Hindawi

Research Article

Minor Recurrent Aphthous Ulcer Management with Hyaluronic Acid Gel in an Italian Cohort: A Double-Blind Randomized Clinical Trial

Paolo Savadori [iD],[1] Pooja Mali Rai [iD],[1] Santhosh Tadakamadla [iD],[2,3] Shahnawaz Khijmatgar [iD],[1] Francesco Inchingolo [iD],[1] Christian Greco,[4] Chiara Occhipinti,[1,5] Maggie Stephen Fahim,[1,5] Massimo Del Fabbro [iD],[1,6] and Gianluca Martino Tartaglia [iD][1,5]

[1]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy
[2]School of Medicine and Dentistry, Griffith University, Australia
[3]Menzies Health Institute Queensland, Griffith University, Australia
[4]Unit of Dentistry, Azienda Sanitaria dell'Alto Adige, Merano Hospital, Bolzano, Italy
[5]Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico, 20100 Milan, Italy
[6]IRCCS Orthopedic Institute Galeazzi, Milan, Italy

Correspondence should be addressed to Gianluca Martino Tartaglia; gianluca.tartaglia@unimi.it

Background. Recurrent aphthous ulcer is a common mucosal disease and encompasses diverse interventions for its management of symptoms like pain and discomfort. Since new therapies keep evolving with better outcomes as compared to traditional interventions, one such therapy using hyaluronic acid has been recently explored using clinical studies based on advances in dental therapeutics. Therefore, we designed this clinical study which is double blinded and randomized using minor recurrent aphthous cases. *Objective*. To evaluate the efficacy of hyaluronic acid topical oral gel in the treatment of minor RAS ulcers, with regard to pain relief and reduction in ulcer size. *Design*. A double-blind randomized controlled clinical trial was designed to conduct an experimental research at IRCCS Fondazione Ca' Granda, Ospedale Maggiore Policlinico, Milan. The participants were recruited from the unit of oral maxillofacial surgery and randomly assigned to test (hyaluronic acid gel) and control groups (placebo gel). 1 : 1 computer-generated random sequence was prepared, and opaque closed envelopes were used for allocation concealment. Participants and clinical investigators were blinded. The outcome measures included ulcer size (mm) and the visual analogue scale for pain and healing as a secondary outcome measure (efficacy index). *Results*. The mean baseline score for ulcer size for the test group was 1.85 ± 1 and the placebo group was 1.85 ± 1.2. At day 7, the test group was 1 ± 1.5 and the placebo group was 2 ± 1.5 ($p < 0.001$). There was significant reduction in ulcer size as compared to the placebo group. In addition, there was significant improvement in pain levels ($p < 0.01$) in the test group as compared to the control group. *Conclusion*. In conclusion, there was significant decrease in the size of the ulcer in the test group as compared to the placebo group. Hyaluronic acid seems to have promising effects on the ulcer size and pain relief associated with minor aphthous ulcers. *Trial Registration*. The protocol of this clinical trial was registered with the Clinical Trial Registry of ISRCTN with study ID ISRCTN16509838, registered 30 June 2020. It can be accessed on this URL: 10.1186/ISRCTN16509838

1. Introduction

Oral aphthae, also known as recurrent aphthous stomatitis (RAS), are common inflammatory ulcerative oral mucosal lesions. Thus, the diagnosis and management of these recurring oral lesions are common in dental practice [1, 2]. The onset of RAS seems to peak between the ages of 10 and 19 years before becoming less frequent with advancing age [3].

RAS has three main presentations: minor, major, and herpetiform. The minor form is the most common, and it is characterized by a well delimited, rounded ulcer smaller than 1 cm in diameter. These aphthae present as ulcerative vesicles. They usually last from seven to ten days and are characterized by intense pain and burning sensation, accompanied by difficulty in chewing and speaking. Pain intensity is usually correlated with the size and the number of the lesions [4, 5].

Aetiology is still unknown; many factors have been associated, including trauma, oral infections, nutrition, hormonal factors, allergies, medications, oxidative stress, and psychological stresses [6, 7]. The lesions usually heal spontaneously after one or two weeks but can often recur monthly or a few times per year. The most widely accepted mechanism for the development of RAS suggests a local immune dysfunction, in which T-lymphocytes play a significant role [8].

Without a well-known aetiology, treatment remains symptomatic with the main aim to relieve pain, alleviate inflammation, and accelerate the healing process.

Systemic medications with different drugs such as Colchicine, Levamisole, Dapsone, Thalidomide, and Pentoxifylline have been used when topical therapy is ineffective. An important limitation with the use of these systemic therapies consists of several side effects. Furthermore, there is a lack of strong evidence to support the efficacy of these agents. Therefore, they should be reserved for lesions that are resistant to topical or local therapies [9, 10]. Even the application of mucoadhesive films has been reported to be helpful in shielding the lesions from the stimuli coming from the oral cavity, thus reducing pain and optimizing the effect of the medication [11–13].

Topical medications are considered as proven therapies for providing symptomatic relief [14]. Many different formulations have been proposed, such as natural products (e.g., honey and curcumin), Chlorhexidine, Doxycycline, Lidocaine, or corticosteroids such as Dexamethasone [15–19]. Among these, natural products, if effective, may bring advantages consisting of no to minimum adverse effects. Hyaluronic acid (HA), a natural, nonsulphated glycosaminoglycan, recently gained attention for its effectiveness in wound healing. HA is a linear polysaccharide of the extracellular matrix (ECM) of the skin and connective, epithelial, nerve, and musculoskeletal tissues [20].

Due to interactions with different cell receptors and proteins, and its antioxidant properties, HA can modulate several key factors in tissue formation and wound healing, like cell migration, inflammatory process, and angiogenesis. As an integral part of the ECM, HA promotes proliferation and reepithelization and supports scarless tissue repair [21]. Owing to its positive effects in wound healing, HA has been used to treat a wide range of conditions including oral ulcers [22, 23]. However, only a few studies investigated the efficacy of products containing HA in the treatment of RAS to relieve pain and promote healing [24, 25]. The aim of this double-blind randomized controlled trial (RCT) was to evaluate the efficacy and safety of a HA-based gel for the treatment of RAS, in an Italian cohort.

2. Materials and Methods

The study was a 7-day randomized, double-blind, placebo-controlled parallel clinical trial approved by the Ethical Committee of the University of Milan (Protocol No.: 44/18) and was conducted in accordance with the Declaration of Helsinki.

Patients were consecutively recruited from the Unit of Oral Maxillofacial Surgery and Dentistry, IRCCS Cà Granda Foundation, Polyclinic Senior Hospital, Department of Biomedical, Surgical and Dental Science, University of Milan, Italy. Prior to the start of the study, the trial was registered under the ISRTC registry [26]. The subjects were considered for inclusion if they met the following criteria: 11 to 50 years old, presence of at least one aphthous ulcer in an easily accessible area of the mouth, reporting pain, maintenance of proper and daily oral hygiene like oral rinse after each meal, no in-between meals/snacks or sugars, and brushing only with toothpaste not containing adjuvants. The medical history including previous history of RAU, trauma, drug history, substance abuse, personal, and diet habits were considered.

Exclusion criteria were the following: smoking; xerostomia; nutritional supplements; allergic and immunologic diseases; immunosuppressive drugs; antioxidants; pregnancy and lactation; systemic disease such as Crohn's disease, Behcet's syndrome, or ulcerative colitis; patients with HIV, hepatitis C, and systemic, acute, or chronic infections; genetic disorders; use of other medications or drugs within the past two months; and, specifically, use of any local treatment for their ulcers in the 48 hours preceding the start of the study.

Potential participants were approached and provided information about the study, and those meeting the eligibility criteria and willing to participate signed an informed consent. Patients were assigned to the test or the placebo group with a process of simple randomization, and opaque closed envelopes were used for allocation concealment. The test group was treated with Bexident® gel (Bexident Aftas Gel®, ISDIN, Barcelona, Spain). The medicated product contained 12% polyvinylpyrrolidone (PVP), an inert polymer which enhances the formulation adherence, dispersing and suspending the drugs; 0.2% sodium hyaluronate (tissue lubricant); and few other inert additives.

For preparation of the placebo gel, all previous ingredients were used except for sodium hyaluronate. Both formulations were packed in the same kind of tubes containing 8 ml of product, in a way that prevented both clinical investigators and participants from knowing the actual content.

An investigator not involved in clinical examination randomly divided and assigned a numerical code to each tube.

Then, the codes were assigned to patients by means of a computerized random number generator. And the tubes were allocated to the participants, who were blind to the treatment agents contained inside. Patients were instructed to squeeze approximately 1 millilitre of the product on a finger or a cotton tip and to gently rub it on each lesion three times daily for one week. They were recommended to refrain from eating or drinking for 60 minutes after application. A total amount of at least 21 ml of product was used for each lesion; i.e., each patient was provided with 3 tubes per ulcer.

All the participants were clinically examined by the same calibrated investigator (CO), who was blinded to the group assignment. Participant and clinical investigators were blinded.

Pain and ulcer size were the primary outcomes of this study, and adverse events were considered as secondary outcomes. The size of each ulcer was measured at baseline and 7 days follow-up. A periodontal probe was used to measure the distance between two opposite outer edges of the white margin of the ulcer. Two measurements perpendicular to each other passing through the centre of the lesion were obtained. The widest linear dimension was considered. If the patient showed more than one ulcer, only the widest linear measurement of one was recorded.

A visual analogue scale (VAS) consisting of a 10 cm horizontal line ranking from 0 (no pain) to 10 (unbearable pain) was used by patients to self-assess their pain. On the VAS scale, the patients were instructed to use a diary to mark the pain level every day before, immediately after, twenty, and sixty minutes after each application, from the first till the seventh day, for a total of 84 measurements for each patient.

The efficacy index (EI) for ulcer pain was calculated at each time-point using the following formula: $EI = [(Vx - V1) \div V1] \times 100\%$, with Vx referring to values measured at a particular time-point and V1 referring to the baseline value measured at the first measurement (before the first application) at day 1. EI was evaluated on a 4-rank scale: (1) healed, $EI \geq 95\%$; (2) marked improvement, $EI \geq 70\%$ to $<95\%$; (3) moderate improvement, $EI \geq 30\%$ to $<70\%$; and (4) no improvement, $EI < 30\%$. Patients were considered to show marked improvement rate (MIR) when EI was $\geq 70\%$ and improvement rate (IR) when EI was $\geq 30\%$ [27].

Patients were also asked to keep daily track of any adverse effects and to refrain from using any other product for the treatment of aphthous ulcers while participating in the study or to report it (and in that case, they would have been excluded from the study). Reporting of adverse events was done on a dichotomous response scale of yes/no. If no adverse event was reported, patients were asked to describe what they have experienced. On every follow-up, a recall history of events was recorded in dichotomous data (yes/no).

The data were then analysed by a third operator, who was blinded to the study and did not perform any clinical assessment. Compliance was not assessed because the total product provided to each patient was just sufficient for the designated dose and time frame of treatment. This article conforms to the Consolidated Standards of Reporting Trials guidelines (CONSORT guidelines) [28].

2.1. Statistical Analysis. The sample size was determined considering a power 0.80 for the ulcer size primary outcome of the study, a significant level of 0.05, and an effect size of 0.339 [29]. Based on these parameters, at least 58 patients (29 per group) were required.

All the data were analysed with Medcalc® software, and significance level was set at a level of $p < 0.05$.

Mixed model regression was used to compare VAS scale scores before application between the two groups, on different days, taking into account repeated data for the same patients. VAS before the application of the product on each day was the dependent variable; group of treatment, days, and their interactions were independent variables; and patients were used as the random factor. Means for each day and groups were estimated. Mean differences between the two groups at each day and their confidence intervals (CIs) were calculated.

To evaluate "immediate" relief, the mixed model was applied using change in VAS between 20 minutes after application (time 0) and VAS before application as the dependent variable; VAS value before application, group of treatment, and days and their interactions were used as fixed factors and patients as the random factor.

Mixed model was applied using TOTPAR as the dependent variable, with VAS before application, group of treatment and days, and their interactions as fixed factors and patients as the random factor. Mean differences and their 95% CIs were calculated.

Model assumptions were checked analysing residual distribution. Bonferroni correction was applied to all post hoc tests.

Chi-square test was used to compare the efficacy indices between the test and placebo groups.

Stata 16.1 was used for mixed models. A Mann–Whitney test was performed for assessing significance of ulcer size change within and between groups.

3. Results

A total of 70 Caucasian patients were enrolled in this study with an equal number of subjects being allocated to the test and placebo groups. Seventy patients with the complaint of RAS were enrolled in this study from October 2018 to January 2019.

From the initial sample of seventy patients (test and placebo groups), fifteen patients were excluded: eight from the test group and seven from the placebo group, mainly due to the use of other drugs ($n = 7$) or due to the misuse of the provided product (consumption of the whole amount of gel in less than 7 days, $n = 8$). Figure 1 illustrates the flow of patients. The test group comprised 27 patients (12 males and 15 females) with a mean age of 22.1 ± 11.4 years; the placebo group comprised 28 subjects (13 males and 15 females) with a mean age of 23.7 ± 9.9 years (Table 1).

No statistically significant differences were detected between the groups for age and gender.

Pain score values on each day before the application are presented in Table 2. There were no statistically significant differences in VAS score among the test and control groups,
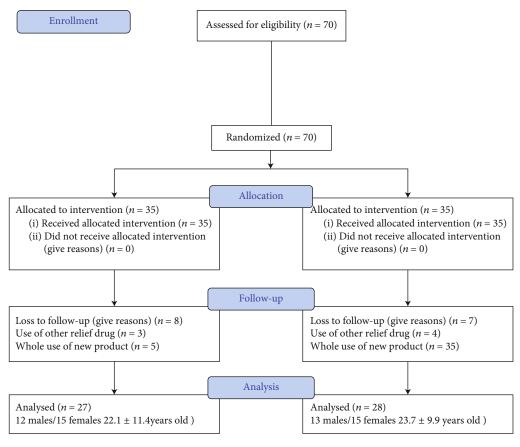
Figure 1: CONSORT flow chart.

Table 1: Demographic characteristics of test and placebo groups.

	Test ($N = 27$)	Placebo ($N = 28$)	p value
Age	22.1 ± 11.4 years old	23.7 ± 9.9 years old	$p > 0.05$
Gender	12 M (44.5%)	13 M (46.4%)	$p > 0.05$
	15 F (55.5%)	15 F (53.6%)	

considering the VAS score in the first 2 days between the placebo and the test group. The pain score decreased significantly during the whole treatment duration in both groups ($p < 0.001$). However, during the last 5 days (third to seventh), pain scores in the test Group were significantly lower than those of the placebo group. The highest difference was observed on the third day (-1.14, 95% CI -1.9; -0.4).

The ulcer size after day 7 was significantly less as compared to day 1 ($p < 0.001$) (Table 3, Figures 2 and 3).

Table 4 represents the proportion of individuals with improvement rates in the test and placebo groups based on the efficacy index values. In the test group, more patients showed a faster improvement rate starting on the third day than the placebo group. Mainly during the fifth and sixth days, marked improvement was significantly higher in the test group. Moreover, a significant increase in the number of totally healed lesions has been reported

from the fifth day. The highest difference was noticed at day 7, with 48.1% of the patients in the test group fully recovered, compared with 17.9% in the placebo group ($p = 0.01$).

Starting from the first application, patients in both groups reported a rapid reduction in their pain scores. Linear comparisons of effect of the HA gel and placebo demonstrated the significant difference between the groups with the HA gel showing reduction in pain score (Figure 4).

Pain relief was calculated as immediate, after 20 minutes and after 60 minutes after the application of the product for all 7 days. Patients in the test group reported a significantly better effect on pain relief right after the application than placebo in all days (Figure 5).

TOTPAR confirmed the significant better pain relief of the treated group than the placebo group in all days except day 7 (Table 5).

Pain relief duration was reported to be better in the test group, as confirmed by the perceived improvement of pain sixty minutes after the application of the products during the first two days. Conversely, on the sixth and seventh days, no significant difference was found (Table 5).

No adverse effects were reported regarding the use of gel in both groups. All participants confirmed the ease of application, tolerability, and the absence of any unpleasant taste.

TABLE 2: VAS marginal means and standard errors estimated by mixed models.

| | Placebo | | Test | | Differences from placebo | | |
	Mean^	Se^	Mean^	Se^	Mean	95% CI*	p value*
Day 1	6.86	0.20	6.67	0.19	-0.19	-0.9; 0.5	1.000
Day 2	5.93	0.22	5.33	0.21	-0.60	-1.4; 0.2	0.342
Day 3	5.14	0.16	4.00	0.22	-1.14	-1.9; 0.4	<0.001
Day 4	4.18	0.16	3.11	0.14	-1.07	-1.6; -0.5	<0.001
Day 5	3.21	0.15	2.19	0.19	-1.03	-1.7; -0.4	<0.001
Day 6	2.25	0.18	1.44	0.16	-0.81	-1.5; -0.2	0.006
Day 7	1.18	0.14	0.56	0.11	-0.62	-1.1; -0.1	0.004

^Estimated by mixed model; *Bonferroni adjustment.

TABLE 3: Comparison of the mean ulcer size, before gel application and at day 7 among the two groups.

Mean/SD	Placebo Ulcer size	Test Ulcer size	Mann–Whitney
At baseline (before gel application)	1.85 ± 1.2	1.85 ± 1	$p > 0.05$
Day 7	2 ± 1.5	1 ± 1.5	$p < 0.001$

FIGURE 2: Preintervention.

FIGURE 3: Postintervention.

TABLE 4: Individuals with improvement rates in test and placebo groups based on the efficacy index values.

Vas	Day 2			Day 3			Day 4			Day 5			Day 6			Day 7		
	Placebo	Test	p	Placebo	Test	p	Placebo	Test	p	Placebo	Test	p	Placebo	Test	p	Placebo	Test	p
	N (%)			N (%)			N (%)			N (%)			N (%)			N (%)		
Healed	0	0		0	0		0	0		0	2 (7.4)		1 (3.6)	4 (14.8)		5 (17.9)	13 (48.1)	
Marked improvement	0	0	0.193	0	0	<0.001	0	1 (3.7)	0.023	1 (3.6)	9 (33.3)	0.001	11 (39.3)	16 (59.3)	0.041	20 (71.4)	14 (51.9)	0.017
Moderate improvement	1 (3.6)	4 (14.8)		6 (21.4)	20 (74.1)		22 (78.6)	26 (96.3)		27 (96.4)	16 (59.3)		16 (57.1)	7 (25.9)		3 (10.7)	0	
No improvement	27 (96.4)	23 (85.2)		22 (78.6)	7 (25.9)		6 (21.4)	0		0	0		0	0		0	0	
Marked improvement rate	0	0	—	0	0		0	1 (3,7)	0.491	1 (3.6)	11 (40.7)	0.001	12 (42.9)	20 (74.1)	0.019	25 (89.3)	27 (100)	0.072
Improvement rate	1 (3.6)	4 (14.8)	0.193	6 (21.4)	20 (74.1)	<0.001	22 (78.6)	27 (100)	0.023	28 (100)	27 (100)		28 (100)	27 (100)		28 (100)	27 (100)	

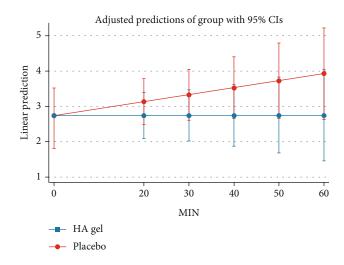Chi-square test or Fisher exact test: N.

Figure 4: Linear predictions for group placebo and the HA gel group with 95% CIs.
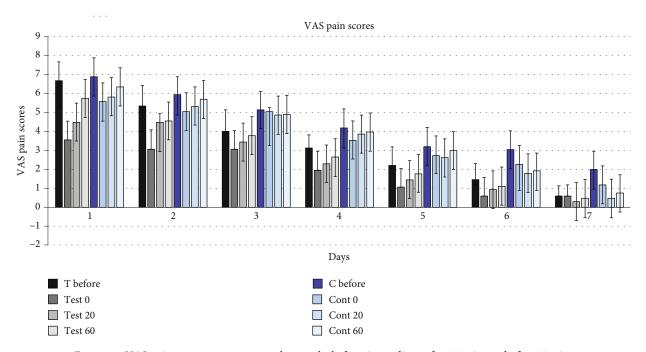

Figure 5: VAS pain scores among test and controls: before, immediate, after 20 min, and after 60 min.

4. Discussion

The results obtained in this RCT showed that a hyaluronic acid-based gel was effective in promoting pain relief and lesion healing, as compared to placebo, for the treatment of active RAS, without any systemic or local side effects.

The clinical results showed that the subjects in the test group reported less pain and better improvement rate from the third until the last day of observation. Moreover, at the end of the seventh day, a significantly higher number of healed lesions has been reported in the test group than in the placebo group.

We may speculate that the absence of between-group difference in reduction of pain reported from patients at day 7 was due to achieved resolution of the painful symptoms.

Several studies reported on the treatment of RAS with similar drug-based products [30–32]. Other therapies are based on the use of Nd:YAG laser or low-level laser therapy. However, laser therapy cannot be compared to treatments based on the use of topical products, which can be applied by the patient without a need for a professional application [32, 33].

To date, the most effective and well-known treatment for RAS is the topical application of corticosteroids. Nonetheless, though topical steroids accelerate the regression and healing of

TABLE 5: Mean TOTPAR differences between test and placebo groups.

| | Differences from placebo | | |
	Mean %	95% CI*	p value*
Day 1	-64.50	-89.2; -39.8	<0.001
Day 2	-58.35	-75.2; -41.5	<0.001
Day 3	-27.68	-43.8; -11.6	<0.001
Day 4	-43.35	-59.2; -27.5	<0.001
Day 5	-43.28	-56.8; -29.7	<0.001
Day 6	23.37	-43.5; -3.2	0.016
Day 7	-0.70	-15.9; 17.3	1.000

*Bonferroni adjustment.

the lesion, they provide only little pain relief. Additionally, the use of topical steroids can be contraindicated for some patients, even for a limited time period [15, 34].

The first studies on the use of topical steroids have been published in 1968 and provided some weak evidence of effectiveness in pain relief [35–38].

Ludlow et al. investigated the topical application of anti-inflammatory and antibacterial drugs. Their study showed similar or even better results in terms of healing and reduction of the size of lesions by, respectively, 75% and 54% after 4 days and 95% and 80% after 7 days. The main difference to be considered when comparing these studies is that our subjects did not report any side effect, whereas the authors of that study pointed out that 8 patients reported adverse effects after the benzylamine hydrochloride, namely, an unwanted and annoying stinging sensation on the tongue [39].

HA gel is considered to be an alternative product for topical treatment. Nevertheless, HA offers advantages over steroids as it is safe in all patients, without risk of toxicity (Becker et al.).

The topical application of 0.2% HA gel has recently been proven to be an effective and safe therapy in patients with RAS in a few clinical trials, all of which showed positive results regarding healing time, pain relief, and absence of side effects [24, 25, 40]. Nolan et al. showed that topical application of 0.2% HA may be of benefit in the pain relief of patients with RAS [24]. Lee et al. investigated the effect of a topical application of a 0.2% HA gel (Gengigel®) in a study that included 16 patients with minor recurrent aphthous ulcers. They reported a decreased value of VAS for pain, namely, 7.4 ± 3.0 to 4.3 ± 4.5, after 14 days. Moreover, almost 20% of the patients still reported no improvement after 14 days. Furthermore, after 7 days of daily application, the product seemed to be still more efficient both in the rate of healing and in pain reduction. They did not evaluate and compare these data with those of a placebo, and the sample size was very limited, but the results are promising [25].

In a more recent study by Tadakamadla et al., published in 2016 [40], the authors compared the use of a HA gel (Aftamed® Oral gel, AktiFarma; Istanbul, Turkey) with a tri-amcinolone acetonide (TA) pomade and placebo, in the treatment of RAS. Pain score in the HA group was statistically lower than that in the TA groups at days 4 and 7 ($p < 0.05$). At day 4, the VAS score was 5.82 ± 1.07 in the TA group and 4.88 ± 0.83 in the HA group. At day 7, VAS score was 2.30 ± 0.90 in the HA group and 3.07 ± 0.97 in the TA group. No other data have been reported by the authors [40]. Once again, the VAS score in our test group was 3.11 ± 0.75 after 4 days and 0.56 ± 0.58 after 7 days. Even if the product tested in the present study might seem to be even more effective than those evaluated in previous studies, comparisons of subjective variables between studies performed in different environmental conditions must be done cautiously.

The results of the present study demonstrated that this gel, from the third day onward, significantly reduced the pain of the patients and led to a significantly faster healing process with no systemic or local side effects. Furthermore, the gel was easy to apply without any bad taste. Some positive effect for pain relief was also observed in the placebo group just 20 min after the application of the product. The slight early effect might be caused by an ephemeral barrier, and because all the patients were blind to the therapeutic agents, it may have also caused some psychologic positive placebo effect. However, the data regarding ulcer size reduction were not statistically significant. This could be attributed to the limitation of the ulcer analysis method; namely, measuring only one ulcer per patient, regardless of the total number of present ulcers, and thus the extent of oral ulcer involvement has not been represented. One of the limitations of the study was the high proportion of subjects lost to follow-up (21.4%), which might represent an attrition bias. Another limitation was the short duration of follow-up. Future studies need to be performed, with longer duration (at least 6 months) and larger sample size, in order to confirm the present results.

In conclusion, HA gel could be considered as an effective, well-tolerated, and safe topical therapeutic agent in clinical practice for the treatment of oral ulcers.

Abbreviations

RAS:	Recurrent aphthous stomatitis
HA:	Hyaluronic acid
ECM:	Extracellular matrix
RCT:	Randomized clinical trial
PVP:	Polyvinylpyrrolidone
VAS:	Visual analogue scale
EI:	Efficacy indices
AUC:	Area under the curve
CI:	Confidence interval
TOTPAR:	Total pain relief
TA:	Triamcinolone acetonide pomade
TGO:	Triester glycerol oxide.

Data Availability

The data used to support the findings of this study may be released upon application to the corresponding author.

Ethical Approval

The study has been performed in accordance with the Declaration of Helsinki and has been approved by the Ethical Committee of the University of Milan (Protocol No.: 44/18).

Consent

Informed consent to participate in the study was obtained from participants before their enrolment.

Disclosure

The funding organization did not have any role in data collection and presentation of the results.

Conflicts of Interest

The authors declare that they have no competing interests.

Authors' Contributions

GMT conceived and planned the experiments. GC carried out the experiments. PS, GMT, MSF, MDF, and FI planned and carried out the simulations. PS, PR, SK, MDF, FI, CO, and ST contributed to the interpretation of the results. PS, PR, and SK took the lead in writing the manuscript. MSF assisted in copyright of the product. All authors provided critical feedback and helped shape the research, analysis, and manuscript. All authors met the criteria and contributed to the manuscript as per ICJE guidelines for authorship.

Acknowledgments

References

[1] J. D. Shulman, "An exploration of point, annual, and lifetime prevalence in characterizing recurrent aphthous stomatitis in USA children and youths," *Journal of Oral Pathology & Medicine*, vol. 33, no. 9, pp. 558–566, 2004.

[2] M. W. Liang and C. Y. Neoh, "Oral aphthosis: management gaps and recent advances," *Annals of the Academy of Medicine, Singapore*, vol. 41, no. 10, pp. 463–470, 2012.

[3] J. A. Ship, E. M. Chavez, P. A. Doerr, B. S. Henson, and M. Sarmadi, "Oral mucosal disease: recurrent aphthous stomatitis," *The British Journal of Oral & Maxillofacial Surgery*, vol. 46, no. 3, pp. 198–206, 2008.

[4] J. A. Ship, "Oxidative stress and cellular immunity in patients with recurrent aphthous ulcers," *Brazilian Journal of Medical and Biological Research*, vol. 47, no. 5, pp. 355–360, 2014.

[5] S. Jurge, R. Kuffer, C. Scully, and S. R. Porter, "Number VI recurrent aphthous stomatitis," *Oral Diseases*, vol. 12, no. 1, pp. 1–21, 2006.

[6] Z. Daněk, J. Gajdziok, P. Doležel, H. Landová, D. Vetchý, and J. Štembírek, "Buccal films as a dressing for the treatment of aphthous lesions," *Journal of Oral Pathology & Medicine*, vol. 46, no. 4, pp. 301–306, 2017.

[7] P. Brocklehurst, M. Tickle, A. M. Glenny et al., "Systemic interventions for recurrent aphthous stomatitis (mouth ulcers)," *Cochrane Database of Systematic Reviews*, vol. 12, no. 9, p. CD005411, 2012.

[8] S. K. Saikaly, T. S. Saikaly, and L. E. Saikaly, "Recurrent aphthous ulceration: a review of potential causes and novel treatments," *The Journal of Dermatological Treatment*, vol. 29, no. 6, pp. 542–552, 2018.

[9] M. G. Arafa, D. Ghalwash, D. M. El-Kersh, and M. M. Elmazar, "Propolis-based niosomes as oromuco-adhesive films: a randomized clinical trial of a therapeutic drug delivery platform for the treatment of oral recurrent aphthous ulcers," *Scientific Reports*, vol. 8, no. 1, p. 18056, 2018.

[10] C. Scully and M. Gorsky, "The diagnosis and management of recurrent aphthous stomatitis: a consensus approach," *Journal of the American Dental Association (1939)*, vol. 134, no. 2, pp. 200–207, 2003.

[11] R. M. Farid, "Promote recurrent aphthous ulcer healing with low dose prednisolone bilayer mucoadhesive buccal film," *Current Drug Delivery*, vol. 14, no. 1, pp. 123–135, 2017.

[12] J. L. Bolognia, "Dermatology," *Section*, vol. 4, pp. 323–332, 2008.

[13] R. A. Deshmukh and A. S. Bagewadi, "Comparison of effectiveness of curcumin with triamcinolone acetonide in the gel form in treatment of minor recurrent aphthous stomatitis: a randomized clinical trial," *Int J Pharm Investig.*, vol. 4, no. 3, pp. 138–141, 2014.

[14] G. Mansour, S. Ouda, A. Shaker, and H. M. Abdallah, "Clinical efficacy of new aloe vera- and myrrh-based oral mucoadhesive gels in the management of minor recurrent aphthous stomatitis: a randomized, double-blind, vehicle-controlled study," *Journal of Oral Pathology & Medicine*, vol. 43, no. 6, pp. 405–409, 2014.

[15] G. S. Vijayabala, A. N. Kalappanavar, R. G. Annigeri, R. Sudarshan, and S. S. Shettar, "Single application of topical doxycycline hyclate in the management of recurrent aphthous stomatitis," *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology*, vol. 116, no. 4, pp. 440–446, 2013.

[16] A. E. Coudert, A. Ostertag, V. Baaroun et al., "Phase III, randomized, double-blind, placebo-controlled trial of topical 2 % lidocaine for the prevention and treatment of oral mucosal pain in children," *Clinical Oral Investigations*, vol. 18, no. 4, pp. 1189–1194, 2014.

[17] C. Liu, Z. Zhou, G. Liu et al., "Efficacy and safety of dexamethasone ointment on recurrent aphthous ulceration," *The American Journal of Medicine*, vol. 125, no. 3, pp. 292–301, 2012.

[18] J. R. Fraser, T. C. Laurent, and U. B. G. Laurent, "Hyaluronan: its nature, distribution, functions and turnover," *Journal of Internal Medicine*, vol. 242, no. 1, pp. 27–33, 1997.

[19] W. Y. Chen and G. Abatangelo, "Functions of hyaluronan in wound repair," *Wound Repair and Regeneration*, vol. 7, no. 2, pp. 79–89, 1999.

[20] M. Casale, A. Moffa, P. Vella et al., "Hyaluronic acid: perspectives in dentistry. A systematic review," *International Journal of Immunopathology and Pharmacology*, vol. 29, no. 4, pp. 572–582, 2016.

[21] M. Casale, A. Moffa, P. Vella et al., "Systematic review: the efficacy of topical hyaluronic acid on oral ulcers," *Journal of Biological Regulators and Homeostatic Agents*, vol. 27, no. 31, pp. 63–69, 2017.

[22] A. Nolan, C. Baillie, J. Badminton, M. Rudralingham, and R. A. Seymour, "The efficacy of topical hyaluronic acid in the management of recurrent aphthous ulceration," *Journal of Oral Pathology & Medicine*, vol. 35, no. 8, pp. 461–465, 2006.

[23] J. H. Lee, J. Y. Jung, and D. Bang, "The efficacy of topical 0.2% hyaluronic acid gel on recurrent oral ulcers: comparison between recurrent aphthous ulcers and the oral ulcers of Behçet's disease," *Journal of the European Academy of Dermatology and Venereology*, vol. 22, no. 5, pp. 590–595, 2008.

[24] C. Occhipinti and M. S. F. Fahim, *The Efficacy of a Topical Gel with Hyaluronic Acid in the Treatment of Oral Ulcers*http://isrctn.com/. Springer Science and Business Media LLC; 2020.

[25] S. J. Pimlott and D. M. Walker, "A controlled clinical trial of the efficacy of topically applied fluocinonide in the treatment of recurrent aphthous ulceration," *British Dental Journal*, vol. 154, no. 6, pp. 174–177, 1983.

[26] K. F. Schulz, D. G. Altman, D. Moher, and CONSORT Group, "CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials," *International Journal of Surgery*, vol. 9, no. 8, pp. 672–677, 2011.

[27] S. V. Rodrigues, A. B. Acharya, S. Bhadbhade, and S. L. Thakur, "Hyaluronan-containing mouthwash as an adjunctive plaque-control agent," *Oral Health & Preventive Dentistry*, vol. 8, no. 4, pp. 389–394, 2010.

[28] J. A. Ship, "Recurrent aphthous stomatitis: an update," *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*, vol. 81, no. 2, pp. 141–147, 1996.

[29] P. Thakrar and S. I. Chaudhry, "Oral ulceration: an overview of diagnosis and management," *Prim Dent J.*, vol. 5, no. 1, pp. 30–33, 2016.

[30] C. Scully and S. Porter, "Oral mucosal disease: recurrent aphthous stomatitis," *The British Journal of Oral & Maxillofacial Surgery*, vol. 46, no. 3, pp. 198–206, 2008.

[31] A. Tezel, C. Kara, V. Balkaya, and R. Orbak, "An evaluation of different treatments for recurrent aphthous stomatitis and patient perceptions: Nd:YAG laser versus medication," *Photomedicine and Laser Surgery*, vol. 27, no. 1, pp. 101–106, 2009.

[32] H. Lalabonova and H. Daskalov, "Clinical assessment of the therapeutic effect of low-level laser therapy on chronic recurrent aphthous stomatitis," *Biotechnol Equip.*, vol. 28, no. 5, pp. 929–933, 2014.

[33] K. Bhalang, P. Thunyakitpisal, and N. Rungsirisatean, "Acemannan, a polysaccharide extracted from aloe vera, is effective in the treatment of oral aphthous ulceration," *Journal of Alternative and Complementary Medicine*, vol. 19, no. 5, pp. 429–434, 2013.

[34] W. T. Mcfall Jr., "Clinical report-effect of flurandrenolone on oral aphthae," *Journal of Periodontology*, vol. 39, no. 6, pp. 364-365, 1968.

[35] R. M. Browne, E. C. Fox, and R. J. Anderson, "Topical triamcinolone acetonide in recurrent aphthous stomatitis. A clinical trial," *Lancet*, vol. 1, no. 7542, pp. 565–567, 1968.

[36] D. A. Miles, S. L. Bricker, T. F. Razmus, and R. H. Potter, "Triamcinolone acetonide versus chlorhexidine for treatment of recurrent stomatitis," *Oral Surgery, Oral Medicine, and Oral Pathology*, vol. 75, no. 3, pp. 397–402, 1993.

[37] J. B. Ludlow, M. J. Kutcher, and A. Samuelson, "Intraoral digital imaging documenting recurrent aphthous ulcer healing in 2-octyl cyanoacrylate versus sham-treated lesions," *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*, vol. 89, no. 4, pp. 425–431, 2000.

[38] D. Ofluoglu, M. Koray, A. Senemtasi, H. İşsever, and M. Yaltirik, "The efficacy of hyaluronic acid gel in pain control of recurrent aphthous stomatitis," *Int J Dent Oral Sci.*, vol. 3, pp. 273–275, 2016.

[39] D. Ofluoglu, S. Ergun, S. Warnakulasuriya, F. Namdar-Pekiner, and H. Tanyeri, "An evaluation of the efficacy of a topical gel with triester glycerol oxide (TGO) in the treatment of minor recurrent aphthous stomatitis in a Turkish cohort: a randomized, double-blind, placebo-controlled clinical trial," *Medicina Oral, Patología Oral y Cirugía Bucal*, vol. 22, no. 2, pp. 159–166, 2017.

[40] S. K. Tadakamadla, V. V. Bharathwaj, P. Duraiswamy, C. Sforza, and G. M. Tartaglia, "Clinical efficacy of a new cetylpyridinium chloride-hyaluronic acid–based mouthrinse compared to chlorhexidine and placebo mouthrinses—a 21-day randomized clinical trial," *International Journal of Dental Hygiene*, vol. 18, no. 1, pp. 116–123, 2020.