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ORIGINAL ARTICLE

Effect of Dentoxol® in the treatment of recurrent mild aphthous ulcers. A prospective observational pilot study.

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ABSTRACT

Background: Recurrent aphthous stomatitis (RAS) is the most common oral ulceration. Its prevalence in the general population varies between 5% and 60%, and during the acute period, it causes pain and interferes with basic activities, such as eating, swallowing and talking. Dentoxol® is a medical mouthrinse that cleans, moisturizes and lubricates the mouth, mechanically stimulating local epithelial regeneration. The aim of this study was to evaluate the efficacy of Dentoxol® in improving the general state of patient with minor RAS using two different treatment schemes. **Material and methods:** Thirty-nine patients with RAS were recruited in a prospective observational pilot study. Two dosing regimens, 5 ml of Dentoxol® twice daily and 5 ml of Dentoxol® three times daily were evaluated. **Results:** Efficacy to improve the general state was significant superior in "Three time daily" group compared with "twice daily" at 72 h (66% vs 33% respectively). No pain was reported in approximately 90% of cases at 96 h of use in both group without significant differences between the groups in any evaluation time-point. **Conclusion:** Despite the limitations of these preliminary data, Dentoxol® shows promising beneficial properties for the management of minor RAS.

KEY WORDS
Recurrent aphthous stomatitis; Mouthrinse; Dentoxol.

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INTRODUCTION

Recurrent aphthous stomatitis (RAS) is the most common ulcerative lesion of the oral mucosa. Its prevalence in the general population varies between 5% and 60%[(1)]. The onset of the condition is commonly seen in people between 10 and 19 years, with no differences between gender. In individuals without underlying pathology, it is characterized by recurrent ulcers seen in the nonkeratinized mucosal surface (labial mucosa, buccal mucosa and floor of the mouth). Traditionally, three types of RAS have been described: minor RAS, major RAS and herpetiform stomatitis[(2)]. The minor variant represents 80% of patients with RAS, is self-limited and resolves in 7 to 10 days[(3)].

Although the lesions return spontaneously, during the acute period, they cause pain and interfere with basic activities, such as feeding, swallowing and talking. The etiology of RAS remains inconclusive, and thus, its treatment is only palliative, limited to reducing the intensity and duration of pain and other associated symptoms during the outbreak. At the time of diagnosis, it is essential to rule out an association with systemic disease (Behçet's syndrome, cyclic neutropenia, celiac disease, IgA deficiency, Reiter's syndrome, etc.) and ensure that there is no dietary deficiency (iron, folic acid, zinc, B vitamins), in which case the corresponding replacement therapy should be established[(4)].

The available therapeutic alternatives aim to combat the symptoms and therefore are very diverse. A recent systematic review[(5)] identified 25 randomized clinical trials that aimed to evaluate the preventive, palliative or curative efficacy of potential systemic interventions to treat RAS.

Twenty-two of the clinical trials used placebo as a control, and eight of the clinical trials compared active products with each other (five trials compared more than two groups). In total, 21 different interventions were evaluated. The main conclusion of this systematic review is that there is no conclusive evidence in the published biomedical literature of sufficient methodological quality regarding the effectiveness (or ineffectiveness) of any of the interventions studied. Only one clinical trial had a low risk of bias[(6)].

A previous systematic review that covered topical treatments[(7)] reached similar conclusions. The authors reviewed 17 clinical trials that were evaluated using the GRADE scale, all of which were classified as "very low-quality evidence". With this in mind, the authors of the systematic review suggested that rinsing with chlorhexidine and topical corticosteroids could reduce the severity and pain caused by ulcers. It was not possible to make any recommendation for the other interventions examined (tetracycline rinse, local analgesics and carbenoxolone gel or rinse).

Dentoxol® is a mouthrinse marketed for human use for the purposes of comfort and oral hygiene. Its primary mode of action is through cleaning, moisturizing and lubricating the mouth and mechanical stimulation of the epithelium, generating optimal conditions for natural cell turnover. Some of the components (eugenol, camphor, parachlorophenol, hydrogen peroxide, purified water, xylitol, sodium bicarbonate, sucralose, and peppermint essence) may have calming and antimicrobial activity[(8,9)]. Recently, a double-blind randomized clinical trial was conducted with the objective of evaluating the efficacy of Dentoxol® in radiation-induced oral mucositis (OM) in patients with head and neck cancer[(8)]. The use of this product was safe and showed a lower proportion of severe OM in Dentoxol® group at weeks 4, 5, and 6 compared with control group[(8)].

Therefore, considering the beneficial properties of Dentoxol®, and the necessity of establishing new products for the treatment of RAS, the aim of the present observational pilot study was to evaluate the efficacy of Dentoxol® in improving the general state of the patient with minor RAS using two different treatment schemes.

MATERIALS AND METHODS

Study design and participant selection

This prospective observational pilot study included a convenience sample of 39 volunteer students with diagnosis of minor RAS from the Faculty of Dentistry of the Universidad Mayor, Chile, recruited between June 14, 2016, and December 28, 2016.

The selected participants for the study meet the following inclusion criteria: acute episode of minor RAS according to Stanley classification[(10)], onset less than 48 hours, previous history of minor RAS, and age between 18 and 26. The exclusion criteria were: systemic disease, major and herpetiform RAS, pregnant or lactating woman, treatment with another mouthwash or any other systemic or topical treatment (including corticosteroids, non-steroidal anti-inflammatory drugs, anesthetics, etc.) the day before or the day of onset. All participants signed an informed consent. The participants were randomly divided into two groups according with the treatment scheme received: Group "Three times daily": Dentoxol® mouthrinse 5 ml every 8 hrs. for 2 minutes and Group "Twice daily": Dentoxol® mouthrinse 5 ml every 12 hrs. for 2 minutes.

Clinical evaluation

Each volunteer was examined by a clinician in Clinical Diagnostic Unit to confirm the diagnosis of minor RAS. A detailed sociodemographic

and clinical data collection form was completed including general history, predisposing factors, previously used topical treatments and history of previous aphthae (severity, number of ulcers, frequency, etc.). Additionally, patient received verbal and written instructions according to the treatment group randomly assigned.

At 24, 48, 72 and 96 hrs. from start the treatment, the following parameters were evaluated: General state evolution (symptoms): described subjectively by patient using a Likert scale using the following categories: Much Worse, Worse, Same, Better and Much better. Pain perception was recorded Verbal Rating Scale: No pain= 0, Mild pain= 1, Moderate pain= 2 and Severe pain= 3. Additionally, the occurrence of adverse events that could arise during the observation period and the degree of patient satisfaction with the use of Dentoxol® were evaluated through an ad hoc questionnaire.

The primary outcome was the efficacy to improve the general state defined as the number of patients who reached "much better" at each visit, divided by the total number of patients in each group. Secondary outcomes included the efficacy to improve pain perception defined as the numbers of patients who reached the category of "No pain" at each visit divided by the total number of patients in that group, and also safety and acceptability of Dentoxol® use.

Statistical analysis

Categorical variables were tabulated and described by absolute frequencies and percentages according to each group. The differences observed between the two groups were obtained using a chi-squared to analyze the trend. The level of significance was adjusted for the four predicted comparisons (one for each visit: 24 h, 48 h, 72 h, 96 h).

RESULTS

Population studied

Thirty-nine patients were recruited, and their demographic characteristics are summarized in Table 1. The "every 8 h" group had a higher proportion of women (46%) than the "every 12 h" group (23.1%). The other characteristics were evenly distributed in the two groups.

All patients adhered to the protocol with respect to the administration and assigned doses, and the patients returned to the scheduled visits and completed the required questionnaires.

Table 1. Characteristic of the participants.

	"Three times daily" group (N=21)	"Twice daily" group (N=18)	Total (N=39)
Females	16 (41%)	9 (23,1%)	25 (64.1%)
Age (years)	22 (20-26)	22 (19-25)	22 (19-26)
Family history	16 (41%)	13 (33.3%)	29 (74.4%)
Allergy	11 (28.2%)	10 (25.6%)	21(53.8%)
Immune pathology	1 (2.6%)	1 (2.6%)	2 (5.1%)
Smoker	5 (12.8%)	5 (12.8)	10 (25.6%)
Stress	20 (51.3%)	14 (35.9%)	34 (87.2%)
Previous treatments			
Topical anesthetic	16 (41%)	14 (35.9%)	30 (76.9%)
Chlorhexidine	7 (17.9%)	2 (5.1%)	9 (23.1%)
Other	11 (28.2%)	10 (25.6%)	21 (53.8%)
Age of onset (years)	13 (5-18)	10 (3-20)	12 (3-20)
Condition duration (days)	7 (4-14)	7 (4-14)	10 (4-14)
Annual recurrence	4 (1-12)	4.5 (1-20)	4 (1-20)

Data are shown as numbers (%) or medians (min-max).

Evolution of the general state

In a purely descriptive analysis, Table 2 shows the frequencies observed at each visit with respect to the self-assessment that patients made regarding their general condition in each group. A clear trend can be observed in the two groups showing an increase in the number of patients feeling "better" or "much better" as time progresses. For example, at 72 h, 100% of the patients in the "three times daily" group were "better" or "much better", whereas only 78% of the patients in the "twice daily" group had improved to the same level.

Table 2. General clinical evolution according to treatment group.

	"Three times daily" group (N=21)				"Twice daily" group (N=18)			
	24 hrs.	48 hrs.	72 hrs.	96 hrs.	24 hrs.	48 hrs.	72 hrs.	96 hrs.
Worse	1	0	0	0	0	1	0	0
Same	11	5	0	1	13	5	4	3
Better	6	11	7	4	4	10	8	5
Much better	3	5	14	16	1	2	6	10
Efficacy (%)	14	24	66	76	5	11	33	56

The difference in efficacy between the two groups studied was nine percentage points (i.e., 14 - 5) at 24 h, 13 percentage points (i.e., 24 - 11) at 48 h, 33 percentage points (i.e., 66 - 33) at 72 h and 20 percentage points (i.e., 76 - 56) at 96 h.

The four comparisons always yielded more improvement over time in the "three times daily" dosage. A chi-squared test was applied to determine similarities in the trend, adjusting the critical value of statistical significance by applying a Bonferroni correction.

Consequently, a "p" value of less than 0.0125 was considered statistically significant. With this rule, the difference of 33 percentage points observed at 72 h was significant, indicating a greater effectiveness in the "three times daily" group than in the "twice daily" group (Chi-squared for trend, p = 0.0097).

The mean values for general state at the different visits, expressed as a score from 0 to 4, are shown in Figure 1. At each visit, the values for the "three times daily" regimen were higher than those of the "twice daily" regimen; as already mentioned, the results at 72 h were the most notable.

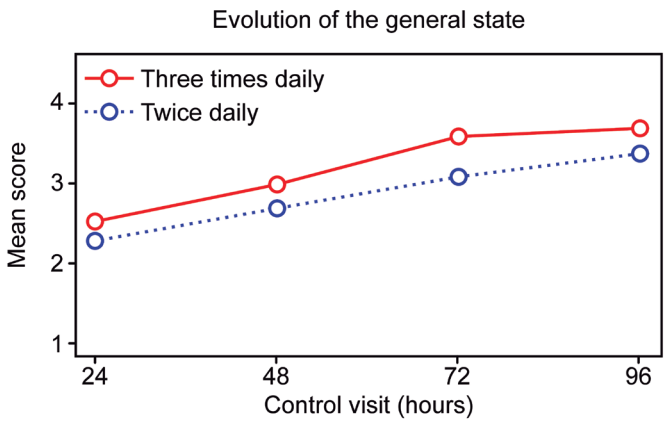

Figure 1. Evolution of general state.

Evolution of pain

Table 3 shows the self-assessment results for each visit regarding the progression of pain. None of the patients reported "Severe pain" at any of the visits.

Again, to analyze efficacy with the most stringent parameter possible, "efficacy" was strictly defined as the number of patients who reached the category of "No pain" at each visit divided by the total number of patients in that group ("Efficacy" column in Table 3).

The difference in efficacy between the groups was six and nine percentage points at 24 and 48 h, respectively, with the "twice daily" regimen

Table 3. Evolution of pain according to treatment group

	"Three times daily" group (N=21)					"Twice daily" group (N=18)				
	Base	**24 hrs.**	**48 hrs.**	**72 hrs.**	**96 hrs.**	**Base**	**24 hrs.**	**48 hrs.**	**72 hrs.**	**96 hrs.**
Severe	15	0	0	0	0	16	0	0	0	0
Moderate	6	10	5	0	0	2	5	3	0	0
Mild	0	10	11	7	2	0	11	9	5	2
No pain	0	1	5	14	19	0	2	6	13	16
Efficacy (%)		5	24	67	90		11	33	72	89

being higher. However, the differences were not significant. The differences in efficacy at 72 and 96 h were reduced by five and two percentage points, respectively. The reduction in pain at this point is not surprising, since the condition evolves spontaneously and always improves, and in 90% of cases, the pain disappears after 96 h (4 d) of use.

The same information is reflected in Figure 2, where the categories are treated as a score from 0 to 4 (where 0 is "No pain" and 4 is "Severe Pain").

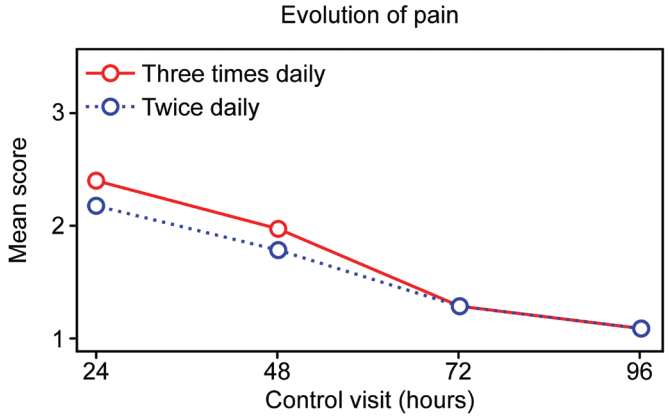

Figure 2. Evolution of Pain.

Safety and acceptability

No severe or moderate adverse events or signs of toxicity were observed in patients exposed to Dentoxol® in this study. Mild adverse events were reported by seven patients: two reported itching or burning, and five patient each reported one of the following: altered taste, pain, increased salivation, sensitivity to cold and redness of the lesion.

Acceptability of the product, evaluated with a simple questionnaire during the last visit, showed that 82% of the participants rated the mouthrinse as good and the remaining 18% rated it as acceptable.

DISCUSSION

The present prospective observational pilot study is the first to evaluate the efficacy of Dentoxol® in minor RAS, showing improvement of general state and pain perception associated with safe and acceptable use of the product applying two different therapeutic schemes "three times daily" and "twice daily" . Despite the effect of Dentoxol® on minor RAS cannot be directly inferred from this study, because there was no control group with placebo or without treatment, the product has a well-supported history of efficacy against other severe oral lesions, such as oral mucositis, supporting its action in this type of oral condition[8]. A randomized clinical trial performed in patients with oral mucositis reported that use of Dentoxol® 5 times per day was safe and resulted in significantly fewer time-points with severe oral mucositis and delayed its onset compared with a control group[8]. These favorable results have been associated to the cleansing, moisturizing, and lubricating effects conferred by Dentoxol®. Some of its active components eugenol a phenolic chemical constituent found in various plants and principally obtained from clove oil have been associated with several beneficial effects such as anti-inflammatory, analgesic, antibacterial and immunomodulatory activity, among others[11]. Another component of Dentoxol®, sodium bicarbonate is able to neutralize the acid produced in the mouth and act as an antiseptic preventing infections and inhibiting some inflammatory triggers[12].

The literature about the clinical management for RAS, after considering a systemic cause, is focused on pain control, decreasing the size and number of ulcers, promoting ulcer healing, and reducing the frequency of ulcer recurrence. The drugs used for topical or systemic therapy include corticosteroids, antimicrobials, analgesics, anti-inflammatory agents, immunomodulating agents, etc.[13]. It is worth noting that the only product approved by the US FDA for this indication is Amlexanox. The marketing authorization of this product was granted based on efficacy, which was defined as complete remission of the lesions at day 4 of treatment. The effect size observed in this confirmatory study was 10 percentage points (i.e., 27% with Placebo versus 37% with Amlexanox at day 4 of treatment)[7].

The two therapeutic regimens with Dentoxol evaluated in this study showed an improvement in the general state (symptoms) with superior results for the group "three-times daily", exposing the impact of Dentoxol associated with a higher dose independent of the absence of a control group. In this context, Dentoxol® was developed, an aqueous solution used as a mouthwash, whose main mode of action is the mechanical detachment of the superficial epithelial cell layer of the oral mucosa, thus stimulating local regeneration of the epithelium. The interaction of its components (purified water, xylitol, sodium bicarbonate, eugenol, camphor, parachlorophenol and essence of peppermint), in specific concentrations, detaches and eliminates damaged cells as well as particles and debris present in the oral cavity, such as like bacteria and organic debris. The observed clinical effect is the result of the interaction of its components acting on the different aspects of the physiopathogenesis of RAS (antioxidant, bacteriostatic and bactericidal, anti-inflammatory, moisturizing and stimulating properties of mucosal regeneration). As a result, Dentoxol® is able to efficiently treat RAS, physically moisturizing and lubricating the oral mucosa to provide flexibility and strength. In this way, it affects several pathways that influence the course of RAS as well as its severity.

Also, both groups showed a decrease in pain perception over time without significant differences between the groups. However, 90% approximately of the patients in both groups did not have pain at 96 h.

Additionally, the safety of Dentoxol use was similar to the obtained in the previous clinical trial of oral mucositis no reporting severe or moderate adverve events.

The main strength of this study is the evaluation centered-patient, exploring the principal parameters that affect the quality of life and which are the principal reason for clinical consultation. On the other hand, the major limitation of this study includes the absence of a control group.

As conclusion and despite the limitations the preliminary data obtained show Dentoxol® as a promising new product for the management of minor RAS, principally related to the improvement of the general state of the patient. Based on the results of the present observational study, we can conclude that a greater effectiveness of Dentoxol treatment is achieved when used 3 times a day and that at 96h of treatment it showed a reduction in pain in 90% of the treated cases. More studies well designed including a control group are necessary to evaluate the real impact of this therapy, exploring new dosis and obtaining new parameters to evaluate for example the efficacy in the healing of ulcers.

CONFLICTS INTERESTS

David Rosenberg and Tomás Galván participate as scientific advisers to Ingalfarma SpA.

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