

**Efficacy of Rebamipide Therapy in Aphthous Ulcers: A Prospective Study**Amrutha V Das<sup>1</sup>, Anchal Kumar Jain<sup>2</sup>, Aditya Goel<sup>3</sup>, Indraprakash Prajapati<sup>4</sup>, Rimsha Khan<sup>5\*</sup><sup>1</sup>MS-ENT, Senior Resident, Department of ENT, Chirayu Medical College, Bhopal, Madhya Pradesh, India<sup>2</sup>MS-ENT, MGM Medical College, Indore, Madhya Pradesh, India<sup>3</sup>MS-ENT, Gandhi Medical College, Bhopal, Madhya Pradesh, India<sup>4</sup>MS-ENT, MGM Medical College, Indore, Madhya Pradesh, India<sup>5</sup>MS-ENT, Senior Resident, Department of ENT, Chirayu Medical College, Bhopal, Madhya Pradesh, India

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**Abstract:****Background:** Recurrent aphthous stomatitis (RAS) poses a considerable challenge within the Otorhinolaryngology domain, impacting patients' quality of life.**Aim and Objectives:** This prospective study aimed to assess the efficacy of Rebamipide therapy in managing RAS over 3 months.**Methods:** A cohort of 60 patients with recurrent aphthous ulcers was enrolled, receiving Rebamipide therapy orally in a Tertiary care center of Central India. Clinical evaluations, pain scores, and ulcer healing rates were recorded at baseline, 1 month, 2 months, and 3 months. Statistical analyses were conducted to assess changes over time.**Results:** Rebamipide therapy demonstrated a significant reduction in the frequency and severity of aphthous ulcers, with pain scores decreasing progressively over the 3-month period. Ulcer healing rates exhibited a consistent upward trend, reaching substantial levels by the study's conclusion. Adverse events were minimal, with 5% of patients reported gastrointestinal discomfort.**Conclusion:** This study contributes evidence supporting Rebamipide as an effective and well-tolerated therapeutic option for RAS. Positive outcomes regarding reduced ulceration, improved pain scores, and enhanced ulcer healing rates underscore its potential clinical utility.**Keywords:** Aphthous Ulcers, Rebamipide Therapy, Recurrent Aphthous Stomatitis, Pain Scores, Ulcer Healing.This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.**Introduction**

Recurrent aphthous stomatitis (RAS), a common disorder affecting the oral mucosa, represents a significant clinical challenge in Otorhinolaryngology. Characterized by recurrent, painful ulcers with distinct clinical features, RAS imposes a substantial burden on affected individuals due to its recurrent nature and associated discomfort. [1] Despite being benign, the recurrent nature of these ulcers can severely compromise oral function, nutritional intake, and overall quality of life. Traditional therapeutic approaches have yielded varied success, prompting the exploration of novel interventions to alleviate symptoms and enhance the healing process. [2]

Rebamipide, a quinolinone derivative initially developed for treating gastric ulcers, has gained attention for its mucosal protective properties. [3, 4] While most studies have focused on its efficacy in gastrointestinal conditions, limited research has

investigated its potential role in managing oral mucosal disorders, particularly recurrent aphthous ulcers. Rebamipide therapy's rationale is its ability to stimulate mucin and prostaglandin synthesis, enhance mucosal defense mechanisms, and promote tissue repair. [5]

Given the dearth of comprehensive studies in the field of Otorhinolaryngology exploring the effectiveness of Rebamipide in treating recurrent aphthous ulcers, this prospective study aims to bridge this gap by investigating the therapeutic potential of Rebamipide in a cohort of 60 patients over a 3-month duration. By evaluating clinical outcomes, pain scores, and ulcer healing rates, this research contributes valuable insights into the potential role of Rebamipide as a novel therapeutic option for patients suffering from recurrent aphthous stomatitis within the ENT setting. The findings of this study may not only enhance our understanding

of the pathophysiology of RAS but also pave the way for improved management strategies that align with the goals of providing symptomatic relief and fostering rapid ulcer resolution.

### Materials and Methods

In this prospective, single-center, open-label study, the efficacy of Rebamipide therapy in managing recurrent aphthous stomatitis was investigated over a 3-month period in a tertiary care center of Central India. Sixty participants, consisting of 32 males and 28 females, diagnosed with recurrent aphthous stomatitis, were enrolled after obtaining informed consent, and the study received ethical approval from the Institutional Ethics Committee.

Participants underwent a specific Rebamipide intervention, involving oral administration at 100 mg orally three tablets per day for 14 days with a gap of 7 days and then again for 14 days till ulcer clears. As this was an open-label study, no control group was included. The primary outcome focused on the reduction in the frequency and severity of aphthous ulcers, with secondary outcomes assessing pain scores and ulcer healing rates.

Clinical evaluations were conducted monthly, encompassing the recording of the number of ulcers and pain scores, while ulcer healing rates were determined at each time point. Data on the number of ulcers, pain scores, and ulcer healing rates were collected through standardized assessments at monthly intervals.

Adverse events, including frequency and severity, were monitored throughout the study. Mild gastrointestinal discomfort, reported by 5% of patients, was the most common side effect, and it did not necessitate treatment discontinuation. Data handling involved recording information in a standardized electronic database with built-in validation checks, and regular quality assurance checks were performed to ensure data accuracy and integrity.

**Statistical Analysis:** Statistical analyses employed descriptive statistics for baseline characteristics, with paired t-tests or Wilcoxon signed-rank tests for within-group comparisons and independent t-tests or Mann-Whitney U tests for between-group comparisons, considering significance at  $p < 0.05$ . The significance level for statistical analysis was set at  $p < 0.05$ .

### Results

Sixty patients with recurrent aphthous stomatitis, comprising 32 males and 28 females, were enrolled in the study. The mean age of the participants was 34.5 years (range: 18 to 55 years). All patients completed the 3-month Rebamipide therapy as per the study protocol.

**Clinical Response:** Clinical evaluation at monthly intervals revealed a progressive reduction in the frequency and severity of aphthous ulcers throughout the study period. Table 1 summarizes the clinical response data at each time point.

**Table 1: Clinical Response to Rebamipide Therapy**

Time Point (Months)	Number of Ulcers (Mean $\pm$ SD)	Pain Scores (Mean $\pm$ SD)
Baseline	3.2 $\pm$ 1.1	7.8 $\pm$ 1.5
1	1.8 $\pm$ 0.9*	5.2 $\pm$ 1.3*
2	1.2 $\pm$ 0.7*†	3.6 $\pm$ 1.0*†
3	0.6 $\pm$ 0.5*††	1.5 $\pm$ 0.8*††

Significant compared to baseline ( $p < 0.05$ ), † Significant compared to month 1 ( $p < 0.05$ ), †† Significant compared to month 2 ( $p < 0.05$ )

Ulcer healing rates increased significantly over the 3 months, with 80% of patients experiencing complete resolution of ulcers by the end of the study.

**Pain Scores:** Patients reported a notable reduction in pain scores following Rebamipide therapy. Table 2 illustrates the trend in pain scores over the study duration.

**Table 2: Pain Scores Over 3 Months of Rebamipide Therapy**

Time Point (Months)	Pain Scores (Mean $\pm$ SD)
Baseline	7.8 $\pm$ 1.5
1	5.2 $\pm$ 1.3*
2	3.6 $\pm$ 1.0*†
3	1.5 $\pm$ 0.8*††

Significant compared to baseline ( $p < 0.05$ ), † Significant compared to month 1 ( $p < 0.05$ ), †† Significant compared to month 2 ( $p < 0.05$ )

**Ulcer Healing Rates:** Table 3 depicts the progressive improvement in ulcer healing rates observed during the study.

**Table 3: Ulcer Healing Rates Over 3 Months of Rebamipide Therapy**

Time Point (Months)	Ulcer Healing Rates (%)
Baseline	0
1	40
2	65
3	80

**Adverse Events:** Rebamipide therapy was well-tolerated, with no reported severe adverse events. Mild gastrointestinal discomfort, the most common side effect, was reported by 5% of patients but did not necessitate treatment discontinuation.

#### Discussion:

The present study aimed to evaluate the effectiveness of Rebamipide therapy in managing RAS within the ENT department, utilizing a prospective design with a 60-patient cohort over a 3-month duration. Our findings revealed a significant reduction in the number and severity of ulcers, an improvement in pain scores, and a high rate of ulcer healing, indicating the potential of Rebamipide as an effective treatment for RAS.

Comparing our results with existing literature, similar positive outcomes were noted in studies investigating Rebamipide's effects on oral mucosal conditions. For instance, Suzuki et al. explored Rebamipide's efficacy in patients with oral mucositis induced by radiotherapy, reporting reduced pain and an accelerated healing process. [6] This aligns with our findings, suggesting that Rebamipide may exhibit consistent mucosal protective properties across oral conditions.

Furthermore, Nakamura et al. investigated Rebamipide in patients with erosive oral lichen planus, revealing a significant reduction in lesion size and improved clinical symptoms. [7] While the etiology of recurrent aphthous stomatitis differs from lichen planus, our study's positive impact of Rebamipide on oral mucosal healing echoes the potential of this agent in managing diverse oral mucosal disorders.

However, it is crucial to acknowledge specific differences between our study and the cited literature. While Suzuki et al. and Nakamura et al. primarily focused on different oral conditions, the present study focused on recurrent aphthous stomatitis. Despite Rebamipide's positive effects on mucosal healing observed in our research, it is essential to note that the mechanisms underlying its efficacy in RAS may differ from those in other oral disorders. The specific pathways by which Rebamipide influences mucin and prostaglandin synthesis, leading to improved mucosal defense and tissue repair, warrant further investigation in the context of RAS.

Another study by Matsuda et al., which investigated the efficacy of rebamipide against oral aphthous

ulcers in 35 patients with Behçet's disease (BD), reported moderate or marked improvement in aphthae count and a 65% reduction in pain. This study concluded that Rebamipide is well tolerated and improves BD patients' aphthae count and pain score. [8]

The variations in study populations, including demographic characteristics, severity of the conditions, and treatment protocols, could also contribute to outcome differences. Additionally, the short-term nature of our study may limit the ability to capture long-term effects or relapse rates associated with Rebamipide therapy in RAS.

Limitations notwithstanding, our study contributes valuable insights into the potential of Rebamipide as a therapeutic option for recurrent aphthous stomatitis within the ENT setting. Larger, multicenter studies with extended follow-up periods are warranted to validate Rebamipide's sustained efficacy and safety in managing RAS. Further research should also explore the specific mechanisms underlying Rebamipide's efficacy in RAS compared to other oral mucosal disorders, providing a more nuanced understanding of its role in routine clinical practice.

#### Conclusion

This prospective study underscores the potential of Rebamipide as an effective and well-tolerated therapeutic approach for managing RAS. The observed reduction in ulcer frequency and severity, coupled with improvements in pain scores and high ulcer healing rates, suggests that Rebamipide holds promise for alleviating the burdensome symptoms of RAS. While our findings align with existing literature on Rebamipide's positive effects in oral mucosal disorders, the study also emphasizes further research to elucidate specific mechanisms and assess long-term outcomes.

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