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Original Article

Dentistry Section

Efficacy of Rebamipide and Levamisole in the Treatment of Patients with Recurrent Aphthous Ulcer - A Comparative Study

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ABSTRACT

Context (Background): Recurrent aphthous stomatitis is an inflammatory condition of unknown aetiology characterized by painful recurrent, single or multiple ulcerations of the oral mucosa.

Aims: To compare the efficacy of rebamipide, a gastro-protective agent and levamisole, an immunomodulating agent in the treatment of recurrent aphthous stomatitis.

Materials and Methods: Hundred patients diagnosed with recurrent aphthous stomatitis were enrolled in the study. Fifty patients were assigned randomly to each of the two treatment groups. After the clinical diagnosis and ulcer measurement, a subjective evaluation of symptoms was done for each subject. Both the drugs were given orally at specified intervals. Ulcer measurements and subjective evaluations were made at day one.

Statistical Analysis: Analysis was done using various test like Mann Whitney and t-test.

Results and Conclusion: The overall results showed mean number of episodes whose values were not statistically significant (p=0.43), neither were the mean number of ulcers (p=0.75), or values for mean size of ulcers (p=0.91). However, the overall results suggested that efficacy of rebamipide is almost same as that of the efficacy of previously proved drug levamisole. The current study with a three months follow up, including patients with high scores of pain, aphthae count, ulcer size and frequency of occurrence showed better results in both the study groups. However, rebamipide is suggested to be well tolerated and may therefore be useful in the treatment and prevention of frequently recurrent aphthous ulcers not restricted to Behcet's disease.

Keywords: Aphthous ulcer, Behcet's disease, Levamisole, Oral ulcer, Rebamipide

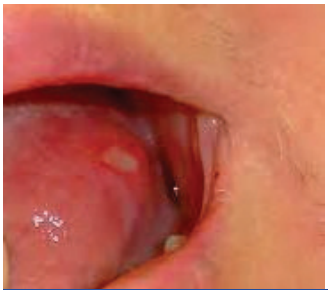
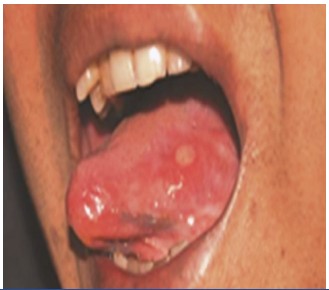
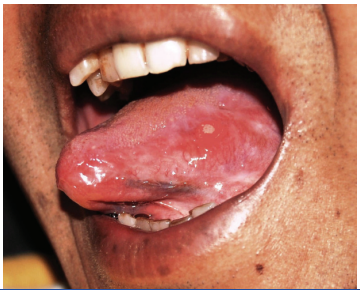
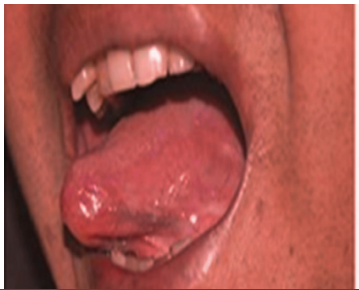
INTRODUCTION

Recurrent aphthous stomatitis (RAS) is a common condition characterized by multiple recurrent small, round or ovoid ulcers with circumscribed margins, erythematous haloes, and yellow or grey floors. It typically presents first in childhood or adolescence [1], being one of the common diseases affecting non keratinized oral mucosa. The aetiology of RAS is not entirely unblemished. Despite many studies have been attempted to identify a causal microorganism for RAS, it does not support an infectious source [2]. Due to this lack of knowledge about the causative factor of RAS, various drugs have been tried and tested to cure RAS. Rebamipide is a known gastroprotective drug that has been successfully used in cases of gastric ulcers, while levamisole is one of the immunomodulators. As RAS is considered to be an immune-mediated disorder, pilot study was conducted to determine the response of patients with RAS to treatment with rebamipide, and with levamisole. The study also aimed to evaluate and compare the efficacy of the two drugs in the treatment of RAS.

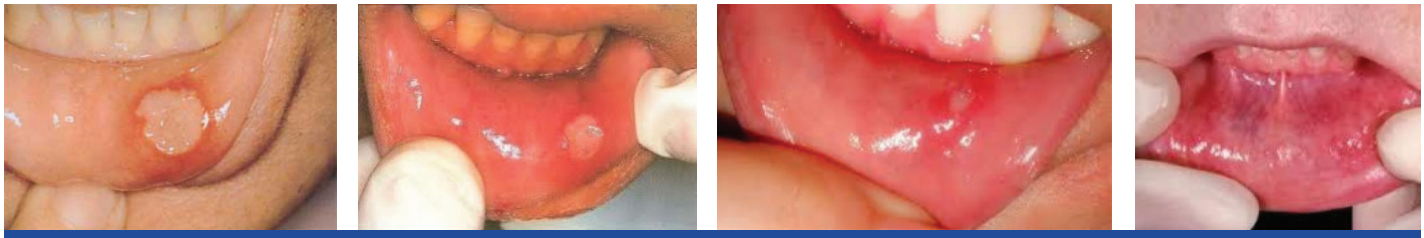
MATERIALS AND METHODS

The current pilot study included in all 100 patients suffering with RAS, with an age group from 15 y and above. Only those patients who gave a history of recurrence of aphthous stomatitis atleast every two months; patients in whom the initial presenting lesions were not more than three days old and patients who were not under any medication for the condition either previously or throughout during the trial period were included in the study. Pregnant or lactating women and females in their child bearing age group; patients with known or suspected history of hypersensitivity to any of the ingredients of the preparation of the drugs used; patients with history of chronic systemic diseases like renal or liver dysfunction or any other condition considered risky by the clinician were excluded from the study.

The patients were principally divided into 2 study groups, 50 in each group. Provisional diagnosis of recurrent aphthous ulcer was made on the basis of clinical examination described by Stanley [1]. Levamisole was administered orally to the first group of patients at a dose of 50 mg thrice daily for three consecutive days per week for three weeks. Rebamipide was given orally to the second group of patients at a dose of 100mg thrice daily for one week. The day of RAS presentation and drug administration was considered as the first episode. Both the groups were followed up regularly after week one, week two and week three, respectively considered as

[Table/Fig-1a]: Clinical photograph of a recurrent aphthous ulcer on the tongue before treatment with rebamipide **[Table/Fig-1b]:** Clinical photograph of a recurrent aphthous ulcer on the tongue during 1st week of treatment with rebamipide **[Table/Fig-1c]:** Clinical photograph of a recurrent aphthous ulcer on the tongue during 2nd week of treatment with rebamipide **[Table/Fig-1d]:** Clinical photograph of a recurrent aphthous ulcer on the tongue during 3rd week of treatment with rebamipide



[Table/Fig-2a]: Clinical photograph of a recurrent aphthous ulcer on the lower labial mucosa before treatment with levamisole **[Table/Fig-2b]:** Clinical photograph of a recurrent aphthous ulcer on the lower labial mucosa during 1st week of treatment with levamisole **[Table/Fig-2c]:** Clinical photograph of a recurrent aphthous ulcer on the lower labial mucosa during 2nd week of treatment with levamisole **[Table/Fig-2d]:** Clinical photograph of a recurrent aphthous ulcer on the lower labial mucosa during 3rd week of treatment with levamisole

episodes two, three and four. There was no drop-out in the study and all the patients were followed up at regular intervals. Compliance was monitored by asking the patient to record the time at which each drug was taken. Patients administered with rebamipide and levamisole were monitored simultaneously at day one, week one, week two and week three for recording the changes of frequency, duration, size and number of oral recurrent aphthous ulcerations. The changes noticed in the ulcers after administration of the two drugs are depicted in [Table/Fig-1a-d] and [Table/Fig-2a-d], respectively. Response to the treatment was assessed using clinical parameters such as pain due to ulcers, number of ulcers, size of the ulcers and frequency of the ulcers. The pain scores were recorded as per the format containing scoring from 0 to 3 (0- no pain, 1- mild pain, 2- moderate pain, 3- severe pain). Any changes occurring during each episode i.e. the time interval between two follow-ups were noted by the patients themselves. Further follow-up was conducted to check for further recurrence of ulcers.

ETHICS

Ethical committee clearance was obtained from Institutional Ethics Committee, P.M.N.M. Dental College and Hospital, Bagalkot, Karnataka, prior to this study (No: 57/2013).

STATISTIC ANALYSIS

Data are presented as mean, standard deviation (SD) and 95% confidence interval (CI) of the mean difference. Comparison of clinical parameters between the groups was carried out by Pairwise comparison done by using Student's unpaired t-test. Chi square test has been used to find the significant association of study parameters between the groups. Correlation between variables carried out by using Pearson's correlation coefficient 'r'. All levels of significance were set at $p < 0.05$.

Following formulae were applied to calculate mean, SD and t-values:

Mean = $\Sigma x/n$

SD = $\sqrt{[\Sigma (x - x)^2]/n}$

x = variable; x = mean; n = no. of samples; Σ = summation

Student's t- test, $t = \frac{x_1 - x_2}{SE(x_1 - x_2)}$

$SE(x_1 - x_2) = S = \sqrt{[1/n_1 + n_2]}$

S = combined standard deviation

Mann-Whitney U-test was applied to find out pair wise comparison between two genotype groups.

RESULTS

The results obtained in the current study have been tabulated as follows [Table/Figure 3-6].

DISCUSSION

Definitive treatment of RAS is an enigma, which has puzzled the medical and dental professions since the recognition of the condition. Because of the multiple theories of cause, the treatment of RAS varies considerably. Many medications including antibiotics, corticosteroids, vitamins, and levamisole have been employed in the treatment of RAS [3,4]. Locally, topical an aesthetics and analgesics, topical steroids in the form of cream or lotions, tetracycline suspension, medicated toothpaste with enzymes amynoglucosidase, are standard treatment in simple cases of RAS. However, in severe cases, topical modalities fail to decrease the interval between the attacks. Hence, systemic immunomodulatory agents have been employed in resistant cases of major RAS or aphthosis with systemic involvement [5].

Levamisole is an antihelminthic drug, a compound that possesses a wide variety of immunological effects both in vivo and in vitro. Since levamisole acts apparently as an immunosuppressant at prolonged dosages, and as an immunopotentiator at lower dosages or on intermittent administration, it has been designated as an immunomodulator. Therefore, levamisole has been used in clinical trials in the therapy of RAS. However, its immunomodulating effect on the immune system of patients of RAS has not been established [6-8].

Rebamipide, a gastro protective agent, is recommended as a long-term treatment for recurrent oral aphthous ulcers. Rebamipide is often used to treat Behcet's disease, an inflammatory disease involving chronic recurrent oral aphthous ulcers (aphthae), uveitis,

Group	N	Mean	SD	t-value	p-value	Significance
Rebamipide	50	2.40	0.76	0.7794	0.4376	NS
Levamisole	50	2.28	0.78	0.7796	0.4377	NS

[Table/Fig-3]: Comparison of Rebamipide and Levamisole groups with respect to mean number of episodes by t-test, *NS = not significant*

Variable	Group	N	Mean	SD	t-value	p-value	Significance
Episode 1	Rebamipide	50	3.12	0.85	0.3095	0.7576	NS
	Levamisole	50	3.06	1.08	0.3090	0.7579	NS
Episode 2	Rebamipide	50	1.58	0.50	1.4000	0.1647	NS
	Levamisole	50	1.44	0.50	1.3998	0.1643	NS
Episode 3	Rebamipide	50	0.56	0.54	0.3689	0.7130	NS
	Levamisole	50	0.52	0.54	0.3683	0.7127	NS
Episode 4	Rebamipide	50	0.16	0.37	1.6025	0.1123	NS
	Levamisole	50	0.06	0.24	1.6023	0.1127	NS

[Table/Fig-4]: Comparison of Rebamipide and Levamisole groups with respect to mean number of ulcers according to episode wise by t-test

Period	Group	n	Mean	SD	t-value	p-value	Significance
1 day	Rebamipide	50	1.2254	0.8147	1.3327	0.1857	NS
	Levamisole	50	1.0198	0.7254	1.3324	0.1852	NS
1 week	Rebamipide	50	0.6987	0.4874	-0.1134	0.9100	NS
	Levamisole	50	0.7099	0.5004	-0.1131	0.9103	NS
2 week	Rebamipide	50	0.3654	0.3214	-1.2225	0.2245	NS
	Levamisole	50	0.4421	0.3058	-1.2221	0.2239	NS
3 week	Rebamipide	50	0.0654	0.0552	-0.6321	0.5291	NS
	Levamisole	50	0.0748	0.0895	-0.6326	0.5293	NS

[Table/Fig-5]: Comparison of Rebamipide and Levamisole groups with respect to size of ulcers at different time points by t-test

Period	Group	Sum of ranks	U-value	Z-value	p-value	Significance
1 week	Rebamipide	2507.50	1234.50	-0.1210	0.9043	NS
	Levamisole	2542.50	1232.50	-0.1206	0.9040	NS
1 week	Rebamipide	2700.00	1077.00	-1.2071	0.2281	NS
	Levamisole	2350.00	1075.00	-1.2064	0.2277	NS
2 week	Rebamipide	2574.00	1203.00	-0.3373	0.7351	NS
	Levamisole	2476.00	1201.00	-0.3378	0.7355	NS
3 week	Rebamipide	2650.00	1123.00	-0.8620	0.3883	NS
	Levamisole	2400.00	1125.00	-0.8617	0.3888	NS

[Table/Fig-6]: Comparison of Rebamipide and Levamisole groups with respect to pain due to ulcers at different time points by Mann-Whitney U-test (Non-parametric)

skin lesions and genital ulcers. But, it might also be useful in preventing and treating frequently recurrent oral aphthous ulcers generally, as suggested by Kudur et al., [9]. The drug improves both aphthae count and pain score, and is also well tolerated and easily administered. It acts by the decrease in oxygen radicals, increase in blood flow and production of protective prostaglandins in ulcer mucosa, which accelerates the process of healing [9]. The investigators assessed the efficacy of rebamipide in patients with Behcet's disease whose main symptom was oral aphthosis [10,11].

The present pilot study group comprised of 100 cases that were diagnosed as recurrent aphthous ulcers made on the basis of clinical examination described by Stanley [1]. RAS has been described under three different clinical variants as classified by Stanley.

Minor RAS is also known as Miculicz's aphthae or mild aphthous ulcers. It is the most common variant, constituting 80% of RAS. Ulcers vary from 8 to 10 mm in size and are most commonly seen on the non-keratinized mucosal surfaces like labial mucosa, buccal mucosa, and floor of the mouth. These ulcers heal within 10–14 d without scarring [7].

Major RAS is also known as periadenitis mucosa necrotica recurrens or Sutton's disease. It affects about 10–15% of patients. Ulcers exceed 1 cm in diameter and the most common sites of involvement are lips, soft palate, and fauces. Masticatory mucosa like dorsum of tongue or gingiva may be occasionally involved. The ulcers persist for up to six weeks and heal with scarring [10].

Herpetiform ulceration is characterized by recurrent crops of multiple ulcers; may be up to 100 in number. These are small in size, measure 2–3 mm in diameter. Lesions may coalesce to form large irregular ulcers and they usually last for about 10–14 d. Unlike herpetic ulcers, these are not preceded by vesicles nor do they contain viral infected cells. These are more common in women and have a later age of onset than other clinical variants of RAS [12].

Maximum patients fall in the age range of 21-25 y that constitutes 47% of the study population. In one study onset of RAS seems to peak between the ages of 10-19 y before becoming less frequent with advancing age [1]. In another study prevalence of RAS was seen in patients below the age of 10 y, whereas no patients were reported below the age of 10 years in the present study [12]. In another study it was documented that in about 80% of patients with RAS the condition develops before 30 y of age and the onset in later years suggests a possibility of definite predisposing factor leading to RAS or that ulceration is not simple RAS, but rather a part of more complex disorder such as Behcet's disease [11].

Most favorable site of occurrence is buccal mucosa with 30% of the total cases, followed by labial mucosa and floor of the mouth that constitutes 20% of the study population. Least common site of occurrence was alveolar mucosa, tongue, gingival and soft palate, constituting only about 7%. According to a study, 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 [11]. RAS spares the dorsum of the tongue, attached gingiva and hard palatal mucosa which are keratinized [10]. The site for occurrence of RAS in the present study was in accordance with the previous studies as 80% of the cases were minor aphthae, those occurring on non-keratinized mucosa.

The present study comprised of 53% male patients and 47% female patients, depicting male predominance. In contrast a study showed a female predominance with prevalence of RAS in males being 48.3% and females being 57.2%[1]. Another study revealed RAS with predilection for females in age group of 10-15 y, at the onset of puberty or after 50 y of age, hormonal changes after menopause being the reason for increased occurrence of RAS in females. RAS most frequently occurs in females as systemic factor associated with RAS like haematinic deficiencies are more common in females of older age group [11], but the present study comprised of majority of patients in younger age group. Another study for decreased incidence of RAS among males states that smoking had inverse relationship with the occurrence of RAS as it causes keratinization and renders the mucosa less susceptible to ulceration [12]. Although no study states clear predilection for males and females. It is the local and systemic factors and genetic predisposition that determines the gender predilection for RAS.

In the present study, maximum patients had minor aphthous ulcers which constituted 80%, 13 major aphthous ulcers constituted 13% and only 7% subjects had herpetiform aphthous ulcers. In an epidemiological survey it was concluded that minor aphthous ulcer is the most common type of RAS and constitutes about 80%. Major aphthous ulcer is about 13% and herpetic form 7% in accordance with the present study [11]. In a study it was documented that minor aphthous ulcer constitutes 75-85% of total RAS cases whereas major aphthous ulcer is about 10-15% and herpetiform type is the smallest group with only 5% [13].

The present pilot study has been performed with the gastro protective agent rebamipide to examine its effect on the management of RAS in comparison with an immunomodulating agent levamisole. This showed the rate of marked improvement in aphthae count, pain, size and frequency in both the groups in three months follow up. These findings are similar to the other reported studies.

Sun et al., [10] showed that levamisole can modulate both the serum interleukin (IL)-6 and IL-8 levels in RAS patients. IL-8, like IL-6, is also a useful serum marker in evaluating therapeutic effects of levamisole on RAS patients. The reason for the above could be healing of RAS lesions after levamisole therapy may give rise to a reduction of the number of altered keratinocytes that can secrete IL-8 in the local lesional tissues [2].

Matsuda et al., [11] concluded that rebamipide is well tolerated and improves the aphthae count and pain score in Behcet's disease patients. It may therefore be useful in the treatment and prevention of frequently recurrent oral aphthous ulcers (not restricted to Behcet's diseases). Administration of rebamipide is not cumbersome, and it does not cause any discomfort, which, corticosteroid ointments for example may do; there are no specific adverse drug reactions. Rebamipide is therefore recommended as a long-term treatment for recurrent oral aphthous ulcers [12].

Ishiyama et al., [13] conducted a study to confirm the effect of rebamipide on experimentally induced stomatitis in a rat acetic acid induced oral ulcer model. Buccal mucosal lesions were induced by local injection of 50µl of 99.7% acetic acid into the buccal mucosa, which produced a single large ulcer in each of the treated rats. The ulcer remained up to 14 d. Repeated dose of rebamipide (3-100 mg/kg) dose-dependently decreased the ulcer area [13]. Histopathologically, increased fibrosis and regenerated epithelium were observed in the rebamipide-treated group. In contrast, indomethacin, a cyclooxygenase inhibitor, impaired the healing of ulcers. They have successfully established an improved method

for the administration of acetic acid to induce oral ulcers, and rebamipide accelerated the ulcer healing [14].

Due to the unknown aetiology of RAS most of the treatment is symptomatic. Literature shows that aphthous ulcers are best treated with levamisole as it decreases healing time, pain, number, size and prevents recurrence. Though the clinical efficacy of rebamipide has shown reduced pain, number, size and frequency of recurrent aphthous ulcers, it is in par with levamisole but lacks literature documentation [13]. An efficient as well as diagnostic value for both the drugs has been proposed in the current pilot study with certain limitations.

CONCLUSION

Based on the inherent difficulties associated with treatment of aphthous ulcers, the clinician should individualize treatment to each patient by considering a number of relevant factors, including the potential psychological benefits of treatment, the degree of patient discomfort experienced, the probability of patient compliance with required application procedures and trade-offs between the enhanced rate of recovery and the economic burden of purchasing the treatment. Levamisole and rebamipide are, thus suggested to be effective drugs in treatment of RAS. In conclusion, the findings of the study put forward the need for extensive studies to be conducted to evaluate the clinical efficacy of these two drugs using similar clinical parameters with control groups.

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