SINGLE APPLICATION OF A DESSICATING AGENT IN THE TREATMENT OF RECURRENT APHTHOUS STOMATITIS

D. LAURITANO[1], M. PETRUZZI[2], G.M. NARDI[3], F. CARINCI[4], G. MINERVINI[5], D. DI STASIO[5] and A. LUCCHESE[5]

[1]Department of Translational Medicine and Surgery, Neuroscience Center of Milan, University of Milano Bicocca, Monza, Italy; [2]Dental School, Section of Oral Pathology and Medicine, University of Bari, Bari, Italy; [3]Department of Stomatology and Maxillofacial School of Medicine and Dentistry, Sapienza University of Rome, Rome, Italy; [4]Department of Morphology, Surgery and Experimental Medicine, University of Ferrara, Italy; [5]Multidisciplinary Department of Medical and Dental Specialties, Second University of Naples, Naples, Italy

Recurrent aphtous stomatitis (aphthae, canker sores) is ones of the most common and painful oral mucosal inflammatory ulcerative conditions; etiopathogenesis is uncertain and only symptomatic therapy is available. We used a dessicating agent based on a concentrated mixture of sulfates. The rationale for use of this product on canker sores is that it cauterises the epithelial tissue affected by the immune response. The aim of this study was to evaluate the topical application of this dessicating agent on aphtous ulcers, and verify its efficacy in reducing pain. Fifty-seven patients, with oral minor aphtous lesions and a history of recurrent aphtous stomatitis were enrolled into this study and were assigned into two groups: 30 patients were treated with a single topical application of a dessicating agent and 27 without any treatment. A subjective evaluation of symptoms was completed by each patient using a visual analog scale (VAS) of 0-10. Patients' oral lesions were clinically observed at days 0 (before entering the study) and at day 6. We found that from day three the mean differences in pain score between the two groups was about 16.33% with a decrease of symptoms of 49.57% compared with pretreatment VAS score at baseline (P<0.001). Unfortunately, if we compare the mean differences from baseline in the range of 6 days of pretreatment until day 6 in the group treated with the dessicating agent and in the one receiving no treatment, performing an unpaired *t*-test, no significant differences appeared (P>0.05). These data suggest that a single application of this medicament could become a valid support in the management of recurrent aphtous stomatitis.

Recurrent aphthous stomatitis (RAS) is a common condition that is characterized by multiple recurrent small, round, or ovoid ulcers with circumscribed margins, erythematous haloes, and yellow or gray floor (1), with a wide range of reported prevalences from 5 to 50% in different populations (2). These ulcers appear on the non-keratinized (or less keratinized) oral mucosal tissues, and usually regress spontaneously within 14 days (3). Recurrent aphthous stomatitis is one of the most common painful oral mucosal conditions seen among patients (4). The frequent aphthous ulcers can increase the severity of patient discomfort and cause functional complications, including difficulties in speaking, tooth brushing and eating (5). The

Key words: recurrent aphtous stomatitis, dessicating agent, oral pain

Mailing address: Dr. Dorina Lauritano,
Department of Neuroscience and Biomedical Tecnologies,
University of Milan- Bicocca Monza, Via Cadore, 48
20052 Monza (MI), Italy
Tel.:+ 0392 339892
Fax: +39 02 64488250
email: dorina.lauritano@unimib.it

0393-974X (2015)
Copyright © by BIOLIFE, s.a.s.
This publication and/or article is for individual use only and may not be further reproduced without written permission from the copyright holder.
Unauthorized reproduction may result in financial and other penalties
DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

aetiology of aphtous lesions is still not clear (2). The histopathological changes in the preulcerative stage include infiltration of the epithelium by lymphocytic cells; oedema develops, followed by keratinocyte vacuolisation and localised vasculitis causing localised swelling that ulcerates and is infiltrated by neutrophils, lymphocytes, and plasma cells before there being a healing phase and regeneration of the epithelium (6, 7). Treatment is symptomatic, since the etiology is unknown and because of its recurrent nature. The goal is to: decrease symptoms, reduce ulcer number and size, increase disease-free periods (8). Topical and sistemic corticosteroids can reduce the duration and severity of RAS ulcers (8, 9). However, a therapy with corticosteroid is not always easy to manage and can cause some side effects, therefore new therapeutic strategies are always welcome. For example, dessicating agents have been suggested to reduce and accelerate healing of the ulceration of RAS (3, 10).

The product that we used was HybenX™ (Epien Medical s.r.l) which is a concentrated mixture of sulfates, a dessicating agent, consisting of 50% sulfuric acid and 28% sulfonated phenolics. This product is an adjunctive agent to assist in the removal of plaque biofilm associated with standard mechanical dental hygiene procedures. Porter et al. demonstrated the effectiveness of HybenX™ in treating oral ulcers of recurrent aphtosis (10). The rationale for use of this agent is that it cauterizes the epithelial tissue affected by the immune response (3, 6). The purpose of this study is to analize the pain caused by minor aphtous lesions using a Virtual Analogue Scale test after a single application of HybenX™ compared with a control group that received no treatment.

MATERIALS AND METHODS

Sixty patients, with oral minor aphtous lesions, aged over 18 years and with a history of RAS were enrolled into this clinical trial. Patients included in the study were casually allocated into 2 groups, Group A and Group B. In Group A, 30 patients received HybenX topically whereas in Group B, 30 patients received no treatment. The Group A comprised 16 females and 14 males, aged over 18 years, the mean age was 21.06 years; the Group B comprised 14 females and 16 males with a mean age of 20.73 years. All subjects had had at least two episodes in the past 12 months and a history of recurrent bouts of ulceration of the non-keratinised oral mucosa. A single clinician, basing on the clinical characteristics of the minour recurrent aphtous lesion, made a definitive diagnosis of RAS. None of the subjects had any local cause for the ulceration or any condition that may mimic classic aphtae or had received any medication likely to precipitate oral mucosal ulceration (8) as shown in the exclusion criteria. Moreover, all subjects agreed to abstain from using other mouth ulcer treatments during the course of the study.

For the patient to be enrolled in the study, the RAS ulcer had to be less than 48 hours old. The subjects had not been medicated with antibiotics, anti-inflammatory agents, or analgesics within the 2 weeks prior to the study.

Exclusion criteria

- Patients with systemic diseases (patients with HIV disease, Sindrome di Beçet, MAGIC syndrome, Sweet's syndrome, PFAPA syndrome, cyclic neutropenia)
- Patients with major aphthous lesions
- Pregnancy or lactating (negative serum or urine pregnancy test within 14 days prior to enrolment).
- Smokers
- Patients allergic to sulfur-containing materials in any form

Inclusion criteria

- Adult patients with minor recurrent aphthous lesions located only at the buccal mucosa and mucosal zone of the lips.

All participants were informed of the aim and design of the study, benefits of the pharmacologic therapy, possible adverse effects, and possibility of being allocated to the control group at the start of the study. Patients, who adhered to the study, signed an informed consent.

Application of topical medication

The topical medication that was administered was of a liquid consistency, violet color, slightly pungent odor and was composed of: sulfonated phenols 30-60%, 25-35% sulfuric acid and water.

Each subject was randomly assigned to either Group A (treatment group) or Group B (control group). The application of HybenX™ was then performed by a single clinician on the ulcers only once at day 0, after an accurate clinical examination, on the aphtae with a cotton swab, including margins, for 10 seconds (Fig. 1). Then the operator proceeded with professional irrigation and aspiration of the product. A sensation of pain was felt by all the patients when the medicament was applied, as also reported by Porter et al. (10).

Clinical observations and pain scoring

The initial appointment consisted of collecting the

clinical data, a history of patient's past experiences with the lesions, clinical examination and pretreatment photographs. Treatment was administered on the day of the initial visit. All patients' data are shown in Table I and Table II.

The oral lesions were clinically observed at day 0 (pretreatment) and at day 6; in this first visit we recorded the duration of each ulcer (the day of onset of the first prodromal symptom of each ulcer). All subjects were instructed to complete a 10-mm Visual Analogue Scale (VAS scale) with 1 mm division, where '0' is no pain and '10' is worst possible pain. Patients filled in the form just before the topical administration of the medicament (pretreatment), and every day at home, to estimate the intensity of the pain for the following 6 days (from day 1 to day 6), until the next control carried out by our working group. After 6 days, in fact, the patients were requested to return the VAS scale records (Table I and Table II). Patients were questioned about any adverse effects following drug therapy. The VAS scale sheet was collected from the patient and post-treatment photographs were taken for comparing with the baseline.

Statistical analysis

Pain reduction was compared between the HybenX group and Control group by testing changes from baseline in VAS pain score at all designated time points. Response to the drug therapy was assessed on the basis of pre- *vs* post-treatment scores (Table III, Table IV). Intragroup comparisons of post-treatment pain reduction were performed using paired *t*-test (Fig. 2). The differences in pain scores were also compared between the two groups by unpaired *t*-test (Fig. 3). In view of the absence of adverse events in the HybenX group, no statistical analysis was performed to compare their incidence in the two treatment groups.

RESULTS

Three subjects of Group B were ultimately excluded as they developed new ulcers during the course of the study, in violation of the study protocol and thus the final Control group comprised 27 patients, 13 females and 14 males with a a mean age of 10.66 years. Group A was unchanged. Finally, a total of 57 patients were enrolled in the study: 29 females and 28 males.

Pain incidence in VAS before and after treatment

The mean VAS score at baseline for the patients of Group A was 7.867±0.90. After treatment at day 1 the mean VAS score was 6.5±1.14 with a percentage of reduction from baseline of 17.38%. At day 2 the mean VAS score was 5.167±1.14 with 34.32% of reduction. At days 3, 4, 5 and day 6 the mean VAS score was 3.967±1.14, 2.867±1.14, 1.367±1.14, 0.333±1.14, respectively, with a progressive reduction percentage of 49.57%, 63.56%, 82.62% and 95.75%. All data are for $P<0.001$ (Table III).

The mean VAS score at baseline for the patients of Group B was 7.926±0.675. At day 1 the mean VAS score was 6.852±1.027 with a reduction of 13.55%. At day 2, we had a mean VAS score of 5.704±1.137 and a 28.03% reduction from baseline. At days 3, 4, 5 and 6 the mean VAS score was 4.741±1.228, 3.667±1.301, 2.222±1.281, 1.333±0.679, respectively. All data are for $P<0.001$ (Table IV)

Differences in pain scores between the two groups

Comparing the two groups at each time point, the mean pain scores at pretreatment and the 2 days following treatment were not statistically different: $P= 0.781$ (pretreatment), $P= 0.22731$ at day 1 and $P= 0.0944$ at day 2. The comparison between the means in the two groups becomes statistically significant at day 3 ($p = 0.0234$) with a difference of 16.33% compared with control group and 49.57% compared with pretreatment VAS score baseline ($P<0.001$).

From day 5 the difference of mean pain score between two groups was about 38.48% ($p = 0.0106$) and on day 6 symptomatology in patients treated with HybenX had almost disappeared, with a difference of 75.02% regarding the control group ($P<0.001$) and 95.75% of mean VAS score reduction from baseline ($P<0.001$).

These results seem to indicate a greater and faster pain reduction in Group A. However, if we compare the mean differences from baseline in the range of 6 days since pretreatment until day 6 in the group treated with the cauterizing agent and in the one treated without treatment, performing an unpaired *t*-test, no significat differences appeared ($P>0.05$), as shown in the diagram.

DISCUSSION

We performed this case-controlled study to verify the effectiveness on painful symptom of RAS, the

Table I. *Patients in Group A treated with dessicating agent.*

Vas pretreatment	day 1	day 2	day 3	day 4	day 5	day 6	age	sex
8	7	7	5	3	0	0	20	F
7	7	6	5	4	2	1	18	F
9	5	4	3	2	1	0	21	F
8	7	7	4	2	0	0	22	M
9	7	6	5	4	3	0	37	M
8	6	6	5	5	3	1	18	F
9	7	6	6	4	2	0	18	F
8	8	6	5	3	3	0	18	F
7	7	5	4	4	2	1	18	M
8	8	6	5	4	3	1	21	M
9	8	6	4	4	2	0	23	F
8	6	4	4	2	0	0	18	M
7	6	5	4	2	1	0	18	M
8	5	3	2	0	0	0	21	F
9	8	8	7	5	3	2	30	F
7	5	3	3	1	0	0	18	M
6	5	4	3	3	2	0	18	F
8	6	5	4	3	2	1	18	M
9	7	5	3	2	0	0	23	F
8	5	5	4	3	0	0	25	F
7	5	3	1	1	0	0	32	M
7	6	4	2	1	0	0	18	F
8	8	6	5	3	3	0	18	M
7	7	5	5	3	2	1	21	M
8	8	6	5	4	2	1	20	M
9	8	6	4	4	1	0	19	F
6	5	4	3	3	1	0	18	F
8	6	5	3	3	2	1	21	M
9	7	5	3	2	0	0	24	M
7	5	4	3	2	1	0	18	F

All patient data including VAS values recorded by patients of the Group A

main cause of disconfort for the patient suffering from this disease (11). Once applied on the ulcer, HybenX leaves an ischemic halo which makes it very diffcult to perform double-blinded placebo studies.

Treatment for recurrent aphthous stomatitis has traditionally been palliative and/or has involved anti-inflammatory agents. Topical steroids and chemical dessicating agents have been used previously to treat oral mucosal disorders, such as RAS, sometimes with limited success. Baccaglini et al. reports that chemical cauterization may provide fairly rapid pain relief, attributed to disruption of local nerve endings or reduction in inflammatory mediators (12). However, these therapies require repeated

Table II. *Patients in Group B (control group) who did not received any treatment.*

Vas pretreatment	day 1	day 2	day 3	day 4	day 5	day 6	age	sex
8	5	5	4	4	3	2	23	M
7	7	6	5	5	4	2	18	F
9	7	6	6	5	4	2	18	M
8	7	6	6	5	3	1	23	M
8	8	6	5	3	3	0	24	F
8	7	6	5	4	3	2	18	M
8	8	6	5	4	3	2	18	F
9	8	7	6	5	3	1	22	F
8	6	4	4	2	0	2	18	M
8	7	6	5	5	2	1	18	M
8	5	3	2	0	0	1	21	M
9	8	8	7	6	4	2	32	F
8	7	6	5	3	2	1	18	F
7	6	5	4	3	2	1	18	F
8	8	7	5	4	3	2	21	M
8	7	6	5	4	2	1	22	M
8	5	5	4	3	0	0	24	F
8	6	4	3	3	2	1	18	M
7	6	4	2	1	0	1	18	F
8	8	7	6	4	3	1	18	F
8	7	6	6	5	3	2	22	M
8	8	6	5	4	2	1	23	M
8	7	6	5	4	3	2	18	M
6	5	4	3	3	1	2	19	F
8	7	6	4	3	2	1	26	M
7	7	6	5	3	0	0	22	F
9	8	7	6	4	3	2	18	F

All patient data including VAS values recorded by patients of Group B

Table III. *Differences in mean VAS score in Group A.*

Time interval	Mean VAS	SD	Difference from baseline	SD	% reduction from BL	*t*	*P* Value
Pretreatment	7.867	0.900	-	-	-	-	-
day 1	6.5	1.137	-1.367	1.033	-17.38%	7.244	P<0.001
day 2	5.167	1.234	-2.7	1.119	-34.32%	13.218	P<0.001
day 3	3.967	1.273	-3.9	1.269	-49.57%	16.833	P<0.001
day 4	2.867	1.224	-5	1.313	-63.56%	20.857	P<0.001
day 5	1.367	1.159	-6.5	1.383	-82.62%	25.735	P<0.001
day 6	0.333	0.547	-7.533	1.042	-95.75%	39.612	P<0.001

Table IV. *Differences in mean VAS score in Group B.*

Time interval	Mean VAS	SD	Difference from baseline	SD	% reduction from BL	*t*	*P* Value
Pretreatment	7.926	0.675	-	-	-	-	-
day 1	6.852	1.027	-1.074	0.917	-13.55%	6.088	P<0.001
day 2	5.704	1.137	-2.222	0.974	-28.03%	11.855	P<0.001
day 3	4.741	1.228	-3.185	1.001	-40.18%	16.527	P<0.001
day 4	3.667	1.301	-4.259	1.196	-53.74%	18.506	P<0.001
day 5	2.222	1.281	-5.704	1.137	-71.97%	26.059	P<0.001
day 6	1.333	0.679	-6.593	0.888	-83.18%	38.561	P<0.001

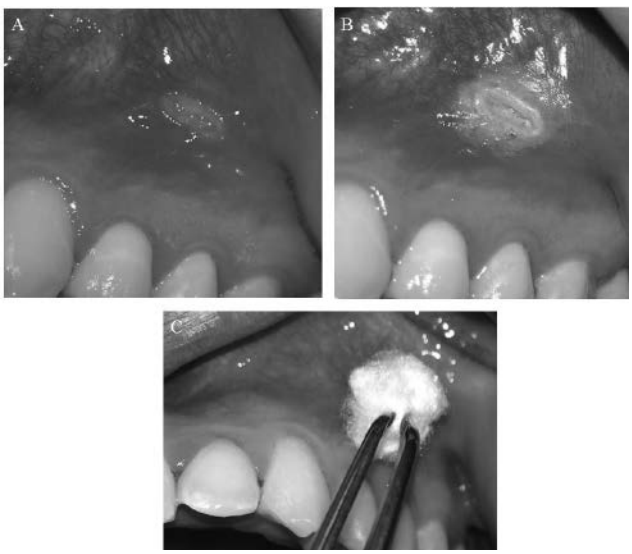

Fig. 1. *Application of the dessicating agent on the aphtae. The figure shows the application of dessicating agent on canker sore using a cotton ball. Once applied on the ulcer, this medicament leaves an ischemic halo.*

dental visits, which are not feasible long-term or for frequent RAS (11).

However, a previous pilot study conducted by Rhodus et al. on a chemical coagulation agent reported that a single application of Debacterol, a chemical dessicating agent, induces faster healing of RAS compared with topical corticosteroid paste or no treatment (3). Later also Porter et al. carried out a study to test the efficacy of a single application of HybenX compared with a daily application of another medicament used for RAS therapy (10).

Our data seem to confirm that a single application of this dessicating agent might be an avaible treatment in order to reduce pain symptoms of recurrent aphtous stomatitis. Indeed, the data show that:

i) the VAS scale values in the Group A were constantly lower in comparison with VAS scale values of Group B (Fig. 2).

ii) from day 3 the VAS scale values in Group A become statistically significantly lower than VAS scale values in Group B (Fig. 2).

The application of this medicament induces

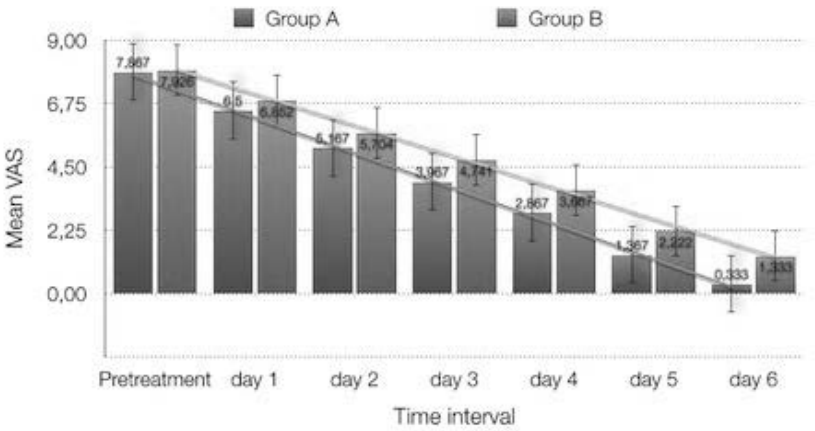

Fig. 2. *Intragroup comparisons of post-treatment pain reduction were performed using paired t-test. The VAS scale values in Group A are constantly lower in comparison with VAS scale values of Group B. From the third day onwards, the differences between the two groups became more significaqnt.*

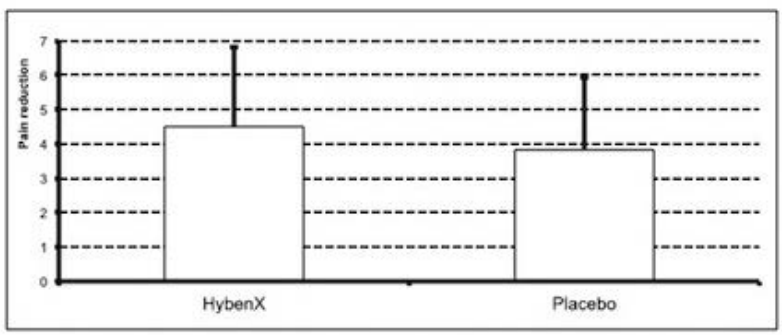

Fig. 3. *The differences in pain scores compared between the two groups by unpaired t-test. Comparing the mean differences of VAS values from baseline in the range from day 0 to day 6 in the two groups, perfoming an unpaired t-test, no significat differences appeared (P>0.05).*

denaturation, precipitation and coagulation of tissue debris, forming a protective layer of tissue fragments coagulated on the surface of the ulcer, so as to reduce the local painful stimuli, as reported by Porter and coworkers (10). The present results regarding VAS scale values (i.e. the patient perceptions), showed that even a single application of this agent had a positive effect on the painful symptomatology, compared to the control group.

However, comparing the mean differences of VAS values from baseline in the range from day 0 to day 6 in the two groups, perfoming an unpaired t-test, no significant differences appeared (P>0.05), as shown in Fig. 3. These results indicate that immediate and significant relief of the pain was achieved in the group treated with HybenX compared to the control group.

It is important to emphasize that the use of such therapeutic agent makes it very difficult to implement a double-blinded study because of the ischemic feature of the HybenX. As a matter of fact, it may create a bias in the analysis of data collection on the VAS scale of the two groups. Therefore, further

studies are needed to clarify the effectiveness of HybenX not only at the level of symptoms perceived subjectively by the patient but also to histologically investigate the epithelial wound-healing process (on animal model) after treatment with HybenX.

ACKNOWLEDGEMENTS

We thank all those who contributed to the drafting of this article, and patients who have undergone the treatment.

REFERENCES

1. Chavan M, Jain H, Diwan N, Khedkar S, Shete A, Durkar S. Recurrent aphthous stomatitis: a review. J Oral Pathol Med 2012; 41(8):577-583.
2. Jurge S, Kuffer R, Scully C, Porter SR. Mucosal disease series. Number VI. Recurrent aphthous stomatitis. Oral Dis 2006; 12(1):1-21.
3. Rhodus NL, Bereuter J. An evaluation of a chemical dessicating agent and an anti-inflammatory ointment for the treatment of recurrent aphthous stomatitis: a pilot study. Quintessence Int 1998; 29(12):769-773.
4. Preeti L, Magesh K, Rajkumar K, Karthik R. Recurrent aphthous stomatitis. J Oral Maxillofac Pathol 2011; 15(3):252-256.
5. Arabaci T, Kara C, Cicek Y. Relationship between periodontal parameters and Behcet's disease and evaluation of different treatments for oral recurrent aphthous stomatitis. J Periodontal Res 2009; 44(6):718-725.
6. Wu RQ, Zhang DF, Tu E, Chen QM, Chen W. The mucosal immune system in the oral cavity-an orchestra of T cell diversity. Int J Oral Sci 2014; 6(3):125-132.
7. Scully C, Porter S. Oral mucosal disease: recurrent aphthous stomatitis. Br J Oral Maxillofac Surg 2008; 46(3):198-206.
8. Scully C, Gorsky M, Lozada-Nur F. The diagnosis and management of recurrent aphthous stomatitis: a consensus approach. J Am Dent Assoc 2003; 134(2):200-207.
9. Porter SR, Scully Cbe C. Aphthous ulcers (recurrent). BMJ Clin Evid 2007; 2007.
10. Porter SR, Al-Johani K, Fedele S, Moles DR. Randomised controlled trial of the efficacy of HybenX in the symptomatic treatment of recurrent aphthous stomatitis. Oral Dis 2009; 15(2):155-161.
11. Alidaee MR, Taheri A, Mansoori P, Ghodsi SZ. Silver nitrate dessicating in aphthous stomatitis: a randomized controlled trial. Br J Dermatol 2005; 153(3):521-525.
12. Baccaglini L, Lalla RV, Bruce AJ, Sartori-Valinotti JC, Latortue MC, Carrozzo M, Rogers RS, 3rd. Urban legends: recurrent aphthous stomatitis. Oral Dis 2011; 17(8):755-770.