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CLINICAL AND BIOCHEMICAL ASPECTS OF LOCAL THERAPY FOR CHRONIC RECURRENT APHTHOUS STOMATITIS

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КЛИНИКО-БИОХИМИЧЕСКИЕ АСПЕКТЫ МЕСТНОЙ ТЕРАПИИ ХРОНИЧЕСКОГО РЕЦИДИВИРУЮЩЕГО АФТОЗНОГО СТОМАТИТА

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The item dwells on issues related to local treatment of the oral mucosa lesions in patients with chronic recurrent aphthous stomatitis. The authors used an adhesive medicine based on a specially engineered formula. The treatment effectiveness was evaluated through the absence of complaints reported by the patients, the rate of aphthae epithelialization, the duration of remission, and some indicators for the oral fluid before and after treatment. The results of the clinical and biochemical studies have shown that the proposed medicine effectively accelerates the disease remission and epithelialization of damaged oral mucosa with the normalization of biochemical and immunological parameters.

Key words: stomatitis, mucous membrane, treatment, healing

Рассматриваются вопросы местной терапии поражений слизистой оболочки полости рта при хроническом рецидивирующем афтозном стоматите. Авторы использовали адгезивное лечебное средство с оригинальной рецептурой. Эффективность лечения оценивали по исчезновению жалоб больных, скорости эпителизации афт, продолжительности периода ремиссии, некоторым показателям ротовой жидкости до и после проведенного лечения. Результаты клинико-биохимического исследования показали, что использование предложенного средства эффективно ускоряет ремиссию заболевания и эпителизацию поврежденной слизистой оболочки полости рта с нормализацией биохимических и иммунологических показателей.

Ключевые слова: стоматит, слизистая оболочка, лечение, заживление

Chronic recurrent aphthous stomatitis (CRAS) is quite a common occurrence in dental practice [9, 10]. The disease has a wave-like course, sometimes with frequent recurrences, the severity and endurance of which increase depending on the duration of the disease. Sometimes CRAS transforms into a permanent issue. Its treatment still remains a relevant question [1, 2, 3, 9]. Most of the means of local therapy tried in case of CRAS are not effective enough; they get easily washed away by saliva and do not provide accelerated epithelialization of the damaged oral mucosa within a short time. This fact explains the need for constant search for new medicines and their rational combinations [5, 6, 7, 8].

It is obvious that an effective treatment of oral mucosa lesions under CRAS takes drugs and substances approved for use in medical practice,

with well-known properties (e.g., adhesive), as well as the development of novel promising therapeutic agents possessing universal features [4, 7, 11].

Given these facts, research into pathogenetic mechanisms for local treatment of oral mucosa lesions in patients with CRAS, as well as elaboration of differentiated treatment principles under this disease is an urgent issue in the modern dentistry.

Aim: to evaluate the effectiveness of the treatment of oral mucosa lesions in patients with chronic recurrent aphthous stomatitis using novel medicine.

Material and Methods. Two groups of patients were formed for the trial – the main one and the control one. The clinical studies involved 42 patients of the main group (22 women and 20 men) diagnosed with CRAS.

Depending on the severity of the clinical manifestations of the disease, the local therapy for the patients with CRAS implied a developed adhesive medicine (DAM); single lesions were observed in 28 patients; multiple lesions – in 14 patients. In the control group (12 patients) the local therapy was based on the Cholisal® gel. Besides, to obtain objective biochemical data of oral fluid and blood properties, a group of 30 healthy individuals was examined.

The treatment and examination of the patients were carried out in the frame of a multicenter study at the Department for Stomatology, Stavropol State Medical University, as well as the Department for Propedeutics and Prevention of Dental Diseases, the Department for Fundamental and Clinical Biochemistry, Kuban State Medical University.

The ingredients of the DAM included glycerin, essential oils of *Lavandula angustifolia*, *Thymus vulgaris*, garden sage, peppermint, linden blossom, kolanhoe juice, stinging nettle, glucosamine hydrochloride, Polysorb-MP, pectin and dimethyl sulfoxide, all taken at certain ratios (Patent of Russian Federation № 2542469, from 20/12/2012).

The DAM is a homogeneous transparent gel, from light yellow to brown in color with a pleasant refreshing herbal mint-and-spicy scent. The DAM was administered as follows: a thin layer was applied to the affected mucosa after every meal and teeth brushing, morning and evening.

The objective assessment of the clinical efficacy of these local treatment methods was performed by daily measurements in the areas of the affected oral mucosa (aphthae and erosions) with a millimeter mesh using the formula: $S = m^2_1 + m^2_2 + m^2_3 + m^2_4 / n$, where m^2_1 , m^2_2 , m^2_3 , m^2_4 is the total area of erosions on the inner surface of the cheeks (1), palate (2), gums (3) and the lips (4), and n is the number of measurements.

The treatment effectiveness was also judged by the disappearance of the patients' complaints, the rate of aphthae epithelialization, the duration of remission, as well as some biochemical parameters of oral fluid.

The common treatment in all the groups was similar and included treatment of opportunistic diseases, oral cavity sanitation, elimination of factors that cause

the appearance of aphthae, and desensitizing therapy (Loratadine or Cetirizine).

The research data were subjected to mathematical processing on the PC using the statistical software package Exel 2007, Statistica for Windows 5.0. Results are provided as the arithmetic mean and its standard error ($M \pm m$). The significance of the differences (p) between the values at various times within each group was assessed using T-Wilcoxon test (for comparing the values measured in two different conditions in the same samplings). To compare two, three or more empirical distributions of the same characteristic χ^2 Pearson's criterion was used.

Results and Discussion. An analysis of the results from the clinical observations showed that in the presence of oral aphthae none of the patients was able to carry out proper oral care, because they were afraid of injuring the mucous membrane, as well as because of the soreness that embarrassed hygienic care. Using the DAM improved the hygienic condition of the oral cavity in the patients with CRAS, which could be accounted for both by a direct antimicrobial action of the DAM components and by their capacity to stimulate salivation and enhance local immunity.

Clinical case. Patient T., 35 years old, Medical Record №1451; reported complaints of pain when opening the mouth, painful lesions in the oral mucosa (appeared about 7 days before), pain on swallowing, chewing and deep breath. Straight after the appearance of the aphthae the patient's condition deteriorated rapidly, the body temperature increased significantly to 38.5–39°C, and non-specific symptoms of acute phase response appeared: weakness, lassitude, apathy, headache, dizziness, nausea and single vomiting. Food and water intake was limited.

Objective data: the mouth opening is narrowed. The mucous membrane of the mouth, lips, palate and tongue bear characteristic elements of destruction in the shape of spots and aphthae of different maturity. The cheeks display spots with a hyperemic focus in the oral mucosa while on the tongue and the palate mucosa the spots appear like ischemic areas. The spots are round and oval in their shapes, clearly detached from the unchanged tissues of the oral mucosa. Apart from the spots there are aphthae observed in the oral cavity that are foci of violated integrity in the mucosal epithelium surface layers (Fig. 1).

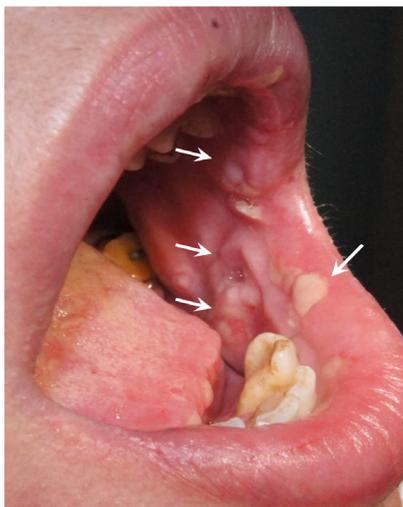


Fig. 1. Patient T. Aphthae on the mucous membrane of the lower lip, the corners of the mouth, upper lip, cheeks

When palpated the aphthae feel as soft in consistency and sharply painful. Around aphthae there are areas of redness. On the surface of the aphthae there is whitish coating to be observed, which is quite tightly connected to their bottoms. A spatula scraped slightly over the surface of the aphthae did not move away the coating. Harder attempts to remove the coating caused bleeding in the aphthae.

The highest number of aphthae is observed in the oral vestibule – in the transitory folds, mucosal coating of lips and cheeks, and in the bottom of the oral cavity (Fig. 2a). On palpation of the aphthae in their base there is infiltration, the hyperemic rim is swollen. Several big aphthae are found on the front and lateral surfaces of the tongue (Fig. 2b).



a



b

Fig. 2. Same patient. a – multiple aphthae in the oral mucosa; b – aphthae on the tip and the lateral surfaces of the tongue and in the hyoid region

The lesions at the mucous membrane of the cheeks are rough and deforming, with scars developing after healing of tissues, and appearing as coarse, extensive, deep defects. The presence of such scarring in the mouth limits mouth opening in the patient also causing microstomia phenomenon – a sharp shrinkage in the volume of the oral cavity (Fig. 3)

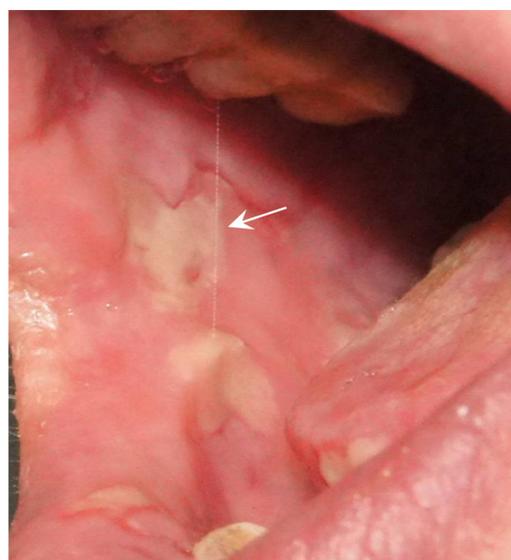
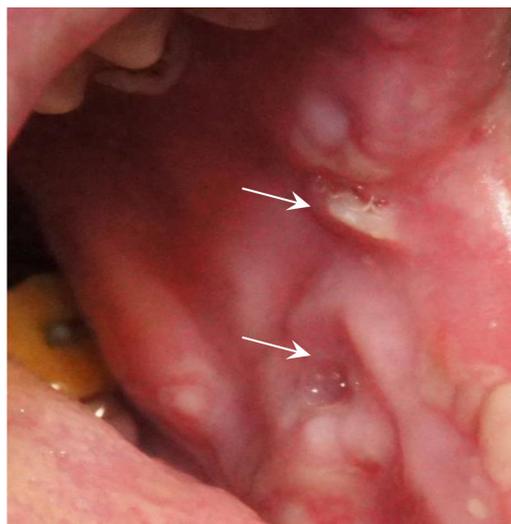


Fig. 3. Same patient. Cicatrizing aphthae on the mucous membrane of the cheeks

Provisional diagnosis: chronic recurrent aphthous stomatitis. To verify the provisional diagnosis the patient underwent the following tests: general and biochemical blood check-up, blood glucose test, common urine analysis, allergological examination with determination of the total and specific IgE, immunological studies, blood serology (WR) test, and blood test for HIV antibodies.

All the tests above helped determine the *final diagnosis:* deforming variant of chronic recurrent aphthous stomatitis.

General treatment. The patient was administered desensitizing therapy, vitamin supplements (vitamins C, D, calcium carbonate), and abundant liquid consumption.

Local treatment: antiseptic treatment, dead tissues removal from the mucosal surface of the aphthae with a spatula as well as chemically by enzymatic preparations, DAM applications (5–6 times a day).

Treatment outcome: as early as on the second day of using the developed medicine the patient reported reduced pain and a decrease in the size of aphthae on the tongue and the palate, together with relief in the acute phase response symptoms. 5 days into using the DAM the patient mentioned reduced pain on swallowing, decreased bleeding and smaller sizes of

the ulceration foci on the lips (Fig. 4). After 7 days the patient presented no complaints. Hygiene index – 1.03 points (good hygienic status); gingivo-periodontal index – 0.83 points (good state of the gums and periodontium). The patient received regular outpatient check-up for another 2 months yet no complaint was registered. The data serve evidence to rapid remission of the disease as soon as DAM application was started, and accelerated epithelialization of the damaged oral mucosa.



Fig. 4. Same patient, 5 days into treatment. Reduced sizes of aphthae and ulcerations in the upper lip

The patient was recommended a diet to stick to through recurrences (non-irritating foods and drinks), oral cavity and chronic infection foci sanitation at least 2 times a year, regular check-ups with a dentist, and using the DAM in case any pathological elements show up.

Study results in the groups with CRAS.

Good adhesion of the DAM allowed using it on all the surfaces of the oral mucosa in all the patients of the experimental group. Blood biochemical analysis performed in patients of the experimental and the control groups revealed an increase in the amount of histamine alongside reduced amount of protective enzyme lysozyme, and IgA in the oral fluid. Mention to be made here that prior to the treatment, the patients with CRAS demonstrated levels of sialic acids, IgA and IgG, as well as the value of the coefficient of local immunity factors balance (CoB) in the oral fluid that were much higher than in the group of healthy individuals.

An analysis into the levels of total calcium, inorganic phosphorus, lysozyme and sIgA, and alkaline phosphatase activity in oral fluid composition 5 days after the onset of the treatment with the DAM and with the comparison drug confirmed their statistically significant decrease to the levels comparable to those identified in the group of healthy individuals.

Increased CoB in the patients with CRAS found in the study of biochemical and immunological parameters of oral fluid prior to the treatment points at a decrease in the local immunity in the mouth cavity and in the protective activity of the oral fluid; a reduced alkaline phosphatase level, in turn, is associated with chronicity of inflammation in the mouth cavity.

It is known that protective and adaptive responses feature an active role of total calcium and inorganic phosphorus, which are to be detected via examination of the biochemical and immunological parameters of the oral fluid. The results of the presented analysis show that in case of CRAS these parameters go up at first, while later on the levels of calcium and phosphorus go down, which may prove it reasonable to treat CRAS with calcium supplements in combination with cholecalciferol.

The biochemical data yielded through the study stand proof of a significantly higher content of urea and uric acid in the patients with CRAS if compared to the healthy group (6.91 ± 0.32 mol/l vs. 5.05 ± 0.13 mol/l, respectively, $p < 0.05$), yet low creatinine (65.02 ± 3.02 μ mol/l vs. 73.09 ± 1.94 μ mol/l, respectively, $p < 0.05$).

The thymol test was higher (3.78 ± 0.13 u vs. 2.32 ± 0.54 U, respectively, $p < 0.05$), while beta-lipoproteins and glucose were lower than in the group of healthy individuals (3.32 ± 0.05 g/l and 3.54 ± 0.15 mol/l, vs. 3.27 ± 0.51 g/l and 4.22 ± 0.14 mol/l, respectively).

The level of sialic acids was also higher than in the group of the healthy individuals (701.11 ± 5.12 U vs. 629.11 ± 3.42 U, respectively). 5 days after the treatment was started, the analyzed biochemical blood parameters in the patients with CRAS using the DAM were as close as possible to those in the group of the healthy individuals ($p < 0.05$); in case of the comparison drug a similar trend was observed by Day 7 only.

The observed increase in the levels of total protein, when compared to the group of the healthy individuals is obviously due to the fact that acute inflammation comes along with an increased synthesis of the acute phase proteins mediated by the interleukin -1, -6, -8 and followed by oncotic tissue dehydration. Chronic pathology is characterized by activation of the immunological process and increased synthesis of immunoglobulins.

Therefore, the clinical studies held in remote follow-up terms (1 year after) showed that the number of recurrences per year in the control group remained similar to that prior to the treatment – 4 times per year on the average. In the group using the DAM the recurrence rate dropped down to 2 per year. Besides, the use of developed adhesive medicine for comprehensive treatment of the patients with CRAS significantly shortened the time of lesions' epithelialization in the oral mucosa to 5–6 days (compared to 14–21 days in the control group).

Conclusions. The study described above showed that the introduction of the developed adhesive medicine into the comprehensive treatment of the patients with chronic recurrent aphthous stomatitis improves the hygienic status of the oral cavity, eliminates the symptoms of hypoptyalism, dysbiosis, and inflammation through activating protective properties of the oral fluid.

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ENDOTHELIAL DYSFUNCTION AND MELATONIN

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ЭНДОТЕЛИАЛЬНАЯ ДИСФУНКЦИЯ И МЕЛАТОНИН

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The item offers independent and referential data on the role that melatonin plays in the regulation of endothelial function. There is also an analysis of the impact that melatonin has on cardiovascular system activity, which is related to restriction of arterial hypertension, atherosclerosis, metabolic syndrome with hyperlipidemia and diabetes mellitus, and enhanced platelet hemostasis. There is a discussion of a set of mechanisms on the cellular level (counteraction to oxidative stress) as well as on the systemic level – psychotropic and chronotropic effects of melatonin.

Key words: melatonin, endothelial dysfunction