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A COMPARATIVE STUDY OF THE EFFICACY OF 5% AMLEXANOX IN THE MANAGEMENT OF RECURRENT MINOR APHTHOUS ULCERS

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ABSTRACT

Background: Recurrent minor aphthous ulcer (RAU) is a common oral disorder which is multifactorial in origin and difficult to treat. Goals of treating aphthous ulcers include; accelerating the healing of ulcers, pain relief and prevention of recurrences. **Aim and Objective:** The aim of this study was to study the efficacy of 5% Amlexanox paste in treatment of Recurrent minor aphthous ulceration (RAU) and compare the results with those of 2% Lignocaine anesthetic gel. **Materials & Methods:** 60 patients with diagnosis of minor recurrent aphthous ulcers were included in this clinical study. The individuals were randomly divided into Group 1 (5% Amlexanox oral paste) and Group 2 (2% Lignocaine gel). The number, size, erythema and pain level of ulcers were measured and recorded on treatment days 1st, 3rd and 6th. Finally, the results were compared using student unpaired t test. **Results:** On comparison between the two groups significant difference was observed on 6th day in reduction of number of ulcers. Amlexanox oral paste significantly reduced ulcer size and erythema ($p \leq 0.05$ for day 3 and day 6). 2% Lignocaine gel was less beneficial in reducing ulcer size and erythema. When overall comparison of the VAS was made, the study group had lower pain scores than the control group on 6th day. (P value < 0.05, statistically significant). **Conclusion:** Amlexanox oral paste is as effective and safe in the treatment of apthous ulcers. It can reduce the frequency, duration and symptoms associated with the disease with no side-effects attributed to the drug.

KEYWORDS: Recurrent apthous ulcer, 5% Amlexenox paste, 2% Lignocaine gel.

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is one of the most common oral mucosa diseases. It can affect both men and women of all ages, races and geographic regions. Minor Recurrent aphthous ulcer (RAU) is the most common form, which accounts for approximately 70% to 87% of the population with RAS.[1,2] They are white ulcerative lesions that may be single or multiple and round or oval. Two to eight crops of lesions occur per year, lasting 7 to 14 days and then heal without scars.[3] For 24–48 hours preceding the appearance of an ulcer, most patients have a pricking or burning sensation in the affected area. The ulcer usually occurs on the nonkeratinized oral mucosa, including the lips, the buccal mucosa, the floor of the mouth, the soft palate and the ventral surface of the tongue. Regions of keratinized oral mucosa, such as the hard palate, the gums and the dorsal surface of the tongue, are uncommon locations. For RAS patients, the ulcer pain associated with each episode may interfere with eating, speaking and swallowing.

Several factors are suspected including genetics, stress, nutritional deficiencies (iron, vitamin B, or folate), diet, hormonal changes and immunological disorders.[4,5] However, the majority of subjects who have recurrent aphthous ulceration tend to be otherwise healthy without signs of systemic disease. Due to the often-uncertain aetiology of recurrent aphthous ulceration and the unpredictable course of the disease, the primary goals of therapy are to control the pain of the ulcer, promote ulcer healing and prevent recurrence.[5,6]

Current treatment options include topical agents, systemic and topical steroids, corticosteroids, cauterization, antibiotics, mouth rinses containing active enzymes, laser treatments and combination therapy.[7,8]

Although topical agents do not prevent ulcer recurrence they are arguably the most commonly used treatment modalities. A multitude of topical agents are available for symptomatic relief including antibiotics, local anaesthetics, antihistamines, non-steroidal anti-inflammatory drugs, enzymatic preparations, gammaglobulins and immunosuppressants.[8-14]

However, the problem remains that the efficacy of many of these agents has not been fully evaluated in adequately designed and controlled clinical trials and contradictory results are reported in the literature.

Of the topical agents that are available for the treatment of recurrent aphthous ulceration, Amlexanox being amongst them. Amlexanox is 2-amino-7-isopropyl-5-oxo-5H-(1) benzopyrano-(2,3-b)-pyridine-3-carboxylic acid, a topical anti-inflammatory and anti-allergic drug. It is available as a 5% paste.[15,16] There have been a number of studies of the efficacy and safety of 5% amlexanox paste in the management of recurrent aphthous ulceration. These studies have demonstrated that 5% amlexanox paste accelerates ulcer healing and resolution of pain with subjects experiencing only minor, transient adverse effects.[17-20]

The purpose of this study is to evaluate the efficacy of 5% Amlexanox in promoting ulcer healing, decreasing ulcer number, size, erythema, resolving pain and recurrence associated with RAS when applied topically.

MATERIALS AND METHODS

This study was conducted on 60 patients with minor aphthous ulcers who visited the Department of Oral Medicine and Radiology.

Inclusion criteria

1. Patients giving history of recurrence ulcers in the oral cavity with at least 2 episodes per year and with no signs of any systemic disease.
2. Patients with one to three ulcers of less than 48 hours duration

Exclusion criteria

1. Patients with known drug hypersensitivities
2. Patient who had applied any topical corticosteroid, topical antimicrobial drug or any other topical medication to the area of treatment within two weeks before day 1 of the study
3. Patients who had taken non steroidal anti inflammatory agents or systemic steroids before day 1 of the study
4. Patients with ulcerative colitis, Crohn's disease, Behcet's syndrome or anaemia
5. Patients undergoing orthodontic therapy
6. Patients who had undergone dental surgery of any type within two weeks before the study
7. Pregnant and lactating mothers.

The patients were randomly divided into 2 groups- - Group 1 patients were treated with 5% Amlexanox oral paste. Group 2 patients were treated with 2% Lignocaine gel. A Clinical examination was performed. The ulcer's size was measured by using a calibrated dental probe with millimeter markings on treatment days 1, 3 and 6. When subjects presented with multiple ulcers, evaluation for all ulcers were averaged. erythema was assessed using erythema scale 0,1,2,3. To evaluate pain, a visual analog scale (VAS) consisting of a 10-cm horizontal line between poles connoting no pain (origin) to unbearable pain was used. Subjects were told to mark the line with a vertical line at the point that best represented the present pain level of the ulcer. For analysis of subjects with healed ulcers, all treated ulcers had to have healed completely for the subject to be counted as healed.

Patients were instructed to apply the ointment to the ulcer 4 times a day (after meals and before bedtime) for 6 days (day 1 to day 6).

RESULTS

Repeated measures ANOVA with Bonferroni test for comparison of parameters obtained at different time periods within the group itself was used. Student's t-test was used for comparison of the study and the control group. A p-value of ≤ 0.05 was taken as statistically significant.

Table 1: Results obtained on different days using 5%Amlexenox paste

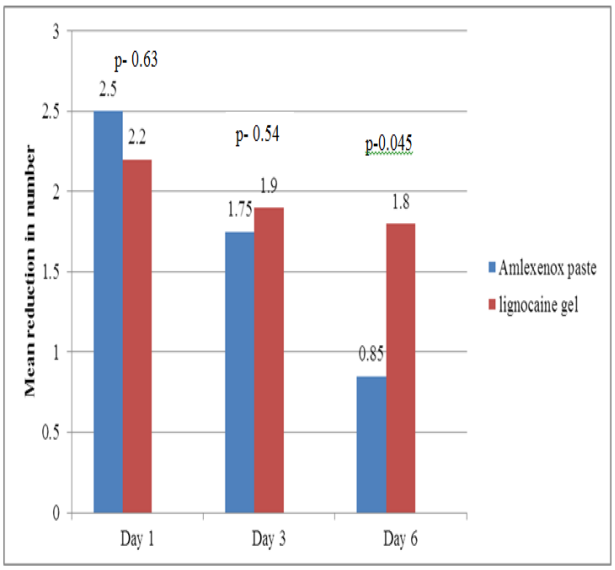
		1st DAY	3rdDAY	6th DAY	P value
Number of ulcers	Mean	2.5	1.75	0.85	0.034
	SD	±0.064	±0.035	±0.013	
Size of ulcers	Mean	2.033	1.5	0.433	0.023
	SD	±0.176	±0.115	±0.92	
Erythema	Mean	1.633	1.067	0.067	0.019
	SD	±0.112	±0.046	±0.035	
Pain in VAS	Mean	3.067	1.667	0.167	0.03
	SD	±0.046	±0.011	±0.09	

Table 2: Results obtained on different days using 2%lignocaine gel

		1st DAY	3rdDAY	6th DAY	P value
Number of ulcers	Mean	2.2	1.9	1.8	0.074
	SD	±0.38	±0.84	±0.94	
Size of ulcers	Mean	1.95	1.75	1.2	0.049
	SD	±0.168	±0.166	±0.156	
Erythema	Mean	1.45	1.17	0.45	0.047

	SD	±0.091	±0.053	±0.043	
Pain in VAS	Mean	3.04	1.5	0.45	0.000
	SD	±0.045	±0.010	±0.012	

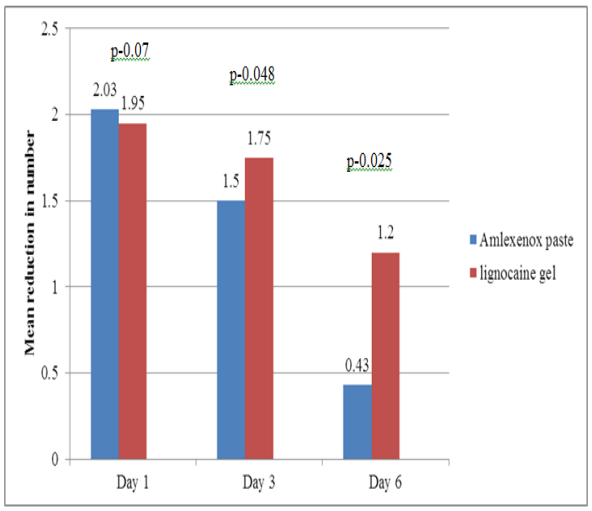
REDUCTION IN NUMBER



Graph 1: Intercomparison between the study and control group (p-value ≤0.05 statistically significant.)

Both groups showed significant results on 6th day, but values were not significant on 1st day and 3rd day. On comparing *between two groups*, there was no significant difference between 1st, 3rd day. Results were significant on 6th day only indicating considerable reduction in number in study group then control group.

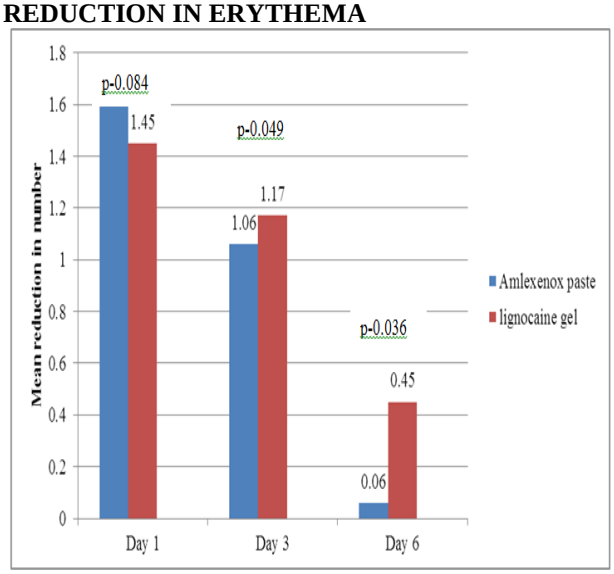
REDUCTION IN SIZE



Graph 2: Intercomparison between the study and control group (p-value ≤0.05 statistically significant.)

Significant reduction was seen in the size of ulcer in both the groups when 3rd, 6th day values were compared with the first day values of respective group. On comparing size of ulcers between two groups, there was significant difference on 3rd, 6th day indicating considerable reduction in study group compared to control group.

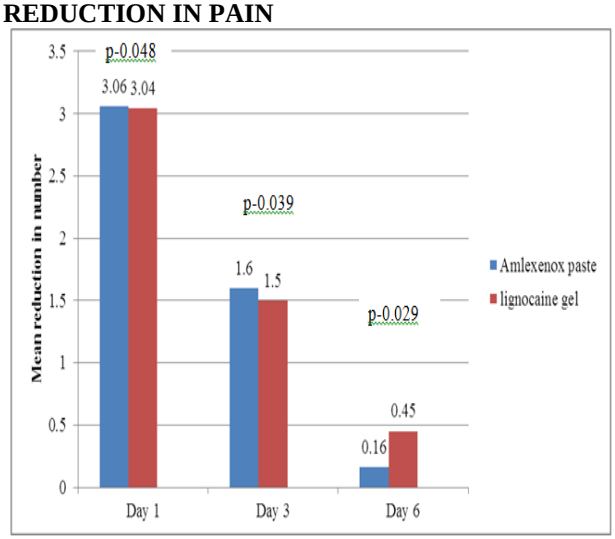
REDUCTION IN ERYTHEMA



Graph 3: Intercomparison between the study and control group (p-value ≤0.05 statistically significant.)

There was also significant reduction in the erythema of ulcer in both the groups when 3rd, 6th day values were compared with the first day values of respective group. On comparing between the groups significant difference was noted on 3rd, 6th day showing good results in the study group than control group.

REDUCTION IN PAIN



Graph 4: Intercomparison between the study and control group (p-value ≤0.05 statistically significant.)

Mean maximum pain scores recorded were similar for both treatment groups at beginning of the study (3.06 for Group 1 and 3.04 for Group2). In Group 1 there was a reduction of pain score from 3.06 to 1.6 and 0.16 at

the end of second and third visit respectively. Group 2 however, showed almost similar pain score as that of Group 1(1.5 at day 3). But on 6th day control group showed higher mean pain score of 0.45 which was more than that of group 1.

DISCUSSION

The beneficial effects of 5% Amlexanox paste, in accelerating ulcer healing and resolution of pain has been demonstrated in well controlled clinical studies. Although Amlexanox has been shown in preclinical studies to have both antiallergic and anti inflammatory properties, the mechanism by which 5% Amlexanox accelerates the healing of aphthous ulcers is unknown.[19]

Amlexanox potentially inhibit the formation and release of histamine and leukotrienes from mast cells, neutrophils and mononuclear cells. Histamine and leukotrienes are vasoactive inflammatory mediators which can only increase the permeability of vessels and therefore cause swelling of the involved tissues, but also contribute to inflammation by affecting the functions of other leukocytes in the involved area.[20]

In present study patient on Amlexanox reported reduced number of ulcers on comparison to pretreatment period and in control group though the number reduced it was not of that significance, indicating greater ulcer free days in study group. (Graph 1) Size and erythema also reduced in both the groups. On comparision between the groups the size and erythema was lower in the study group than the control group. (Graph 2,3) This reduction was not significant on the 1st day of ulcer size and 1st, 3rd day of erythema which showed near approximation with previous studies done by Jie Liu et al,Greer et al and Girish et al.[17,21,22]

Signs and symptoms in both the groups had reduced which was noted by reduction in the VAS scores throughout treatment and post-treatment period. This indicates that both drugs could bring about reduction in the pain. However, on comparing between two groups, the patients on amlexanox had a significant lower VAS values than the control group on 6th day(Graph 4) which is similar to the previous studies performed.[19,20,21]

The only type of adverse event reported by some studies on treatment with Amlexanox was local transient stinging at the application site.[20] In this study however, none of the patients reported any adverse effects with the use of Amlexanox.

In conclusion, the results of this study provide evidence that 5% Amlexanox is a well-tolerated effective treatment modality for minor aphthous ulceration. This study has shown reduction in number, size, erythema, pain associated with ulcers and also the reduction in recurrence of ulceration with no side-effects attributed to the drug. A larger sampled study is advised to confirm the findings of present study.

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