



## CELL ADHESION MOLECULES IN THE PATHOGENESIS OF RECURRENT APHTHOSIS STOMATITIS

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**Relevance.** According to WHO experts, about 20% of the population of our planet is currently affected by diseases of the oral mucosa of the oral cavity, but other researchers 16 specify that 20% of the population aged 20 to 40 years cited by WHO experts have aphthae at different periods of their lives. . It was especially emphasized that before puberty, diseases are diagnosed in both sexes, but after puberty (in adults), women predominate among patients [2, 10, 11, 15].

Numerous studies have established that one of the most frequently diagnosed nosological units of OM is RAS, which is increasingly attracting the attention of dentists, since there is no tendency to reduce this disease. We draw attention to the fact that immune processes play the most important role among a number of pathogenic factors among several in the genesis of the onset and development of ASD [1, 3, 16,17,18]. Moreover, it should be especially emphasized that a number of diseases of somatic origin can complicate the clinical course of ASD [5, 6,19,20,21, 23]. In connection with the above, a detailed visual diagnosis of patients by dentists and specialists from related

disciplines improves the effectiveness of the treatment of patients with ASD.

Recurrent aphthous stomatitis (RAS) is a multifactorial pathology in which stationary disturbances of many homeostatic mechanisms are observed, inevitably accompanied by the appearance of adhesion molecules, which are important markers of systemic inflammation [12, 22, 27, 33].

The development of systemic inflammation, which inevitably accompanies manifestations of ASD, is associated with the progression of system-wide reactions with the accumulation of inflammatory mediators, pathological immunological reactions, cytokine phenomena, and adhesion factors [8, 13].

The severity of local and systemic inflammatory reactions is associated with an increase in the concentration of adhesion molecules, which play an important role in the implementation of intercellular contacts [14].

The degree of expression of adhesive molecules is maintained by proinflammatory cytokines, lipid peroxidation products, low molecular weight tissue breakdown products, etc. [8].

Activation of the inflammatory reaction, adhesion and extravasation of neutrophils is determined by the level of adhesion molecules [17, 32].

Thus, adhesion molecules reflect the activation of the endothelium in response to damage and the nature of intercellular interactions between the endothelium and blood cells [7].

It is believed that the expression of adhesion molecules on the endothelium is an important stage in the development of the inflammatory response, since it promotes the adhesion of activated leukocytes to the endothelium [28].

According to modern concepts, ASD is an immune-mediated disease associated with a perverted reaction of various parts of the immune system. Cytokines penetrating the oral mucosa during the development of an erosive-ulcerative lesion determine the course of the pathological process [24, 25, 26, 29].

Neopterin is a marker of activation of the monocytic component of cellular immunity; its determination allows assessing the state of cellular immunity [28, 17].

### **Materials and methods**

In 2021-2022 the control group of patients undergoing treatment at the polyclinic of the Tashkent State Dental Institute was 40 healthy people.

The subject of the study consisted of mixed saliva and blood serum for immunological (immunoglobulins and cytokines) and biochemical (LPO-AOS products; markers of allergic reactions) studies in the process of diagnosis and treatment of recurrent aphthous stomatitis.

Research methods. The study used clinical, biochemical, immunological and statistical

research methods. The scientific novelty of the study is as follows: the association of the severity of the course of the RAS disease with the prevalence of comorbid pathology, which can not only initiate local and systemic immunometabolic changes, but also pseudo-allergic reactions, has been proven;

a new concept of the pathogenesis of recurrent aphthous stomatitis is substantiated, according to which, along with immunological changes, increased proteolysis, pro-inflammatory cytokinemia, and an increase in lipid peroxidation products, adhesion molecules and indicators of pseudo-allergic load play an important role in the formation of the severity of the disease;

for the first time, a new method of treatment has been developed, including, combined with basic therapy, the differentiated use of antihistamines with different pharmacological directions depending on the severity of the course of the disease;

pathogenetically substantiated criteria for the severity of the course of the disease and the effectiveness of treatment were determined, including the levels of adhesion molecules, histamine and the enzyme counteracting histamine diamine oxidase;

developed a new complex method for the treatment of recurrent aphthous stomatitis at the local (mixed saliva) and systemic (blood serum) levels.

The practical results of the study are as follows: the introduction of modern methods for diagnosing recurrent aphthous stomatitis in clinical practice has made it

possible to conduct a number of screening studies in Uzbekistan;  
 this allowed for a detailed assessment of the pathologies of the gastrointestinal tract, kidneys and vascular system in the process of systemic inflammation;  
 early diagnosis of recurrent aphthous stomatitis allows not only to completely cure the patient, avoid complications, but also to assess the low effectiveness of traditional treatment.

The reliability of the results of the study is confirmed by the use of modern theoretical methods and approaches in the scientific study, methodologically correct studies, a sufficient number of patients; using modern methods, based on complementary clinical, biochemical, immunological and statistical methods, features of the development of pathogenetic therapy for recurrent aphthous stomatitis. The results of foreign and domestic studies were also compared, the conclusions and the results obtained were confirmed by the authorized structures.

Scientific and practical significance of the research results. The theoretical significance of the study results lies in a significant enrichment of knowledge on the evaluation of clinical and dental studies, the results of studying various background somatic pathologies, early diagnosis, pathogenetic mechanisms for the prevention and treatment of chronic recurrent aphthous stomatitis, IL-4 and IL-10 concentrations, with a decrease in the number of anti-inflammatory mediators there is an increase in the concentration of pro-inflammatory cytokines.

Table 1 Concentration of adhesion molecules in biological fluids in patients with ASD.

Indicators	Control	Patients with ASD, course of ASD
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**Results.**

Cell adhesion molecules are proteins through which cells interact.

Of the wide range of adhesion molecules, selectins that regulate the adhesion of leukocytes to the endothelium are of the greatest interest. At the same time, an increase in the adhesiveness of the endothelium plays an important role in the pathogenesis of inflammatory processes [7, 32].

It should be noted that under physiological conditions, the endothelium does not produce adhesion molecules; an increased content of adhesion molecules initiates pathogenic factors that prove the role of pro-inflammatory cytokines, lipid peroxidation products, thrombin, histamine, complement, and many other factors [28].

It is obvious that the assessment of the molecular mechanisms of the development of pathology will help not only to assess the pathophysiological mechanisms of its development, but will also make it possible to identify predictors of the development of multifactorial pathology and substantiate pathogenetically oriented therapy.

As can be seen from the data presented in Table 1 and Figure 1, the increase in the severity of ASD was accompanied by a significant ( $p<0.05$ ) increase in the concentration of adhesion molecules, more pronounced at the local (mixed saliva) level. So, in the oral fluid, the concentration of VCAM-I in mild course was increased by 69.58% ( $p<0.01$ ), in moderate course - by 99.99% and in severe course - by 169.78% ( $p<0.01$ ). 0.01);



		lung	average	heavy
<b>Mixed saliva</b>				
VCAM-1, ng/ml	231.42 ±9.9	392.44* ±17.24	462.81* • ±20.51	634.32 * • <sup>X</sup> ±25.62
ICAM-1, ng/ml	204.31 ±7.51	421.31* ±18.42	621.25* • ±28.61	851.31* • <sup>X</sup> ±37.81
sp, ng/ml	25.31 ±1.03	52.33* ±2.33	71.34* • ±2.55	102.37* • <sup>X</sup> ±4.25
neopterin, n/mol/mg	2.41 ±0.11	4.29* ±0.15	5.25* • ±0.17	7.31* • <sup>X</sup> ±0.37
<b>blood plasma</b>				
VCAM-1, ng/ml	495.21 ±19.32	605.32* ±25.14	669.32* • ±27.11	744.03* • <sup>X</sup> ±31.25
ICAM-1, ng/ml	521.3 ±24.11	604.03* ±30.02	683.42* • ±25.81	781.08* • <sup>X</sup> ±37.42
sp, ng/ml	107.24 ±4.25	131.42* ±6.08	163.07* • ±6.05	192.11* • <sup>X</sup> ±6.35
neopterin, n/mol/mg	6.12 ±0.25	7.11* ±0.32	7.51* • ±0.31	9.03* • <sup>X</sup> ±0.44

Note: \* - p<0.05 - in relation to the control;

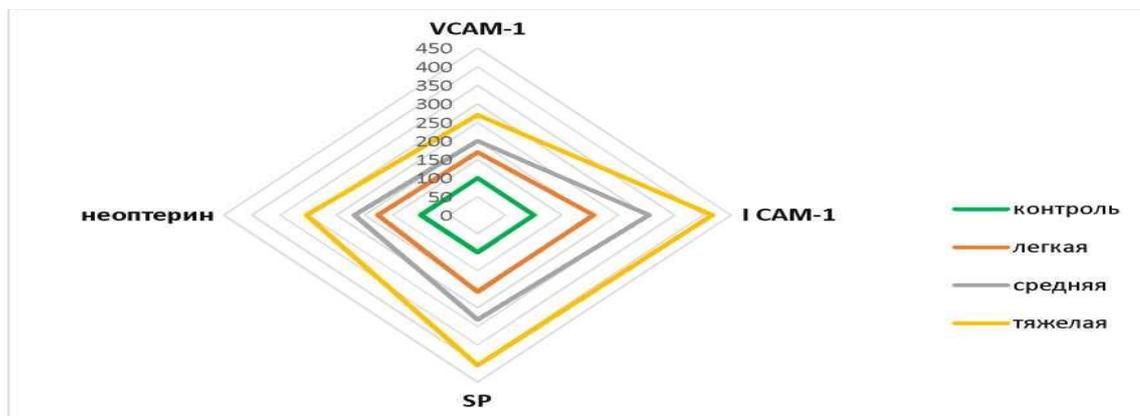
• - p<0.05 - in relation to severe course;

<sup>X</sup> - p<0.05 - in relation to the course of moderate severity.

The corresponding dynamics of ICAM-1 was 106.21% (p<0.01); 204.07% (p<0.01) and 316.68% (p<0.001); similarly 106.76% (p<0.01);

181.86% (p<0.01) and 304.47% (p<0.01); and neopterin, respectively, by 76.63% 217.84% and 203.32% (table 4.3, figure 4.3).

**Mixed saliva**



**Плазма крови**

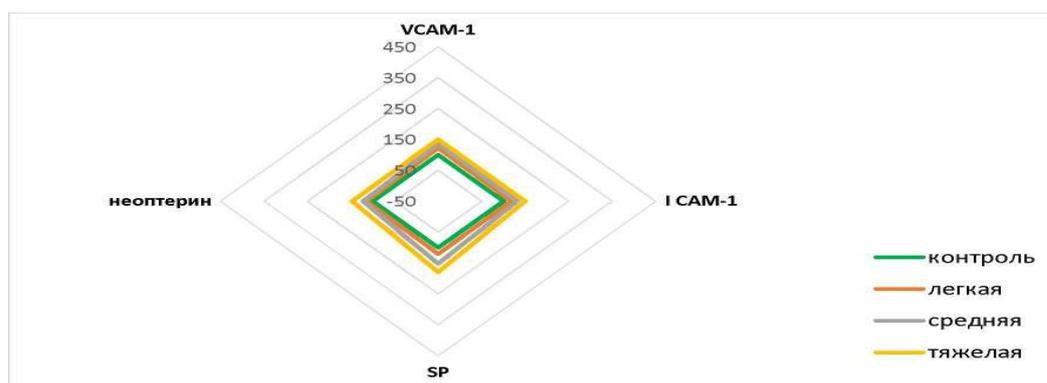


Fig.1. Dynamics of the concentration of adhesion molecules in patients with ASD (in % in relation to the control group -100%).

When compared during this period of studies in blood plasma, the concentration of USAM-1 in mild ASD was increased by 22.24% ( $p<0.05$ ), in moderate severity - by 35.16% ( $p<0.05$ ) and in severe cases - by 50.24% ( $p<0.01$ ); similar dynamics ICAM - I was 17.75% ( $p<0.05$ ), 31.09% ( $p<0.05$ ) and 49.83% ( $p<0.01$ ); increase in SP concentration respectively by 22.5%

( $p<0.05$ ); 52.10% ( $p<0.01$ ) and 79.14% ( $p<0.01$ ); and neopterin - by 14.14% ( $p<0.05$ ); 22.71% ( $p<0.05$ ) and 47.55% ( $p<0.05$ ), respectively (Table 1 and Fig. 1).

The established increase in the concentration of adhesion molecules with increasing severity of ASD indicates their pathological significance.

At the same time, high concentrations

of ICAM-I, VCAM-I and SP indicate the activation of the endothelium. In this regard, higher concentrations of adhesion molecules in the oral fluid seem logical, reflecting the local level of the inflammatory response.

At the same time, high concentrations of the studied parameters in the blood flow system indicate the participation of systemic processes in the development of the disease.

The obtained data suggest that constantly present high concentrations of the studied molecules can make a significant contribution to the destructive processes of the endothelium of the oral mucosa and project exacerbations of the disease.

The constant presence of background diseases is a risk for the development of disorders of many homeostatic mechanisms, while an increase in the concentration of adhesive molecules initiated by a chronic inflammatory process can be a diagnostic marker of the inflammatory development of relapses and their severity.

Thus, the presence of foci of chronic infection in ASD patients can initiate endothelial dysfunction.

The quantitative levels of adhesion molecules in the studied biological fluids also have a high diagnostic value for the differential diagnosis of the severity of the ASD process. Adhesion molecules in the dynamics of treatment. The continuing interest

in the treatment of ASD is probably due to the fact that, despite the numerous proposed methods of treatment, there is no decrease in the intensity and prevalence of the pathology [3, 4, 7, 31].

Numerous recent studies confirm the multifactorial nature of the disease with immuno-metabolic changes characterizing the severity of inflammatory-erosive damage to the oral mucosa and the involvement of a systemic inflammatory response in the disease.

It is known that adhesion molecules determine the severity and course of the local and systemic inflammatory response, stimulate the adhesion of leukocytes from the blood to the site of inflammation [7, 28, 32]

Obviously, their interaction with the endothelium in the pathogenesis of RAS, in the pathogenesis of erosive and ulcerative lesions of the oral mucosa and the formation of aphthous elements is to a certain extent determined by the activation of adhesion molecules.

A study was made of the influence of the main proposed methods of therapy on the levels of cell adhesion molecules in the blood and mixed saliva. A positive effect of all applied methods of treatment on the course of ASD and the formation of clinical remission was established, which was accompanied by a decrease in the concentrations of adhesion

molecules.

It can be assumed that the positive effect of different methods of therapy on the course of RAS is due to the ability of different groups of drugs to suppress various inflammation mechanisms, indirectly reducing leukocyte-endothelial interactions.

It should be noted that before the start of treatment in the concentrations of VCAM-I, ICAM-1 and SP, there were no significant differences between the groups ( $p>0.05$ ), which allowed a comparative assessment of treatment methods.

Significant differences were established between the analyzed groups after treatment ( $p<0.05$ ). At the same time, the maximum effect of therapy was registered in the 3rd main group and the minimum - in the 1st comparison group (conventional

treatment).

So, in mixed saliva in patients of the 3rd main group, the level of VCAM-I was increased by 25.18% ( $p<0.05$ ); ICAM-1 - by 22.85% ( $p<0.05$ ); and SP - by 33.61% ( $p<0.05$ ); the corresponding dynamics in the 2nd main group was slightly lower and amounted to 18.68% ( $p>0.05$ ), 14.16% ( $p>0.05$ ) and 13.04% ( $p>0.05$ ); the minimum effectiveness of treatment compared with the value before treatment was established with standard therapy - 1 comparison group, in which in patients the average level of VCAM-I decreased by only 10.44% ( $p>0.05$ ), ICAM-1 - by 8, 02% ( $p>0.05$ ) and SP - by 9.55% ( $p>0.05$ ) (Table 2). The concentration of adhesion molecules and the activity of neutroptin in the comparison groups before and after treatment ( $M\pm m$ ).



Show whether	Control healthy	Groups					
		1 comparison		2 main		3 main	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
<b>Mixed saliva</b>							
VCAM-I, ng/ml	231.42 ±9.05	466.92 ±22.14	325.11* <sup>x</sup> ±15.25	464.31 ±21.43	305.32* <sup>x</sup> ±14.52	465.81 ±27.43	240.31* <sup>Chole</sup> ±11.42
ICAM-I ng/ml	204.3 ±17.51	624.32 ±30.18	411.24* <sup>x</sup> ±15.00	628.11 ±30.11	296.25* <sup>x0</sup> ±12.8	625.31 ±30.14	208, 22 * <sup>0</sup> <sub>l</sub> ±10.35
SP neopteryn Nmol/mg	25.31 ±1.03	72.03 ±3.11	54.41* <sup>x</sup> ±1.65	71.65 ±2.95	40 44* <sup>x0</sup> ±1.66	71.44 ±2.66	25.66* <sup>0</sup> <sub>l</sub> ±1.21
	2.41 ±0.11	5.31 ±0.23	3.78* <sup>x</sup> ±0.11	5.28 ±0.24	2.86* <sup>x0</sup> ±0.10	5.26 ±0.24	2 43* <sup>0</sup> <sub>l</sub> ±0.09
<b>Serum</b>							
VCAM-I, ng/ml	495.21 ±19.32	670.31 ±31.25	606.31* <sup>x</sup> ±29.52	670.45 ±31.51	545.21* <sup>x</sup> ±26.18	668.44 ±31.14	500.11 <sup>^</sup> ±23.41
ICAM-I ng/ml	521.3 ±24.11	688.41 ±31.42	633.20* <sup>x</sup> ±31.17	685.14 ±32.19	588.14* <sup>x0</sup> ±29.31	687.11 ±30.16	530.03* <sup>0</sup> <sub>l</sub> ±25.80
SP neopteryn Nmol/mg	107.24 ±4.25	166.25 ±7.82	150.38* <sup>x</sup> ±7.71	165.88 ±8.08	144.25* <sup>x</sup> ±6.68	166.00 ±8.80	110, 21 * <sup>0</sup> <sub>l</sub> ±8.66
	6.12 ±0.25	7.71 ±0.33	7.11* <sup>x</sup> ±0.32	7.74 ±0.29	6.52* <sup>o</sup> ±0.25	7.73 ±0.32	6.15 <sup>^</sup> ±0.25

Note: x - p<0.05 in relation to the control group;

\* - p<0.05 in relation to the period before treatment; <sup>0</sup> - p<0.05 in relation to group 1;

L-p<0.05 in relation to the 2nd main group.

The relief of local inflammation and the impact on indicators of systemic inflammation had a positive effect on the levels of adhesion molecules in the systemic circulation. The positive effect of treatment was maximum in the 3rd main group, where after treatment the level of VCAM-I decreased by 48.477% (p<0.01); ICAM-1 - by 66.70% (p<0.01) and SP -



by 64.08% ( $p < 0.01$ ). The corresponding dynamics in the 2nd main group was 33.38 ( $p < 0.05$ ); 52.84% ( $p < 0.01$ ) and 43.56% ( $p < 0.01$ ); and in the 1st comparison group, respectively, 27.03% ( $p < 0.05$ ); 34.13% ( $p < 0.01$ ) and 24.46% ( $p < 0.05$ ) (Table 5.5; Figure 5.3).

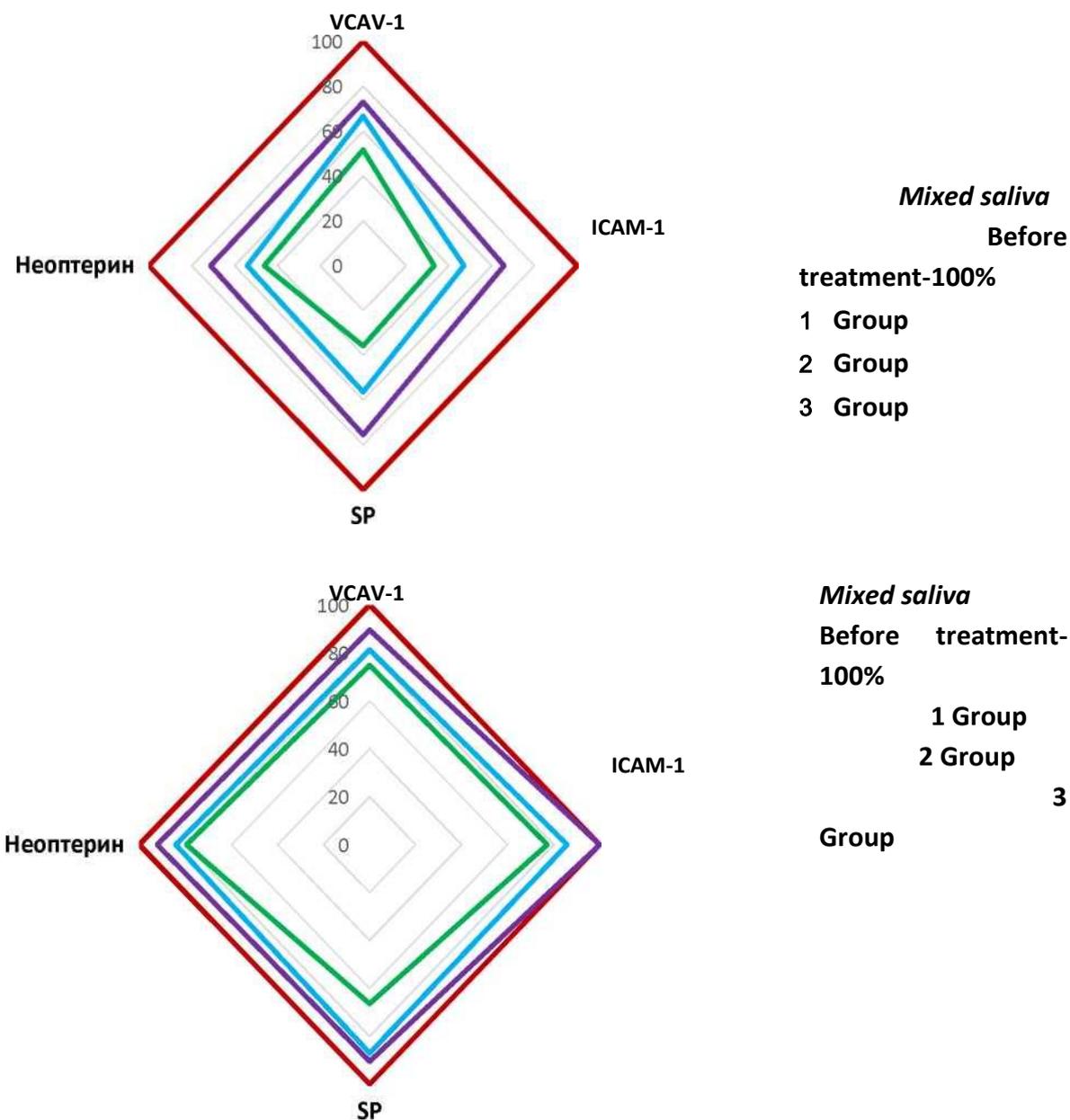


Fig.2. Comparative data on the dynamics of adhesion molecules in the compared groups (in % relative to the value before treatment).

It should be noted that more significant levels of decrease in adhesion molecules in the blood serum reflect the systemic nature of the lesion.

ORM in patients with ASD and involvement in the process of mucosal lesions of many systemic processes initiating local lesions of the oral cavity. Against the background of a decrease in the levels of adhesion molecules, a decrease in the activation of the monocytic immune response, assessed by the activity of neopterin, was registered.

Restoration of neopterin activity with maximum efficiency occurred in the 3rd main group, amounting to 20.44% in mixed saliva ( $p>0.05$ ); in blood serum - 53.80% ( $p<0.01$ ); the corresponding dynamics in the 2nd main group was 15.76% ( $p<0.05$ ) and 45.83% and in the 1st comparison group, respectively, 7.78% ( $p>0.05$ ) and 28.84% ( $p<0, 05$ ) (table 2, fig.2)

Evaluation of the effectiveness of treatment relative to the comparison group showed that a higher efficiency of the treatment is recorded at the local level (mixed saliva).

Thus, the effectiveness of treatment in the 3rd main group in mixed saliva exceeded the conventional treatment >in terms of reducing the level of VCAM-I >41.38%; ICAM-1 >48.06%; SP >55.78% and neopterin by >44.86%; similar dynamics in blood serum was >28.40%; > 32.30%; > 44.75% and > 30.20%. The corresponding excess of conventional therapy in the 2nd main group in mixed saliva in terms of VCAM-I >18.68%; ICAM-1 > 14.16%; SP >13.04% and neopterin >15.76%; the corresponding excesses in blood serum were >10.51%; >21.64%; >28.08% and >22.79% (Table 3).

At the same time, the average total effectiveness of treatment in normalizing the level of adhesion molecules in relation to the 1st comparison group in the mixed saliva of the 3rd main group exceeded the effectiveness of the 2nd comparison group> 47.51; in the 2nd main group >26.34; in blood serum, respectively >33.91% and >20.76% (Table 5.6).

Table.3. Efficacy of treatment (in%) in comparison groups by molecular level adhesion.

Indicators	Comparison group before treatment	Main groups			
		2 main		3 main	
		K before treatment	K 1 group	K before treatment	K 1 group
<b>Mixed saliva</b>					
VCAV-1	10.44	18.68	>28.29	15.18	>41.38
ICAM-1	8.02	14.16	>27.68	22.86	>48.06

SP	9.55	13.04	>15.49	33.61	>55.75
neopterin	7.78	15.76	>33.90	20.44	>44.86
S, sum			105.36		190.05
M cf.			>26.34		>47.51
Place 3			2		1
<b>Serum</b>					
VCAV-I	27.03	33.38	>10.51	48.47	>28.40
ICAM-I	34.13	52.84	>21.64	66.70	>32.30
SP	24.46	43.56	>28.08	64.08	>44.75
neopterin	28.84	45.83	>22.02	53.80	>30.20
S, sum			82.02		135.65
M cf.			>20.76		>33.91
Place 3			2		1

Thus, after the treatment of ASD, there is a tendency to normalize initially elevated local (oral fluid) and plasma (blood serum) adhesive molecules.

A higher positive effect of antihistamine therapy is due to the suppression of pseudo-allergic inflammation in response to therapy with drugs that act on the key links in the development of allergic reactions.

### CONCLUSIONS

The use of a new method of ASD therapy makes it possible to achieve a significant improvement in the indicators of the main pathogenetic mechanisms that determine the severity of the course of ASD. Thus, after treatment, the average total efficiency of normalization of

immuno-metabolic disorders with the inclusion of an immunoregulator, probiotic, sorption and antioxidant therapies in the treatment of ASD exceeds the effectiveness of basic treatment in mixed saliva by more than 20.01%; in blood serum - more than 20.81%; with the additional use of antihistamine therapy, this efficiency increases by 20.81% and 35.32%, respectively.

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