ORIGINAL RESEARCH

Local Formula with Mucoadhesive Property: A Randomized Clinical Trial of a Therapeutic Agent for the Treatment of Oral Aphthous Ulcers

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Abstract

Background: Recurrent or occasional aphthous lesions represent a painful oral condition with high prevalence. Since the etiology is still unclear and most likely related to a dysfunction in the local immune system, several treatment strategies have been proposed, including systemic agents, local agents, and laser therapy, to reduce the pain and discomfort for the patient without acting on the causes.

Materials and methods: The purpose of the present randomized study was to assess the clinical efficacy of a new topical gel with mucoadhesive property to reduce the pain and the dimension of the aphthosis lesions. Fifty patients presenting at least one minor ulcer were randomized to a control group (placebo prescription), a first test group (topical agent with laser), and a second test group (topical agent only). The healing rate, the visual analog scale (VAS) score for pain, and the diameter reduction were monitored for 10 days.

Results: Both test groups showed better results than control group, significant clinical efficacy, and a median total reduction time of 4 days with no significant adjunctive benefit from the use of laser.

Conclusion: The clinical results are encouraging; nevertheless other studies are needed to valid this kind of treatment.

Clinical significance: The present randomized clinical study suggested that the use of topical mucoadhesive agents could represent a valid therapy for minor aphthous lesions.

Keywords: Adjuvant therapy, Laser therapy, Mucoadhesive gel, Oral aphthous ulcers, Recurrent aphthosis.

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Introduction

Aphthous stomatitis is a common recurrent condition of the oral cavity, statistically affecting 5–25% of the population.[1] Clinically, patients present painful lesions characterized by an initial necrotic ulcer, with well-defined limits surrounded by erythematosus area. Even though the etiology is not clear, a number of local and systemic factors seem to favor the onset of oral aphthae, including dysfunction, genetic factors, microbiota, allergy, trauma of the mucosa, stress, hormonal changes, certain chemical substances, food additives/preservatives (e.g., cinnamaldehyde and sodium benzoate), and smoking cessation. Moreover, many systemic diseases, such as Behçet's syndrome, gastrointestinal diseases, hematological disorders, vitamin deficiencies, cyclic neutropenia, and Reiter syndrome, have been associated with oral aphthous lesions.[2] Those lesions are located on the oral mucosa (keratinized and non-keratinized) and affect most frequently subjects between 10 years and 40 years of age. The disease uses to manifest in the form of outbreaks, with a chronic and self-limiting lesion. Two clinical subtypes of aphthous lesions have been established according to size, number, and duration of the outbreaks: minor aphthous and major aphthous lesions.[3] Minor lesions are most common (80%) and are characterized by ulcers surrounded by a thin erythematous halo and smaller than 8 mm in diameter. They are commonly located in the non-keratinized mucosa and have an average healing time between 10 days and 14 days. Major aphthous lesions represent the most severe form of the disease, affecting the 10–15% of patients and are characterized by ulcers in diameter larger than 10 mm in the keratinized mucosa with an average healing time of 2–8 weeks. Pain is the most relevant symptom, but it often seems to be not even related to ulcer dimension. The onset of the lesion may be caused by a several local events, including local trauma, unfitted prothesis, stress for anesthesia injection, vitamin

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deficiencies (B_{12}, folic acid), iron deficiency, possible sensitivity to sodium lauryl-sulfate, and other iatrogenic factors.[4] Since the etiology of the lesion is not known, during the years, many different treatment strategies and drugs have been suggested in order to accelerate the ulcer's healing process and to mitigate the symptoms: topical analgesic pastes, benzydamine hydroclotite mouthrinse, protective bioadhesives, 0.12% chlorhexidine mouthrinse but even topical corticosteroid agents, usually in combination with antifungal prophylaxis and/or systemic medication, vitamin B replacement, and laser therapy.[5] The use of laser to treat these lesions was proposed, particularly in biomodulation protocols for the effects in terms of stimulation of wound healing and analgesic effect.[6] It is used with different wavelengths and different parameters.[7] Drugs muco-adhesion has the property to settle on the oral mucosa with enough stability to create a protective pellicular above the injuries. The advantages of this type of administrations are mainly related to the avoidance of stomach acidity and the prompt action to the target site. In addition to that, this type of products is well-tolerated by patients. In the last years, we are witnessing an ecological retrofit of the therapeutic approach toward several oral conditions; therefore, it is important to explore the clinical efficacy of new non-pharmaceutical agents in rigorous trial designs. The purpose of the present randomized controlled clinical study was to evaluate the clinical effectiveness of a new topical product with mucosal delivery on healing rate and reducing pain of aphthous lesions at a 10 day period when compared to no treatment and to laser therapy.

Materials and Methods

This randomized clinical study followed the Declaration of Helsinki so that a written informed consent was signed by all the participants before starting the study. The clinical activities were carried out between January 2018 and July 2018 at the Tuscan Stomatologic Institute, Forte dei Marmi, Italy.

Sample size was computed according to the results of the study by Yilmaz et al.[8] A sample size of 40 patients would have been sufficient to detect a significant difference between a test and a control group in the healing rate efficacy.

A total of 50 patients with recurrent aphthous stomatitis were included in the present study and completed the intended follow-up. Participants were 18 years and older with a validated history of recurrent aphthous stomatitis. The presence of at least one minor aphthous lesions in the buccal or labial non-keratinized oral mucosa with a duration of maximum 3 days was the main inclusion criterion. Exclusion criteria were as follows: traumatic ulcers, the presence of systemic diseases that predispose to oral mucosa lesions that could be misunderstood as aphthosis lesion, major herpetic lesions, and ulcers caused by systemic medications or other iatrogenic factors.

The new adhesive oral gel that was put to test is called dermovitamina aftaclin (Pasquali Healthcare s.r.l.). This new product is an adjuvant agent that creates a protective film on the wound reducing pain and discomfort for aphthosis making a faster healing.

Each subject with aphthous lesions have been randomly assigned by the toss method to three groups:

- Test group I: Topical application of the new product two times a day after toothbrushing + oral instructions + professional Er,Cr:YSGG laser irradiation at first appointment.
- Test group II: Topic application of the new product two times a day + oral instructions.
- Control group: Topic application of a placebo product two times a day + oral instructions.

Patients were encouraged to apply the elect product as many times as required to achieve relief during the day and they were asked to report this frequency on a questionnaire.

Patients scored their pain and discomfort level for each aphthous lesion by marking a point on a visual analog scale (VAS) score with 10 points. Visual analog scale scores have been recorded immediately and at 4 control sessions, at days 1, 3, 7, and 10 after treatment.

The clinician who recorded the data at 1, 3, 7, and 10 days did not know the group of treatment as well as the patient who obviously did not know about the composition of domiciliary gel (placebo or Dermovitamina Aftaclin). For these reasons, the study could be defined as double blinded: only the first clinician at T0 who performed the randomization and did the first treatment knew about the groups.

The investigator assessed the healing process of aphthous lesions by a four-point scale (range 1–4) at which grade I means totally healing, grade II represents moderate healing (50% of aphthous lesions healed and epithelialized), grade III defines slightly healing (50% of aphthous lesions healed and epithelialized), and grade IV means no healing.

The ulcer diameter was measured with a standard periodontal probe and intraoral digital photographs.

Each value was recorded into an electronic database and the conversion of data into an executable file allowed statistical computing on a free software environment (R Studio 3.3.1). Summary statistic was done first to obtain mean and standard deviation of each variable.

Results

At the initial visit (0 day), no differences between groups were reported regarding age, gender, ulcer size, and pain intensity. Table 1 shows the baseline data of patients enrolled in different groups. One patient in the test group I had diagnosticated the

Table 1: Mean values for the explored outcomes at each time-point for each group

	Laser + topic formula	*Topic formula*	*Placebo*
Baseline			
Maximum diameter (mm)	5.60 ± 1.17	5.65 ± 1.62	4.62 ± 0.76
Pain (VAS)	8.70 ± 1.16	8.00 ± 1.94	9.38 ± 0.80
1 day			
Maximum diameter (mm)	4.19 ± 1.60	3.76 ± 2.51	4.46 ± 0.59
Pain (VAS)	3.90 ± 1.20	2.47 ± 2.15	7.62 ± 0.51
3 days			
Maximum diameter (mm)	2.40 ± 1.07	2.00 ± 2.06	3.69 ± 0.75
Pain (VAS)	2.30 ± 1.25	1.41 ± 1.62	5.23 ± 0.92
7 days			
Maximum diameter (mm)	1.10 ± 1.37	1.12 ± 2.12	1.23 ± 0.43
Pain (VAS)	0	0	1.38 ± 0.76

VAS, visual analog scale

Behçet's syndrome and one patient in the test group II had diabetes since 2010. A total of 50 patients were included and 48 completed the follow-up; the anamnestic data were homogeneous in the three groups of treatment (male:female 1:2 in every group).

When compared to baseline, all patients showed significant clinical improvement in the explored parameters (p value = 0.001), with the overall best results revealed at days 7–10.

Diameter

When implemented on the Brunner and Longer model, the data showed a significant relation between time and lesion shrinkage in both the test groups (p value = 0.004). The maximum reduction in diameter occurred at a 3 day evaluation. There were no significant differences in diameter reduction between the two test groups. There was a significant difference between test groups and the placebo group (p value < 0.0001). When the onset of ulcer size reduction was evaluated, a statistically significant difference was found between the two test groups and placebo group (p < 0.0001). In the intervention groups, there was a significant reduction in ulcer size on the third day of treatment in most patients, while for the placebo group, no decrease in ulcer size was observed on these days, and a size reduction was observed only after 7 days (Fig. 1).

Visual Analog Scale

The VAS score for pain showed a significant reduction over time in both the test groups (p value < 0.0001) with no differences between them (p value 0.0552) (Fig. 2). Most of the patients reported no pain (VAS = 0) after 3 days of topic application of the new formula no matter if they were not treated with laser. There was a significant difference between test groups and the placebo group (p value < 0.0001). Below is reported the plot of the relative treatment effects on VAS of time × treatment (Fig. 3).

Pain reduction

Patients were asked to answer whether the pain relief was immediate and how efficient it was. The two test groups behaved similarly: the pain was reduced immediately, and the analgesic effect sustained during the 3 days afterward. There was a significant difference with the control group in which no relief was recorded at all (Fig. 4).

The efficacy onset was sensibly higher in both the test groups without adjunctive benefit from laser. Both the test groups were significantly more efficient than the placebo (Fig. 5). The mean onset time for lesions with <10 mm diameter was 0.77 ± 0.97 minutes.

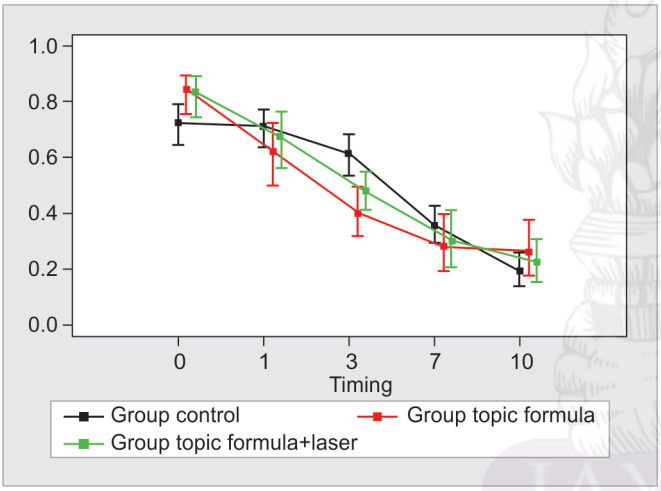

Fig. 1: Plot of the relative treatment effects on diameter of time × treatment

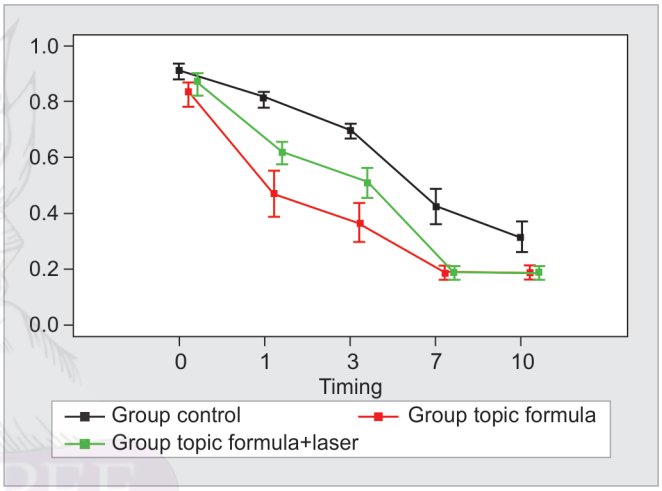

Fig. 2: Plot of the relative treatment effects on visual analog scale of time × treatment

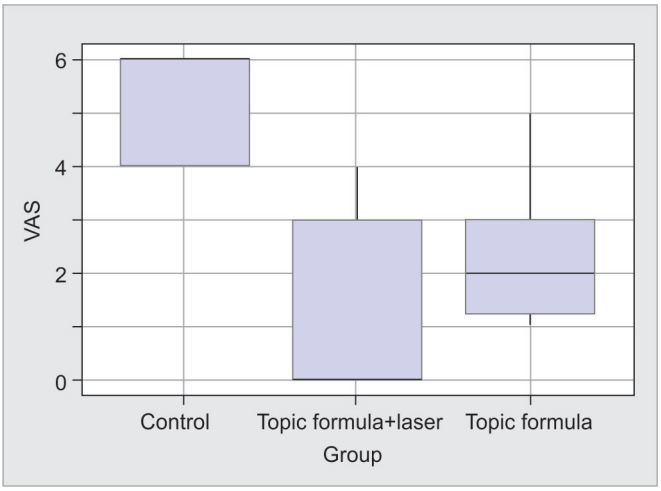

Fig. 3: Histogram of the mean visual analog scale value at a 3-day evaluation for each group

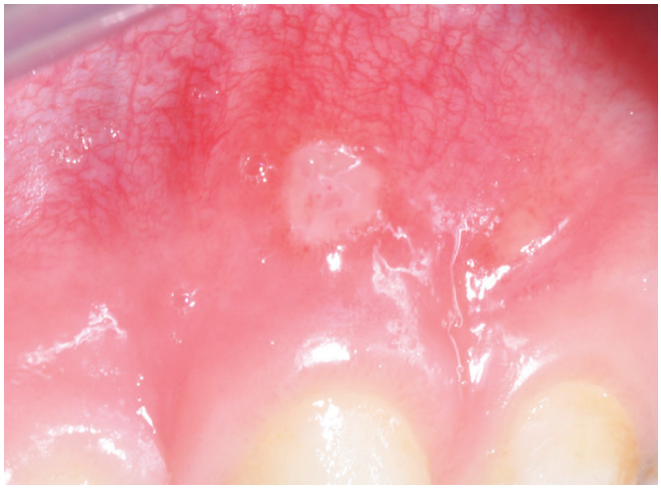

Fig. 4: Clinical case of minor aphthosis lesion treated by topic formula

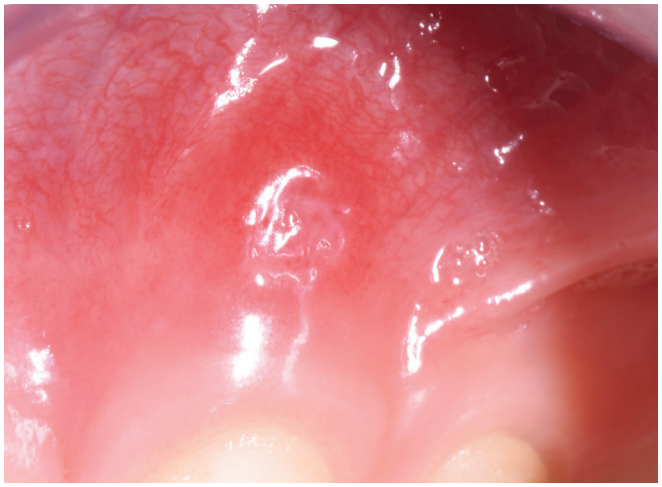

Fig. 5: Clinical case of minor aphthosis lesion treated by topic formula after 1 day (T1)

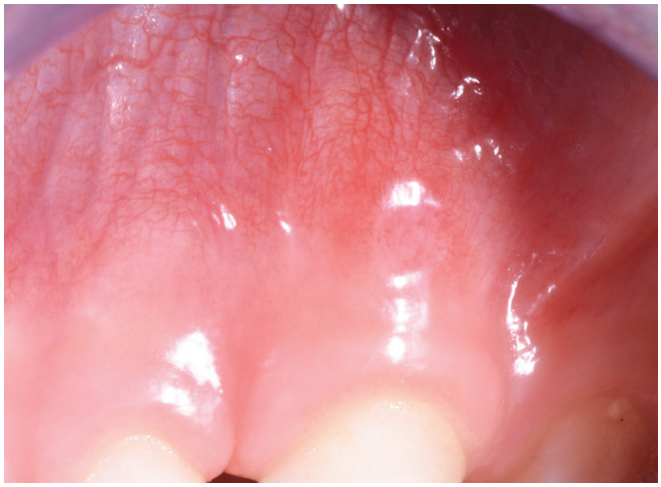

Fig. 6: Clinical case of minor aphthosis lesion treated by topic formula after 3 days (T2)

Figure 6 shows the frequency of distribution of patients according to the efficacy onset time recorded.

The intervention group showed a significantly shorter time to complete ulcer healing than the placebo group ($p = 0.001$). Most patients from the intervention groups recorded complete ulcer healing during the first 7 days; on the contrary, no patients in the placebo group recorded healing of ulcers during the first 5 days of treatment.

Level of patient satisfaction was scored on a VAS with 10 values. The intervention group was significantly more satisfied than the placebo group ($p = 0.0005$). All patients in the intervention group recorded high scores. The clinicians reported high appreciation for the gel performance in terms of clinical efficacy and ease of use.

Discussion

The present analysis inquired the clinical effect of a topical agent against aphthous lesions in a randomized cohort clinical study. The new formula was compared with a placebo and with the laser therapy which is, by far, considered the most powerful method in non-respondent oral aphthous lesions. However, laser therapy comes in professional-use only and implies higher costs for the clinician due to the precious "chair-side time". For these reasons, the laser therapy is often not used to treat minor lesions, because of the cost and the time. Moreover, the patients' needs to manage problems at home and to use domiciliary products are increasing in last years and clinicians have to consider also this aspect to have a good compliance in the treatment plan.

The results of the present study suggested that topical agents adhering to the oral mucosa might be considered as the first choice of treatment in minor ulcers. In Figures 4 to 6 is shown a minor aphthosis lesion at T0, T1, and T2 after the use of the oral gel with Dermovitamina Aftaclin. According to the clinical results of the present study and as shown in pictures, the ulcer healed in 3 days (T2). The topical agent was also compared with the use of both the agent and laser therapy. In both groups, the median healing time after treatment was 4 days with no adjunctive benefit in terms of pain reduction, diameter shrinkage, or efficacy onset from the laser supplement. Despite the limitation of the present study, such as the small size sample, the present findings agreed with the results from Zand et al. who achieved a mean healing time of 4.8 ± 2.4 days using laser and 7.6 ± 2.5 days in the placebo group.[9] The same authors stated the fact that low-level laser therapy (LLLT) remains controversial since the exact biochemical mechanisms are not completely understood and the positive effects are not explained. On the contrary, the use of topical mucoadhesive agents is a novel, promising method against mechanical trauma and inflammation at the ulcer site. In fact, this new product is an adjuvant agent that creates a protective film on the wound reducing pain and discomfort for aphthosis making a faster healing. This kind of home-care therapy is classified as a proactive therapy because it helps the patients to defend himself and heal thanks to his own endogenous anti-inflammatory, antioxidant, and healing mechanism.

Creating a mechanical film on the lesion protects the patients from pain, stabilizes the coagulum improving the healing, and prevents supra infection so that patients do not have to intake other medications (antimycotics or antibiotics). Other type of local domiciliary proactive therapy could be the ozone therapy because it modulates immune response, reduces inflammation, and promotes healing of the damaged tissues.[10]

Even though, other limitations of the present clinical study defined as a pilot study could be the nature of arthouses lesions that can heal even without treatment and the VAS that measures the pain thanks to a patients' outcome so that very variable according to patients' perception.

Moreover, the treatment modality of aphthous lesions should always be related to disease severity, patients' medical history, the frequency of flare-ups, size, and number of ulcers.[11,12] A variety of topical therapeutic agents have been used in the management of aphthous lesions for years, including various anti-inflammatory agents, immunomodulatory agents, antimicrobials, and analgesic drugs. Non-pharmaceutical products are a promising source for the innovation of new therapeutic agents, also because of the fewer adversative properties or side effects than traditional medication.[13,14] In recent decades, for example, the bee product propolis has attracted interest from clinicians and researchers, and several studies have been conducted to investigate the its biological properties exploring its potential for the development of new drugs with clinical efficacy toward different oral conditions.[15,16]

One other frequent oral mucosa lesion may be present in patients with prolonged antitumoral therapy.

In order to treat this kind of lesions, oncologic patients are often monitored by dentists together with general doctors and oncologic to control complications and to avoid those lesions became chronic.[17] Sometimes, local therapy could be more efficient and less invasive than pharmacologic one. Non-pharmaceutical products might be useful to facilitate healing process, preventing systemic complications such as dehydration, malnutrition, and interaction with other drugs and allergies.

One of the main advantages of topical agents is the patients' compliance and the kinship contributory factor: patients usually stick to the therapeutic indications with loyalty if they feel immediate relief ease of use.

Conclusion

The patients in the intervention groups were greatly satisfied with the effect of the topic agent and with its effects on their quality of life, as this accelerated the onset of ulcer size reduction, prolonged the duration of pain relief, and accelerated the lesions healing time.

Further studies with larger sample sizes and with the inclusion of major aphthous lesions are recommended to support these scouting findings.

Clinical Significance

The present randomized clinical study suggested that the use of topical muco-adhesive agents could represent a valid therapy for minor aphthous lesions with great performance in terms of pain relief and healing rate.

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