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Original Research

Clinical evaluation of a hyaluronic acid-based medical device in counteracting aphthous stomatitis in adults

Abstract

Oral mucosal ulcers are quite common in an otherwise healthy population, and can determine a real worsening of the quality of life.
Conventional therapy is not appropriate since ulcers often recur and, even if not needed, therapy lasting not less than 2–3 weeks carries a high risk of serious side effects. The use of hyaluronic acid applied as an adhesive gel over the lesions seems to have potential in terms of efficacy and the avoidance of side effects. Of course, hyaluronic acid-based formulations show different effects and tolerability.
In our study, we retrospectively report the results obtained using a medical device, Bloxaphte®, applied for 14 days to counteract ulcers in adults.
Our data clearly demonstrate the healing capability and safety profile of the product in reducing the number and size of the ulcers within the first week of daily application.

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Introduction

Due to the presence of a painful burning sensation that worsens during speaking, eating or drinking, oral ulcers represent a very common and unpleasant mouth mucosal disease that reduces the patient's quality of life [1]. Likely causes of mouth ulcers include physical trauma, radiation, chemical injury and microbial infection (bacterial, viral and fungal). In some patients, due to an uncertain aetiology and to causes that are not fully elucidated, occasional ulcerations become recurrent, representing a diagnosis of recurrent aphthous stomatitis (RAS), also known as aphthae or canker sores [1]. Commonly observed histopathological changes in the pre-ulcerative stage include infiltration of the epithelium by lymphocytic cells and oedema formation, followed by keratinocyte vacuolization and focal vasculitis, both provoking tissue swelling and tumefaction. The ulcerated area is then infiltrated by neutrophils, lymphocytes and plasma cells until healing and epithelium regeneration starts to occur [2]. Although both the histology and the disease progression of the aphthous lesions follow a common pattern, triggers and stimuli vary between individuals and may include nutritional deficiencies, local trauma, stress, hormonal influences, allergies, genetic predisposition or other unknown factors [3]. From an epidemiological standpoint, the incidence of canker sores is approximately 25% within the general population [4], and the most widely used drugs to counteract these are anti-inflammatories, corticosteroids, analgesics and antimicrobials, in addition to lubricating and healing-promoting agents [5]. Notably, oral ulcer conditions can last for several years, with recurrent episodes. Therefore, long-term exposure to this type of medication may not be appropriate due to the occurrence of severe side effects. Unfortunately, limited success has been achieved by using vitamins, silver nitrate and/or botanicals, substances described as being almost devoid of side effects [6–9].

More recently, topically applied mucosal protectants have been developed. This strategy corresponds to an attempt to form a temporary physical barrier over the ulcerous lesion, thereby protecting it from the milieu of the oral cavity, and from food and beverage constituents.

This "mechanical protecting action" should foster the healing process. The molecule most likely to be effective when applied to this strategy is certainly hyaluronic acid (HA). It has been clinically demonstrated to reduce healing time as well as to increase the relief of pain without any serious reported side effects [10–14].

However, even if HA efficacy is well accepted within the scientific community, its effectiveness is also affected by patient compliance and by the strength of the HA retention over the oral mucosa. This last feature is affected by formulation and may vary between different products and between different methods of administration. Last, but not least, patient compliance is influenced by product features such as taste, texture and ease of use, which all compromise adherence to therapy, and therefore, the success of the product.

We have thus decided to retrospectively report the results obtained from our recent experience in the clinical use of a newly developed HA-based medical device intended to counteract oral ulcers.

Materials and methods

Tested product

The medical device tested is a gel (Bloxaphte®, Bausch & Lomb, France) intended for oral use and developed to counteract oral mucosal ulcers, both recurrent and episodic. The medical device is manufactured at Farmaceutici Procemsa S.p.A. in a facility

located at Nichelino, Italy and it is distributed by Laboratoire Chauvin, Montepellier, France.

The exact qualitative composition of the gel, ranked by weight is: xylitol, glycerin, Rosa damascena petal extract, xanthan gum, polycarbophil, hyaluronic acid sodium salt (0.24%), pectin, potassium sorbate, sodium benzoate, panthenol, *Aloe barbadensis* leaf extract, stevia.

Study protocol and endpoints

The study is the retrospective report of the routine practice when treating patients with oral ulcers. The study was conducted in a clinical outpatient facility located in Milan under the supervision of a medical doctor and in accordance with the Declaration of Helsinki.

A total of 39 adult subjects attending our medical clinic between September 2018 and June 2019, without ethnic limitations, of both sexes and between the ages of 18 and 65, with a diagnosis of aphthous stomatitis, but considered otherwise healthy, have been analyzed retrospectively. Nineteen of these subjects were treated with the tested HA-based medical device and 20 were treated with a chlorhexidine-based mouthwash preparation (chlorhexidine gluconate at a concentration of 0.2%).

The subjects were considered eligible for our retrospective statistical analysis only after providing signed informed consent, with the relevant declarations of privacy and confidentiality. At the time of enrolment, to establish eligibility, all subjects were also informed that both the clinical report and the statistical analysis would be performed under conditions of total anonymity to guarantee the subsequent possible publication of the data obtained. All of the subjects taking part in this retrospective analysis declared they had not been previously placed on immunosuppressive, cytotoxic, cortisone, antibiotic, antifungal and hormone therapy (including birth-control pills) for at least 45 days prior to the use of the HA-based medical device. All subjects, at the beginning of treatment, were obviously recommended to abstain from eating any foods capable of producing burning pain in the oral mucosa (mint, spices, coffee or extremely hot foods, highly salted foods, some fruit such as pineapple, and so on). We considered only subjects demonstrating to have at least one easily measurable ulceration eligible for this report and for the statistical analysis.

Any ulceration established as being measurable was evaluated as the average of the two largest diameters. In subjects with multiple lesions, we took the sizes of the two lesions of larger dimensions that could be measured with greater precision.

The measurements were taken according to the two major perpendicular axes and the average value of the two measurements expressed in mm was used. An approximation degree of 0.5 mm was considered acceptable. Ulcers were measured in the morning by 12.00, for a total period of not less than 14 days from the day when treatment started and with no fewer than 6 measurements. The first measurement was taken 30 minutes before applying the first treatment. The scheme envisaged for the measurements was therefore: t=1; t=3; t=6; t=9; t=12 and t=14. This scheme was not always adhered to due to small variations that could not have been foreseen at the time of enrolment and due to there being days where the evaluation of the subjects was difficult (Saturdays, Sundays, holidays, unforeseen events). However, in these few cases, the measurements were taken with a delay of one or two days, at most. In addition to measuring the major diameters of the lesions, the total number of mouth ulcers was evaluated for any single subject. The measurement of aphthous lesion diameters and the numerical evaluation over time were considered primary endpoints in our retrospective report. Tolerability, compliance, therapeutic adherence and the appearance of collateral events were considered secondary

endpoints. These secondary endpoints were verified by reading the notebooks containing the daily transcription performed by each subject and through the analysis of the residual product content for the treatments prescribed.

Statistical analysis

To test the difference between uncorrelated groups, treated subjects versus controls, we used the non-parametric Wilcoxon rank-sum test. Data are represented as the mean ± standard deviation and the median value. JMP 10 for Mac OsX was used for statistical analysis and statistical significance was set at 95% (p<0.05).

Results

According to our retrospective report and analysis, the two groups were found not to differ in terms of age (Group A: 35.2 ± 12.4; Group B: 35.2 ± 12.0) and sex (Group A: 9 males and 10 females; Group B: 11 males and 9 females), and therefore, we considered them statistically comparable. As shown in **Tables 1** and **2**, treatment with the HA-based oral gel determined better results both in terms of the number of oral lesions and in terms of lesion sizes. Regarding the number of lesions, the results are significant even after 6 days of treatment, while 3 days are enough to differentiate the two groups with respect to lesion sizes.

Day	Group A	Group B	*p*
T=1	2.9±1.0 [3]	2.8±0.8 [3]	n. s.
T=3	.7±0.9 [3]	2.7±0.8 [3]	n. s.
T=6	2.0±0.8 [2]	2.5±0.6 [2]	<0.05
T=9	1.6±0.8 [2]	2.4±0.7 [2]	<0.01
T=12	0.8±0.6 [1]	2.1±0.7 [2]	<0.001
T=14	0.4±0.5 [0]	.9±0.6 [2]	<0.001
n. s.: Not significant			

Table 1 Number of oral lesions (mean ± standard deviation; median in square brackets) observed in subjects (N=19) treated with hyaluronic acid-based gel (Group A) and in those (N=20) treated with chlorhexidine gluconate (Group B)

Day	Group A	Group B	*p*
T=1	7.3±2.0 [7]	7.3±0.9 [7.25]	n. s.
T=3	5.2±1.7 [5]	7.1±0.9 [7]	<0.001
T=6	3.6±1.5 [4]	6.5±1.4 [7]	<0.001
T=9	2.4±1.3 [2]	5.9±1.3 [6]	<0.001
T=12	1.0±1.0 [1]	4.9±0.7 [4.75]	<0.001
T=14	0.3±0.5 [0]	3.5±0.9 [3]	<0.001
n. s.: Not significant			

Table 2 Size (mm) of oral lesions (mean ± standard deviation; median in square brackets) observed in subjects (N=19) treated with hyaluronic acid-based gel (Group A) and in those (N=20) treated with chlorhexidine gluconate (Group B)

The same results are likely more striking for the reader observing **Figures 1** and **2** where the same findings, albeit only the means without standard deviations and medians, are reported in graph form.

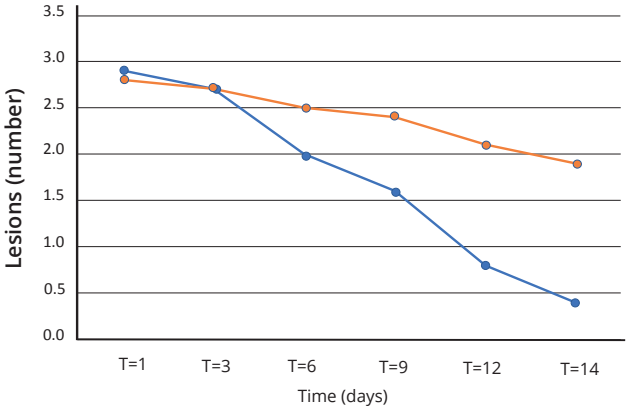

Figure 1 Average number of oral lesions in the group (N=19) treated with hyaluronic acid-based gel (blue line) and in the group (N=20) treated with chlorhexidine gluconate (orange-brown line)

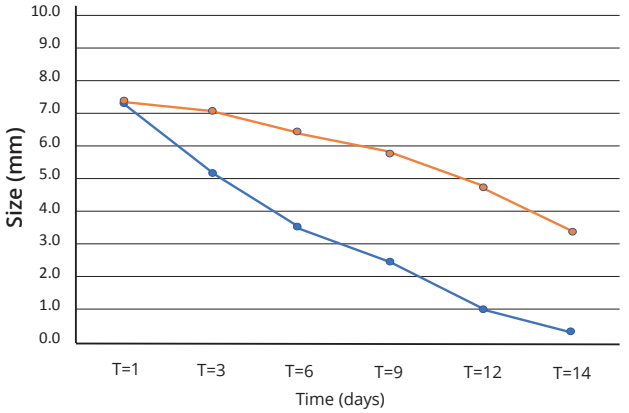

Figure 2 Mean size (in mm) of oral lesions in the group (N=19) treated with hyaluronic acid-based gel (blue line) and in the group (N=20) treated with chlorhexidine gluconate (orange-brown line)

In contrast, tolerability, compliance and adherence to therapy were found to be completely overlapping between the two groups (**Table 3**). However, the incidence of side effects (**Table 3**) was slightly different, with the HA-based gel being apparently safer.

	Tolerability	Compliance	Adherence	Side effects
Group A	9.6±2.3 [10]	9.5±2.2 [10]	93.2	2/19°
Group B	9.2±1.2 [10]	9.2±1.1 [9.5]	94.0	6/20^
°Migraine and constipation; ^inappetence (2), migraine (3), diarrhoea (1)				

Table 3 Tolerability, compliance (mean ± standard deviation; median in square brackets), therapy adherence (%) and side effects (number of subjects with side effect/total subjects) observed in subjects (N=19) treated with hyaluronic acid-based gel (Group A) and in those (N=20) treated with chlorhexidine gluconate (Group B)

The difference is not significant but just shows a tendency that would require a higher number of subjects for statistical confirmation.

Finally, the expected side effect of chlorhexidine treatment, black staining, often reported in similar trials, was avoided probably due to the diligence of the doctors involved in the study in selecting which chlorhexidine-based product to administer as a control [15].

Discussion

Oral ulcers are quite common within the general population and recurrence is common as well, with RAS being the most common form of recurrent oral ulcers. Recurrent or not, such mouth ulcers are characterized by painful lesions with a round or ovoid appearance and inflammatory halos. Oral ulcers can sometimes be deep, affecting also the keratinized mucosa and needing several weeks to heal. Our results demonstrate a trend towards better healing of the lesions if these are treated with a HA-based gel. In our study, subjects could choose freely between the HA-based gel or the chlorhexidine mouthwash formulation, based on their individual preference and irrespective of their initial clinical situation. Both formulations were shown to be well tolerated but our findings clearly indicate a better clinical outcome when the HA-based gel is used. The observed efficacy cannot be due only to the presence of HA. More probably, the formula as a whole makes a global contribution to this efficacy.

In this regard, polycarbophil has been appropriately added to the final formula to guarantee the correct and proper adhesivity to the oral mucosa, making the gel work as a surgical patch [16]. *Aloe barbadensis* contributes to the overall anti-inflammatory properties of the device [17]. In any case, *Aloe* without a proper formula is ineffective [18]. Similarly, some findings indicate anti-inflammatory properties associated with *Rosa damascena* extract [19]. In this case also, it is likely that these properties become medically apparent only in the context of a highly complex formula. It is our hypothesis that a daily and continuous application of the HA-based gel could reduce the frequency of recurrent ulcers. However, the effect on recurrence frequency was not investigated in our study and this would need to be investigated differently using a prospective design. Regarding the methodological aspects of the study, a limitation of our retrospective report is lack of a negative control or of a placebo group. Nevertheless, we believe that our statistical analysis is sufficiently robust to render our results useful for medical practice. Oral ulcer pathological conditions are generally widespread, so physicians, dentists or dental practitioners and nutritionists could use the results of our study to better manage those patients where the occurrence of ulcers worsens their quality of life and limit drug therapy and/or dietary prescription.

Conclusions

Within the limitations of the retrospective design and the absence of a placebo group, our study reports the efficacy and the tolerability

of Bloxaphte® in counteracting oral ulcers in adults. Application of the product for at least 14 days has a clear healing effect on the mucosa.

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