

TO EVALUATE THE EFFICACY OF REBAMIPIDE ON CLINICAL RESOLUTION AND RECURRENCE OF MINOR RECURRENT APHTHOUS STOMATITIS

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ABSTRACT:

Introduction: Recurrent aphthous minor are common recurrent painful ulcerations of the oral mucosa. The efficacy of Rebamipide, a gastroprotective drug, against recurrent aphthous minor was prospectively investigated.^[1,2,24,42]

Material And Methods: A single-blind, placebo-controlled study, 60 patients with recurrent aphthous minor, were randomised to receive rebamipide 300 mg/day or placebo for 7 days between December 2012 and octomber 2012. Oral aphthous minor count and pain score were recorded on first visit (day 0), second visit (day7) and third visit (day 60). The pain score was measured by visual analog scale.

Result And Discussion: Rebamipide showed a statistically significant higher efficacy rate than Placebo in terms of clinical resolution i.e. reduction in size of ulcers, reduction in pain score and rate of recurrence of minor recurrent aphthous stomatitis. No adverse events were reported with use of Rebamipide. Rebamipide is therefore recommended as a treatment for recurrent oral aphthous ulcers.

Keywords: Minor recurrent aphthous stomatitis, Rebamipide, clinical resolution, pain scores, recurrence, Visual Analog Scale.

INTRODUCTION:

Minor recurrent aphthous stomatitis is a common oral disease. Minor recurrent aphthous stomatitis are common superficial recurrent ulcerations of the nonkeratinized oral mucosa. The ulcer size is between 2 mm - 10 mm. The appearance of the lesion is that of an erythematous halo with yellowish or grayish centre. Pain is the obvious characteristic symptom of the lesion. It will be painful and last about 10-14

days.^[11,12] The exact cause of aphthous ulcers is unknown.^[1,2,24]

It causes pain, which worse by eating, drinking and talking. This disrupts the day to day functioning of an individual.^[6,12] Therapeutic options for Minor recurrent aphthous stomatitis include management with topical anesthetic agent, corticosteroids, antibiotics, immunomodulators and

others. But recurrence is seen after stoppage of treatment.^[12]

Rebamipide is a cytoprotective agent. Rebamipide was selected as the most effective drug for gastric ulcer healing. It is well tolerated and improves the gastric ulcer and pain score with no specific adverse drug reactions. This drug stimulates prostaglandin generation in gastric mucosa and improves not only the speed but also the quality of ulcer healing. In addition, it increases gastric mucus glycoprotein components, stimulates migration and proliferation of wounded epithelial cell monolayers, increases expression of epidermal growth factor and its receptor in normal and ulcerated gastric mucosa, and scavenges active oxygen radicals. The drug also attenuates the activity of neutrophils and that leads to ulcer healing.^[41,42,62]

Therefore, this study was conducted to assess the potential of Rebamipide in resolution and prevention of recurrence of minor recurrent aphthous stomatitis.

MATERIALS AND METHODS

AIMS:

1) To study the effect of Rebamipide on clinical resolution, pain scores & recurrence of minor recurrent aphthous stomatitis.

2) To study the effect of Placebo on clinical resolution, pain scores & recurrence of minor recurrent aphthous stomatitis.

3) To compare the roles of Rebamipide and Placebo on clinical resolution, pain scores & recurrence of minor recurrent aphthous stomatitis.

4) To record adverse events if any, associated with short term use of Rebamipide.

OBJECTIVE: Minor recurrent aphthous stomatitis causes varying degrees of pain and recurrence in patients. Over the years, many drugs have been tried, but are not satisfactory in resolving and preventing recurrence of these ulcers. Therefore, this single blind study was undertaken to explore the efficacy of Rebamipide in resolution of minor recurrent aphthous stomatitis ulcers and reducing their rate of recurrence and also to check the safety of the drug as a therapeutic option in this condition.

The trial was conducted in the department of Oral Medicine and Radiology, Bharati Vidyapeeth Deemed University Dental College and Hospital, Pune. Minor recurrent aphthous stomatitis, which was diagnosed on the basis of history and clinical examination, was considered for inclusion in the study. Total 60 individuals became participants for the study, out of which 30 patients randomly were given tablet Rebamipide and remaining 30 patients were given placebo and following outcomes were evaluated:

1. Duration of clinical resolution of minor recurrent aphthous stomatitis ulcers.

2. Reduction in pain scores using a ten point visual analog scale (VAS).

3. Reduction in rate of recurrence of minor recurrent aphthous stomatitis.

Pre-designed case record forms were used to record all the data.

STUDY POPULATION:

The target population for the prospective clinical trial included all self reporting cases to the Department of Oral Medicine and Radiology.

CRITERIA FOR SELECTION:

1. Inclusion criteria

- Patients within the age group of 18-50 years.
- Patients, who were capable of understanding the supplied information.
- Those who gave informed consent to participate in the study and agreed to report for follow-ups on the designated dates.

2. Exclusion criteria

- Pregnant and lactating women.
- Individuals with oral ulcers due to trauma.
- Patients taking any other medication.

Patients were enrolled as participants into the trial, subject to fulfilment of criteria mentioned above.

METHODOLOGY:

1. Patients reporting with painful sensation on the oral mucosa or referred for evaluation of oral lesions from other departments were examined and diagnosis was made after history and clinical examination.

2. From among these patients, only those fulfilling the inclusion criteria were considered for participation and were explained the need and procedure of the study. An informed consent was obtained from each participant.

3. Instructions were given to participants and information.

4. Total 60 individuals became participants for the study, out of which 30 patients randomly formed the study group and were given a commercially available TABLET REBAGEN 100mg (REBAMIPIDE 100 mg, Macleods Pharmaceuticals Ltd.®) and remaining 30 patients formed the control group and were given placebo. All participants were unaware of the contents of `medicine` they were advised to take.

5. The Placebo tablet having the same size, shape and colour like that of Rebamipide drug. It was prepared at POONA COLLEGE OF PHARMACY PUNE and contained the following excipients:

- Lactose I.P
- Starch I.P
- Talc I.P
- Magnesium stearate I.P

6. After noting down the size, location of ulcers and pain scores, at first visit (Day 0) every patient was asked to take the given tablet three times daily for 7 days. Effects of the Rebamipide and Placebo on clinical resolution of the minor recurrent aphthous stomatitis and its symptoms were studied after 7 days. This visit was considered as the second visit (Day 7). Effects of the Rebamipide and Placebo on recurrence of minor recurrent aphthous stomatitis were studied after 60 days or on the day of recurrence before Day 60. This was considered as the third visit.
7. The interventional material (Rebamipide or Placebo) and instructions for its use were delivered to the participants at first visit. The interventional material was given in plastic packet [figure: 1(A)]. Placebo similar in colour and size to that of active drug was also given in plastic packet [figure: 1(B)]. Every patient was given 21 tablets of either Rebamipide or placebo.
8. Participants were interviewed and examined for occurrence of adverse effects like constipation, bloating, diarrhea, nausea, vomiting, rash and pruritus.

CRITERIA FOR ASSESSMENT OF OUTCOMES:

1. For the purpose of this trial, complete clinical resolution was defined as total disappearance of a lesion. Also, site of the lesion and its size in millimeters (mm) was recorded at first visit (Day 0), size was measured again at second visit

(Day 7) and site and size of recurrent lesion if any, was noted at the third visit (before / on Day 60). The dimensions of the lesions were measured by adapting a dental floss across largest dimension of the lesion and the length of floss then being determined on the measuring scale [figure: 2(A&B)].

2. The pain sensation in each participant was recorded on a ten point Visual Analog Scale (VAS) at every visit.

Visual Analog Scale (VAS) has been described by D. Gould et al⁶³ to convert the subjective symptom / characteristic or attitude of persons to pain, into an objective measurement.

“Operationally a VAS is usually a horizontal line, 100 mm in length, anchored by word descriptors at each end, as illustrated below. The patient marks on the line the point that they feel represents their perception of their current state. The VAS score is determined by measuring in millimetres from the left hand end of the line to the point that the patient marks.”⁶³



3. To observe and record adverse events, if any, associated with use of Rebamipide.

ARMAMENTARIUM USED FOR CLINICAL EVALUATION (FIGURE: 3):

- Stainless steel tray
- 2 mouth mirrors
- Tweezers
- Metallic scale
- Sterile cotton
- Disposable gloves
- Disposable face mask
- Dental floss

DATA ANALYSIS AND STATISTICS

The data entered in the proforma was tabulated, sorted and analysed statistically in view of the aims and objectives of the study using the Mann-Whitney U test and Chi-Square test.

The sample analysed in the present trial consisted of minor recurrent aphthous stomatitis patients and considering the eligibility as per the inclusion criteria, 60 patients were considered for the trial. Out of which 30 patients formed the study group and were given a commercially available Tablet Rebagen 100mg (Rebamipide 100 mg, Macleods Pharmaceuticals Ltd.®) and remaining 30

patients formed the control group and were given placebo. All patients completed the process of informed consent and thus became participants to the trial. Demographic and study parameters data were gathered as per the predesigned proforma.

Minor recurrent aphthous stomatitis is not a life threatening disease and stress appears to play an important role in formation of minor recurrent aphthous stomatitis. Placebo was used to manage minor recurrent aphthous stomatitis in the control group, which may be helpful to reduce this factor.

At first visit every patient was asked to take given tablet three times daily for 7 days. Participants were assessed on Day 7 and on Day 60 or on the day of recurrence, whichever was earlier.

The outcomes assessed were:

1. Complete clinical resolution of minor recurrent aphthous stomatitis ulcers.
2. Reduction in pain scores using a ten point visual analog scale (VAS).
3. Reduction in rate of recurrence of minor recurrent aphthous stomatitis.

Adverse events if any, associated with short term use of Rebamipide were also recorded.

The data recorded on first visit (Day 0) was the number, location, size of ulcers

in millimetres (mm) and scores for pain on the Visual Analog Scale (VAS).

The data recorded on second visit (Day 7) was in terms of ulcer number, size and pain sensation.

At third visit effects of the Rebamipide and Placebo on recurrence of minor recurrent aphthous stomatitis were recorded on / before Day 60.

Drugs associated adverse events, if any, were recorded during the course of the trial.

RESULT:

Table 1 and Graph 1 show that, out of 30 patients in the study group 27 patients had single ulcer in oral cavity and only 3 patients had two ulcers in oral cavity at first visit.

Table 2 and Graph 2 show that the mean ulcer size was 4 mm at Day 0, which completely disappeared (size 0 mm) at Day 7 in the study group. In the control group the mean ulcer size was 5 mm at Day 0, which decreased to 2 mm at Day 7. (p value < 0.05, Mann-Whitney U test).

Table 3 and Graph 3 shows the mean VAS score for ulcer pain was 2 at Day 0, which was reduced to 0 at Day 7 in the study group. In the control group the mean VAS for ulcer pain was 2 mm at Day 0, which was decreased to 1 at Day 7. (p value < 0.05, Mann-Whitney U test).

Table 4 and Graph 4 shows, recurrence of minor recurrent aphthous stomatitis was prevented in 26 patients of the study group and recurrence was seen in remaining 4 patients of the study group in 2 months. Table and Graph also showed, recurrence of minor recurrent aphthous stomatitis was prevented in only 7 patients of the control group and recurrence was seen in remaining 23 patients of the control group in 2 months. (p value < 0.05, Chi-square test).

DISCUSSION:

The results of this single blind, randomized Placebo-controlled study demonstrate that, Rebamipide showed a statistically significant higher efficacy rate than the Placebo in terms of, clinical resolution i.e. reduction in size (figure 4&5), reduction in VAS score for pain and reduction of recurrence of minor recurrent aphthous stomatitis.

No adverse events were reported with use of Rebamipide given three times daily for one week.

Over the years, many drugs have been tried, but are not satisfactory in resolution and prevention of recurrence of minor recurrent aphthous stomatitis.

Rebamipide stimulates prostaglandin & endothelial growth factor generation in mucosa. It also scavenges active oxygen radicals and attenuates the activity of neutrophils; and that leads to ulcer healing.^[41,42,62]

In this single blind randomized study, the effect of Rebamipide on clinical resolution, pain scores & recurrence of ulcers in minor recurrent aphthous stomatitis was evaluated. Total 60 individuals became participants for the study, out of which 30 patients randomly formed the study group and were given Rebamipide 100 mg and remaining 30 patients formed the control group and were given placebo. At first visit (Day 0) the location, number, size and pain scores of ulcers were recorded. Patient was asked to take the given tablet three times daily for seven days. Patient was recalled after completion of the course of medicine. Effects of Rebamipide and Placebo on clinical resolution and pain scores of minor recurrent aphthous stomatitis ulcers were checked on Day 7. This visit was considered as the second visit. Patients were advised to report immediately, if they noticed any recurrent ulcer and if there was no recurrence, they were recalled after 60 days. This was marked as the third visit.

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This time participants were interviewed and examined for occurrence of adverse events due to consumption of drug.

Rebamipide showed a statistically significant higher efficacy rate than Placebo in terms of, clinical resolution i.e. reduction in size of ulcer, reduction in pain score and rate of recurrence of minor recurrent aphthous stomatitis.

CONCLUSION:

Our study was carried out with seven days regime of 300 mg Rebamipide per day. Minor recurrent aphthous stomatitis patients were benefitted in terms of, reduction in size of ulcer, reduction in pain score and rate of recurrence of by this regimen. No adverse events were reported with short term use of Rebamipide.

ACKNOWLEDGMENT:

I extremely & gratefully acknowledge Poona College of Pharmacy Pune, for providing tablet Placebo of similar size and colour to that of tablet Rebamipide.

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TABLES:

Figure: 1

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Rebamipide tablets in plastic packet

(A)



Placebo tablets in plastic packet

(B)

(B)

Figure: 2



Measurement of the longest dimension of lesion by adapting dental floss across the lesion. Length of floss being determined on the measuring scale.

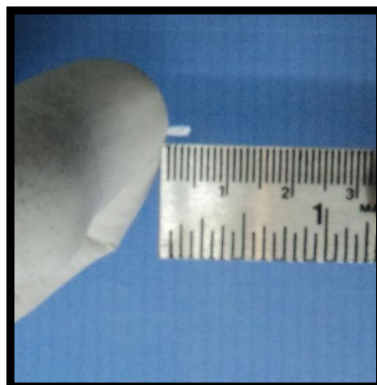


Figure: 3
Armamentarium



FIGURE: 4 STUDY GROUP

First visit: Two ulcers measuring 2mm. and 3mm. in diameter seen on ventral surface of tongue bilaterally.



Second visit: Complete resolution of ulcers.



FIGURE: 5 CONTROL GROUP

First visit: Single 2mm. sized ulcer seen on left side of maxillary labial mucosa.



Second visit: Reduction in size of ulcer to 1mm.

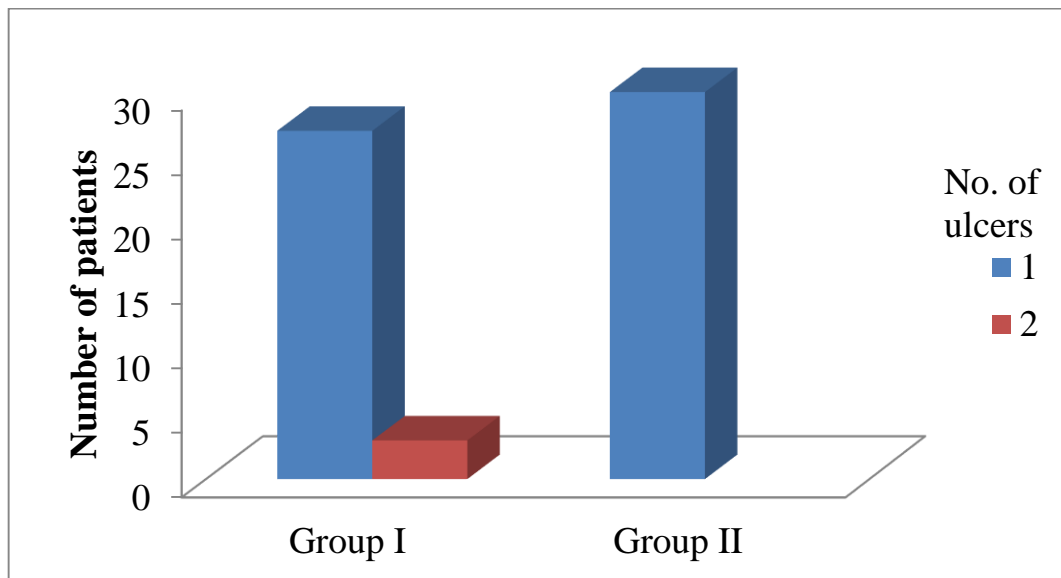


ULCER COUNT IN PATIENTS

TABLE 1

Visit	Group	Number		Total
		1	2	
First	Group I	27	3	30
	Group II	30	0	30

GRAPH 1

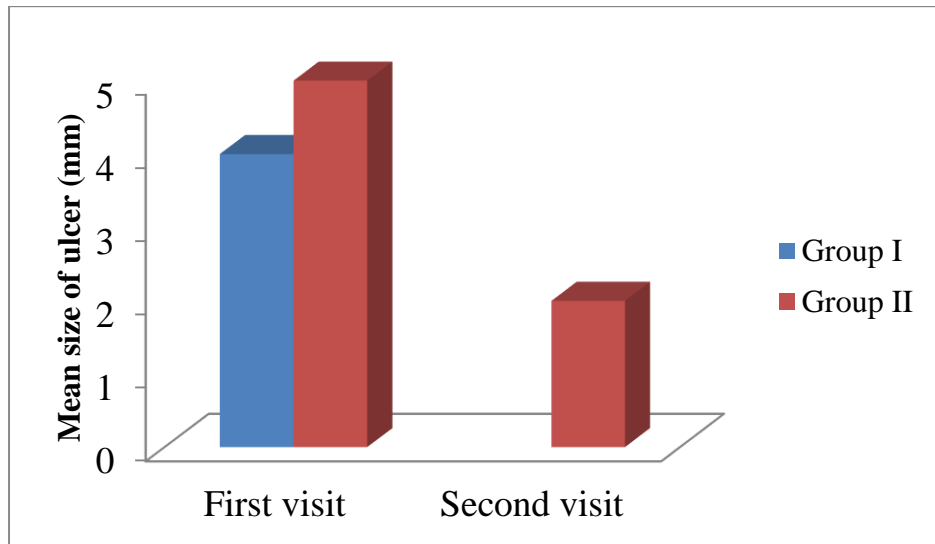


REDUCTION IN SIZE OF ULCERS

TABLE 2

Visit	Mean Size of ulcer (mm)	
	Group I	Group II
First	4	5
Second	0	2

GRAPH 2

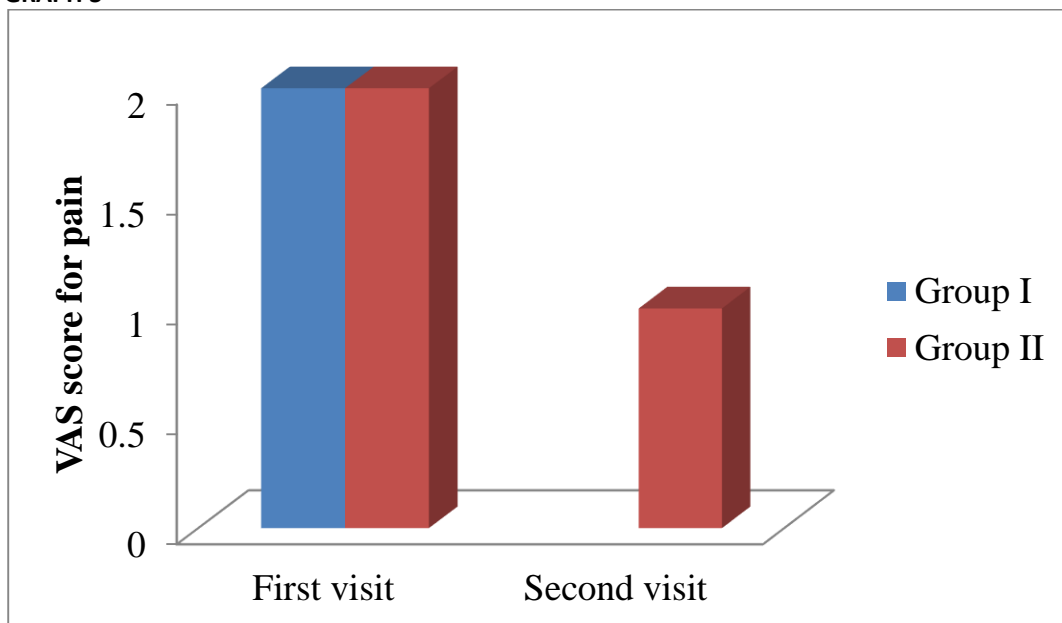


VAS SCORE FOR PAIN

TABLE 3

Visit	mean VAS score	
	Group I	Group II
First	2	2
Second	0	1

GRAPH 3



RECURRENCE OF ULCER

TABLE 4

	Recurrence		Total
	Yes	No	
Group I	4	26	30
Group II	23	7	30

GRAPH 4

