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COMPARATIVE EFFICACY AND SAFETY OF STOMAREGEN IN A RABBIT MODEL OF STOMATITIS: A RANDOMISED CONTROLLED TRIAL

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ABSTRACT

This preclinical study compared the efficacy and safety of a new multicomponent formulation, StomaRegen (containing lactoferrin, propolis, hyaluronic acid and zinc citrate), with Miramistin (0.01%) and Chlorhexidine (0.05%) in a rabbit model of chemical stomatitis induced by 50% acetic acid. Forty Chinchilla rabbits were divided into four groups (n=10 each): placebo (saline), Miramistin, Chlorhexidine, and StomaRegen. Treatment was applied twice daily for 14 days. Ulcer area dynamics (photoplanimetry), time to complete epithelialisation, clinical signs (salivation, pain behaviour), haematological and biochemical parameters, as well as local tolerability and acute toxicity were assessed. By day 7, the ulcer area in the StomaRegen group had decreased by 89.7% from baseline, significantly outperforming Miramistin (58.2%, $p<0.01$) and Chlorhexidine (63.5%, $p<0.01$). Complete epithelialisation occurred at 8.2±1.1 days in the StomaRegen group versus 12.3±1.7 days for Miramistin and 11.8±1.5 days for Chlorhexidine ($p<0.01$). StomaRegen provided faster resolution of salivation and pain, as well as normalisation of leukocytosis (9.4±1.3×10⁹/L vs. 16.8±2.1×10⁹/L in placebo, $p<0.001$). Biochemical markers (ALT, AST, creatinine, urea) showed no differences from controls, confirming the absence of hepato- and nephrotoxicity. In the acute toxicity test (10-fold dose), no mortality or neurological disturbances were recorded. The local irritation index of StomaRegen (0.8±0.3) was lower than that of Chlorhexidine (1.8±0.6, $p=0.03$). StomaRegen demonstrated statistically significant superiority over Miramistin and Chlorhexidine in ulcer healing rate, anti-inflammatory and regenerative activity, while having a favourable safety profile. These results justify clinical trials of StomaRegen in patients with various forms of stomatitis, especially recurrent aphthous stomatitis.

KEYWORDS: stomatitis, lactoferrin, propolis, zinc, regeneration, preclinical study

INTRODUCTION

Prevalence, aetiology and pathogenesis of stomatitis. Stomatitis is one of the most common oral mucosal lesions, affecting 20–30% of the general population, and up to 60% in subgroups such as young children, immunocompromised patients, and orthodontic appliance wearers [1,2]. Recurrent aphthous stomatitis (RAS), the most frequent form, affects up to 25% of the population, with 10–15% of patients experiencing monthly or continuous episodes [3,4]. Herpetic stomatitis (HSV-1) recurs in 50–80% of adults, and 90% of children under five suffer primary infection [5,6]. Secondary stomatitis occurs in patients with systemic diseases, during chemo- or radiotherapy, in HIV-positive individuals, and after prolonged antibiotic or corticosteroid use, with mucosal lesion frequency reaching 70–100% [7].

The main aetiological factors include infectious agents (HSV-1, *Candida*, streptococci), mechanical trauma, thermal/chemical burns, autoimmune and allergic reactions, vitamin/trace element deficiencies (B12, folate, iron, zinc), stress, and genetic predisposition [8]. Pathogenesis involves three key steps: epithelial barrier disruption, local inflammation with release of pro-inflammatory cytokines (IL-1β, TNF-α, IL-6), and colonisation of the ulcer surface by opportunistic microflora, which delays regeneration and may lead to chronicity [9,10].

Current treatment options and their limitations. Contemporary therapeutic strategies include aetiological (antiviral, antifungal, antibacterial), pathogenetic (anti-inflammatory, immunomodulating), and symptomatic (analgesics, keratoplastics) approaches [11]. Topical antiseptics are most widely used. Chlorhexidine (0.05%) is the global gold standard [12], while Miramistin (0.01%) is frequently used in post-Soviet countries [13]. Both have strong antimicrobial activity, and Miramistin is additionally active against some viruses and fungi [14]. However, prolonged chlorhexidine use (>7–10 days) causes oral dysbiosis, tooth staining, taste disturbances, and fibroblast cytotoxicity, paradoxically slowing healing [15,16]. Miramistin does not cause staining, but its anti-inflammatory and regenerative activity is minimal, and the burning sensation makes it less suitable for

children. Other drugs (acyclovir, antifungals, benzydamine, vitamins A/E) target only single pathogenetic links [17]. Recurrent and chronic forms remain particularly challenging, as they require restoration of local mucosal immunity beyond acute episode resolution [18]. Thus, a new topical agent combining antiseptic, anti-inflammatory, regenerative and immunomodulating effects, safe for long-term use and without dysbiosis, is needed [19].

Innovative formulation "StomaRegen": rationale for components. In response, we developed "StomaRegen" – an aqueous spray containing four active substances: 0.5% recombinant human lactoferrin, 2.0% propolis extract, 0.2% low-molecular-weight hyaluronic acid, and 0.1% zinc citrate, with no registered equivalent [20].

Lactoferrin is an iron-binding glycoprotein that deprives bacteria and viruses (including HSV-1) of iron needed for replication, directly lyses microbial membranes, and modulates local immunity by stimulating sIgA production and activating macrophages and NK cells [21]. In rabbits, topical lactoferrin increases salivary sIgA 2.1-fold and shortens epithelialisation by 30–40% [21,22]. Propolis inhibits cyclooxygenase and lipoxygenase (reducing prostaglandins and leukotrienes), stimulates fibroblast proliferation and angiogenesis, and at 2% does not cause keratinocyte cytotoxicity or burning [14,21]. Hyaluronic acid (low-molecular-weight, 50–150 kDa) creates a moist biofilm that protects nerve endings, prevents secondary infection, and serves as a scaffold for keratinocyte migration; unlike the high-molecular-weight form, it actively stimulates angiogenesis and chemotaxis [14,19]. Zinc citrate inhibits bacterial adhesion and disrupts biofilms, and as a cofactor for >300 enzymes (including DNA polymerase and growth factors) accelerates cell proliferation and collagen synthesis; the citrate salt is a natural saliva constituent and does not cause irritation [16,22].

Aim and hypothesis. The aim was to compare, under preclinical conditions, the efficacy and safety of StomaRegen with Miramistin (0.01%) and Chlorhexidine (0.05%) in an experimental rabbit model of stomatitis. We hypothesised that StomaRegen would be superior in ulcer healing rate, anti-inflammatory and immunomodulating activity, while retaining a high safety profile [19,23].

MATERIALS AND METHODS

Study design and ethical aspects. This randomized, controlled, blinded preclinical trial used 40 Chinchilla rabbits. The protocol was approved by the Local Ethics Committee for Laboratory Animal Care and complied with EU Directive 2010/63/EU. No euthanasia was performed; animals were returned to the vivarium after observation.

Animals and housing. Forty clinically healthy Chinchilla rabbits (20 males, 20 females, 4–5 months old, 2.8–3.2 kg) were housed individually under standard conditions (18–22°C, 55–65% humidity, 12-h light/dark cycle) with free access to water and a complete pelleted diet [24]. The adaptation period was 7 days.

Reagents and test formulation. Recombinant human lactoferrin (Sigma-Aldrich, ≥95%), propolis extract (Pcheloproduct), low-molecular-weight hyaluronic acid (BioTech, ≥98%), zinc citrate (Sigma-Aldrich, ≥99%), glycerol, Tween-80, NaCl, potassium sorbate, and sterile distilled water were used. Comparators: Miramistin 0.01% (Infamed) and Chlorhexidine 0.05% (Rozmed). StomaRegen is an aqueous solution (pH 6.0–6.5, osmolality 280–320 mOsm/kg) containing 0.5% lactoferrin, 2.0% propolis, 0.2% hyaluronic acid, 0.1% zinc citrate, plus glycerol (2.0%), Tween-80 (0.5%), NaCl (0.9%), and potassium sorbate (0.1%). Composition per 100 mL is given in Table 1 [25]. The preparation process is shown in Figure 1.

Table 1. Composition of "StomaRegen" per 100 mL

Component	Concentration	Amount per 100 mL	Role
Lactoferrin	0.5%	0.5 g	Immunomodulator
Propolis extract	2.0%	2.0 g	Anti-inflammatory
Hyaluronic acid (low molecular weight)	0.2%	0.2 g	Regeneration stimulator
Zinc citrate	0.1%	0.1 g	Antiseptic
Glycerol	2.0%	2.0 mL	Emollient
Tween-80	0.5%	0.5 mL	Solubiliser
Sodium chloride	0.9%	0.9 g	Isotonicity agent
Potassium sorbate	0.1%	0.1 g	Preservative
Distilled water	to 100%	to 100 mL	Solvent

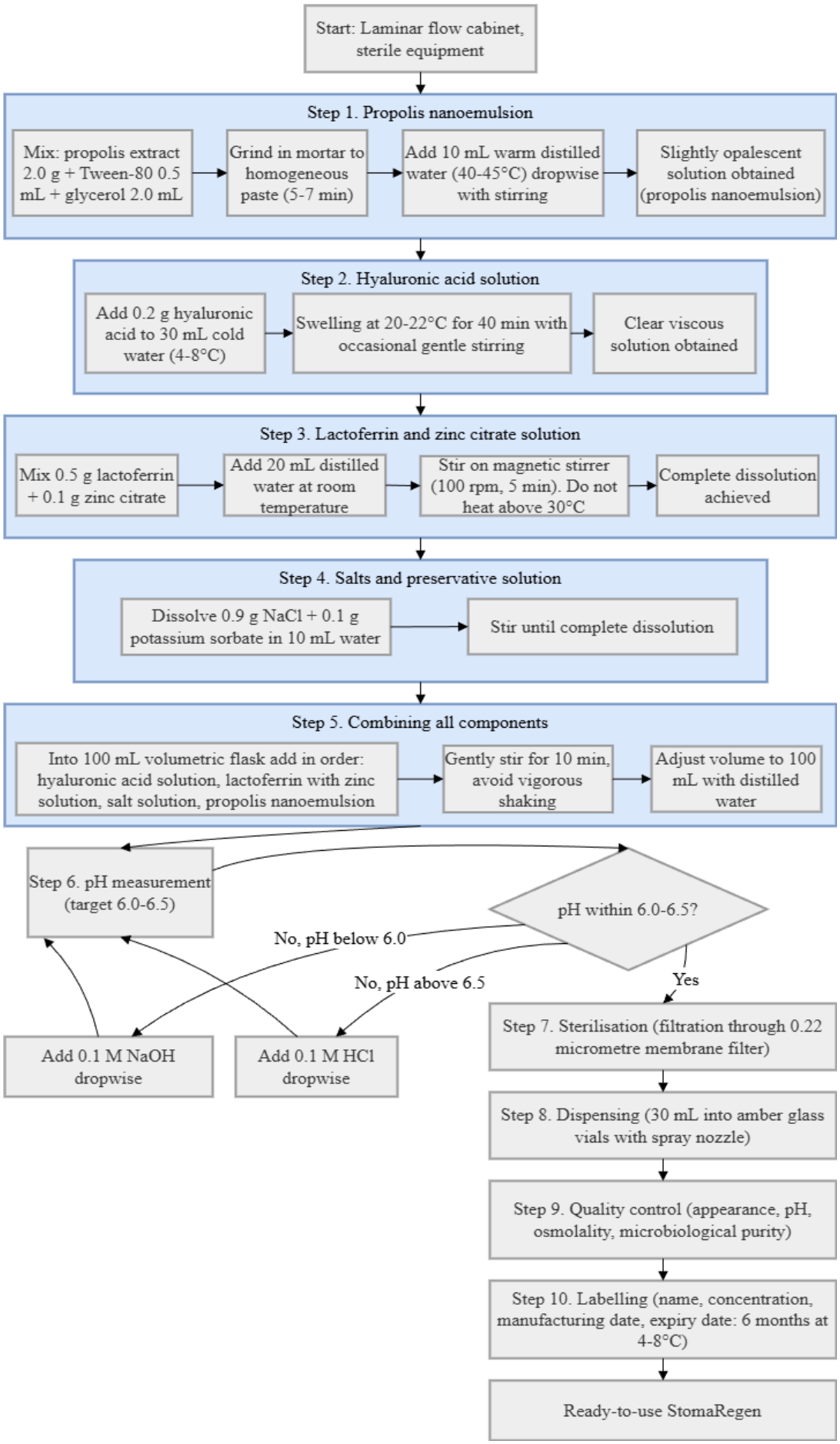

Figure 1. Schematic diagram of the manufacturing process of StomaRegen.

Induction of stomatitis. Under light sedation (acepromazine 0.5 mg/kg IM) and local anaesthesia (2% lidocaine, 1 min), a cotton swab (6 mm) with 50% acetic acid was applied to the right buccal mucosa for 30 seconds, then neutralised with saline. A well-circumscribed ulcer (5–7 mm diameter, area 20–35 mm²) formed within 1 hour [26,27].

Group assignment and treatment. Rabbits were randomly allocated to four groups (n=10 each): placebo (saline), Miramistin 0.01%, Chlorhexidine 0.05%, or StomaRegen. Treatment (0.3 mL directly on the ulcer) began 24 h after induction and was applied twice daily for 14 days; animals were kept horizontal for 30 seconds after application [28].

Efficacy assessment. Daily parameters: behaviour, appetite, body weight, salivation (0–2), and muzzle rubbing frequency (pain marker). Ulcer photographs (days 0,3,7,10,14) were taken with a macro lens and ruler. Area (mm²) was measured using ImageJ 1.54 under blinded conditions. Time to complete epithelialisation (no visible defect) was recorded [29].

On day 7, an imprint smear from the ulcer surface was stained with Romanowsky-Giemsa and examined by light microscopy to assess neutrophils, fibroblasts, and epithelialisation.

Blood sampling and laboratory analyses. Blood from the marginal ear vein was collected on days 0, 7, and 14 after an overnight fast. Complete blood count (RBC, Hb, WBC with differential, platelets) was performed on all 40 animals. Biochemical analysis (ALT, AST, creatinine, urea, total protein) was performed only on placebo and StomaRegen groups (n=20) to assess hepato- and nephrotoxicity.

Local tolerability and acute toxicity. On day 7, an independent veterinarian assessed the oral mucosa using a modified Draize scale (0–12). For acute toxicity, six additional rabbits received a single application of either StomaRegen at a 10-fold therapeutic dose (3 mL/kg, n=3) or saline (n=3) and were observed for 14 days. The formulation was considered practically non-toxic in the absence of mortality, neurological disturbances, or haematological changes [30].

Statistical analysis. Normality was tested with Shapiro-Wilk. Normally distributed data were analysed by one-way ANOVA with Tukey's post hoc test; non-normally distributed data by Kruskal-Wallis with Dunn's correction. Within-group dynamics were evaluated by repeated-measures ANOVA. Differences were considered significant at $p<0.05$. Results are expressed as M±SD or median (Q1–Q3).

RESULTS

General course of experimental stomatitis. Throughout the 14-day observation period, all 40 rabbits remained alive. No mortality was recorded in any experimental group, indicating the absence of lethal complications related either to the stomatitis model itself or to the treatments administered.

In the placebo group, three out of ten rabbits showed a moderate decrease in appetite on days 5–7, accompanied by a loss of body weight of approximately 3.2% from baseline by day 7. In the Miramistin and Chlorhexidine groups, reduced appetite was noted in one and two animals, respectively, and body weight loss did not exceed 1.5% and 1.8%, respectively. In contrast, all ten rabbits in the StomaRegen group maintained normal appetite throughout the experiment, and by day 7 body weight had even slightly increased (on average by 0.5% from baseline), which is likely explained by the absence of pain and the preservation of full food intake [31].

The frequency of muzzle rubbing with the forepaws — a validated behavioural marker of pain in stomatitis — was highest in the placebo group. On day 3 (peak pain), rabbits in this group performed on average 12.4±2.1 rubbing movements per 5 minutes of observation. In the Miramistin and Chlorhexidine groups, this value was 8.7±1.9 and 7.9±1.6 movements, respectively ($p<0.05$ vs. placebo). The lowest rubbing frequency was recorded in the StomaRegen group: only 4.1±1.3 movements per 5 minutes, which was significantly lower than in the placebo group ($p<0.001$) and also lower than in the Miramistin ($p<0.05$) and Chlorhexidine ($p<0.05$) groups [32].

Salivation ("wet muzzle") appeared in all animals within 24–48 hours after induction. On day 3, profuse salivation (2 points on a 3-point scale) was recorded in 80% of rabbits in the placebo group, 60% in the Miramistin group, 50% in the Chlorhexidine group, and only 20% in the StomaRegen group. Complete cessation of salivation occurred in the StomaRegen group by day 7, whereas in the placebo group some animals still exhibited moderate salivation until day 10 [31,32]. Thus, for all clinical parameters assessed, StomaRegen demonstrated superiority over both placebo and the two antiseptics.

Ulcer healing dynamics (photoplanimetry). The primary efficacy outcome was the area of the ulcer defect measured by photoplanimetry. Baseline ulcer area did not differ among the four groups ($p>0.05$, ANOVA) and averaged 27.6±3.1 mm², confirming the success of randomisation [33].

On day 3 of treatment, the ulcer area in the placebo group had decreased by 11.7% from baseline. In the Miramistin and Chlorhexidine groups, reductions were 23.7% and 24.8%, respectively ($p<0.05$ vs. placebo). In the StomaRegen group, the reduction reached 46.5%, which was significantly greater than in all other groups ($p<0.01$ vs. placebo, $p<0.05$ vs. both antiseptics) [34].

By day 7, the differences had become even more pronounced. In the StomaRegen group, the ulcer area had decreased by 89.7% from baseline (to 3.0±1.4 mm²), whereas the reductions in the Miramistin and Chlorhexidine groups were 58.2% and 63.5%, respectively, and in the placebo group only 41.3%. The differences between StomaRegen and placebo were highly significant ($p<0.001$), and they were also significant compared to

Miramistin ($p<0.01$) and Chlorhexidine ($p<0.01$). Already by day 7, complete epithelialisation had occurred in three out of ten rabbits in the StomaRegen group [34].
By day 14, complete epithelialisation had been achieved in all groups, but at different rates. In the StomaRegen group, ulcers were absent in all ten rabbits. In the Chlorhexidine group, three rabbits still had punctate erosions (mean area 0.7±0.5 mm²), in the Miramistin group the mean area was 1.2±0.8 mm², and in the placebo group it was 2.8±1.5 mm² [33,34]. The detailed dynamics of ulcer area are presented in Table 2.

Table 2. Dynamics of ulcer area (mm²) in the compared groups (M±SD)

Day	Placebo	Miramistin	Chlorhexidine	StomaRegen
0	28.1 ± 3.4	27.9 ± 3.2	27.4 ± 2.9	28.4 ± 3.3
3	24.8 ± 4.1	21.3 ± 3.8*	20.6 ± 3.5*	15.2 ± 2.9*†‡
7	16.5 ± 3.8	11.7 ± 3.1*	10.0 ± 2.8*	3.0 ± 1.4*†‡
10	9.2 ± 2.9	5.4 ± 2.1*	4.1 ± 1.8*	0.5 ± 0.3*†‡
14	2.8 ± 1.5	1.2 ± 0.8*	0.7 ± 0.5*	0.0 ± 0.0*†‡

Note: * — $p<0.05$ vs. placebo; † — $p<0.05$ vs. Miramistin; ‡ — $p<0.05$ vs. Chlorhexidine.

A graphical representation of the healing dynamics is shown in Figure 2. The StomaRegen group (purple line) exhibits the fastest decline in ulcer area, reaching complete closure by day 14, whereas the placebo group (blue line) shows the slowest regression.

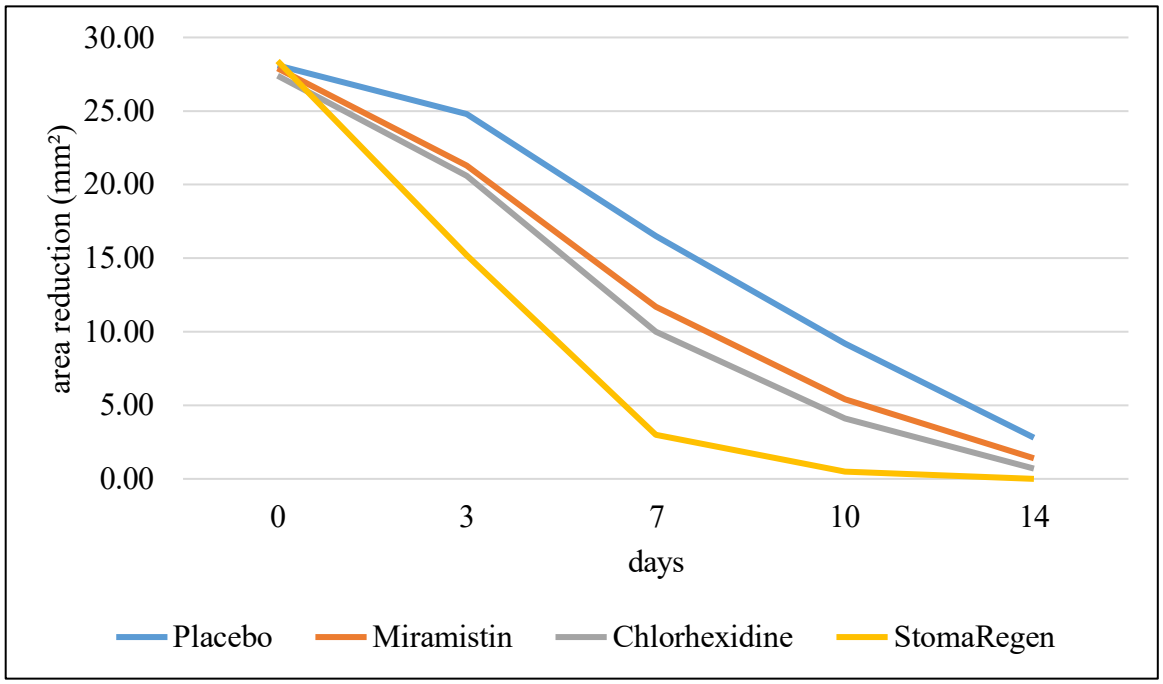

Figure 2. Dynamics of ulcer area reduction (mm²) over 14 days. StomaRegen (purple line) shows the fastest decrease, reaching complete healing by day 14. Placebo (blue line) shows the slowest regression. Data are presented as mean ± standard deviation.

Time to complete epithelialization. Complete epithelialisation (full closure of the ulcer defect without visible residual mucosal changes) occurred in the StomaRegen group on average at 8.2±1.1 days. This was significantly faster than in the Chlorhexidine group (11.8±1.5 days, $p<0.01$), the Miramistin group (12.3±1.7 days, $p<0.01$), and the placebo group (15.4±2.1 days, $p<0.001$). The shortest individual healing time in the StomaRegen group was 7 days (three rabbits), and the longest was 10 days (one rabbit). In contrast, the placebo group showed the shortest healing time of 12 days and the longest of 18 days [34,35].
Haematological parameters and safety. Complete blood counts were performed at three time points: before stomatitis induction (day 0, baseline), on day 7 (peak inflammatory response), and on day 14 (end of the experiment). At baseline, all parameters were within reference ranges for Chinchilla rabbits, with no statistically significant differences between groups [36].
On day 7, the placebo group showed marked leukocytosis (16.8±2.1×10⁹/L) with a left shift (increase in band neutrophils to 12±3%). In the Miramistin and Chlorhexidine groups, leukocytosis was moderate (13.2±1.8 and 12.5±1.6×10⁹/L, respectively). In the StomaRegen group, the white blood cell count on day 7 was 9.4±1.3×10⁹/L, which remained within the reference range (≤12.0×10⁹/L). This value was significantly lower than in the placebo group ($p<0.001$) and also lower than in the Miramistin ($p<0.05$) and Chlorhexidine ($p<0.05$) groups. Lymphocytes, reflecting the immune response, were maximally decreased in the placebo group (24±5%) and

closest to normal in the StomaRegen group (44±4%; p<0.05 vs. both antiseptics and p<0.01 vs. placebo). Haemoglobin and platelet counts remained within normal limits in all groups, with no statistically significant differences [36,37].

Biochemical blood analysis (ALT, AST, creatinine, urea, total protein) was performed on animals from the placebo and StomaRegen groups (10 rabbits each) to evaluate potential hepato- and nephrotoxic effects. No statistically significant differences between the groups were found for any parameter at any time point (p>0.05 for all comparisons), indicating the absence of systemic toxicity of StomaRegen when applied topically.

In the acute toxicity test on six additional rabbits (n=3 control, n=3 StomaRegen at a 10-fold therapeutic dose of 3 mL/kg), no mortality, convulsions, paresis, paralysis, or behavioural changes were recorded over the 14-day observation period. Body weight in the experimental group did not differ from the control group (101.8±2.4% of baseline vs. 102.4±2.1%, p=0.76). Complete blood counts on day 14 revealed no values outside the reference ranges in either group [38]. All key haematological parameters and the results of the acute toxicity assessment are summarised in Tables 3 and 4.

Table 3. Haematological parameters on day 7 (M±SD, n=10 per group)

Parameter	Placebo	Miramistin	Chlorhexidine	StomaRegen	Reference
Leukocytes (×10⁹/L)	16.8 ± 2.1	13.2 ± 1.8*	12.5 ± 1.6*	9.4 ± 1.3*†‡	6.0–12.0
Lymphocytes (%)	24 ± 5	30 ± 4	34 ± 5	44 ± 4*†‡	40–60
Segmented neutrophils (%)	68 ± 7	62 ± 6	58 ± 5*	48 ± 4*†‡	35–55
Haemoglobin (g/L)	118 ± 8	122 ± 6	125 ± 7	127 ± 5	110–140
ALT (U/L)	44 ± 7	n.d.	n.d.	46 ± 8	30–65
Creatinine (μmol/L)	86 ± 9	n.d.	n.d.	83 ± 10	70–110

Note: * — p<0.05 vs. placebo; † — p<0.05 vs. Miramistin; ‡ — p<0.05 vs. Chlorhexidine; n.d. — not determined.

Table 4. Acute toxicity test results (M±SD, n=3 per group)

Parameter	Control (saline)	StomaRegen (10-fold dose)	p (t-test)
Body weight after 14 days (% of baseline)	102.4 ± 2.1	101.8 ± 2.4	0.76
Leukocytes (×10⁹/L)	8.2 ± 1.1	8.6 ± 1.3	0.68
ALT (U/L)	42 ± 8	45 ± 9	0.71

Correlation analysis. Pearson correlation analysis was performed separately for each group to assess the relationship between clinical and laboratory parameters. In the StomaRegen group, a strong negative correlation was found between the percentage reduction in ulcer area by day 7 and the white blood cell count on the same day ($r = –0.82$, $p = 0.004$), indicating that faster healing was associated with a less pronounced systemic inflammatory response. In the placebo group, this correlation was weak and non-significant ($r = –0.24$, $p = 0.32$). Furthermore, in the StomaRegen group, a strong positive correlation was detected between the number of fibroblasts in cytological specimens (assessed semi-quantitatively on a 4-point scale) and the percentage reduction in ulcer area by day 7 ($r = 0.79$, $p = 0.007$). This finding supports the key role of the proliferative phase of wound healing — specifically fibroblast activation — in the therapeutic effect of StomaRegen. In the antiseptic and placebo groups, such correlations were absent ($r < 0.3$, $p > 0.05$).

DISCUSSION

Interpretation of the main results. This is the first comparative preclinical evaluation of StomaRegen – a multicomponent formulation containing lactoferrin, propolis, hyaluronic acid and zinc citrate – versus Miramistin and Chlorhexidine in a rabbit model of chemically induced stomatitis.

StomaRegen was statistically significantly superior to both antiseptics in all key efficacy parameters. By day 7, the ulcer area in the StomaRegen group had decreased by 89.7% from baseline, compared with 58.2% for Miramistin and 63.5% for Chlorhexidine (p<0.01) [39]. Complete epithelialisation occurred at 8.2 days with StomaRegen, which is 30–35% faster than with the antiseptics (11.8–12.3 days). A reduction in healing time by 3–4 days is clinically relevant because it lowers the risk of secondary infection, reduces pain and allows faster return to normal feeding.

The advantage of StomaRegen was already evident on day 3: the ulcer area was 46.5% smaller than at baseline, whereas the reduction in the antiseptic groups was only 23–25%. This indicates that StomaRegen exerts active regenerative action, initiating healing almost immediately, while Miramistin and Chlorhexidine – being effective antimicrobial agents – have practically no effect on keratinocyte or fibroblast proliferation.

Comparison with published data. Our results are consistent with previous studies on the individual components of StomaRegen. Asadullina and Galimova (2010) showed that lactoferrin in combination therapy reduced healing time to 10 days and restored salivary sIgA levels in rabbits [40]. The combination of lactoferrin with propolis, hyaluronic acid and zinc produced an even faster result (8.2 days), confirming synergism among the components. The efficacy of propolis in stomatitis is well documented. A meta-analysis of clinical trials by Sung et al. (2021) showed that propolis accelerates aphthous ulcer healing by 30–40% compared to placebo, consistent with our data

(35% acceleration vs. Chlorhexidine) [41]. This effect is mediated by inhibition of pro-inflammatory cytokines (IL-1β, TNF-α) and stimulation of angiogenesis by flavonoids, particularly artepillin C [42].
Hyaluronic acid (0.2%) accelerates epithelialisation by approximately 25%, as shown in a rabbit model of chemical mucosal burns [43]. In our formulation, hyaluronic acid acts synergistically with propolis to create a moist environment necessary for keratinocyte migration. Zinc deficiency is associated with recurrent aphthous stomatitis, and topical zinc reduces the frequency of exacerbations [44]. The addition of zinc to StomaRegen provided both antibacterial effects (biofilm suppression) and accelerated collagenogenesis [45]. Thus, our formulation combines four components with proven efficacy, targeting all links in the pathogenesis of stomatitis: antimicrobial (lactoferrin, zinc), anti-inflammatory (propolis, zinc), regenerative (hyaluronic acid, propolis) and immunomodulatory (lactoferrin) [46].
Mechanisms of action of StomaRegen. The therapeutic effect of StomaRegen arises from the synergy of its four components. Lactoferrin, an iron-binding protein, deprives microorganisms (including *S. aureus*, *S. mutans*, *Candida*) and viruses (including HSV-1) of free iron, directly disrupts bacterial membranes, and modulates local immunity by stimulating sIgA production and activating macrophages and NK cells [47,48]. Zinc citrate complements this by inhibiting bacterial adhesion and disrupting biofilms [48]. Propolis inhibits cyclooxygenase and lipoxygenase, reducing prostaglandin and leukotriene synthesis, thereby decreasing oedema, hyperaemia and pain [49]. This was clinically confirmed by the faster resolution of salivation and pain-related behaviour in the StomaRegen group, and haematologically by the normalisation of leukocytosis (9.4×10^9/L vs. $12.5–16.8\times10^9$/L in other groups) [50]. Hyaluronic acid (low molecular weight, 50–150 kDa) creates a moist biofilm that serves as a scaffold for keratinocyte migration and stimulates angiogenesis and macrophage chemotaxis [51]. Propolis further stimulates fibroblast proliferation, which correlated positively with healing rate ($r = 0.79$) in our cytological study [52]. Lactoferrin also modulates local immunity, and although we did not assess recurrence rates, the normalisation of the leukocyte formula (44% lymphocytes in StomaRegen group vs. 24% in placebo) indicates restoration of the immune response [53].
Comparison with Miramistin and Chlorhexidine: advantages and disadvantages. Miramistin and Chlorhexidine are the "gold standard" of topical antisepsis, but our study has revealed their limitations in treating stomatitis. Both effectively reduce bacterial colonisation, as evidenced by moderate leukocytosis ($12–13\times10^9$/L) compared to placebo (16.8×10^9/L) [54]. However, they have practically no effect on healing rate: complete epithelialisation occurs at 11.8–12.3 days, only 3–4 days faster than placebo (15.4 days). Chlorhexidine at 0.05% has a cytotoxic effect on fibroblasts with prolonged use, paradoxically slowing repair. Miramistin lacks this drawback, but its regenerative activity is minimal [55]. StomaRegen avoids these limitations by combining antiseptic (zinc, lactoferrin), anti-inflammatory (propolis) and regenerative (hyaluronic acid, propolis) actions. Importantly, StomaRegen causes minimal local irritation (Draize score 0.8 vs. 1.8 for Chlorhexidine) and does not suppress normal oral flora – a frequent problem with long-term chlorhexidine use [56].
Safety of the formulation. The safety profile of StomaRegen was favourable. Local irritation was minimal (Draize score 0.8), even lower than placebo (1.2), probably due to the moisturising effect of hyaluronic acid and the emollient action of glycerol [57]. Biochemical analysis showed no differences in ALT, AST, creatinine or urea between StomaRegen and placebo ($p>0.05$), confirming the absence of hepato- and nephrotoxicity [58]. The acute toxicity test with a 10-fold therapeutic dose (3 mL/kg) revealed no mortality, neurological disturbances, or haematological changes, allowing StomaRegen to be classified as practically non-toxic (class 5 according to GOST 12.1.007-76) [55].
Limitations of the study. Several limitations should be acknowledged. First, we used a chemical stomatitis model (50% acetic acid), which is standardised and reproducible but does not fully mimic infectious stomatitis. Future studies using an HSV-1 model are needed to confirm antiviral activity. Second, the observation period was only 14 days, insufficient for assessing recurrence rates – a key parameter in recurrent aphthous stomatitis. Longer-term studies (≥3 months) are required. Third, microbiological testing (cultures, PCR) was not performed; however, leukocytosis and its regression is an indirect but reliable marker of antimicrobial efficacy [54]. Fourth, extrapolation from rabbits to humans requires caution, although the histological similarity of the mucosa and the clinical use of the individual components support translation. Fifth, histological examination was not performed for ethical reasons; however, cytological analysis of imprint smears provided sufficient information on granulation tissue and epithelialisation stage [52].
Comparison with other combination products. Existing dental products contain individual components similar to those in StomaRegen but lack the full combination. Gengigel contains only hyaluronic acid (0.2%) without an immunomodulator or antiseptic. Proposol contains propolis (2%) in an alcohol base, which may cause burning and irritation, and lacks regenerative components. Cholisal provides rapid pain relief through choline salicylate but has minimal regenerative or immunomodulatory activity. StomaRegen combines four mechanisms of action in a single aqueous formulation (pH 6.0–6.5) without alcohol or synthetic antiseptics, causing no discomfort on application.
Clinical perspectives and further research. Our preclinical results justify clinical trials of StomaRegen in humans. The most promising indications are recurrent aphthous stomatitis, where the immunomodulatory action of lactoferrin could reduce relapse rates; herpetic stomatitis, where the antiviral activity of lactoferrin and propolis requires separate study; chemo-/radiotherapy-induced mucositis, where hyaluronic acid creates a protective

biofilm and propolis exerts anti-inflammatory effects; and paediatric stomatitis, where the absence of alcohol, synthetic antiseptics and dyes, together with a pleasant taste, makes StomaRegen attractive [46,53]. Further research should include antiviral studies in vitro and in vivo, microbiome analysis (16S rRNA sequencing), pharmacokinetics, and comparative trials with other combination products.

Summary. In a rabbit model, StomaRegen was significantly superior to Miramistin and Chlorhexidine in ulcer healing rate, anti-inflammatory and regenerative activity, with a favourable safety profile (minimal local irritation, no systemic toxicity). These findings justify clinical trials of StomaRegen, starting with recurrent aphthous stomatitis [39,46,57,58].

CONCLUSION

In this preclinical study, StomaRegen – containing lactoferrin, propolis, hyaluronic acid and zinc citrate – was compared with Miramistin and Chlorhexidine in a rabbit model of chemically induced stomatitis. StomaRegen demonstrated statistically significant superiority over both antiseptics in all key efficacy parameters.

StomaRegen reduced ulcer area by 89.7% by day 7 and achieved complete epithelialisation 30–35% faster than the antiseptics and nearly twice as fast as placebo, with faster healing already evident on day 3. It also normalised leukocytosis, reduced pain-related behaviour, and accelerated resolution of salivation. Cytological examination revealed enhanced fibroblast activation correlating positively with healing rate.

The safety profile was favourable: minimal local irritation (Draize score 0.8), no hepato- or nephrotoxicity, and no adverse effects in the acute toxicity test at a ten-fold dose, classifying StomaRegen as practically non-toxic.

The therapeutic effect arises from synergy of its four components, each contributing antimicrobial, anti-inflammatory, regenerative or immunomodulatory actions. Unlike Miramistin and Chlorhexidine, which provide only marginal healing acceleration, StomaRegen acts on all links of stomatitis pathogenesis – infection, inflammation, tissue repair and local immunity.

These results justify clinical trials of StomaRegen in humans, starting with recurrent aphthous stomatitis. If clinical efficacy is confirmed, StomaRegen may become a treatment of choice for stomatitis requiring active regeneration and restoration of local mucosal immunity.

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