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Use of mixed saliva in the diagnosis of recurrent herpetic stomatitis in patients with dental problems: An interventional single-center, prospective, randomized, uncontrolled study

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ABSTRACT

BACKGROUND: Recurrent herpetic stomatitis, also known as oral herpes, is one of the most common viral diseases of the oral cavity. Currently, saliva is widely used in innovative diagnostic methods. However, there are only limited data supporting the diagnostic value of salivary biomarkers in herpes infections.

AIM: To establish the informative value of using the wedge-shaped dehydration method and the express method for determining salivary amylase activity in patients with recurrent herpetic stomatitis.

MATERIALS AND METHODS: Diagnosis of recurrent herpes stomatitis was carried out based on the results of a clinical examination and confirmed using molecular genetic (PCR with real-time detection) and serological studies (ELISA — VectoHSV-IgG test system). For non-invasive diagnosis of recurrent herpetic stomatitis, we used crystallography methods — wedge-shaped dehydration of oral fluid and an express method for determining salivary amylase activity. The study included 26 patients with HHS in the acute stage (frequency of exacerbations of 4 or more per year) and 14 patients in the control group with no history of episodes of herpetic stomatitis.

RESULTS: The results of crystallography of mixed saliva and determination of salivary amylase activity in patients diagnosed with recurrent herpes before and after treatment are presented. Specific changes in facies in the protein zone were established during wedge-shaped dehydration during the exacerbation period and an increase in salivary amylase activity in patients with recurrent herpetic stomatitis in the acute stage.

CONCLUSION: To confirm the diagnosis of recurrent herpetic stomatitis at a dental appointment, a non-invasive method of wedge-shaped dehydration using samples of mixed saliva is recommended, and to determine the effectiveness of treatment, along with clinical indicators, the most informative is a rapid test based on a study of the level of amylase in mixed saliva.

Keywords: recurrent herpetic stomatitis; wedge-shaped dehydration; amylase; mixed saliva.

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Использование смешанной слюны в диагностике рецидивирующего герпетического стоматита у стоматологических пациентов: интервенционное одноцентровое, проспективное, выборочное, неконтролируемое исследование

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АННОТАЦИЯ

Обоснование. Рецидивирующий герпетический стоматит (РГС), также известный как оральный герпес, является одним из наиболее распространённых вирусных заболеваний полости рта. В настоящее время слюна широко используется в инновационных методах диагностики. Однако имеются лишь ограниченные данные, подтверждающие диагностическую ценность биомаркёров слюны при герпесных инфекциях.

Цель исследования — установить информативность использования метода клиновидной дегидратации и экспресс-метода определения активности амилазы слюны у пациентов с РГС.

Материалы и методы. Диагностику РГС проводили по результатам клинического осмотра и подтверждали с использованием молекулярно-генетических и серологических исследований. Для неинвазивной диагностики РГС нами применялись методы кристаллографии — клиновидная дегидратация смешанной слюны и экспресс-метод определения активности α -амилазы слюны. В исследование были включены 26 пациентов с РГС в стадии обострения (частота обострений 4 и более в год) и 14 пациентов контрольной группы, не имеющие эпизодов герпетического стоматита в анамнезе.

Результаты. Представлены результаты кристаллографии смешанной слюны и определения активности α -амилазы у пациентов с диагностированным рецидивирующим герпесом до и после лечения. Установлены специфические изменения фаций в белковой зоне при клиновидной дегидратации в период обострения и повышение активности α -амилазы слюны у пациентов с РГС в стадии обострения.

Заключение. Для подтверждения диагноза РГС на стоматологическом приёме рекомендован неинвазивный метод клиновидной дегидратации по образцам смешанной слюны, а для определения эффективности лечения, наряду с клиническими показателями, наиболее информативен экспресс-тест, основанный на исследовании уровня α -амилазы в смешанной слюне.

Ключевые слова: рецидивирующий герпетический стоматит; клиновидная дегидратация; амилаза; смешанная слюна.

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BACKGROUND

Recurrent herpetic stomatitis (RHS), also called oral herpes, is a common viral diseases in the oral cavity. A study showed that about 3.6 billion people are infected with oral herpes, with an overall prevalence of 63.6% (95% uncertainty interval (UI): 59.0–66.0) [1]. Railean et al. reported that RHS typically occurs twice a year (79.3%), and more than half (65.5%) of cases occur in the winter–spring period [2].

Currently, cell cultures, serological studies, and polymerase chain reaction (PCR) are widely used for diagnosing herpes virus infection. The PCR test is the most common test to confirm herpes simplex [3, 4]. However, the labor intensity and high cost of reagents and equipment for these tests present problems in diagnostics.

It is crucial to develop new methods for diagnosing RHS, considering the following characteristics: noninvasiveness, simplicity, use in real time, high accuracy, low cost of analysis, and possibility of use at a dental appointment.

At present, mixed saliva is commonly used in innovative diagnostic methods. Biomarkers of mixed saliva are of interest to researchers as indicators of health and disease, owing to its components that can be used to detect systemic diseases or signs of exposure to various toxic and mutagenic chemicals. The use of mixed saliva for research is beneficial in collecting samples easily, noninvasively, and rapidly, thereby increasing the capabilities of screening studies [5, 6].

However, data confirming the diagnostic value of mixed saliva biomarkers in herpes infections are limited. Notably, some of these biomarkers can be influenced by salivary proteins and expressed in lower concentrations or cannot be detected at all [7].

For noninvasive diagnostics of recurrent herpetic stomatitis, the use of mixed saliva research methods is promising, namely, crystallography (wedge-shaped dehydration [8]) and rapid method for determining α -amylase activity [9].

The crystallography method is increasingly used for express diagnostics of somatic diseases and the assessment of the general condition the body [10]. Moreover, it allows determining pathological changes at the earliest stages. In this case, the macrostructure of the biological fluid formed during the transition from a liquid to a solid state is assessed [11].

Microcrystallization of mixed saliva has been widely used in dental diseases such as caries [12] and periodontal diseases [13]. The crystallographic method is used as an auxiliary technique in assessing the dynamics and effectiveness of treatment of patients with lichen planus [14]. However, studies on its use in herpes simplex virus (HSV) infections in the oral cavity were not found.

Mixed saliva contains the protein α -amylase, which is a heterogeneous calcium-dependent metalloenzyme with a molecular weight of 54–62 kDa. Amylase is a digestive enzyme secreted by the pancreas and salivary glands. Up to 70% of α -amylase in the oral cavity is secreted by the parotid glands. The secretion of α -amylase is regulated by the sympathetic nervous system. Studies have shown that the measurement of amylase activity of mixed saliva causes stress-induced changes in the autonomic nervous system (NS) and can be used to monitor sympathetic NS activity [15, 16]. Hence, along with cortisol, salivary α -amylase is used as a marker in diagnosing stress and anxiety disorders [16–20]. An increase in α -amylase of mixed saliva has been observed in patients with rheumatoid arthritis [21], squamous cell carcinoma of the oral cavity or precancerous lesions [22, 23], and diabetes mellitus [24]. An increase in salivary α -amylase was detected in patients with periodontitis [25, 26] and oral lichen planus [27].

In a study by Honarmand et al., the level of α -amylase was significantly higher during the relapse of labial herpes than during the recovery period and in the control group. Obtained data indicate a relationship between α -amylase levels in mixed saliva and labial herpes [28].

The present study aimed to establish the informative value of using the wedge-shaped dehydration and express methods for determining the activity of α -amylase in mixed saliva in patients with RHS.

MATERIALS AND METHODS

Diagnostics of RHS was performed based on the results of a clinical examination and using molecular genetic studies (PCR with detection in real time) and serological studies (ELISA, test system VectoHSV-IgG [Vector-Best, Russia]).

Samples of mixed saliva in a volume of 1.0 ml were collected from patients on an empty stomach in 1.5 ml Eppendorf microcentrifuge tubes, with subsequent freezing at a temperature of -20°C .

When studying the microcrystallization of mixed saliva in RHS patients, the wedge-shaped dehydration method was used, which is a method of dehydration of a biological fluid placed on a plane [8].

In the laboratory, mixed saliva was defrosted and centrifuged at 3000 rpm for 10 minutes. Then, 20 μl was applied to the test card of the diagnostic kit “Lithos system” (Russian Research Institute of Gerontology of the Federal Agency for Healthcare and Social Development, Moscow, Russia). After dehydration, a facies of mixed saliva was obtained in the form of a dried film. The structure-forming elements of the dried film were studied in direct light using a Mikmed-5 medical microscope (LOMO, Russia). The natural samples of dried facies and their images at different magnifications ranging from $\times 40$

to $\times 100$ before treatment and 4 weeks after its completion were examined.

The activity of α -amylase of mixed saliva was assessed using the Wohlgemuth method, based on determining the activity of starch residues in the sample, improved by Godovalov et al. in 2019 [29]. Additionally, the reagent kit "AMILAZA-VITAL" was used.

Study design

An interventional single-center, prospective, selective, uncontrolled study of the accuracy of diagnostic and prognostic methods in RHS patients was conducted.

The study was performed according to the ethical principles of the Declaration of Helsinki "Ethical principles for medical research involving human subjects" (Fortaleza, 2013), GOST R 52379-2005 "Good clinical practice", and "Rules of clinical practice in the Russian Federation", and was approved by the Order of the Ministry of Health of the Russian Federation (dated 04/01/2016, no. 200n). All subjects signed an informed consent for the publication of data obtained as a result of the studies, excluding personal identification.

Eligibility criteria

Criteria for inclusion of patients in the study:

- Age >18 years
- Exacerbation of extraoral and intraoral herpes at the present time
- Current episodes of exacerbation of extraoral and intraoral herpes in the anamnesis four times a year or more
- Signed informed consent for the publication of data obtained as a result of the studies, excluding personal identification

Non-inclusion criteria:

- Concomitant decompensated general somatic pathology
- Intake of narcotic and psychotropic drugs
- Refusal of treatment

Conditions

The study was conducted at the Research Institute of Dentistry and Maxillofacial Surgery of the I.P. Pavlov First Saint Petersburg State Medical University (Saint Petersburg) and at the Department of Internal Medicine of the Faculty of Dentistry; in the dental clinic "Renaissance Dent" (Saint Petersburg); and at the Department of Propedeutics of Dental Diseases of the A.N. Sokolov Medical Center (Saint Petersburg).

Study duration

After the treatment, the patients were examined and tested four times, that is, immediately after the treatment course, after 2 and 4 weeks, and after 6 months.

Description of medical intervention

RHS patients were treated using recombinant interferon preparations (human recombinant interferon gamma at 500,000 IU 1 time/day subcutaneously, every other day). The course of treatment involved five injections. For systemic medication, vitamins B and C were prescribed. In addition to their primary purpose, they actively influence various functions, affecting metabolism and neuroreflex regulation, and provide a positive effect in various somatic diseases (e.g., RHS). Local treatment of RHS consisted of antiviral and anti-inflammatory therapy: rinsing the mouth with antiseptic solution (0.2% chlorhexidine solution) and painkillers (benzylamine hydrochloride spray at 0.255 mg); taking antiviral drugs (acyclovir) in the first hours of disease development (up to 72 hours maximum); and applying agents that stimulate rapid healing of the mucous membrane (keratoplastic therapy), such as oil solution of vitamin A, beta-carotene, or dental adhesive paste.

Main outcome of the study

Determination of the activity of α -amylase of mixed saliva in the course of treatment of patients with RHS using the method of wedge-shaped dehydration of mixed saliva.

Subgroup analysis

The study included 26 patients with RHS in the acute stage (19 women and 7 men; mean age: 41.7 ± 3.5 years), with the incidence of exacerbations of four or more per year. The control group consisted of 14 patients without RHS (10 women and 4 men; mean age: 39.8 ± 3.9 years).

Statistical analysis

Data processing was performed on a personal computer PC Pentium IV using STATISTICA 6.0 (StatSoft Inc., USA) and MS Excel 2003 (Microsoft, USA). Student's *t*-test was used to compare independent groups with a normal distribution of the trait. Differences were considered significant at $p \leq 0.05$ (95% confidence interval).

RESULTS AND DISCUSSION

Clinical examination revealed swelling and redness of the oral mucosa. Herpetic elements (painful ulcers) were mainly localized in the area of the tongue, gums, and the oral cavity floor (perioral herpes). In some cases, damage to the lips was noted (labial herpes; Fig. 1).

To confirm the diagnosis, PCR with detection in the real-time mode and determination of Ig G to HSV-1 were performed (Table 1).

Crystallography showed that shortened radial lines (SRL; Fig. 2) are characteristic of the oral fluid facies in patients with acute RHS.

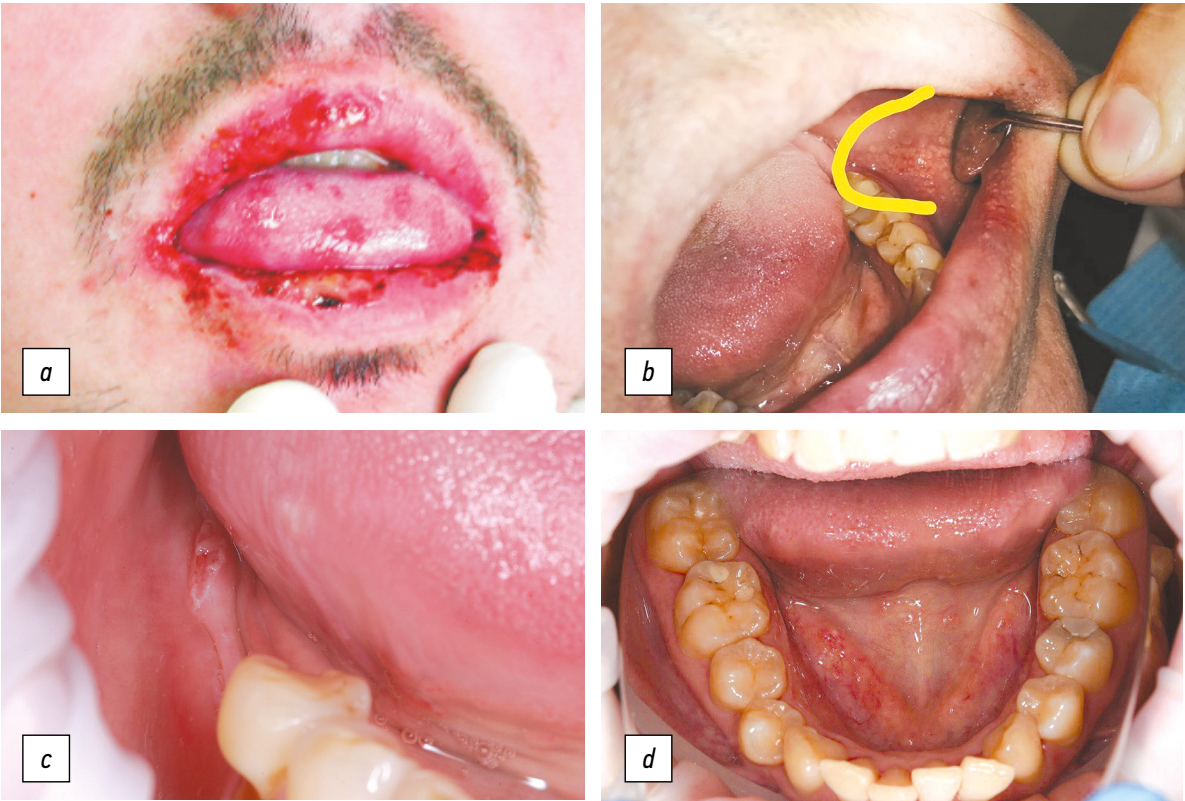


Fig. 1. Clinical picture of recurrent herpetic stomatitis: *a* — red border of the lips, *b* — buccal mucosa, *c* — gums and alveolar ridge, *d* — floor of the mouth.

Table 1. HSV-1 and Ig G to HSV-1 concentrations in patients of the main and control groups

Patient group	HSV-1 concentration (n/COV) <1.000*	Antibodies (Ig G) to HSV-1 (U/ml) <1*
Main (<i>n</i> =26)	14,1±1,8	109,2±18,6
Control (<i>n</i> =14)	0,33±0,07	1,99±0,22

* reference values.

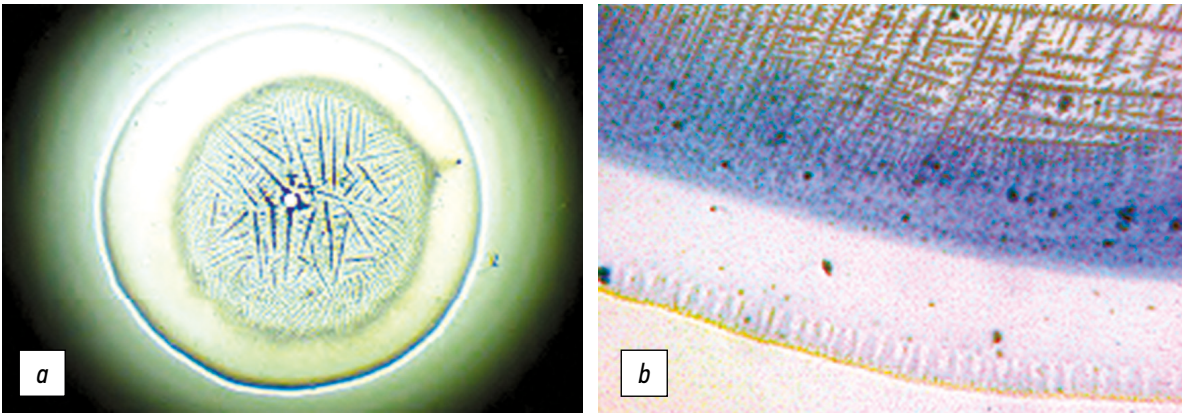


Fig. 2. Images of the protein zone of oral fluid facies during wedge-shaped dehydration in patients with recurrent herpetic stomatitis during an exacerbation: *a* — control group, *b* — patients in the acute stage.

Thus, indirect signs of an increase in colonies of persistent herpes viruses are accompanied by a violation of the state of mixed saliva with the formation of specifically altered facies with wedge-shaped dehydration, the detection of which can be used to confirm herpes virus carriage.

After treatment, the SRL in the (protein) zone disappeared, and a set of different lines (straight, horizontal, disk-shaped, and branched cracks) appeared on the periphery of the central zone of the salivary facies,

which began in the marginal zone, indicating a chronic infection (Fig. 3, Table 2).

Table 2 shows that patients with RHS often had branched cracks with three nodes, followed by branched cracks with two nodes and disk-shaped cracks.

During the inflammatory process, a change in the synthesis and activity of α -amylase in mixed saliva is expected. In patients with RHS, an increase in its activity was detected during an exacerbation (Table 3).

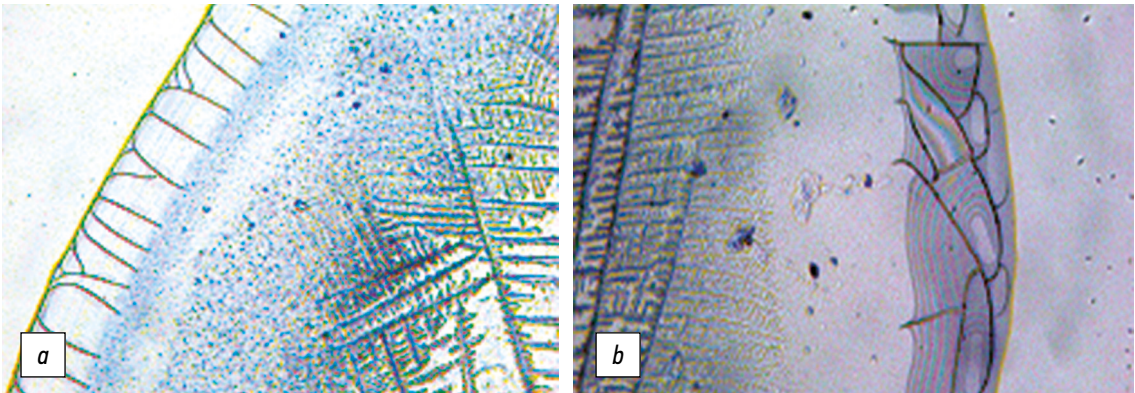


Fig. 3. Images of oral fluid facies during wedge-shaped dehydration after completion of treatment in patients (inter-relapse period): *a* — before treatment, *b* — after treatment.

Table 2. Markers of pathology in the peripheral zone of oral fluid facies during its wedge-shaped dehydration after completion of treatment

RHS, <i>n</i> =26	Total	Straight	Branched fissures			Horizontal	Disc-shaped
			1 node	2 nodes	3 nodes		
After treatment	131±6,9	9,6±1,33	18,0±1,6	30,4±1,0	44±3,9	3,8±0,7	25±4,8

Note. RHS — recurrent herpes stomatitis.

Table 3. α -Amylase activity before and after treatment in patients

Groups	Amylase activity U/ml (normal 160–640 U/ml)					
	Before treatment		After treatment			
	remission	exacerbation	2 weeks	1 month	1,5 months	2 months
Main (RHS), <i>n</i> =26	570±12,8*	1156±11,3*	1110±22,4*	808±24,3*	625±17,4*	592±13,2*
Control, <i>n</i> =14	418±21,9					

* differences are statistically significant in $p \leq 0,001$.

During the month, the activity of α -amylase did not decrease. The change in its activity was not associated with the relapses of herpes simplex per year, but was determined by the disease severity and individual characteristics of the body. Complete rehabilitation occurred within 2 months from the onset of the disease and depended on the processes of body recovery after intoxication and on the possibility of the disease transitioning to a chronic form. This transition led to a decrease in α -amylase activity and an increase in remission time.

CONCLUSION

Indirect signs of an increase in colonies of persistent herpes viruses are accompanied by a disturbance in the state of mixed saliva with the formation of specifically altered facies with wedge-shaped dehydration, the detection of which can be used to confirm herpes virus carriage. This diagnostic method is noninvasive, informative, and therefore can be used to justify therapy and choose the time for dental sanitation.

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ADDITIONAL INFORMATION

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