Research materials and methods. During 2016-2018, 60 patients with chronic generalized periodontitis (CGP) aged from 25 to 60 years old were examined, who were treated in the clinic dental department No. 1 of Chita State Medical Academy. All patients had the moderate chronic generalized periodontitis. 4 clinical comparison groups were formed for the research: the 1st Group - 15 patients aged 25-44 years old with CGP receiving standard treatment; Group 2 - 15 CGP patients aged 45-60 years old receiving standard treatment; Group 3 - 15 patients aged 25-44 years old with CGP receiving Cortexin (a dose of 10 mg 10 days, intramuscularly) in standard therapy; Group 4 - 15 patients aged 45-60 years old with CGP receiving Cortexin (a dose of 10 mg 10 days, intramuscularly) in

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Table 1

The effect of therapy on the state of hemostasis system in patients with CGP [Me (25-75 0/00)]

Indicator	Control (n = 15)	Standard treatment (n = 15)		Standard treatment + Cortexin (n = 15)	
		before treatment	after treatment	before treatment	after treatment
CGP patients of young age (25-44 years old)					
APTT, c	43.10 (40.5; 44.9)	38.9* (37.8; 39.7)	39.6*▲- (38.8; 39.8)	37.9* (37.5; 39.5)	40.95▲▪ (40.6; 41.4)
MHO	1.05 (1.0; 1.1)	1.2* (1.2; 1.2)	1.1 (0.95; 1.21)	1.19* (1.1; 1.3)	1.05▲ (1.0; 1.14)
Thrombin time, s	17.2 (17.2; 17.3)	15.8* (15.6; 16.2)	16.1*▲ (15.7; 16.6)	15.0* (14.5; 15.4)	17.1▲ (16.9; 17.4)
Fibrinogen, g/l	2.75 (2.3; 3.0)	4.3* (3.9; 4.6)	4.1*▲ (3.8; 4.4)	4.2* (3.9; 4.4)	3.5▲▪•
FMC, mg/100 ml	3.00 (2.90; 3.0)	5.1* (5.0; 5.8)	5.3*▲ (5.0; 5.4)	5.2* (5.0; 5.5)	3.5▲▪•
Fibrinolysis, min	141.00 (138.0; 147.0)	178.5* (177.0; 182.5)	164.00*▲ (159.0; 167.0)	179.2* (176.0; 182.0)	146.0▲▪•
CGP patients of young age (45-60 years old)					
APTT, s	43.10 (40.50; 44.90)	34.8* (29.5; 36.5)	37.60*▲ (36.4; 38.5)	34.7* (32.5; 36.5)	40.4▲▪•
INR	1.05 (1.00; 1.10)	1.2* (1.13; 1.2)	1.2* (1.11; 1.21)	1.2* (1.13; 1.2)	1.07▲▪ (1.0; 1.1)
Thrombin time, s	17.20 (17.20; 17.30)	14.8*▪ (14.3; 14.9)	15.40*▲•	14.6*▪ (14.3; 14.6)	16.9▲▪ (16.5; 17.0)
Fibrinogen, g/l	2.75 (2.30; 3.00)	5.4* (5.1; 5.6)	5.3*• (5.2; 5.6)	5.5* (4.8; 5.7)	3.2▲▪• (3.1; 3.5)
FMC, mg/100 ml	3.00 (2.90; 3.00)	6.1* (6.0; 6.6)	6.0*▲ (5.8; 6.2)	6.0* (5.8; 6.2)	4.10*▲▪ (3.8; 4.20)
Fibrinolysis, min	141.00 (138.0; 147.0)	189.1* (183.0; 194.5)	177.00*▲ (175.0; 180.0)	188.9* (181.8; 189.8)	154.0▲▪• (152.25; 158.0)

Note: n is the number of examined; * - the significance of differences compared with control (Mann-Whitney test); ▲ - differences in values compared to the baseline (Wilcoxon test); ▪ - differences in values between groups; • - differences in values between treatment options (Mann-Whitney test).

standard therapy. The control group was 15 practically healthy individuals without acute and chronic periodontal diseases at the time of research aged from 18 to 24 years old.

Standard treatment of patients with CGP included: hygiene training of oral cavity, professional hygiene and sanitation of oral cavity, antiseptic processing of tissues of the parodont with 0.06% Chlorhexidine solution, hardening bandage with Cholisal and "Metrogyl Denta" for 20 min. 2 times a day within 10 days, the Vector therapy, ozonterapy, a selective grinding, splinting with "GlasS-pan". Cortexin was used intramuscularly in complex treatment with a dose of 10 mg, the course of treatment was 10 days in the 3rd and 4th clinical groups.

The tissue factor of plasminogen (t-PA) and PAI-1 was determined in blood plasma and oral fluid by a set of reagents "Cloud-Clone Corp." (USA) with ELISA sandwich method. To examine hemostasis, donor blood from the ulnar vein was taken with a wide needle into centrifugal siliconized tubes with addition of 3.8% sodium citrate solution in a ratio of 1:9. To obtain platelet-rich and platelet-depleted plasma, sodium citrate-stabilized blood was centrifuged at 1000 rpm for 7 minutes and 3000 rpm for 15 minutes, respectively.

Coagulation hemostasis was evaluated by the following tests: activated partial thromboplastin time (Larrien M.G., Weillard C., 1957), prothrombin time (Quick A.J., 1943), thrombin time (Syrmai E., 1957). Euglobulin fibrinolysis was investigated by M. Kowarzhyk (1953). Fibrinogen concentration was determined coagulometrically. Fibrin monomer complexes (FMC) content was determined by phenatroline test. All methods used in this research were published in hemostasis system instructions [1, 5-7].

Statistical processing was carried out in the program "StatSoft Statistica 10.0 Advanced" (StatSoft Ins., USA) (License No. AXAR507G794202FA-B). According to the results of visual and quantitative analysis according to the Shapiro-Wilk statistics for compliance with the normal distribution, some indicators were not to the law of normal distribution. In case of non-compliance with the normal distribution, according to the recommendations of A.M. Grizhbovsky et al. (2016), a median quartile assessment was performed. Wilcoxon criterion was used for analyzing dependent samples. Mann-Whitney criterion was used for comparing independent samples.

Results and discussion. The obtained data of the hemostasis system indicate that there is an increase in the coagulation blood properties in young and middle age patients with moderate CGP. Concentration of compounds having procoagulant activity and inhibiting fibrinolysis in oral fluid was increased in those patients compared to healthy ones.

After standard therapy, hypercoagulation signs decreased in blood of young patients, but maintained a shortened APTT (Table 1). The latter indicates that the internal coagulation pathway remains initiated. At the same time, INR reached the normal level, and the concentration of fibrinogen and fibrin clot lysis time approached the control values. It should be especially noted that there was an increased concentration of FMC in this group of patients, which indicated an increase in constant intravascular blood coagulation and microcirculatory disorders. After Cortexin therapy, all the examined indicators of the hemostasis system in young patients reached control values, which contributed to the restoration of microcirculation in periodontal tissues.

In middle-aged patients, after standard treatment, shortened APTT, increased INR and reduced thrombin time were preserved. At the same time, in patients, compared with healthy ones, the concentration of fibrinogen and FMC remained increased, as well as suppressed fibrinolysis, which indicated serious microcirculation damage and thrombus preservation. Meanwhile, the dynamics of hemostasis system indicators in complex treatment with Cortexin was more pronounced. Thus, APTT, thrombin time and fibrinogen content approached the normal level, INR achieved control indicators, and fibrinolysis accelerated by more than 18% compared to conventional therapy.

In young patients with CGP, standard therapy led to a decrease in the concentration of procoagulants in the oral fluid, an extension of APTT, prothrombin and thrombin time, as well as an acceleration of fibrin clot dissolution in comparison to the course of treatment. The procoagulant activity of saliva was increased with Cortexin treatment, which is characterized by approaching the APTT values and prothrombin time to the normal level, as well as normalization of thrombin time and fibrinolysis (Table 2). In the oral fluid of middle-aged patients after standard therapy, procoagulant activity increased poorly and the antifibrinolytic effect remained at the same level, but Cortexin therapy led to the restoration of APTT, INR and thrombin time in the bloodstream to reference values, and at the

Table 2

Effect of oral fluid on blood clotting and fibrinolysis during the therapy in patients with CGP [Me (25-75 0/00)]

Indicator	Control (n = 15)	Standard treatment (n = 15)		Standard treatment + Cortexin (n = 15)	
		before treatment	after treatment	before treatment	after treatment
CGP patients of young age (25-44 years old)					
Prothrombin time, %	75.8 (74.6; 78.6)	62.1* (59.0; 63.0)	68.4* (62.10; 69.5)	62.7* (59.5; 63.6)	72.3*▲■ (68.60; 74.40)
APTT, %	80.1 (79.8; 81.8)	59.2* (58.3; 61.0)	71.0*▲ (67.9; 70.8)	59.7* (58.3; 61.0)	77.8*▲■ (76.6; 79.4)
Thrombin time, %	80.3 (78.8; 82.8)	63.4* (62.2; 65.3)	68.3* (65.6; 70.65)	63.3* (62.4; 65.6)	75.3▲■ (73.3; 79.4)
Fibrinolysis, %	73.5 (73.0; 75.5)	86.1* (84.0; 89.0)	82.8* (82.0; 83.5)	87.0* (84.00;90.0)	78.1▲■ (77.00; 80.00)
CGP patients of young age (45-60 years old)					
Prothrombin time, %	75.80 (74.63; 78.60)	62.0* (58.0; 64.3)	67.1*▲ (64.4; 67.90)	61.7* (59.8; 61.9)	71.1▲■ (69.2; 71.5)
APTT, %	80.10 (79.80; 81.80)	65.0* (57.2; 69.5)	69.2*▲ (67.3; 70.75)	65.1* (57.4; 68.5)	79.5▲• (76.8; 81.0)
Thrombin time, %	80.28 (78.80; 82.81)	63.3* (62.2; 63.8)	68.5*▲ (65.7; 70.65)	63.3* (62.5; 63.5)	77.6▲■ (73.3; 78.4)
Fibrinolysis, %	73.50 (73.00; 75.75)	85.7* (85.0; 89.0)	83.0*▲ (82.0; 84.0)	85.8* (85.3; 88.4)	76.5■ (74.5; 81.0)

Note: n is the number of examined; * - the significance of differences compared with control (Mann-Whitney test); • - differences in values compared to the baseline; ■ - differences in meanings between treatment options.

Table 3

Dynamics of tPA and PAI - 1 content in blood plasma in patients with CGP moderate severity [(Me (25-750 / 00)]

Indicator	Control (*n*=15)	Standard treatment		Standard treatment + Cortexin (*n*=15)	
		before treatment (*n*=15)	after treatment (*n*=15)	before treatment (*n*=15)	after treatment (*n*=15)
CGP patients of young age (25-44 years old)					
tPA, нг/мл	0,728 (0,537; 0,825)	5,07* (4,482; 5,197)	1,849*• (1,59; 1,925)	5,395* (4,482; 5,585)	3,592*▪ (2,667; 4,115)
PAI – 1, пг/мл	585,35 (556,05; 591,3)	28325,00* (27195; 28850)	13780*• (12850; 13920)	26810* (26540; 26960)	8570*•▪ (8212; 8820)
CGP patients of young age (45-60 years old)					
tPA, нг/мл	0,728 (0,537; 0,825)	5,246* (5,07; 5,615)	1,438*• (1,219; 1,608)	5,525 * (4,125; 6,825)	4,608* (3,425; 5,315)
PAI – 1, пг/мл	585,35 (556,05; 591,3)	30196* (28998,5; 31005)	18250*• (17923; 18550)	29590* (28954; 30440)	14020*•▪ (13445; 14880)

Note. n is the number of examined; * - the significance of differences compared with control (Mann-Whitney test); • - differences in values compared to the baseline; ■ - differences in meanings between treatment options; p <0.05.

Table 4

Dynamics of the content of tPA and PAI - 1 content in oral fluid in patients with CGP moderate severity [(Me (25-750 / 00)]

Indicator	Control (*n*=15)	Standard treatment		Standard treatment + Cortexin	
		before treatment (*n*=15)	after treatment (*n*=15)	before treatment (*n*=15)	after treatment (*n*=15)
CGP patients of young age (25-44 years old)					
tPA, нг/мл	0.06 (0.052; 0.078)	0.19* (0.15; 0.21)	0.24* (0.17; 0.28)	0.17* (0.13; 0.19)	0.073•▪ (0.065; 0.078)
PAI – 1, пг/мл	156.072 (135.5; 169.6)	1800.5* (1676; 1936)	1677* (1535; 1717)	1802* (1697; 1929)	1621* (1575; 1763)
CGP patients of young age (45-60 years old)					
tPA, нг/мл	0.06 (0.052; 0.078)	0.457* (0.374; 0.493)	0.48* (0.44; 0.55)	0.445* (0.363; 0.472)	0.186*•▪ (0.174; 0.199)
PAI – 1, пг/мл	156.072 (135.5; 169.6)	2165* (2097.0; 2206)	1555*• (1435; 1641)	2180* (2112; 2321)	1738* (1617; 1944)

same time a weakly expressed inhibition of fibrinolytic activity was preserved. The effect of oral fluid on the examined indicators of the hemostasis system when using Cortexin had practically no difference in comparison to healthy people.

The research revealed a high blood content of plasminogen activator inhibitor (PAI-1) in young patients, which decreased by 2 times with standard treatment and by 3 times with Cortexin (Table 3) after the treatment. The level of tissue factor plasminogen (tPA) was increased 4-5 times before treatment, and decreased 2.5 (standard treatment) and 1.5 times (standard treatment with Cortexin) after therapy. A high content of plasminogen activator inhibitor (PAI-1) in blood was also detected in patients aged 45-60 years old, which after treatment decreased by 1.5 (standard treatment) and 2 times (standard treatment and Cortexin). The tissue factor of plasminogen (tPA) in patients receiving standard therapy decreased 3.5 times from the original, and it remained the same in patients using Cortexin.

There is a high content of plasminogen activator inhibitor (PAI-1) in the oral fluid of patients with CGP aged 25-44 years old, which decreased in both methods of treatment. The tissue factor of plasminogen (tPA) with standard treatment remained the same, and the use of Cortexin normalized these indicators (Table 4). After treatment in patients aged 45-60 years old, the oral fluid showed a decrease in the content of the plasminogen activator inhibitor (PAI-1) with standard treatment and with the use of Cortexin. The tissue factor of plasminogen (tPA) with standard treatment remained at the same level, and Cortexin decreased it by 2 times. Standard therapy reduced the content of activator inhibitor and tissue factor plasminogen, but the effect in complex with "Cortexin" was significant.

Conclusion. The obtained data indicated hemostasis system disorders in chronic generalized periodontitis of moderate severity in patients of young and middle age, which was confirmed by the researches.

Standard treatment improved blood

hemostasis - INR and fibrinogen reached the normal level, but at the same time, APTT was shortened and the concentration of FMC was increased. Tissue factor and plasminogen activator inhibitor decreased but did not reach control numbers. A similar situation was observed in the indicators of hemostasis in the oral fluid. Complex Cortexin treatment in young and middle-aged patients led to a significant reduction or elimination of hypercoagulation shifts and restoration of procoagulant and antifibrinolytic activity of oral fluid. Use of "Cortexin" in patients of young age with chronic generalized periodontitis of moderate severity led to normalization of the analysed parameters of the hemostasis system in the bloodstream and oral fluid.

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ANTI-RELAPSE TARGETED CHEMOEMBOLIZATION AS AN ADJUNCT TO RENAL CANCER RESECTION

Aim: to assess the saturation of the surgical margin of the kidney resection with a chemotherapy drug in order to determine the effectiveness Aim: to assess the saturation of the surgical margin of the kidney resection with a chemotherapy drug in order to determine the effectiveness of targeted balloon chemoembolization during parenchymal organ resection for the prevention of tumor recurrence

Materials and methods. The study is based on the results of experimental experiments on laboratory animals. The concentration of the marker in the parenchyma of the organ was determined for 8 days with its transarterial administration when simulating the resection process followed by wound closure.

Results and discussion. The data obtained clearly demonstrated the prolonged fixation of the marker in the tissues of the surgical edge of the resected organ.

Conclusion. Transarterial balloon embolization with a targeted drug for resection of the parenchymal organ may be effective for the prevention of tumor recurrence due to the duration of high concentrations in the surgical margin of resection.

Keywords: Kidney cancer, renal tumor recurrence, targeted balloon chemoembolization

Introduction. Kidney cancer occupies 2–3% of all human malignant neoplasms, and 90% of kidney tumors are localized in the renal parenchyma. The annual global increase in the incidence of kidney tumors is 2%, [13]. In Russia, this figure is slightly higher and amounts to about 3-4% [2]. Given the high growth rates of this pathology, the search for the most effective methods of treatment is an urgent problem of modern medicine.

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Rudolf Virchow in 1865 noted the abundant blood supply to tumor tissue, but only 100 years later J. Folkman in 1971 suggested the dependence of tumor growth on the development of capillary blood supply, under the influence of certain substances produced by the tumor itself [7]. Since that time, an extensive search for angiogenesis inhibitors and their use in the treatment of oncological diseases began. For a long time, it was believed that a tumor mass with a volume of less than 2 mm3 does not have its own blood supply and that vital functions in it are supported by its own supply of energy substrates and diffusion of oxygen from the surrounding tissue. When a tumor grows beyond this volume, oncocytes located in the center of the formation undergo acute hypoxia and stimulate the processes of oncoangiogenesis [8]. The results of studies of C. Li showed that oncoangiogenesis is triggered in a formation consisting of 100-300 cells, when microvessels are formed to feed the tumor mass [12]. Substances that activate angiogenesis were first described by N. Ferrara in 1989 and constitute a group of vascular endothelial growth factors (VEGF) [6].

When VEGF interacts with the corresponding receptor on the endothelial cell surface, the receptor is activated, which leads to the launch of a cascade of intracellular mediators reaching the cell nucleus and the final result of which is the initiation of genes responsible for angiogenesis [15]. Disclosure of the mechanisms of onconeoangiogenesis led to the creation of a whole group of drugs that block angiogenesis in malignant tumors of various localization [1].

The first targeted drug, bevacizumab, which is a monoclonal antibody, was presented in 2003 and showed an increase in oncological patient survival in clinical studies [9, 14]. In the treatment of advanced renal cell carcinoma, the use of bevacizumab led to a decrease in tumor size and increased the duration of the relapse-free period [5]. Inhibitors of vascular endothelial growth factors block the site that binds to the corresponding receptor and thereby prevent its activation and further transmission of the angiogenic impulse, which in turn inhibits the proliferation of endothelial cells, preventing the formation of a pathological vascular network. In addition, the action of bevatsimab induces apoptosis of endothelial cells of tumor vessels [4]. It is noteworthy that the effect of antiangiogenic therapy