

Clinical Efficacy of Aloe Vera and Triamcinolone Acetonide in the Management of Minor Recurrent Aphthous Stomatitis- A Randomised Double-Blind Clinical Study

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Abstract

Aim: To compare the therapeutic effects of Aloe Vera and triamcinolone acetonide in alleviating the healing duration and pain in recurrent aphthous ulcers.

Methodology: A double-blind clinical trial was carried out on 60 clinically diagnosed RAS patients in the department of Oral Medicine and Radiology. Patients were selected by simple random sampling technique; the study sample was divided into three groups with 20 patients in each group. Group A received placebo, group B Aloe Vera and group C triamcinolone acetonide 0.1% respectively. Treatment outcome was evaluated and improvement in the size and pain score of the ulcer was evaluated. The statistical analysis was done using ANOVA and Chi-square test where $p < 0.05$ was statistically significant.

Results: The results of the study showed female preponderance (68.3%) as compared to males (31.6%) and affecting younger age group (21-25 years) for RAS. Although triamcinolone acetonide was effective in

alleviating the pain score in initial stage of the study with mean and standard deviation 1.40 ± 1.14 as compared to Aloe Vera (2.65 ± 1.79) $p < 0.05$. However at the end of the study no statistically significant difference was observed between the groups. Topical Aloe Vera gel showed almost similar response with respect to reducing the RAS size and healing compared to triamcinolone acetonide and was equally effective in alleviating the pain associated with RAS.

Conclusion: The results of the present study show evidence that Aloe Vera gel is well tolerated and effective in treating recurrent aphthous stomatitis (RAS).

Keywords: Recurrent Aphthous Stomatitis, ulcer size, pain, Aloe Vera, Triamcinolone acetonide.

Introduction

Recurrent aphthous stomatitis (RAS) is one of the most common lesions of the oral cavity, with a wide range of reported prevalence from 5 to 50% in different populations. [1-4] RAS is one of the most common and poorly understood mucosal disorders. It is found in men

and women of all ages, races, and geographic regions. [5] It occurs more frequently in times of stress. [6,7] Much progress has been made over the last four decades on the epidemiology, clinical description, predisposing factors, and symptomatic treatment of RAS. Considerable research attention has been devoted to elucidating the etiology of RAS. Currently, the most widely accepted etiology is that it is a localized immunological disorder. It is estimated that at least 1 in 5 individuals is afflicted with RAS and usually begins in adolescent and teenage years.[8] There is no curative therapy to prevent the recurrence of ulcers and all available treatment modalities can only reduce the frequency or severity of the lesions. Although, RAS may be a marker of an underlying systemic illness such as coeliac disease or may be present as one of the features of Behçet's disease (International Study Group for Behçet's Disease 1990), in most cases no additional body systems are affected, and patients remain otherwise fit and well. [9]

Aphthous ulcers have been reported in 2–4% of HIV-seropositive patients, although these patients suffer from larger and more frequent aphthae in advanced stages of their disease. [10]In patients with advanced HIV disease, aphthous ulcers may exacerbate weight loss. While most aphthae are small and heal within 7–10 days, larger ulcers can persist for weeks or months.[11] The ulcer usually occurs on the non-keratinized oral mucosa, including the lips, the buccal mucosa and the floor of the mouth, the soft palate, and the ventral surface of the tongue, it may cause pain and may interfere with eating, speaking and swallowing. Consequently, the goal of therapy for the disease of recurrent aphthous stomatitis (RAS) is to reduce the severity of pain, healing time and the frequency of occurrence of new ulcers.

The mainstay of treatment of RAS patients is local therapy (topical) and systemic therapy. Topical steroids have been

used for decades to treat aphthous ulcers to some extent in the mouth effectively; however long-term use of steroids is associated with several ill-effects. Another limitation is that the steroids are not FDA- approved for this use although there are many studies that demonstrate their effectiveness and safety for treating oral diseases. [12] The use of natural products in the prevention and treatment of oral conditions has increased recently and could be of benefit to low socioeconomic level in urban and rural communities. In this context various naturally occurring products like, turmeric, myrrh, tea, liquorice, Aloe Vera etc., have been widely explored. Aloe Vera is a well-known medicinal plant belonging to the Liliaceae family. It is a cactus-like plant that grows readily in hot dry climates. The mucilaginous tissue in the centre of the Aloe Vera leaf (Aloe Vera gel) has traditionally been used for treatment of digestive tract disorders, sunburn and wounds. [13]

A double-blind therapeutic study was planned to study the effect of Aloe Vera gel in the management of recurrent aphthous ulcers and to compare its effects with most widely used Triamcinolone Acetonide oral gel. Hence the purpose of the study was to conduct a comparative double-blind therapeutic study between Aloe Vera gel, Triamcinolone and a placebo in the management of minor recurrent aphthous stomatitis.

Materials and Methods

A double-blind therapeutic study was conducted in the Department of Oral Medicine and Radiology, Navodaya Dental College and Hospital, Raichur, Karnataka from March 2014 to Oct 2015. The study sample comprised of 60 subjects with clinically diagnosed recurrent aphthous ulcer drawn from the out-patient Department of Oral Medicine and Radiology.

Patients were selected by simple random sampling technique and the study sample was divided into three

groups with 20 patients in each. Group A received placebo, group B Aloe Vera and group C triamcinolone acetonide 0.1% respectively.

The criteria for inclusion of subjects was patients with minor recurrent aphthous lesion on their oral mucosa without any other medical complications who had noticed oral lesions during the last two days and patients with history of recurrent aphthous ulcers; with at least one episode per month on an average. These were randomly assigned to receive Aloe Vera gel, triamcinolone acetonide and placebo.

In the patients clinically diagnosed the parameters assessed for the inclusion were-size, duration of the ulcer, the healing time (days after gel application) and patient's pain score to be recorded using Visual Analogue Scale (VAS). While the patients suffering with any other systemic diseases or any allergic conditions, on medication and pregnant women were excluded from the study. Ethical clearance was obtained from the ethical committee and informed consent was taken from each patient. A standard Performa was used to record the clinical signs and symptoms in all the cases.

History of the previous occurrence of ulcers and duration of the ulcers was recorded and intra-oral examination findings such as presence of ulcers, number, shape, size, margins were noted. The ulcer size was measured at maximum and minimum diameters of the ulcer by using a sliding calliper. Clinical examinations were carried out at the initial visit (day 1), day 3 and day 7. The 2 measurements were multiplied to calculate surface area of the ulcer (mm^2). To evaluate pain, a visual analogue scale (VAS) between the poles of "no pain" to "unbearable pain" was used. Patients were told to mark the score by encircling at the point that best represented the present pain level between the scores of 1-10 of the ulcer, at days 1, 3 and 7. The products were placed into three identical

opaque containers and were labelled as A, B and C respectively coded by the operator external to the study. The patients were randomly allocated into three groups. One group received Aloe Vera gel (prepared freshly from aloe Vera juice extract). Second group received triamcinolone acetonide 0.1% (Abbot Pharmaceuticals, India- KENACORT 0.1%) and third group received a placebo [gelatine, pectin, carboxy methyl cellulose, triethanol amine, alcohol (95%), methyl paraben, purified water (Q.S)]. The patients were asked to apply the gel on the ulcer three times a day for 7 days and were advised not to eat or drink anything till 30 minutes. They were advised to maintain a chart of frequency of application of the gel. Patients were assessed after an interval of 3 and 7 days. Improvements in the ulcer size cure length and pain score was recorded up to two visits and analysed. The containers were decoded at the end of the study, patients' median VAS scores [Visual Analogue scale], RAS healing period with mean size of lesion and inflammation diameters were compared between the three groups. Patients with stimulated pain score of 1 and lesion diameter less than 1mm were considered healed.

Statistical analysis was done using ANOVA and Chi-square test. P value (<0.05) was considered to be statistically significant at 95% confidence interval.

Effectiveness indices were evaluated on a 4-rank scale:

- 1) Healed; $EI \geq 95\%$
- 2) Marked improvement; $EI \geq 70\%$ to $<95\%$
- 3) Moderate improvement; $EI \geq 30\%$ to $<70\%$
- 4) No improvement; $EI < 30\%$

Marked improvement rate (MIR) referred to $EI 1+2$ ($EI \geq 70\%$)

Improvement rate (IR) referred to $EI 1+2+3$ ($EI \geq 30\%$)

Results

An in-vivo, double-blind study was done among patients suffering from minor recurrent aphthous ulcers to study the clinical efficacy of topical application of Aloe Vera and triamcinolone acetonide. The sample size comprised of 60 patients between the age group of 14-47 years. They were divided into three groups A, B and C each comprised of 20 subjects. On completion of the study the samples were decoded, and results were obtained.

The subjects were divided into 4 age groups with an interval of 5 years. The age wise distribution showed maximum number of subjects in the age group of 21-25 years, 36(60%) among all the three groups. In the present study out of 60 subjects, the total number of males was 19 (31.6%) and the total number of females was 41(68.3%).

Among the 60 subjects, the most frequently involved oral mucosal site for the occurrence of RAS was labial mucosa 25 (41.66%), followed by tongue 12 (20%), alveolar mucosa 10 (16.66%), buccal mucosa 6 (10%), floor of the mouth 3 (5%), vestibule 1 (1.66%) and commissure of the lip 1 (1.66%) in decreasing order of frequency. [graph 1]

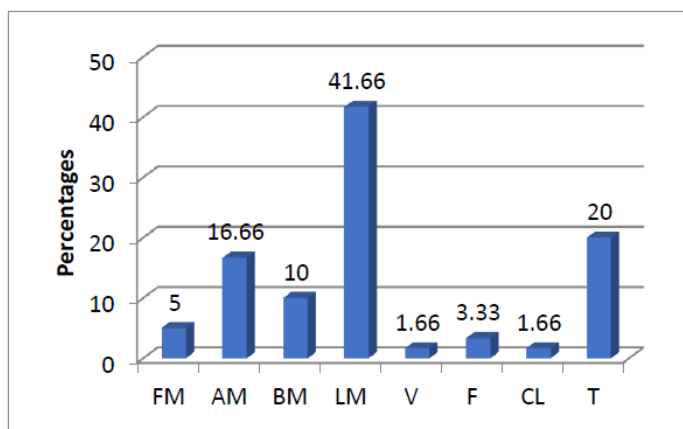


Figure 1: Frequency of Ras at Different Locations in the Oral Cavity.

FM- Floor of the mouth, AM- Alveolar mucosa, BM- Buccal mucosa, LM-Labial mucosa, V- Vestibule, F-Frenum, CL- Commissure of lip, T-Tongue.

The duration of the present study was distributed into 3 visits where Day 1 depicted 1st visit, Day 4 depicted 2nd visit and Day 7 depicted 3rd visit. The following graphs [graph 2, graph 3 and graph 4] show the comparison of size of RAS between the 3 groups at 1st visit, 2nd and 3rd visits. Although, the mean size of RAS among the 3 groups during the 3 visits varied. However, it was statistically not significant ($p > 0.05$).

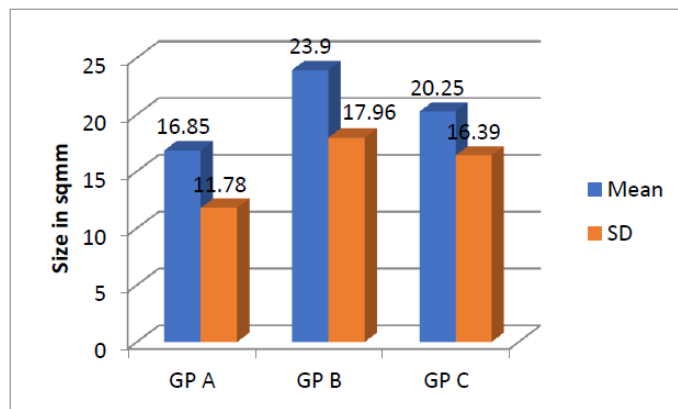


Figure 2: Comparison of Mean Size of RAS at 1st Visit (Day 1) Among Group A, Group B and Group C.

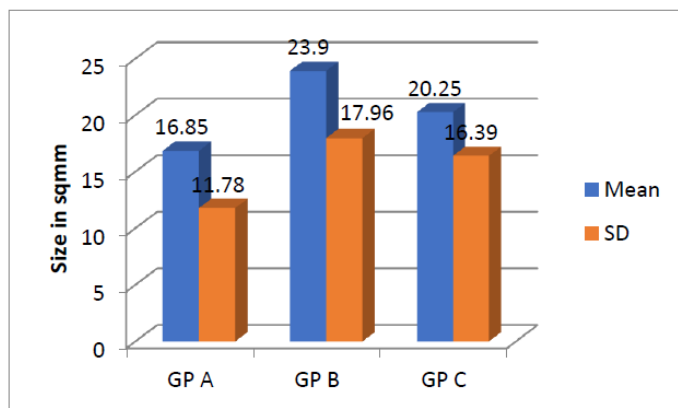


Figure 3: Comparison of Mean Size of RAS at 2nd Visit (Day 3) Among Group A, Group B and Group C

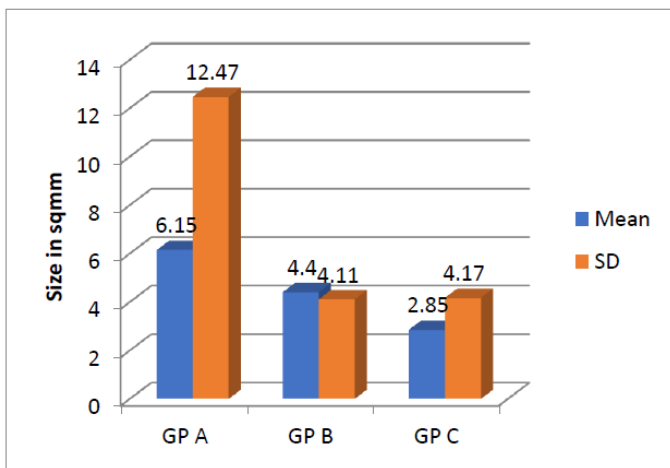


Figure 4: Comparison of Mean Size of RAS at 3rd Visit (Day 7) Among Group A, Group B and Group C

On comparison of pain score (VAS) of RAS between the 3 groups at 1st (Day 1), 2nd (day 3) and 3rd visit (day7) respectively, it was found that the mean pain score (VAS) on 2nd visit was statistically significant with $p < 0.05$. However, between 1st and 3rd visit the mean pain score (VAS) was statistically insignificant with $p > 0.05$. [graph 5, graph 6 and graph 7]

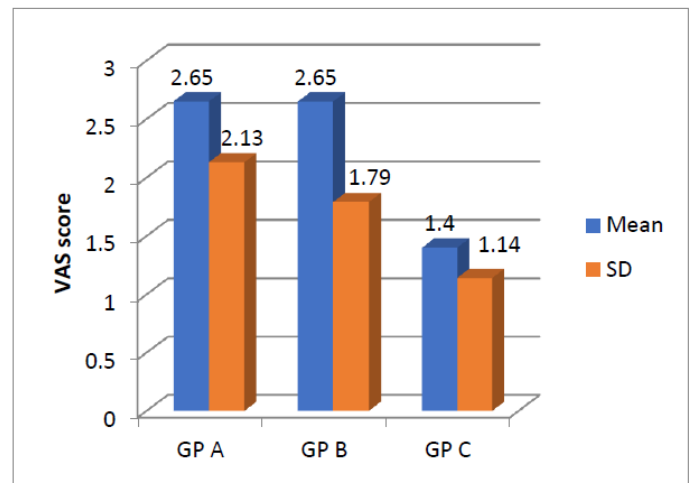


Figure 6: Comparison of Pain Score (VAS) At 2nd Visit (Day 3) Between the 3 Groups.

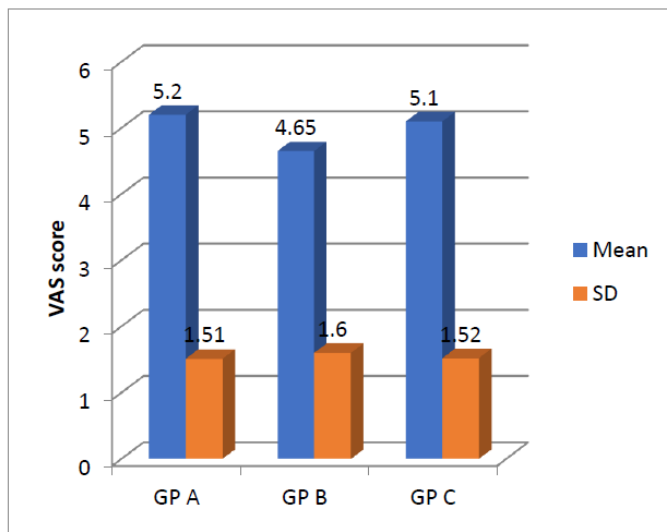


Figure 5: Comparison of Pain Score (VAS) At 1st Visit (Day 1) Between the 3 Groups

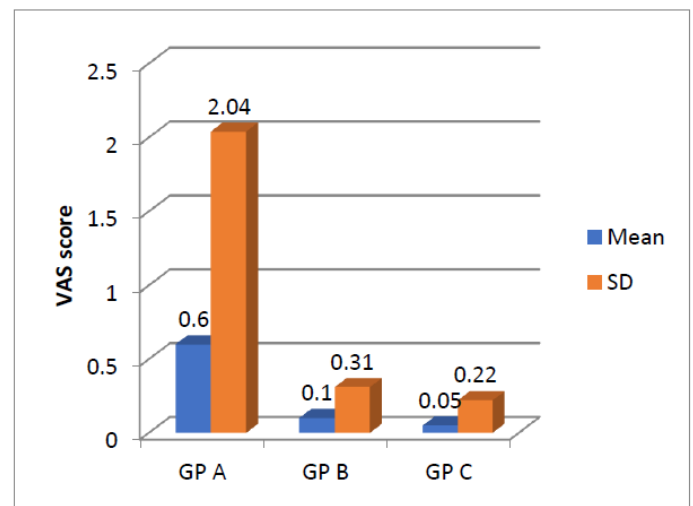


Figure 7: Comparison of Pain Score (VAS) At 3rd Visit (Day 7) Between the 3 Groups.

	1 ST VISIT	2 ND VISIT	3 RD VISIT	F	P	INFERENCE
GP A	16.85±11.78	11.20±8.95	6.15±12.47	4.594	.014 (<0.05)	SIGNIFICANT
GP B	23.90±17.96	15.85±9.97	4.40±4.11	13.130	0.0001 (<0.001)	HIGHLY SIGNIFICANT
GP C	20.25±16.3	9.10±7.43	2.85±4.17	13.66	0.0001	HIGLY
	9			8	(<0.001)	SIGNIFICANT
F	1.022	3.052	0.862	-	-	-
P	0.36 (>0.05)	0.055 (>0.05)	0.428 (>0.05)	-	-	-
INFERENCE	NS	NS	NS	-	-	-

Table 1: Comparison of size between all the 3 groups at 1st visit 2nd visit and 3rd visit

Mean size, SD-Standard deviation, F-ANOVA value

	1 ST VISIT	2 ND VISIT	3 RD VISIT	F	P	INFERENCE
GP A	5.20±1.51	2.65±2.13	0.60±2.04	29.031	0.0001 (<0.001)	HIGHLY SIGNIFICANT
GP B	4.65±1.60	2.65±1.79	0.10±0.31	53.462	0.0001 (<0.001)	HIGLY SIGNIFICANT
GP C	5.10±1.52	1.40±1.14	0.05±0.22	112.047	0.0001 (<0.001)	HIGHLY SIGNIFICANT
F	0.722	3.454	1.293	-	-	-
P	0.490 (>0.05)	0.038 (<0.05)	0.282 (>0.05)	-	-	-
INFERENCE	NS	SIGNIFICANT	NS	-	-	-

Table 2: Comparison of Pain Score (VAS) Between All the 3 Groups at 1st Visit 2nd Visit and 3rd Visit

Mean size, SD-Standard Deviation, F-ANOVA value

The effectiveness index was calculated in order to evaluate the reduction in the diameter of the size of the RAS among group A, group B and group C on Day 4 (2nd

visit) and Day 7 (3rd visit).The statistical analysis was not significant (p>0.05). [Table 3]

	DAY 3			DAY 7		
	GRP A(n=20)	GRP B(n=20)	GRP C(n=20)	GRP A(n=20)	GRP B(n=20)	GRP C(n=20)
(1) Healed completely	0	0	1	8	6	9
(2) Marked Improvement	1	0	6	6	10	8
(3) Moderate Improvement	10	10	7	4	3	3
(4) No Improvement	8	10	6	2	4	0
P	11.75*			2.79**		
Marked Improvement Rate (MIR)	1%	0%	7%	14%	16%	17%
Improvement Rate (IR)	11%	10%	14%	18%	19%	20%

Table 3: Effectiveness Index in Ulcer Size Reduction

The effectiveness index was calculated in order to evaluate the reduction in the pain score of RAS among group A, group B and group C on Day 4 (2nd visit) and Day 7 (3rd visit).The results were statistically insignificant (p>0.05) [table 4].

None of the study groups showed any adverse effects to the prescribed therapeutic agents.

	DAY 3			DAY 7		
	GRP A(n=20)	GRP B(n=20)	GRP C(n=20)	GRP A(n=20)	GRP B(n=20)	GRP C(n=20)
(1) Heal	3	2	1	17	18	19
(2) Marked Improvement	1	1	6	2	2	1
(3) Moderate Improvement	12	12	7	0	0	0
(4) No Improvement	4	5	6	1	0	0
P	9.54*			3.46**		
Marked Improvement Rate (MIR)	4%	3%	7%	19%	20%	20%
Improvement Rate (IR)	4%	15%	14%	19%	20%	20%

Table 4: Effectiveness Index in Ulcer Pain Reduction.

Discussion

Recurrent aphthous ulcers are accompanied by inflammation and pain which interfere with the patients’ quality of life. It is characterized by necrotizing ulcers of the oral mucosa that persist, remit and recur for variable periods of time. Pain and ulceration may disable patients and prevent them from performing their daily activities. [14]

Dolby in 1968 pointed out that corticosteroids such as hydrocortisone may be effective in aphthous stomatitis through interference with the formation of autoantibodies and the stabilization of lysosomes that in turn reduce the necrosis of the mucosa and inflammatory symptoms.

Triamcinolone acetonide is a synthetic intermediate acting corticosteroid. Its cream (0.1%) and ointment (0.1%) forms are available for topical use. The topical preparation of triamcinolone acetonide (0.1%) in RAS has been reported by various authors. [15-18]The use of natural

products in the prevention and treatment of oral conditions has increased recently and could be of benefit to low socioeconomic level in rural and urban communities. Aloe Vera gel has been applied topically by ancient and modern times throughout the world for its anti-inflammatory and wound healing properties. More recently, in the west, it has been widely used as an oral preparation for its supposed anti-inflammatory effects. [19] Thompson in 1991 reported that topical application of aloe Vera-derived allantoin gel stimulated fibroblast activity and collagen formation. [20] Despite its widespread popularity, scientific evidence on the aloe Vera gel remains sparse. Aloe Vera gel is regarded as safe if applied topical with only a few allergic reactions being reported. [21-23]

All the patients in this study were in the age group of 16-47 years. The age wise distribution showed maximum number of subjects in the age group of 21-25 years (60%) among all the three groups. Since the present study was carried out in an institution it comprised majority of the patients in this age group. The results were similar to those of Parvathi et al who reported 47% of population of her study in the age range of 21-25 years. [24] In another study it was documented that in about 80% of patients with RAS the condition develops before 30 years of age. [25]

Based on the gender distribution, the present study showed female predilection for RAS (68.3%) compared to the males (31.6%).These results were in accordance with the study carried out by Jurge S et al, which showed a female predominance with prevalence of RAS in females being 57.2% and males being 48.3% .[25] T Matsuda et al revealed RAS is found to be more in females with age of 10-15 years that is at the onset of puberty or after 50 years of age. They suggested that the reason for increased occurrence of RAS in females is due to hormonal changes.[26]Mc Cartan et al also showed

decreased incidence of RAS among males and concluded that smoking had inverse relationship with the occurrence of RAS as it causes keratinization and renders the mucosa less susceptible to ulceration.[27] In contrast, Parvathi et al in their study showed a male predominance among patients of RAS with 53% male patients and 47% female patients.[24] With consideration of the above mentioned studies the literature shows inconsistent reports with regard to the gender predilection in recurrent aphthous ulcers.

The most common site of RAS in the present study was labial mucosa 25 (41.66%), followed by tongue 12(20%), buccal mucosa 10(16.66%), floor of the mouth 3 (5%), frenum 2 (3.33%). The least common site of occurrence was on commissure of lip and vestibule having 1 (1.66%) of RAS each. T Matsuda et al stated that ulcers are confined to the non-keratinized mucosa of the mouth regardless of the type of RAS occurring more commonly on buccal mucosa and labial mucosa, followed by maxillary and mandibular sulci, non-attached gingiva, and floor of the mouth, ventral surface of the tongue, soft palate and tonsillar fauces.[26] The site for occurrence of recurrent aphthous ulcer in the present study was in accordance with the previous studies as 80% of the RAS were those occurring on the non-keratinized mucosa.

The present study comprises of 2 follow up visits of the patients on day 3 and day 7 i.e., 1st and 2nd visit respectively. On comparing the mean size of the ulcers at different time interval among the subjects in group A (placebo), group B (aloe Vera) and group C (triamcinolone acetonide) there was an overall improvement in the mean size and pain score for the ulcers at Day 3 and Day 7 which was statistically significant ($p < 0.001$) suggesting that all the 3 therapeutic modalities were effective in reducing the ulcer size and alleviating the pain score. [Graph-2,3,4,5 and 6] On

subsequent follow up visits it was observed that on comparing the mean between group B and group C, the patients receiving aloe Vera showed marked reduction in the ulcer size on Day 3 and Day 7 respectively, as compared to triamcinolone acetonide on Day 3 and Day 7 respectively with $p < 0.05$ [Table-1] Our results were similar to Mansur G et al who concluded that aloe Vera was superior in reduction of ulcer size, erythema and exudation when compared to myrrh.[23] Similar results were found by Babae et al who stated that the duration of complete wound healing, pain score, wound size and inflammation zone diameter in the Aloe Vera treated group were significantly lower than the control group ($p \leq 0.05$) on specific time points after treatment.[22] This marked reduction in size could be due to the wound healing properties of aloe Vera which resulted in an overall reduction in the healing duration throughout the study as compared to triamcinolone acetonide.

In the present study on subsequent following visits on comparing the mean between group B (Aloe Vera) and group C (triamcinolone acetonide) it was observed that triamcinolone acetonide showed marked reduction in the pain score with a mean and standard deviation of 1.40 ± 1.14 and 0.05 ± 0.22 on Day 3 and Day 7 respectively, as compared to aloe Vera which showed mean and standard deviation of 2.65 ± 1.79 and 0.10 ± 0.31 on Day 3 and Day 7 respectively, which was statistically significant ($p < 0.05$)[Table 1 and 2].

Triamcinolone acetonide showed initial effective reduction in pain score whereas aloe Vera had a more sustained and long-lasting effect. This difference might be due to recognized feature of the steroid in reducing pain. [18] Similarly, in a study done by Rhodus and Bereuter 20% of patients treated with triamcinolone acetonide reported pain reduction in the first 3 days of treatment. [28]

In this study the effectiveness index of reduction in ulcer size and pain score between Aloe Vera, Triamcinolone acetonide and placebo on day 3 and day 7 was not significant with similar MIR and IR values [Table 3 and 4]. Manifer et al reported no changes in the effectiveness index of pain reduction of ulcer in between turmeric and triamcinolone acetonide in the initial visit and towards the 7th day turmeric showed better improvement. Similar results were found in reduction of the size of the ulcer. [29]

The overall, effects of aloe Vera on RAS lesions is considered curative as it decreased the healing time to less than seven days.[22]The immunomodulatory roles of some polysaccharides in AloeVera (A.V) gel is a possible mechanism involved in its anti-inflammatory properties that could facilitate the wound healing process as well.[30]Acemannan; a mucopolysaccharide derived from A.V.gel, has shown immunomodulatory properties and might have a major contribution in A.V. wound healing effects.[31]Even though steroids are found to be more potent in reducing the duration and pain of aphthous ulcers, they come with certain adverse drug reactions. Aloe Vera on the other hand being a natural product serves to be a safer and better choice. The highly selective character of the sample studied, and the relatively small population investigated, makes any comparison with other studies unsafe. Further studies involving larger sample sizes and evaluating the effects of Aloe Vera at the cellular level are recommended in order to understand the mechanism and the efficacy of Aloe Vera on the recurrence of RAS.

Conclusion

In conclusion, the present study findings demonstrate that topical application of the Aloe Vera gel was able to decrease the intensity of pain and reduce the ulcer size there by accelerating the healing without any side effects.

Thus topical Aloe Vera could be safe and a better alternative to topical steroid for RAS.

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