

## Comparison of Efficacy of *Aloe vera* Gel With 5% Amlexanox Oral Paste in the Treatment of Minor Recurrent Aphthous Stomatitis: A Randomized Clinical Trial

Hemcle Shalma G\* and Sushmini Hegde

\*Department of Oral Medicine and Radiology, The Oxford Dental College, Bengaluru, Karnataka, India.

Received June 14, 2019; Accepted June 27, 2019; Published October 11, 2019

### ABSTRACT

**Background:** Recurrent aphthous stomatitis (RAS) is one of the most common oral mucosal conditions. Most of the currently available treatment modalities aim at symptomatic relief hasten healing and prevent recurrence of ulcers. The aim of the study is to compare the efficacy of *Aloe vera* gel with 5% Amlexanox oral paste in the treatment of minor RAS.

**Materials and methods:** 64 patients diagnosed to have minor recurrent aphthous ulcers were randomly divided into Group A (*Aloe vera* gel group -32) and Group B (Amlexanox oral paste group - 32). The base line parameters were recorded on day of first visit which included ulcer size, pain and erythema. Evaluation of reduction in ulcer size, pain and erythema were made on day 3 and day 7. The recurrence rate of ulcer was evaluated for 6 months at monthly intervals.

**Results:** In both group A and group B, marked improvement was observed in ulcer size, pain and erythema between baseline and day 3, baseline and day 7 and day 3 and day 7. Both the groups were found to be effective in reducing ulcer size, pain and erythema but *Aloe vera* gel group when compared with Amlexanox group has significant reduction in ulcer size and VAS score ( $P < 0.001$ ).

**Conclusion:** *Aloe vera* proved to have multiple unique properties with very less side effects. *Aloe vera* gel group when compared with Amlexanox group has significant reduction in ulcer size and VAS score hence proving to be clinically beneficial in treatment of minor RAS.

**Keywords:** RAS, *Aloe vera*, Amlexanox, Efficacy

### INTRODUCTION

Recurrent aphthous stomatitis (RAS) is a disorder characterized by recurring ulcers confined to the oral mucosa in patients with no other signs of disease and can cause pain on eating, swallowing and speaking [1,2]. The pathophysiology of aphthous ulcers is poorly understood [3-5]. The diagnosis is primarily based on the history and clinical criteria [5]. RAS can be clinically classified mainly into three groups: Minor aphthae, major aphthae and recurrent herpetiform ulcers [3,4]. Various treatment modalities of RAS include systemic therapies, topical agents, physical therapies, laser therapy, etc. Topical agents are the first choice of management for RAS. They are cost effective, safe and easily available. Amlexanox ( $C_{16}H_{14}N_2O_4$ ) is one of the most extensively studied topical agents available for the treatment of RAS. It has an anti-inflammatory, anti-allergic action which inhibits the formation and release of histamine and leukotriene's from mast cells, neutrophils and mononuclear cells [4]. *Aloe vera* (AV- *Aloe barbadensis* Miller) is one amongst the natural herbal medicine which is used as an alternative therapy for RAS. The transparent gel derived from *Aloe vera* leaves

contains a series of natural components which has immunomodulators, anti-inflammatory, wound healing, antioxidant, anti-diabetic and anti-neoplastic properties. These properties lead the researchers to use it in management of minor RAS [6]. Since *Aloe vera* is one of a novel modality with its efficacy and rate of recurrence still under investigations, very few studies were observed during literature search. Hence the present study is designed to compare the efficacy of *Aloe vera* gel with 5% Amlexanox oral paste in the treatment of minor RAS.

**Corresponding author:** Hemcle Shalma G, Department of Oral Medicine and Radiology, The Oxford Dental College, Bengaluru, Karnataka, India, Tel: +91-7200976818; E-mail: shalmajoy@gmail.com

**Citation:** Hemcle Shalma G & Hegde S. (2019) Comparison of Efficacy of *Aloe vera* Gel With 5% Amlexanox Oral Paste in the Treatment of Minor Recurrent Aphthous Stomatitis: A Randomized Clinical Trial. J Oral Health Dent, 2(3): 139-144.

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## MATERIALS AND METHOD

The study was conducted on 64 patients with minor RAS who visited our Department of Oral Medicine and Radiology. The patients were selected according to the specific inclusion and exclusion criteria. The following criteria were utilized to select the patients with minor RAS: age range 18 to 50 years, presenting with single or multiple minor RAS of less than 48 h duration, location of ulcer must be easily accessible. Exclusion criteria comprised of pregnancy and lactation, history of allergies to *Aloe vera* and Amlexanox, patients on NSAIDs, immune modulatory agents or systemic antibiotics, patients on any other oral topical medication, with bleeding disorders and on corticosteroid therapy, ulcers as manifestation of systemic diseases. The whole study process was explained to the patients before and informed consent was obtained. The ethical clearance was obtained from institutional ethical board. The clinical trial registry – India registration number for this trial is CTRI/2018/05/013778. The proforma was distributed among the study subjects, which included demographic data, medical history and study parameters.

The patients were distributed as Group A (*Aloe vera* gel – Forever company, Bangalore, India) or Group B (5% Amlexanox oral paste - Lexanox oral paste, Macleods pharmaceuticals limited, Mumbai- India) through lottery method of randomization. Group A patients were instructed to apply *Aloe vera* gel directly on the ulcer 3 times a day for 10 days (after meals and before bed time) and Group B patients were instructed to apply 5% Amlexanox oral paste on the ulcer 4 times a day for 10 days (after meals and before bed time). The base line parameters were taken and recorded on the day of the first visit. Reduction in ulcer size, pain (VAS score) and erythema were evaluated on day 3 and day 7 and recurrence rate of the ulcer were evaluated for 6 months at monthly intervals. Subjects were instructed that if any allergic reactions occur they should terminate usage of medication and inform the investigator immediately. To

determine the size of the ulcers, a calibrated William's periodontal probe with millimetre markings was used to measure the ulcer size at the maximum diameter of the ulcer. Degree of erythema was evaluated on a 4 point scale ranging from 0 to 3 based on the methods of Greer et al. [7]. Evaluation of recurrence in both the groups was done by monthly follow ups either by clinical examination or by telephonic follow up (for those who could not come for follow up appointment).

## STATISTICAL ANALYSIS

Both the study group and the control group will be compared with respect to all the baseline parameters. The mean differences in the lesion diameter and inflammation diameter between the two groups will be compared at baseline, on day 3, day 7 and at 1 month follow up periods using Independent sample t-test. The mean decline in the lesion diameter and increase in inflammation diameter at different follow up periods, differences along with their 95% CI and p value will be presented. P value<0.05 will be considered statistically significant. IBM SPSS statistical software, version 21 will be used for statistical analysis.

## RESULTS

A total of 64 patients (32 in Group A and 32 in Group B) who were diagnosed with minor recurrent aphthous ulcers were enrolled in this study. There were 2 dropouts from both Group A and Group B. At the end of the study period we had 30 patients each in Group A and Group B. All the findings were subjected for statistical analysis. The gender distribution in the study sample of 60 patients, 12 (40.0%) being males and 18 (60.0%) being females in *Aloe vera* group and 17 (56.7%) being males and 13 (43.3%) being females in Amlexanox group, respectively (**Table 1**). The age range of patients in *Aloe vera* group was 18-50 years and the age range of patients in Amlexanox group was 20-50 years.

**Table 1.** Age and gender distribution of study participants.

| Age and Gender distribution among 2 groups |           |                  |       |                  |       |                   |
|--------------------------------------------|-----------|------------------|-------|------------------|-------|-------------------|
| Variables                                  |           | Aloe vera [N=30] |       | Amlexanox [N=30] |       | P-Value           |
|                                            |           | Mean             | SD    | Mean             | SD    |                   |
| Age                                        | Mean & SD | 29.50            | 6.96  | 28.27            | 7.37  | 0.51 <sup>a</sup> |
|                                            | Range     | 18-50            |       | 20-50            |       |                   |
|                                            |           | n                | %     | n                | %     |                   |
| Gender                                     | Males     | 12               | 40.0% | 17               | 56.7% | 0.20 <sup>b</sup> |
|                                            | Females   | 18               | 60.0% | 13               | 43.3% |                   |

<sup>a</sup> Mann Whitney Test; <sup>b</sup> Chi Square Test

The mean ulcer size at baseline for the patients of group A was  $6.23 \pm 1.48$  and that of group B was  $5.70 \pm 1.90$ . After

using *Aloe vera* gel patients were recalled on the day 3 and day 7. The results revealed significant reduction of ulcer size

in both Group A and Group B on day 3 ( $2.73 \pm 2.90$  and  $3.17 \pm 2.31$ , respectively) and day 7 ( $0.40 \pm 0.97$  and  $1.53 \pm 1.72$ ), respectively. Statistically significant difference

between Group A and Group B was observed in day 7 ( $P=0.001$ ) (Table 2).

**Table 2.** Comparison of mean ulceration size (in mm) between 2 groups at different time intervals.

| Comparison of mean ulceration size [in mm] between 2 groups at different time intervals using Mann Whitney U Test |                  |    |      |      |           |        |         |
|-------------------------------------------------------------------------------------------------------------------|------------------|----|------|------|-----------|--------|---------|
| Time                                                                                                              | Groups           | N  | Mean | SD   | Mean Diff | Z      | P-Value |
| Day 0                                                                                                             | <i>Aloe vera</i> | 30 | 6.23 | 1.48 | 0.53      | -1.679 | 0.09    |
|                                                                                                                   | Amlexanox        | 30 | 5.70 | 1.90 |           |        |         |
| Day 3                                                                                                             | <i>Aloe vera</i> | 30 | 2.73 | 2.90 | -0.43     | -0.889 | 0.37    |
|                                                                                                                   | Amlexanox        | 30 | 3.17 | 2.31 |           |        |         |

\* - Statistically Significant

The mean pain score at baseline for the patients of Group A was  $6.40 \pm 1.87$  and that of Group B was  $5.50 \pm 2.06$ . A marked reduction in pain in both Group A and Group B was noted on day 3 ( $2.60 \pm 2.34$  and  $3.07 \pm 2.33$ ) and day 7 ( $0.23$

$\pm 0.73$  and  $1.20 \pm 1.63$ ), respectively. Statistically significant difference between Group A and Group B was observed in day 7 ( $P=0.001$ ) (Table 3).

**Table 3.** Comparison of mean VAS scores between 2 groups at different time intervals.

| Comparison of mean VAS Scores between 2 groups at different time intervals using Mann Whitney U Test |                  |    |      |      |           |        |         |
|------------------------------------------------------------------------------------------------------|------------------|----|------|------|-----------|--------|---------|
| Time                                                                                                 | Groups           | N  | Mean | SD   | Mean Diff | Z      | P-Value |
| Day 0                                                                                                | <i>Aloe vera</i> | 30 | 6.40 | 1.87 | 0.90      | -1.574 | 0.12    |
|                                                                                                      | Amlexanox        | 30 | 5.50 | 2.06 |           |        |         |
| Day 3                                                                                                | <i>Aloe vera</i> | 30 | 2.60 | 2.34 | -0.47     | -0.794 | 0.43    |
|                                                                                                      | Amlexanox        | 30 | 3.07 | 2.33 |           |        |         |
| Day 7                                                                                                | <i>Aloe vera</i> | 30 | 0.23 | 0.73 | -0.97     | -3.225 | 0.001*  |
|                                                                                                      | Amlexanox        | 30 | 1.20 | 1.63 |           |        |         |

\* - Statistically Significant

The mean erythema score at baseline for Group A was  $1.83 \pm 0.46$  and that of Group B was  $1.77 \pm 0.43$ . A slight reduction in erythema in both Group A and Group B was noted on day 3 ( $0.63 \pm 0.56$  and  $0.80 \pm 0.61$ ) and day 7 ( $0.17$

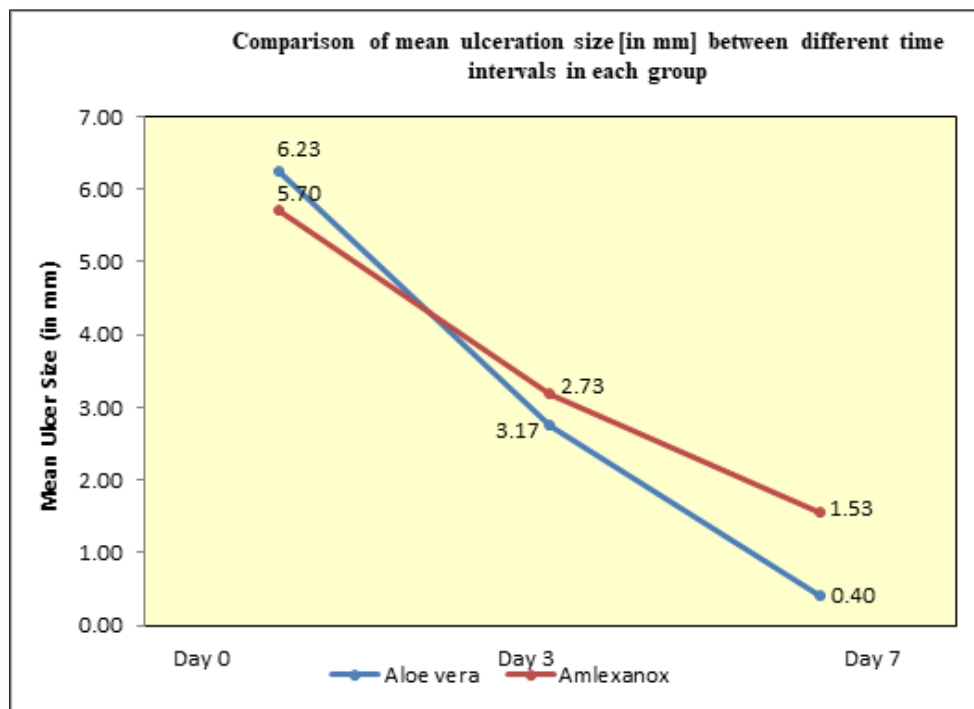
$\pm 0.38$  and  $0.33 \pm 0.48$ ), respectively. No statistically significant difference was observed in day 3 and day 7 in erythema reduction between Group A and Group B (Table 4).

**Table 4.** Comparison of mean erythema score between 2 groups at different time intervals.

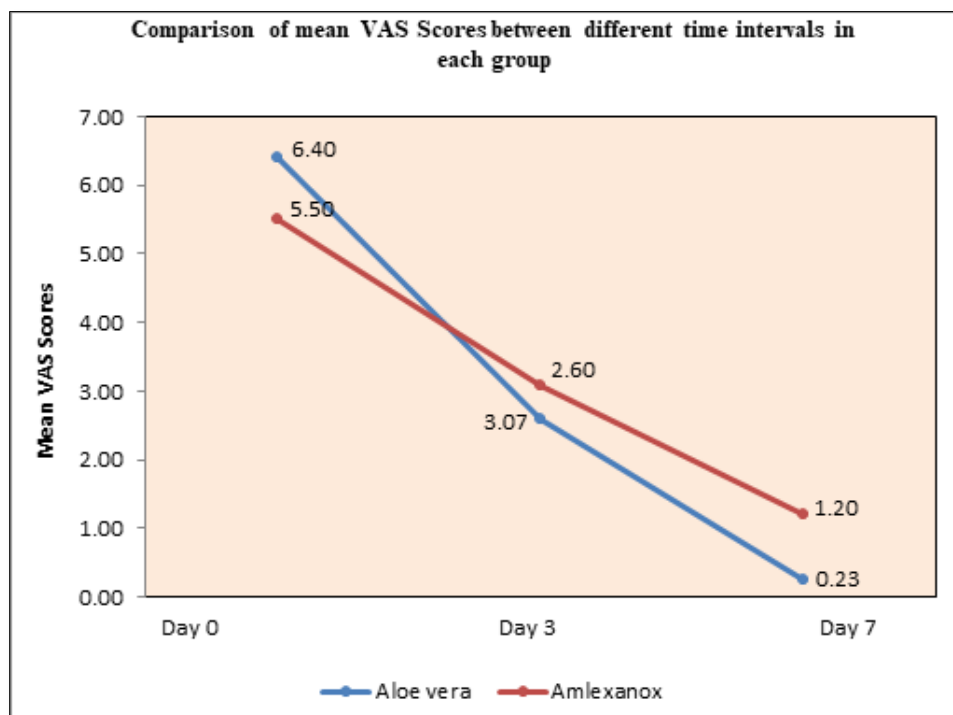
| Comparison of mean Erythema scores between 2 groups at different time intervals using Mann Whitney U Test |                  |    |      |      |           |        |         |
|-----------------------------------------------------------------------------------------------------------|------------------|----|------|------|-----------|--------|---------|
| Time                                                                                                      | Groups           | N  | Mean | SD   | Mean Diff | Z      | P-Value |
| Day 0                                                                                                     | <i>Aloe vera</i> | 30 | 1.83 | 0.46 | 0.07      | -0.553 | 0.59    |
|                                                                                                           | Amlexanox        | 30 | 1.77 | 0.43 |           |        |         |
| Day 3                                                                                                     | <i>Aloe vera</i> | 30 | 0.63 | 0.56 | -0.17     | -1.044 | 0.30    |
|                                                                                                           | Amlexanox        | 30 | 0.80 | 0.61 |           |        |         |
| Day 7                                                                                                     | <i>Aloe vera</i> | 30 | 0.17 | 0.38 | -0.17     | -1.478 | 0.14    |
|                                                                                                           | Amlexanox        | 30 | 0.33 | 0.48 |           |        |         |

On comparison of mean ulceration size, VAS scores and erythema scores between different time intervals in each group signifies that within group A statistically significant difference were observed between baseline and day 3 ( $P$  value= $<0.001$ ), baseline and day 7 ( $P$ = $<0.001$ ) and day 3

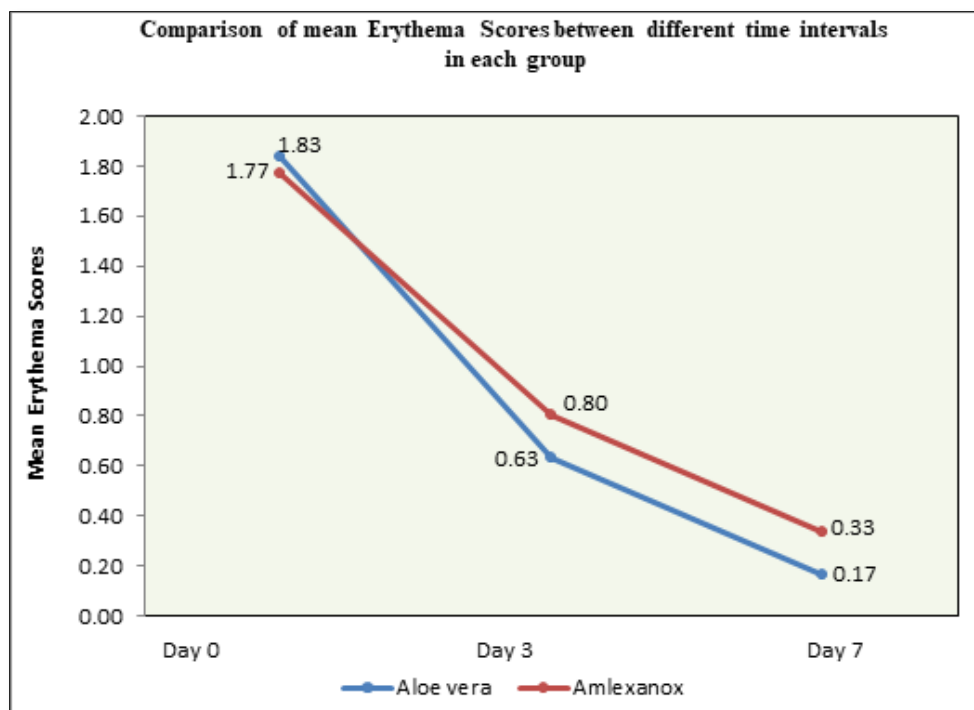
and day 7 ( $P$ = $<0.001$ ) and within Group B statistically significant difference were observed between baseline and day 3 ( $P$  value= $<0.001$ ), baseline and day 7 ( $P$ = $<0.001$ ) and day 3 and day 7 ( $P$ = $<0.001$ ) (Graphs 1-3).



**Graph 1.** Comparison of mean ulceration size between different time intervals in each group.



**Graph 2.** Comparison of mean VAS scores between different time intervals in each group.



**Graph 3.** Comparison of mean erythema scores between different time intervals in each group.

## DISCUSSION

The primary goals of therapy for RAS are relief of pain, reduction of ulcer size and duration and the restoration of normal oral function. Secondary goals include reduction in the frequency and severity of recurrence and maintenance of remission [8]. A wide range of treatments ranging from topical agents to systemic medications, physical modalities, natural remedies, home remedies and homeopathic remedies have been tried in the treatment of RAS [9]. The present study aimed at evaluating the efficacy of *Aloe vera* gel with 5% Amlexanox oral paste in reducing the size, pain and erythema of minor RAS. In our study, female predominance was noted in both the groups which accounts for 51.65%. This is in accordance with Rajmane et al. study where majority of patients were females. Females are more prone to stress and emotional situations which can affect their immune response. They seek medical examination more frequently than males. The hormonal changes during pregnancy and menstruation also play a role [10]. Maximum number of patients belonged to 21-30 years of age group which correlated with the study done by Kareem et al. in which about 80% of patients develop the condition before 30 years of age. The highest incidence is among young people, however the severity and frequency of ulcers decreases with age [11]. A high prevalence and severity of the disease has been found in students with a high socio-economic background. This is because psychological stress acts as a triggering factor for RAS and is typically observed during stressful situations such as school exam and any other significant changes in life [12]. This is in accordance with

Abdullah et al study where majority of patients were students [13].

The ulcer size in both Group A and Group B showed marked improvement between the baseline and day 3, baseline and day 7 and day 3 and day 7. This is in accordance with Babae et al. study where *Aloe vera* gels were found to be effective in reducing ulcer size [14]. There was significant difference between *Aloe vera* gel and Amlexanox oral paste in reducing the size of the ulcer in day 7 ( $P=0.001$ , respectively). According to literature, Glucomannan, a mannose-rich polysaccharide and gibberellin, a growth hormone, interacts with growth factor receptors on the fibroblast, thereby stimulating its activity and proliferation, which in turn significantly increases collagen synthesis after topical application of *Aloe vera* [15].

Both Group A and Group B had marked reduction in VAS scores between baseline and day 3, baseline and day 7 and day 3 and day 7. However on comparing both groups, *Aloe vera* gel showed a significant difference in pain reduction in day 7 ( $P=0.001$ , respectively). This indicates that *Aloe vera* gel has a significant therapeutic effect in reducing the VAS score which is in accordance with the Babae et al. study where *Aloe vera* gel were found to be effective in alleviating ulcer pain [16]. According to literature, *Aloe vera* inhibits the cyclooxygenase pathway and reduces prostaglandin E2 production from arachidonic acid. Recently, the novel anti-inflammatory compound called C-glucosyl chromone was isolated from gel extracts which helps in relieving pain [15].

In our study we have observed obvious improvement in erythema associated with RAS in both the study groups between baseline and day 3, baseline and day 7 and day 3 and day 7 but there was no statistically significant difference between the groups in any of the follow up visits ( $P=0.59$ ,  $P=0.30$ ,  $P=0.14$ , respectively). Amlexanox due to its anti-inflammatory property is equally effective as *Aloe vera* in reducing the erythema. This in accordance with the study done by Katti et al. [16]. During the study period, periodic phone calls were made to the participants to confirm the use of the interventions. *Aloe vera* gel and Amlexanox oral paste were well tolerated by the patients during the study period without any major side effects.

## CONCLUSION

The results of the study suggests that both treatment groups were found to be effective in healing of ulcers, reducing the pain and erythema. *Aloe vera* gel group when compared with Amlexanox group has significant reduction in ulcer size and VAS score hence proving to be clinically beneficial in treatment of minor RAS. However, studies on a larger series of patients for a longer duration may be required in order to determine the true therapeutic effects of *Aloe Vera* and to compare their efficacy in the management and recurrence of minor RAS.

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