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RESEARCH ARTICLE

Assessment of the Effectiveness of a Film-Forming Cream in the Management of Oral Aphthous Ulcers: A Placebo-Controlled Randomized Clinical Trial

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Background: Aphthous stomatitis is a common disease of the oral mucosa and its pathogenesis is associated with several risk factors. Frequently, minor ulcers are idiopathic in nature and often resolve naturally. However, those ulcers are painful and sensibly compromise patients' eating. There are different treatment strategies for the clinical management of oral aphthae.

Methods: The present study assessed the efficacy of a film-forming cream in accelerating the healing and diminishing the pain associated with minor aphthae in a randomized fashion design. The test product (AphtoFix®) was compared with placebo cream in a cohort of patients with a diagnosis of minor recurrent stomatitis. Patients were randomly distributed into two groups and were followed for 10 days. The primary outcomes included the number of days until symptoms were relieved and the number of days to complete healing.

Results: Thirty-six patients completed the follow-up, eighteen per group. All lesions eventually healed within day 10. However, patients in the test group experienced significantly less pain, already from day 1. Patients in the test group also showed a faster healing rate of the lesion with an average of 7 days against the 9 days required for patients in the control group.

Conclusion: The present study supported the utility of a film-forming in cream in relieving the patient from symptoms associated with aphthous stomatitis already at day 1 of product use. Patients also displayed faster healing of the lesions when compared to the control group. Further studies with greater sample size and patient stratification according to age and risk factors are recommended to support the present findings.

Key Words: Aphthous, Oral, Oral hygiene, Pathology, Stomatitis

Introduction

1. Background

Oral aphthous ulcers are painful pathologic lesions of the mucosa with nonspecific etiology. The lesions are round or oval with a necrotic base surrounded by an erythematous halo and varying dimensions[1]. In predisposed patients, oral aphthosis is often recurrent but usually self-limited. Aphthae are variously attributed to stress, trauma, viral infection, dysergy of the immune system, malnutrition, and genetic predisposition[2]. Aphthous ulcers may be minor (diameter less than 5 mm), major, or herpetiform, and, sometimes, may be the sentinel of a worse systemic condition[3].

The diagnosis is clinical. Minor recurrent aphthous stomatitis (RAS), also known as per Mikulicz's aphthae, is the most common form of RAS and represents 70～85% of cases[3]. Minor aphthae are less than 1 mm in diameter and often appear in groups of 1～5 and are characterized by a gray pseudomembrane surrounded by an erythematous area. They usually heal within 7～10 days. Although minor lesions are usually self-limiting, the associated pain can significantly interfere with eating, swallowing, and speaking[4].

The pathophysiology of RAS is ambiguous and it mainly

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involves T-cell immune dysregulation, whereby a Th1-type hyperimmune response leads to inflammation and ulcerations[5]. Given the unclear origin of the pathology, the clinical management of minor aphthous lesions addresses the symptoms, thus, reducing inflammation and pain, and promoting healing[5]. There are many treatment approaches, however, topical corticosteroids are the gold standard. Nevertheless, their continued use can lead to adverse effects, mainly related to a possible systemic absorption of the steroids[5].

Thus, the offer of treatment alternatives for RAS has been expanding and it now includes topical formulae with a prolonged barrier action on the underlying mucosa and no adverse effects, such as AphtoFix®[6].

2. Objectives

The aim of the present placebo-controlled randomized clinical trial was to assess the efficacy of a film-forming cream to control pain associated with minor aphthous lesions and to promote faster healing of the mucosa.

Materials and Methods

1. Study design

The present study is a single-blind, 2-group of treatment, placebo-controlled randomized clinical trial with a 10-day follow-up. This study was conducted in full accordance with the World Medical Association Declaration of Helsinki and it was undertaken with the understanding and written consent of each participant and according to the above-mentioned principles. The Unicamillus (Rome) Ethical Committee gave the approval for this study. The study was approved by the Institutional Review Board of the Unicamillus (IRB no. E00352-2023).

The cohort of patients enrolled in the present trial was at the Tuscan Institute of Stomatology, between May and July 2022, and have been identified following the inclusion and exclusion criteria outlined below as follows. The inclusion criteria included: the presence of recurrent minor aphthous stomatitis. The Exclusion criteria included: smoking more than 20 cigarettes/day; abusing alcohol or drugs; severe psychiatric disorders; pregnancy; head/neck irradiation in the last years; patients with severe stomatitis which was secondary to other conditions.

After written informed consent was obtained, forty patients were enrolled in the study and randomly allocated into two groups of treatment: Patients included in the Test Group were treated with topical application of a film-forming cream (AphtoFix®, bonyf, Liechtenstein) applied three times a day after tooth brushing for 10 days. AphtoFix® is composed of cellulose gum and a copolymer of calcium/sodium and a copolymer of methyl vinyl ether and maleic anhydride (PVM/MA). Patients included in the Control Group were treated with topic application of an inert placebo product (glycerine based) three times a day after tooth brushing for 10 days.

2. Study endpoints

The primary outcomes included the number of days until symptoms were relieved and the number of days to complete healing. Pain was assessed for each patient using a visual analog scale (VAS). A line of 10 cm in length was used, and the patient was asked to select the number which best reflected her/his state for the following assessment times: day 0, day 3, 7, 10. Patients' responses ranged from (0): no pain, to (10): the highest pain level. Then, the assessment of pain was converted into the number of days that occurred until VAS was down to zero for each patient.

Ulcer healing was recorded for each treatment period (day 0, day 3, day 7, and day 10) using a calibrated William's periodontal probe with millimeter markings. Each measurement was taken twice, and the average value was calculated. Then, the assessment of the lesion dimension was converted into the number of days that occurred until the lesion was completely healed.

The eventual side effects due to the treatment (such as local irritations or patient sensitization) were also recorded as well as the lesion location.

Patients were followed for two weeks and five time points were identified: T0 represented the Baseline evaluation. At this time patients were motivated and instructed to follow a specific treatment protocol depending on the group allocation (Test Group, film forming creme, Control Group Placebo).

3. Statistical analysis

Sample size, descriptive, difference, and correlation analysis was performed (R version 4.2.0 [2022-04-22] - "Vigorous Calisthenics", Copyright (C) 2022 The R Foundation for Statistical Computing). Each variable of interest was assigned to the appropriate statistical test according to its nature: independent/dependent, continuous/nominal/time-to-event, and normal/non-normal. The inferential statistic was performed using a nonparametric longitudinal design for the testing of the group (treatment) and time effects, and their interactions.

Results

1. Sample characteristics

Forty patients were initially included in this trial. Four patients were lost during the follow-up period. Thus, thirty-six patients were included in the final analysis, with 18 subjects in each group. Regarding gender distribution, there were 7 males and 11 females in the test group, 7 males and 11 females in the control group. The age ranges were 18 years～42 years, 20 years～45 years, in the test and the control group, respectively. Sample characteristics along with the distribution of lesion location for each group are presented in Table 1.

2. Days to symptoms relief

On average, the days required for symptom relief in the test group was 1 (median) against 4 days reported by patients in the control group, the difference being statistically significant (p-value＜0.05) (Fig. 1). The treatment effect on pain was significant regardless of the time occurred (multivariate analysis p-value＜0.05) (Table 2).

3. Days to complete healing

On average, the days required for the documentation of complete healing of the lesion were 7 (median) in the test group and 9 in the control group, the difference being statistically significant (p-value＜0.05) (Fig. 2). The treatment effect on the healing rate was enhanced over time (multivariate analysis p-value＜0.05). No side effects nor complications were reported in both groups.

Discussion

The present single-blind randomized trial evaluated the efficacy of a film-forming formula AphtoFix® on the clinical management of symptoms and the healing rate of minor aphthous ulcers. Patients who used the AphtoFix®

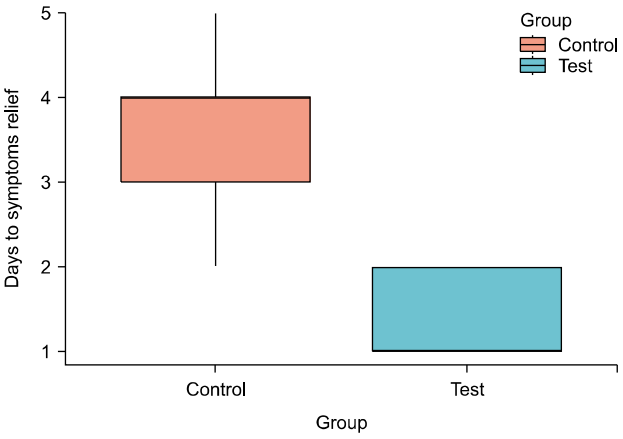

Fig. 1. Box-plot of the days to symptom relief for both the control and the test group.

Table 1. Patients characteristics at baseline

Explanatory variables	Test group (N=18)	Control group (N=18)
Male/Female Ratio	7/11	7/11
Age	37.2±7.41	39.0±4.20
Lesion Location		
Buccal mucosa	3	4
Upper lip	4	3
Lower lip	8	7
Tongue	3	4

Values are presented as number only, or mean±standard deviation.

Table 2. Median values for VAS lesion size at each time point for both groups

Outcome measures	Day 0	Day 3	Day 7	Day 10
Pain (VAS)				
Test	7	0	0	0
Control	7	2	0	0
Multi-way ANOVA	＞0.05	＜0.05	＞0.05	＞0.05
Lesion size (mm)				
Test	4	2	0	0
Control	4	3	2	0
Multi-way ANOVA	＞0.05	＞0.05	＜0.05	＞0.05

Values are presented as number only. VAS: visual analog scale.

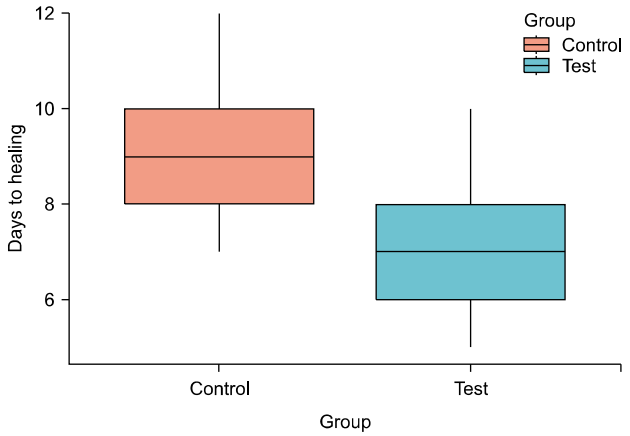

Fig. 2. Box-plot of the days to complete healing for both the control and the test group.

cream experienced less pain and faster healing of the lesions when compared with patients of the placebo group. The median days required for pain relief in the test group was 1 against the 4 days reported by patients of the placebo group.

1. Interpretation

The strong pain relief effect of AphtoFix® might be related to its formula that provides a thin, durable layer when in contact with the oral mucosa. The muco-adhesive property of AphtoFix® is activated on contact with saliva. Acting as an elastic barrier against the oral environment, this durable film may protect the ulcer, thus favoring prompt healing by means of excluding the wound from food debris and bacteria. The muco-adhesive properties of AphtoFix® are due to the presence of cellulose Gum and Calcium/Sodium PVM/MA Copolymer that activate on contact with saliva. This enables the cream to create a protective waterproof and lasting layer over the ulcer area. This durable film also prevents from burning sensation.

2. Key results and comparison with the results of previous studies

The results of the present study are in agreement with those of Sakly et al.[6], who reported a difference between the 3rd and 7th days was −6.29±0.14 points of pain. They also reported a significant reduction of the size of the lesions of 4.08 mm±0.2 mm, on the 7th day. In addition, no adverse reactions were reported which was reconfirmed in this study.

3. Suggestions

In January 2023, Parra-Moreno and colleagues published the results of a systematic review of the available treatment strategies for recurrent aphthous stomatitis[5]. In their results, among all the treatments, the authors emphasized the barrier method based on a compound of cellulose rubber and a calcium/sodium copolymer PVM/MA, namely AphtoFix®, with which the analgesic effect was had an earlier onset when compared to other strategies. Furthermore, domestic formulations are cheaper and more convenient for patients when compared with repeated professional laser sittings, especially in the management of a recurrent lesion, such as aphthosis.

4. Limitations

The present study had some limitations that must be mentioned. The follow-up period was short and did not take into account the natural recurrence of the disease. Patients included in the study did not show multiple lesions and the sample size was relatively small. The oral health-related quality of life was not investigated.

Conclusion

The present study suggested the clinical efficacy of a film-forming cream AphtoFix® in the management of the symptoms (pain relief) and healing rate of minor aphthous lesions when compared with a placebo. Further studies with larger sample sizes and the stratification of data according to the number, diameter, and putative etiology are recommended.

Notes

Conflict of interest

No potential conflict of interest relevant to this article was reported.

Ethical approval

This study was approved by the institutional review board of Unicamillus University (IRB no. E00352-2023).

Author contributions

Conceptualization: Simone Marconcini, Annamaria Genovesi. Data acquisition: Giacomo Oldoini, Annamaria Genovesi. Formal analysis: Enrica Giammarinaro. Funding: Annamaria Genovesi. Supervision: Simone Marconcini, Annamaria Genovesi. Writing-original draft: Simone Marconcini, Enrica Giammarinaro, Giacomo Oldoini, and Annamaria Genovesi. Writing-review & editing: Simone Marconcini, Enrica Giammarinaro, Giacomo Oldoini, and Annamaria Genovesi.

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Data availability

Data files are available upon request.

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