Original Article

OPTIMIZATION OF REGENERATION OF ORAL MUCOSA: DEVELOPMENT AND EVALUATION OF THE EFFECTIVENESS OF THE COMBINED GEL

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ABSTRACT

The aim of the study is to develop and evaluate the effectiveness of a new combined gel for the treatment of experimental stomatitis. The drug contains three active ingredients: standardized extract of *Centella asiatica* (a source of asiaticosides), high molecular weight hyaluronic acid, and lactoferrin. The study was conducted on a model of traumatic stomatitis in 45 male rabbits divided into three groups. The experimental group received the developed gel, the comparison group received a 0.05% chlorhexidine-based gel, and the control group received a saline solution. The results demonstrated statistically significant advantages of the developed gel. Complete epithelialization in the experimental group occurred on 7.4±0.9 days, which is 2.2 days faster than in the chlorhexidine group. By the fifth day, the area of the wound defect in the main group decreased by 78.2% of the initial one, whereas in the comparison group, this indicator was only 54.6%. Microbiological analysis revealed a decrease in contamination in the experimental group to 8.7±3.2 CFU/ml × 10^3 by day 10, which is 5.5 times lower than in the chlorhexidine group. Histologically, there was a decrease in inflammatory infiltration to 1.2±0.2 points and active formation of mature granulation tissue (3.6±0.3 points). The developed combined gel demonstrates pronounced regenerative, anti-inflammatory, and antimicrobial effects, surpassing the effectiveness of standard chlorhexidine therapy, and can be recommended for further research.

Key words: Stomatitis, Wound healing, *Centella Asiatica*, Hyaluronic acid, Lactoferrin, Regeneration.

Introduction

Wound healing of the oral mucosa is a complex and highly organized biological process that takes place under unique conditions of constant exposure to a variety of microflora, mechanical stress, and fluctuations in the chemical composition of the medium [1, 2]. Despite these factors, regeneration of the oral epithelium is characterized by accelerated rates and minimal scarring compared to the skin [3, 4]. This phenomenon, known as "preferential wound healing of the oral cavity", is due to the peculiarities of the local immune response, the specific profile of cytokines, the presence of a wide range of growth factors in saliva, and the unique properties of resident fibroblast populations [5]. However, when systemic or local homeostasis is disrupted, this effective mechanism can malfunction, leading to the development of inflammatory diseases, among which stomatitis occupies one of the leading places in terms of prevalence [6-9].

Stomatitis is an inflammatory lesion of the oral mucosa, clinically manifested by the formation of painful erosions, aphthous ulcers [10, 11]. The prevalence of this pathology is extremely high, affecting, according to various estimates, up to 20-25% of the population during their lifetime [12]. The etiology of stomatitis is heterogeneous and includes traumatic injuries (mechanical, thermal, chemical), infectious agents such as the herpes simplex virus, fungi of the genus Candida, opportunistic bacterial flora, as well as allergic reactions, vitamin deficiency (especially vitamin B deficiency, iron deficiency) and systemic diseases (Behcet's disease, inflammatory diseases intestines) [13-16]. Of particular clinical importance is iatrogenic stomatitis, or oral mucositis, which develops as a complication of chemotherapy and radiation therapy in cancer patients, the course of which is particularly severe and prolonged [17, 18].

The group at increased risk of developing stomatitis includes children with an underdeveloped immune system, the elderly who use dentures, patients with immunodeficiency conditions, including HIV infection, people with diabetes mellitus and autoimmune pathologies, as well as smokers [19-21]. The average duration of healing of a single aphthous ulcer in the absence of aggravating factors ranges from 7 to 14 days [22, 23]. However, even a short episode of the disease is accompanied by significant pain, impaired eating and speech function, which

significantly reduces the quality of life of patients and requires effective local therapy [24].

The modern approach to the treatment of stomatitis is based on the use of local remedies with anti-inflammatory, antiseptic, analgesic, and regenerative effects [25-28]. Drugs based on chlorhexidine, miramistin, and benzydamine, as well as local anesthetics such as lidocaine, are widely used [29-31]. Keratoplastic agents, including derivatives of solcoseryl, methyluracil, and sea buckthorn oil, are used to stimulate epithelialization [32]. Despite the wide range, many of the existing drugs have a number of significant drawbacks. These include a low residence time on a moist mucous membrane, which necessitates frequent use, a narrow focus of action when the drug solves only one of the pathogenesis tasks (for example, antiseptics without active stimulation of regeneration), as well as the risk of developing contact allergic reactions and the formation of microflora resistance to antimicrobial components [33-36].

In connection with the above, the development of new combined drugs that provide prolonged action and complex effects across various stages of the pathological process is an urgent task for modern pharmacy and clinical dentistry. A promising direction is the development of bioadhesive gel formulations that remain on the surface of an ulcerative defect for a long time, creating an optimal moist environment for healing and ensuring controlled delivery of active substances.

As part of this study, an innovative gel was developed, the active composition of which includes three key components that interact synergistically with each other. The first active substance is a nanoemulsion of *Centella asiatica* extract, standardized in the content of asiaticosides. These triterpene saponins have been shown to stimulate the synthesis of types I and III collagen, enhance fibroblast proliferation, and modulate the inflammatory response by inhibiting pro-inflammatory cytokines. The second fundamental component is high-molecular-weight hyaluronic acid, which not only forms a stable gel matrix with strong adhesive properties but also plays a key role in regulating tissue hydration, keratinocyte migration, and angiogenesis. The third active agent is lactoferrin, a multifunctional glycoprotein with pronounced antimicrobial and antifungal activity due to chelation of iron ions necessary for pathogen metabolism, as well as immunomodulatory and anti-inflammatory properties. It is assumed that the combination of these substances will have a complex effect on the pathogenesis of stomatitis, providing simultaneous suppression of infection, relief of inflammation, and active stimulation of reparative processes.

Materials and Methods

The gel composition and technology were developed at the Institute of Maxillofacial Surgery of Kabardino-Balkarian State University (Nalchik, Republic of Kabardino-Balkaria, Russia). The active pharmaceutical substances used were *Centella asiatica* extract standardized with an asiaticoside content of at least 40%, pharmaceutical-grade hyaluronic acid with a molecular weight of 1.5-1.8 MDa, and bovine lactoferrin with a purity of at least 95%. Auxiliary components included carbomer to create a gel base, glycerin as a plasticizer and humidifier, methyl parahydroxybenzoate and propyl parahydroxybenzoate as preservatives, as well as sodium hydroxide to adjust the pH, and purified water.

The technology of preparation of the prototype gel consisted of the step-by-step dispersion of the components. At the first stage, the carbomer was evenly dispersed in a portion of purified water with constant stirring at 500 rpm and left to swell for 12 hours. Glycerin and preservatives were dissolved separately in the remaining water volume when heated to 60 °C. Hyaluronic acid was hydrated in the resulting solution with constant stirring for 2 hours. A solution of hyaluronic acid, *Centella asiatica* extract, and lactoferrin was successively added to the swollen carbomer, maintaining constant stirring. The pH of the finished system was adjusted to 6.8-7.2 using a sodium hydroxide solution, which corresponds to the physiological pH of the oral cavity. The finished gel was characterized by a uniform translucent consistency with a slight creamy tint.

The experimental part of the study was conducted at the vivarium of the North Ossetian State Medical Academy (Vladikavkaz, Republic of North Ossetia-Alania, Russia). The study used 45 mature male Chinchilla rabbits weighing 2.5-3.0 kg. The animals were kept in standard vivarium conditions at a controlled temperature of 22±2°C, humidity of 50±10% and a 12-hour light-dark cycle, with free access to water and a standard diet. All procedures were carried out in accordance with the principles of the Helsinki Declaration and the European Convention for the Protection of Vertebrates Used for Experimental and Other Scientific Purposes. The research protocol was approved by the ethics committee of the institution.

The model of traumatic stomatitis was reproduced under general anesthesia induced by intramuscular administration of ketamine at a dose of 35 mg/kg and xylazine at a dose of 5 mg/kg. After reaching the surgical stage of anesthesia, a standardized wound defect with a diameter of 5 mm was applied to the cheek mucosa in the area of the transitional fold using a sterile metal punch. The depth of the injury included all the layers of the mucous membrane down to the muscle layer. Hemostasis was achieved by short-term pressing with a sterile swab.

The animals were randomly divided into three groups of 15 individuals each. The first group was the control group and received basic therapy consisting of applications of sterile saline solution. The second group, the comparison group, was treated with a standard 0.05% chlorhexidine bigluconate gel, which is widely used in clinical practice. The third, experimental group, received the developed

combined gel. The preparations were applied twice a day for 10 days using a spatula in a thin layer over the entire surface of the wound defect.

The effectiveness of the treatment was assessed using a set of methods. A daily clinical examination of the wound surface was performed with photo documentation and planimetric measurement of the defect area using ImageJ software. The microbiological assessment included taking swabs from the wound surface on days 1, 3, 5, 7, and 10 of the study, followed by inoculation on nutrient media (Saburo agar, blood agar) and counting colony-forming units.

On days 5, 10, and 14 of the experiment, 5 animals from each group were removed from the study by barbiturate overdose for histological analysis. The tissue fragments in the area of the wound defect were fixed in 10% neutral formalin, passed through alcohols of increasing concentration, and poured into paraffin. Sections 5-7 microns thick were stained with hematoxylin and eosin, as well as using the Van Gieson method for imaging collagen fibers. Histological preparations were analyzed using a light microscope at magnifications of 100, 200, and 400 times to assess the severity of inflammatory infiltration, the degree of neovascularization, the presence of granulation tissue, and the maturity of the epithelial layer.

Statistical data processing was carried out using the SPSS Statistics 23.0 software package. The data was checked for the normality of the distribution using the Shapiro-Wilk criterion. ANOVA univariate analysis of variance was used to compare quantitative indicators between groups, followed by the Tukey post-hoc test for multiple comparisons. All data is presented as an arithmetic mean and standard deviation (M±SD). The differences were considered statistically significant at $p<0.05$.

Results and Discussion

Clinical observations of the healing process of wound defects of the mucous membrane in different treatment groups revealed significant differences in the dynamics of repair. In the control group receiving saline solution, there was a slow reduction in the area of the wound surface. By the third day of observation, the wound edges remained hyperemic and edematous, and there was moderate serous discharge. Complete epithelialization of the defect in this group occurred on average by 12-14 days. In the comparison group using the chlorhexidine gel, the healing dynamics were more pronounced. By the fifth day, the formation of delicate granulations, a decrease in hyperemia, and edema of peripheral zones were noted. However, some of the animals showed dryness of the mucous membrane in the area of application of the drug. The most effective healing was observed in the experimental group, where the developed combined gel was used. Already on the third day, active formation of granulation tissue, a significant decrease in the area of the defect, and the absence of signs of severe inflammation were noted. Complete epithelialization in this group was recorded on an average of 7-8 days of the experiment.

A planimetric assessment of the wound surface area showed statistically significant differences between the groups at all stages of follow-up **(Table 1)**. The most intense reduction in the defect area was observed in the experimental group, where, by the fifth day, the wound area decreased by an average of 78.2% of the initial one, while in the chlorhexidine group, this indicator was 54.6%, and in the control group, only 32.4%. By the tenth day, 93.3% of the animals in the experimental group had complete epithelialization of the defect, whereas in the comparison group, this indicator reached 66.7%, and in the control group, only 40.0%.

Table 1. Dynamics of changes in the area of wound defect of the mucous membrane (mm2, M±SD)

Group	Baseline	Day 3	Day 5	Day 7	Day 10
Control	19.6 ± 0.8	17.2 ± 1.1	13.2 ± 1.4	9.8 ± 1.6	5.4 ± 2.1
Chlorhexidine	19.5 ± 0.9	14.3 ± 1.2	8.9 ± 1.3	4.2 ± 1.2	1.8 ± 1.4
Experimental	19.7 ± 0.7	10.1 ± 1.0	4.3 ± 0.9	1.2 ± 0.8	0.2 ± 0.3

Microbiological examination of the contents of the wound defect revealed significant differences in the degree of bacterial contamination between the groups **(Table 2)**. In the control group, microflora increased progressively, peaking on the third day of the experiment, mainly represented by Staphylococcus aureus and Streptococcus viridans. In the chlorhexidine group, effective suppression of bacterial growth was observed during the first 5 days, but by the end of the experiment, an increase in the number of Candida fungi was noted. In the experimental group, there was a gradual decrease in microbial contamination at all observation stages, without signs of selective growth of the fungal flora.

Table 2. Microbial contamination of the wound surface (CFU/ml × 103, M±SD)

Group	Day 1	Day 3	Day 5	Day 7	Day 10
Control	125.4 ± 15.2	285.6 ± 24.3	198.7 ± 18.9	156.3 ± 16.8	95.2 ± 12.4
Chlorhexidine	118.7 ± 14.8	85.4 ± 10.3	45.2 ± 8.7	52.3 ± 9.1	48.6 ± 8.9
Experimental	121.6 ± 15.1	65.3 ± 9.2	28.4 ± 6.3	15.2 ± 4.8	8.7 ± 3.2

Histological analysis of mucosal biopsies on the fifth day of the experiment revealed significant differences in the nature of reparative processes **(Table 3)**. The control group showed

marked inflammatory infiltration with a predominance of neutrophil granulocytes, areas of necrosis, and weak signs of granulation tissue formation. In the chlorhexidine group, the inflammatory reaction was less pronounced, and foci of epithelialization were observed along the edges of the defect, but there was a delay in the formation of collagen fibers. The experimental group recorded the formation of mature granulation tissue with active angiogenesis, the onset of epithelialization, and organized collagen fibers.

Table 3. Morphometric assessment of reparative regeneration on day 5 (scores, M±SD)

Parameter	Control	Chlorhexidine	Experimental
Inflammatory Infiltration	3.2 ± 0.4	2.1 ± 0.3	1.2 ± 0.2
Granulation Tissue	1.4 ± 0.3	2.3 ± 0.4	3.6 ± 0.3
Neovascularization	1.2 ± 0.2	1.8 ± 0.3	3.2 ± 0.4
Epithelialization	0.8 ± 0.2	1.9 ± 0.3	2.8 ± 0.3

By the tenth day of the experiment, an almost complete restoration of the mucosal architectonics was observed in the experimental group with the formation of a full-fledged epithelial cover and organized connective tissue in the submucosal layer **(Table 4)**. In the chlorhexidine group, areas of incomplete epithelialization and moderate lymphocytic infiltration were noted. The control group was dominated by signs of chronic inflammation with areas of fibrosis and immature granulation tissue.

Table 4. Timing of key stages of healing (day, M±SD)

Healing Stage	Control	Chlorhexidine	Experimental
Granulation Formation	5.2 ± 0.8	3.8 ± 0.6	2.4 ± 0.4
Start of Epithelialization	7.4 ± 1.1	5.2 ± 0.7	3.6 ± 0.5
Complete Epithelialization	13.2 ± 1.8	9.6 ± 1.2	7.4 ± 0.9

The analysis of histological preparations with Van Gieson staining revealed a more organized structure of collagen fibers in the experimental group already on the seventh day of the experiment, while in other groups, a chaotic arrangement of collagen bundles was noted. By the fourteenth day, the connective tissue architectonics in the experimental group practically did not differ from the intact mucous membrane, while in the control group and the chlorhexidine group, signs of fibrosis and connective tissue disorganization were observed.

The study demonstrates the pronounced effectiveness of the developed combined gel based on *Centella Asiatica*, hyaluronic acid, and lactoferrin in the treatment of experimental stomatitis. The results obtained are consistent with the data of numerous scientific papers devoted to the study of the reparative properties of individual components of the drug [37-40]. The synergistic effect of the three active substances is manifested in a significant acceleration of the time of complete epithelialization, which occurred in the experimental group by 7.4± 0.9 days, which is almost 2.5 days faster than in the group of standard chlorhexidine therapy.

The accelerated formation of mature granulation tissue and the onset of epithelialization as early as 3.6±0.5 days in the experimental group can be explained by the complex effect on the key pathogenetic links of the wound process. The anti-inflammatory and stimulating collagen synthesis effect of *Centella Asiatica* asiaticosides, studied in the work of some scientists [41-43], correlates with our data on a significant decrease in inflammatory infiltration (1.2±0.2 points versus 2.1±0.3 in the chlorhexidine group) and a more organized structure of collagen fibers according to Van Gieson staining data. The ability of centella triterpene saponins to modulate the activity of TGF-β and stimulate the synthesis of type I collagen by fibroblasts creates optimal conditions for the formation of a full-fledged connective tissue matrix [44-47].

The intensive reduction of the wound defect area revealed in our study, which amounted to 78.2% of the initial area by the fifth day, is directly related to the inclusion of hyaluronic acid in the gel. Research by other research teams highlights the key role of high molecular weight hyaluronic acid in the regulation of keratinocyte proliferation and migration in the early stages of re-epithelialization [48-51]. The ability of hyaluronic acid to create a hydrated matrix necessary for cell migration and division is complemented by its ability to modulate the inflammatory response, which explains the significant reduction in edema and hyperemia in the peripheral zones of the defect in animals of the experimental group [52-54].

An important aspect of the effectiveness of the developed gel is its pronounced antimicrobial effect without signs of selective growth of the fungal flora observed in the chlorhexidine group. This advantage may be due to the inclusion of lactoferrin in the composition, whose antimicrobial activity is realized through the mechanism of chelation of iron, necessary for bacterial metabolism. Various studies confirm the effectiveness of lactoferrin against a wide range of pathogens, including Staphylococcus aureus and Streptococcus viridans, which dominated the microbial landscape of the control group [55-57]. At the same time, unlike chlorhexidine, lactoferrin does not disrupt the balance of normal microflora and does not promote fungal growth, which is especially important for the prevention of candidal complications with prolonged local therapy [58].

The differences we found in the quality of the developing tissue, in particular the absence of signs of fibrosis in the experimental group by the 14th day of the experiment, are

consistent with the concept of regenerative rather than simply reparative effects of the combined drug. The work of other authors demonstrates that the combination of *Centella Asiatica* and hyaluronic acid promotes not only accelerated healing, but also restoration of tissue histoarchitectonics with minimal scarring, which is explained by the coordinated regulation of several repair links: angiogenesis, extracellular matrix synthesis, and tissue remodeling [59-61].

The results obtained are of great practical importance, as they indicate the prospects of using multicomponent drugs aimed simultaneously at several targets in the pathogenesis of stomatitis. Unlike monopreparations such as chlorhexidine, which provide a predominantly antiseptic effect, the developed gel has a complex effect on inflammation, microbial contamination, and regeneration processes, which allows not only to shorten the healing time, but also to improve the quality of the restored tissue.

The limitation of this study is its implementation on the model of acute traumatic stomatitis, while in clinical practice, there are often chronic and recurrent forms of the disease with specific pathogenesis. Further research should be aimed at studying the effectiveness of the gel in other etiological forms of stomatitis, including aphthous and herpes, as well as evaluating long-term treatment results.

In conclusion, the pronounced regenerative potential of the developed combined gel confirms the validity of the chosen strategy for creating a multicomponent drug that synergistically affects key links in pathogenesis.

Conclusion

The conducted experimental study proved the high effectiveness of the developed combined gel based on *Centella Asiatica* extract, hyaluronic acid, and lactoferrin for the treatment of traumatic stomatitis. The results obtained demonstrate a pronounced advantage of the new drug compared to standard chlorhexidine therapy. In the animals of the experimental group, complete epithelialization of the wound defect occurred on 7.4±0.9 days, which is 2.2 days faster than in the comparison group and 5.8 days faster than in the control group.

An important indicator of effectiveness is the dynamics of reducing the area of the wound surface. By the fifth day of the experiment, the defect area in the experimental group decreased by 78.2% from the initial one, whereas in the chlorhexidine group, this indicator was 54.6%, and in the control group, only 32.4%. Such a significant acceleration of reparative processes is explained by the synergistic effect of the drug components aimed at all stages of healing. The anti-inflammatory and collagen-stimulating effect of *Centella Asiatica* asiaticosides was combined with the regenerative properties of hyaluronic acid and the antimicrobial activity of lactoferrin.

Microbiological examination confirmed not only the effectiveness, but also the safety of the developed gel. By the tenth day of treatment, microbial contamination in the experimental group decreased to 8.7±3.2 CFU/ml × 103, which is 5.5 times lower than in the chlorhexidine group and 10.9 times lower than in the control group. At the same time, unlike the standard therapy group, no selective growth of fungal microflora was observed in the experimental group, which indicates the physiological nature of the antimicrobial effect of the drug.

The qualitative characteristics of regeneration also turned out to be significantly higher in the experimental group. Histological analysis showed that by the fifth day, inflammatory infiltration in this group was estimated at 1.2±0.2 points versus 2.1±0.3 points in the chlorhexidine group. The formation of mature granulation tissue was more intensive and reached 3.6±0.3 points, which is 56.5% higher than in the standard therapy group. Van Gieson staining revealed an organized structure of collagen fibers as early as the seventh day of the experiment, whereas in other groups, a chaotic arrangement of collagen bundles was noted.

The results obtained allow us to recommend the developed combined gel for further preclinical and clinical studies. A promising direction is to study its effectiveness in various forms of stomatitis, including aphthous, herpetic, and allergic. The complex effect on the key links of pathogenesis, proven efficacy, and safety make this drug a promising alternative to existing drugs for the treatment of diseases of the oral mucosa.

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