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ORIGINAL ARTICLE

Effectiveness of two oral pastes for the treatment of recurrent aphthous stomatitis

M Rodríguez[1], JA Rubio[2], R Sanchez[3]

[1]*Facultad de Odontología;* [2]*Facultad de Medicina;* [3]*Facultad de Medicina, Instituto de Investigaciones Clínicas, Universidad Nacional de Colombia, Bogotá, Colombia*

OBJECTIVE: To compare the effectiveness of two topical medications to reduce the pain and size of recurrent minor aphthous ulcers.
SETTING: Ten Colombian Dental Faculties' clinics.
DESIGN: A double-blind randomized multi-centre clinical study.
SUBJECTS: Ninety-six patients complaining of at least five acute aphthous ulcers were randomized to two intervention groups. Sample size was calculated using an alpha error of 0.05 and beta of 0.20
MATERIALS AND METHODS: Participants were randomly assigned to receive 5% amlexanox or a 0.05% clobetasol propionate magistral preparation. Observers at the participating institutions were previously trained to standardize clinical diagnosis and data recollection. Ulcer size and pain were measured on treatment days 0, 2 and 5.
RESULTS: No significant differences were found between the two groups studied in any of the studied variables at baseline. Both treatment medications significantly reduced pain magnitude and the index ulcer's size on days 2 and 5 compared with day 0 without adverse reactions (within groups differences). No statistical differences between groups of the study medications were found.
CONCLUSION: The two treatments applied had similar effectiveness as they both relieved pain and reduced the size of recurrent aphthous ulcers.
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Keywords: controlled randomized clinical trial; recurrent aphthous stomatitis; clobetasol propionate; 5% amlexanox

Introduction

Recurrent aphthous stomatitis (RAS) is a type of lesion of the oral mucosa consisting of sudden acute, painful loss of normal mucous tissue, being recurrent and sickening. RAS specific cause is as yet unknown. Reported prevalence of oral aphthous ulcerations in textbooks and much of the literature varies according to study location, patient selection and whether point prevalence (presence of lesions at examination) or period prevalence (history of lesions during a specified period) is reported. Moreover, many studies are based on non-probability (convenience) samples that may also account for the significant variability of the prevalence reported by different groups (Rivera *et al*, 2004).

According to the National Health And Nutrition Examination Survey (NHANES III) and the National Survey of Oral Health in USA Schoolchildren, 1986–1987 (OHSC) (Shulman, 2004) there is a point prevalence of 1.5% and 1.2% in children and adolescents respectively, an annual prevalence of 19.8% (NHANES III) and a lifetime prevalence of 40.2% (OHSC). The last National Oral Morbidity study carried out in Colombia (Ramirez *et al*, 1999) showed a global point prevalence of 1.3% and of 1.5% for the group aged 20–34. This study did not evaluate the lifetime prevalence of RAS in our country.

Reducing pain and healing time for recurrent aphthous ulcers restores the ability to eat, swallow and talk, improving the quality of life of those people suffering from this condition. Amlexanox (an anti-inflammatory and anti-allergic topical medication) showed effective in reducing erythema, pain and the size of lesions in a multi-centre double-blind clinical study on 32 patients suffering from RAS. Global improvement was seen in 98% of those patients treated with 5% amlexanox paste compared with 50% of those patients treated with placebo (Robert *et al*, 1993). Khandwala *et al* (1997) compared 5% amlexanox oral paste against 1% amlexanox and placebo in a randomized, double-blind, controlled clinical multi-centre study involving 1335 patients suffering from RAS of <48 h of appearance. This study evaluated the duration of the ulcer's healing process and pain disappearance. Benefits of applying 5% amlexanox were highly significant when applied during the ulcer's preclinical stage (i.e. when the patient feels the onset of pain).

Correspondence: Mauricio Rodríguez, Universidad Nacional de Colombia, Carrera 30 N° 45-03, Ciudad Universitaria, Bogotá, Colombia. Tel: 57 1 3165527, Fax: 57 1 3165226,
E-mail: mrodriguezgo@unal.edu.co
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Several randomized clinical trials evaluated corticosteroids, such as hydrocortisone, triamcinolon acetonide or clobetasol propionate topically or systemically, and found them effective in treating Aphthous Stomatitis by interfering the formation of auto-antibodies and stabilizing lysosomes thus reducing necrosis of the mucosa and inflammatory symptomatology. Other studies have shown that these treatments tend to reduce the lesions' duration and severity but have no effect on ulcers' recurrence (Dolby, 1968). Topical medications must be directly applied over the lesion to promote healing of the recurrent ulcers, keeping the compound in close contact with the lesion as long as possible by using a barrier to allow it to stay in place (Dale *et al*, 1993).

Lozada and Min (1991) treated seven patients suffering from RAS that responded completely to an adhesive paste of 0.025% clobetasol propionate ointment in combination with other systemic treatments, which were not specified in their report. Lozada *et al* (1994) suggested that clobetasol propionate oral paste could be used alternatively to systemic therapy without adverse effects because of the small surface area where the medication is applied if used for <2 weeks.

Fifty-four patients with a history of oral aphthous ulceration or erosive lichen planus lesions were randomly assigned into three treatment groups with 0.05% topical clobetasol propionate in three different presentations. Each subject scored his or her symptoms daily from most severe (seven) to none (0) by verbal assessments using a categorical scale. The results suggested that topical application of clobetasol mixed in an adhesive denture paste was an effective drug for symptomatic oral vesiculo-erosive and/or ulcerative lesions (Lo Muzio *et al*, 2001).

This study compares the effectiveness of two topical medications: 5% amlexanox oral paste and a locally prepared paste including 0.05% clobetasol propionate for topical use, for shortening of healing time and improving pain control of immunocompetent outpatients from different Colombian Faculties of Dentistry suffering from acute RAS.

Materials and methods

Design
A double-blind, randomized, multi-centre clinical trial.

Study site
Ten Dental Faculties throughout Colombia during the years 2001 and 2002 (Table 1). The study protocol was approved by the ethics committee at each centre. Twenty-three professors of oral medicine with at least 5 years of expertise from 10 dental faculties were chosen as evaluators in their respective centres and were especially trained by the main researcher at their institutions to standardize clinical diagnosis and data collection. The main author and two professors of oral medicine recorded a videotape that was used for additional training in such purpose.

Table 1 Participating centres and number of participants per centre

Centre/faculty	*Evaluators*	*Number of participants*
Universidad Del Bosque	3	6
Colegio Universitario Colombiano	3	16
Universidad San Martin	2	8
Universidad Nacional de Colombia	2	14
Universidad de Cartagena	2	17
Universidad de Antioquia	3	14
Centro De Estudios En Salud (CES)	2	6
Universidad Del Valle	2	5
Universidad Santo Tomás	2	1
Universidad Autónoma De Manizales	2	9

Sample size
Assuming a difference of 10 points in the analogue visual pain scale between the two evaluated treatments, with an alpha error of 0.05 and a power of 80% for two-tailed tests, a sample size of 96 subjects was calculated, 48 to each study group.

Inclusion criteria
Patients at least 18 years old complaining from up to five aphthous ulcers of <48 h of appearance located on reachable sites of the oral mucosa that produced enough pain to limit activities such as talking, eating or carrying out oral hygiene. The most painful ulcer identified by the patient was selected as the index ulcer for study and all data were collected regarding this lesion.

Exclusion criteria
Subjects with less than two episodes of recurrent aphthous ulcers that had lasted more than 7 days on the previous year, clinically evident or documented in medical clinical records systemic disease, under systemic or topical corticosteroid therapy, immune-modulating treatment or having previously received any of the medications under study were excluded from this study. Pregnant women or during breast-feeding were also excluded.

After each patient's general evaluation and clinical diagnosis, they offered to participate in the trial. Once they agreed and signed the informed consent form, they were assigned to each treatment group using a computer-generated random numbers list. Five per cent amlexanox (Aphthasol® Block Drug Company Inc., Jersey City, NJ, USA) and a 0.05% clobetasol propionate, pectine, carboxymethyl cellulose gel and mineral oil magistral preparation were packed in identical looking containers and labelled with a code number. Preparations were similar in colour, flavour and consistency. The ethical committee at the research centres recommended not including a placebo treatment group in order to offer every participant a relieving medication for their disease.

Participants assigned to the treatment A received 0.05% clobetasol propionate oral paste whilst those assigned to treatment B received 5% amlexanox oral paste. Therapeutical regimen was the same for both

groups: topical application of the medication with a standard-sized applicator over the ulcers four times per day for 5 days.

The index ulcer's size was measured on day 0 (when intervention began) and on treatment days 2 and 5 to evaluate the short-term benefits of the intervention as RAS has a self-limited natural history. Adverse effects were recorded on the case report forms whenever the participants referred them.

Data collection and outcomes of interest

Reduction of pain score of the index ulcer on a visual analogue scale (VAS) and reduction in the surface area of the same lesion following treatment were considered the main outcomes of interest. The pain relief outcome was registered by the study subjects after being instructed on how to use the VAS. For the baseline evaluation, we applied a 10 cm vertical line and asked the patients to qualify their pain intensity from 0 = no pain to 10 = very intense pain according to Huskisson's recommendations (Huskisson, 1974). On treatment days 2 and 5, participants were asked to score 0 if they have experienced complete improvement or relief from pain (values registered on the vertical line) up to 10 on the VAS if they have experienced no improvement at all.

Changes of the index ulcer's size during the compared treatments were measured using a similar methodology to the one described by (Khandwala *et al*, 1997) on days 0, 2 and 5. The lesion's greatest diameter was registered when the ulcer was round in shape, and the maximum and minimum diameters were registered when the ulcer had an oval shape. These measurements were carried out using acetate rulers graded in millimeters after removing any residual oral paste. The surface area of the ulcer was calculated by applying a formula according to the shape of lesion (round or oval), obtaining a resulting area in square millimetres.

Statistical analysis

Using STATA 8.0 (Stata Corporation, College Station, TX, USA 2003) *t*-test was performed to compare continuous variables and Fisher's exact test and chi squared test to compare categorical variables. According to data distribution, Fisher test and ANOVA for within subjects repeated measurements were used to compare means and s.d. between treatments as follows: change in the pain-score was evaluated by a within subjects (repeated measurement) analysis of variance method (ANOVA), considering day of evaluation (days 0, 2 and 5) and treatment allocated as the main sources of variation.

Results

Ninety-six subjects accepted participating and were randomized to each treatment group. Table 2 shows the baseline demographic variables and risk factors associated with recurrent aphthous ulcers for the subjects assigned to each group. The number of applications of either medication by the study participants was not evaluated. No statistically significant differences were found in baseline demographic characteristics (Table 2), co-interventions received or adverse effects reported between the treatment groups. Every subject enrolled was followed-up until they completed the study protocol.

Table 2 Demographic and basal characteristics of the studied population

	5% Amlexanox		*0.05% Clobetasol propionate*		
	n	*Percentage*	*n*	*Percentage*	*P-value*
Age (years), mean (s.d.)	48	30.6 (9.0)	48	34.5 (13.7)	0.052[a]
Gender					
Women	34	70.8	30	62.5	0.368[b]
Men	14	29.2	18	37.5	
Dental trauma					
Yes	3	6.3	4	8.3	0.307[b]
No	45	93.7	44	91.7	
Prosthesis					
Yes	8	16.7	2	4.2	0.05[b]
No	40	83.3	46	95.8	
Stress					
Yes	31	64.6	33	68.8	0.665[b]
No	17	35.4	15	31.2	
Hypersensitivity to dentifrices					
Yes	2	4.2	0	0	0.153[b]
No	46	95.8	48	100	
Diarrohea					
Yes	3	6.2	3	6.2	1.0[b]
No	45	93.8	45	93.8	
Melena					
Yes	2	4.2	0	0	0.153[b]
No	46	95.8	48	100	
Anaemia					
Yes	0	0	1	2.1	0.315[b]
No	48	100	47	97.9	
Ulcerative colitis					
Yes	1	2.1	0	0	0.315[b]
No	47	97.9	48	100	
Aphthas in parents					
Yes	15	31.2	12	25	0.496[b]
No	33	68.8	36	75	
Aphthas in brothers and sisters					
Yes	7	14.6	8	16.7	0.779[b]
No	41	85.4	40	83.3	
Aphthas in other family members					
Yes	6	12.5	9	18.8	0.399[b]
No	42	87.5	39	81.2	

[a]*t*-test; [b]Fisher exact test.

Pain-score was significantly different at the 3 days of evaluation depending on the day of evaluation (within groups) [$F\ (2.186) = 149.19$, $P = 0.000$] and not depending on treatment allocated (between groups) [$F\ (1.92) = 0.73$, $P = 0.39$]. There was a marginal interaction effect between applying any treatment allocated and the day of measurement ($F_{2,186)} = 2.83$, $P = 0.0617$) (Figure 1).

Similar results were observed when the difference in the ulcer's surface area was analysed by within subjects (repeated measurements) ANOVA. Considering the day of evaluation and treatment allocated, the index

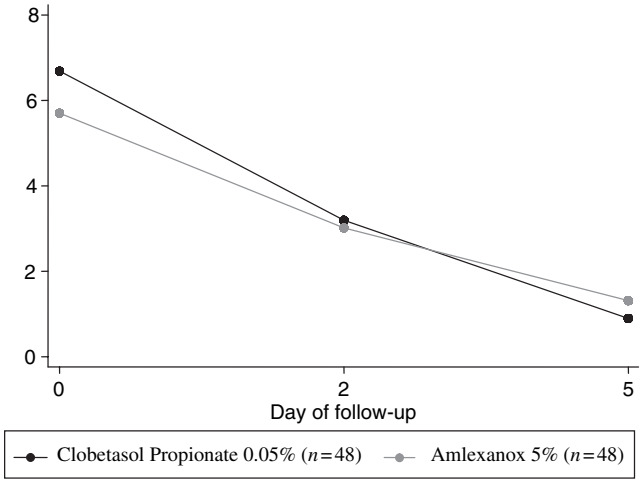

Figure 1 Mean pain score (measured by visual analogue scale) during follow-up reported by all patients included according to treatment allocated

ulcer's size changed significantly across the 3 days of observation within groups. Change in the ulcer's size was related to the day the evaluation was performed. [$F(2.188) = 18.33$, $P = 0.000$] and not related to the treatment allocated (between groups difference) [$F(1.94) = 0.39$, $P = 0.5$]. Gender and location of the ulcer inside the mouth did not affect the results on pain and size reduction according to ANOVA test.

There were no adverse effects reported in any of the treatment groups by the patients or the examiners.

Discussion

Many topical treatments have been used for improving discomfort associated with recurrent minor aphthous ulcers, including corticosteroids, chlorhexidine, hexitidine, low intensity ultrasound, dentifrices, barrier techniques, laser and medications such as 5% amlexanox. Most of these treatments have not been rigorously evaluated. The present study was designed to compare a corticosteroid (0.05% clobetasol propionate) prepared in an oral paste versus 5% amlexanox oral paste, which in large-scale studies carried out in the USA proved effective as treatment of this condition. Clobetasol propionate has been proved to relieve discomfort related to aphthous ulcers and we intended to evaluate a locally produced paste containing this substance. We compared both medications in a head-to-head manner and not against a placebo for ethical reasons. As there was a very short use of clobetasol propionate and small quantities were applied, there is a very low risk of adrenal suppression or any other long-term adverse reaction. During follow up, none of the study centres reported any of these complications.

There is no agreement on how to evaluate relief for this condition on the literature reviewed. Outcomes considered in different studies have included the number of new ulcers appearing within a specific time (4–8 weeks), daily ulcer index (sum of the number of existing ulcers each day during a period of time, i.e. 4–8 weeks), which indicates the episode's severity and average duration of individual ulcers. The latter variable is very hard to evaluate because of the difficulty and uncertainty to determine the exact moment of complete remission (Porter and Scully, 2004). To avoid this problem, the study's follow-up period included only 5 days of observation and evaluation of pain and ulcer-size variables for minor aphthous ulcers considering that these ulcers should resolve spontaneously without treatment within 7–10 days according to the disease's natural history (Regezi and Sciubba, 1989). These findings showed almost complete resolution of both pain and ulcer after 5 days, indicating that treatment shortened the time to symptomatic relief of the affected subjects. As an index ulcer was defined, it was not evaluated if pain relief was related to the number of ulcers present at the oral mucosa or its location within the mouth. The small calibrated rulers guaranteed precise measurement of the ulcer's size when evaluating the reduction in ulcer size. This fact allowed us to determine small changes because of the treatments applied during the short intervals between observations. The absence of a placebo control group does not exclude if the benefits observed with both medications is related or not to the natural history of this disease.

Our alternative topical treatment, at a much lesser cost, was evaluated in our setting and demonstrated that it could help to alleviate the incapacity produced by RAS in people suffering from this situation without adverse effects given the fact that 5% amlexanox is not available in our country. The desired and obtained sample size allows us to state that with a power of 80% both medications compared in this study were not different for relieving pain and reducing the size of minor recurrent aphthous ulcers. Results of the present study showed that early start of any of the two medications (on the first 48 h of onset of the symptoms) decreased the total days of pain suffering.

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