



## Rebamipide to Manage Stomatopyrosis in Oral Submucous Fibrosis

<sup>1</sup>Joanna Baptist, <sup>2</sup>Shrijana Shakya, <sup>3</sup>Ravikiran Ongole

### ABSTRACT

**Introduction:** Oral submucous fibrosis (OSF) causes progressive debilitating symptoms, such as oral burning sensation (stomatopyrosis) and limited mouth opening. The standard of care (SOC) protocol includes habit cessation, intralesional steroid and hyaluronidase injections, and mouth opening exercises. The objective of the study was to evaluate efficacy of rebamipide in alleviating burning sensation of the oral mucosa in OSF in comparison with SOC intralesional steroid injections.

**Materials and methods:** Twenty OSF patients were divided into two groups [rebamipide (100 mg TID for 21 days) and betamethasone (4 mg/mL biweekly for 4 weeks)] of 10 each by random sampling. Burning sensation was assessed every week for 1 month. Burning sensation scores were analyzed using repeated measures analysis of variance (ANOVA) and paired t-test.

**Results:** Change in burning sensation score was significant ( $p < 0.05$ ) in the first four visits. However, score between the 4th and 5th visit was not statistically significant ( $p > 0.05$ ).

**Conclusion:** Our study has shown that rebamipide can be considered as an effective modality to manage burning sensation in patients suffering from OSF.

**Clinical significance:** Considering stomatopyrosis and trismus as a major cause for inability to eat in OSF, use of newer adjunctive modalities, such as rebamipide will ease patients suffering and also encourage them to consume food.

**Keywords:** Betamethasone, Management, Oral submucous fibrosis, Rebamipide.

**How to cite this article:** Baptist J, Shakya S, Ongole R. Rebamipide to Manage Stomatopyrosis in Oral Submucous Fibrosis. *J Contemp Dent Pract* 2016;17(12):1009-1012.

<sup>1,3</sup>Department of Oral and Maxillofacial Surgery, Manipal College of Dental Sciences, Manipal University, Mangaluru, Karnataka India

<sup>2</sup>School of Dental Medicine, University of Colorado, Denver Colorado, USA

**Corresponding Author:** Shrijana Shakya, School of Dental Medicine, University of Colorado, Denver, Colorado, USA, e-mail: shriju79@gmail.com

**Source of support:** Nil

**Conflict of interest:** None

### INTRODUCTION

Oral submucous fibrosis (OSF) is commonly seen in the Indian subcontinent affecting individuals of all age groups. It is a potentially malignant disorder caused almost exclusively by the use of smokeless form of tobacco products. The malignant transformation rates vary from 3 to 19%.<sup>1,2</sup>

Oral submucous fibrosis causes progressive debilitating symptoms affecting the oral cavity, such as burning sensation, loss of cheek elasticity, restricted tongue movements, and limited mouth opening. Oral submucous fibrosis is an irreversible condition and the management strategies are aimed at alleviating the symptoms. The standard of care (SOC) in managing OSF includes habit cessation, intralesional steroid and hyaluronidase injections, and mouth opening exercises.

Oral submucous fibrosis affects the oral cavity and in severe forms can involve the pharynx. The characteristic symptoms of burning sensation and stiffness of the oral mucosa are debilitating and prevent the affected individual from consuming food. Progressive mucosal stiffness is caused by the fibroelastic changes in the lamina propria and the burning sensation in the oral cavity results from juxtaepithelial inflammation and epithelial atrophy.<sup>3</sup>

In the Southeast Asian region, use of smokeless form of tobacco is very popular among young adults. It is believed that 33% of men and 18% of women use smokeless form of tobacco in India,<sup>4</sup> which involves chewing of betel-quid or "paan" (combination of betel nut, tobacco, slaked lime, and flavoring/coloring agents hand-rolled in betel leaf) and gutkha or paan masala<sup>5</sup> (substitute for betel-quid), which is marketed in small single-use sachets widely consumed by young adults.

Areca nut chewing is known to cause local trauma and injury to the oral mucosa due to its abrasive nature. This could be more severe in users of paan masala and gutkha due to their fine particulate nature, with the high probability of particle adhesion to the traumatized mucosa, leading to morphological changes and membrane damage. Areca nut, present in these mixtures, can disturb collagen homeostasis and cause cross-links and accelerate the onset of OSF, a collagen-related disorder, in habitual chewers. This continuous local irritation by paan masala, gutkha, or areca nut can lead to injury-related chronic inflammation, oxidative stress, and cytokine production. Oxidative stress and subsequent reactive oxygen species (ROS) generation can induce cell proliferation, cell senescence, or apoptosis, depending upon the amount of ROS produced. Chronic exposure to such events can lead to preneoplastic lesions in the oral cavity that can subsequently transform into malignancy.<sup>6</sup>

Epidemiological studies have shown that the process of carcinogenesis occurs by generation of ROS, which act by initiating lipid peroxidase. In OSF, lipid peroxidase was found to increase according to the severity of the disease.<sup>7</sup>

The objective of the study was to evaluate the efficacy of rebamipide [2-(4-chlorobenzoyl) amino]-3-(2-oxo-1H-quinolin-4-yl) propanoic acid], essentially a mucosal protective agent, to reduce the oral burning sensation associated with OSF. Apart from having a potent anti-inflammatory property, it inhibits major factors that cause mucosal and submucosal damage, by scavenging hydroxyl radicals, inhibition of increase in lipid peroxidase, and decreasing cytotoxicity of ROS. It also inhibits the infiltration of neutrophils and attenuates tissue damage. Overall anti-inflammatory action is due to the reduction of inflammatory interleukin (IL)-6 and IL-8, reduction of neutrophil migration, and scavenging of free radicals.<sup>8</sup>

**STUDY DESIGN AND METHODOLOGY**

After obtaining the institution ethical committee approval, this prospective clinical study was undertaken among OSF patients reporting to the outpatient clinic at the dental school. The inclusion criteria included all clinically diagnosed immune-competent OSF patients complaining of burning sensation in the mouth. Individuals who were already on some form of treatment for OSF, pregnant or nursing mothers, and those with known systemic illnesses or history of drug allergies were excluded from the study. After providing information about the study and obtaining consent, these individuals were divided into two groups of 10 each using random

sampling method. Patients in the rebamipide group (group I) were prescribed 100 mg tablets of rebamipide thrice a day for 21 days. The other 10 patients (group II) were given SOC, intralesional betamethasone injection 4 mg/mL once a week for 4 weeks, which is SOC in the management of OSF.

Visual analog scale (VAS) with 11 points (0–10) was used to assess burning sensation in the first visit, and change in the burning sensation was assessed after every 7th day on VAS in both the groups. Patients were followed up for 4 weeks and were advised to report adverse events if any. During the follow-up visit, number of tablets remaining was evaluated to ensure compliance to therapy.

**RESULTS**

Following data entry in Statistical Package for the Social Sciences (SPSS) version 11.5, the demographic data were analyzed using descriptive analysis and the evaluation of burning sensation by VAS score was done using repeated measures analysis of variance (ANOVA) and comparison between the rebamipide and betamethasone group was done by using paired t-test.

The age range of the study population was 19 to 65 years, with a mean age of the study population being 32.2 ± 10.09 years. The rebamipide group had eight males and two females, and the SOC (betamethasone) group had nine males and one female.

The VAS scores were evaluated for both the groups on 1st, 7th, 14th, 21st, and 30th day. Repeated measures ANOVA was utilized to evaluate the difference in the VAS score. The improvement in the VAS score in each visit was significant (p < 0.05) in the 1st, 2nd, 3rd, and 4th visit. The VAS score between the 4th and 5th visit failed to reach a statistically significant level (p > 0.05).

Table 1 summarizes the mean VAS scores of burning sensation in both the groups during their weekly follow-up visit. The burning sensation in rebamipide group reduced from 4.7 to 0.8 on day 30. In betamethasone

**Table 1:** Mean VAS scores for burning sensation

Type of treatment	Visit	VAS		95% confidence interval	
		Mean	Std. deviation		
Rebamipide	1	4.700	1.94	3.485	5.915
	2	3.200	1.68	2.179	4.221
	3	1.800	1.68	0.803	2.797
	4	0.800	0.91	0.036	1.636
	5	0.800	0.91	0.136	1.464
Betamethasone	1	5.300	1.70	4.085	6.515
	2	3.900	1.37	2.879	4.921
	3	3.100	1.28	2.103	4.097
	4	2.100	1.52	1.264	2.936
	5	1.600	1.07	0.936	2.264



group, the burning sensation reduced from 5.3 to 1.6 on day 30.

Even though there was a significant difference between the VAS scores in successive visits, the VAS score was not significantly different between the rebamipide and betamethasone group ( $p > 0.05$ ).

## DISCUSSION

Oral submucous fibrosis is a chronic inflammatory condition affecting the oral mucosa, exclusively characterized by mucosal pallor, loss of cheek elasticity, limited mouth opening, limited tongue movements, shrunken uvula, and burning sensation, leading to inability to consume food. Various treatment modalities had been tried with varying results like vitamin A supplementation, lycopene, pentoxifylline, hyaluronidase, corticosteroids, and placental extracts,<sup>9-13</sup> all targeted at reducing inflammation for symptomatic relief to the patient. The total cure of the disease has not been possible till date, which is mainly due to the fact that the etiology of the disease is not fully understood and the disease is progressive in nature.

The use of local injections of dexamethasone and hyaluronic and placental extracts has been described, which acts by opposing the action of soluble factors released by chronic inflammatory cell steroids also acting to reduce the inflammatory process preventing fibrosis by decreasing fibroblast proliferation and deposition of collagen.<sup>9</sup> Submucosal injections of steroids though very popular are purely palliative and have no curative value. It is also believed that repeated injection of the drug may further lead to fibrosis and associated trismus. Patient compliance is also poor due to the repeated painful intraoral injections.

In our study of the 10 patients in the betamethasone injection group, 2 patients had worsening in the mouth opening at the end of the study period, possibly due to the fibrosis induced by the repeated injections.

Rebamipide reduces or blocks the ability of human mast cells to release cyclic adenosine monophosphate phosphodiesterase, an inflammatory mediator. It also blocks proinflammatory substances and the production of substances that cause inflammatory reactions.<sup>14</sup>

Rebamipide has been used as a gastroprotective drug and has demonstrated its ulcer healing properties in animal as well as human studies. It stimulates prostaglandin synthesis in the mucosa and improves the speed and the quality of ulcer healing<sup>15,16</sup> Rebamipide has been used effectively in managing aphthous stomatitis and Behcet's disease.<sup>17</sup>

Patient compliance to rebamipide therapy was assessed by asking the patient to carry the tablet strip with them during their weekly follow-up. All patients in the group completed the treatment. Significant reduction

in burning sensation was seen from the initial visit to the 1-month follow-up, and none of the patients had worsening of the fibrosis or any adverse drug reaction.

## CONCLUSION

Our results showed that rebamipide was equally efficacious if not better than the betamethasone intralesional injections. Better patient compliance and lack of iatrogenic fibrosis caused by repeated mucosal injections make rebamipide a painless alternative to alleviate burning sensation in patients with OSF.

## REFERENCES

1. Sarode SC, Sarode GS. Better grade of tumor differentiation of oral squamous cell carcinoma arising in background of oral submucous fibrosis. *Med Hypotheses* 2013 Oct;81(4): 540-543.
2. Chen HM, Hsieh RP, Yang H, Kuo YS, Kuo MY, Chiang CP. HLA typing in Taiwanese patients with oral sub mucous fibrosis. *J Oral Pathol Med* 2004 Apr;33(4):191-199.
3. Shafer, WG; Hine, MK; Levy, BM. Benign and malignant tumors of the oral cavity. In: Shafer, WG; Hine, MK; Levy, BM, editors, *A textbook of oral pathology*. 4th ed. Philadelphia, PA: WB Saunders; 1983. p. 86-229.
4. World Health Organization. Regional office for South-East Asia global adult tobacco survey (GATS): India country report. New Delhi: WHO-SEARO; 2009 [cited 2014 Mar 25]. Available from: [http://www.searo.who.int/LinkFiles/Regional\\_Tobacco\\_Surveillance\\_System\\_GATS\\_India.pdf](http://www.searo.who.int/LinkFiles/Regional_Tobacco_Surveillance_System_GATS_India.pdf).
5. Willis DN, Popovech MA, Gany F, Hoffman C, Blum JL, Zelikoff JT. Toxicity of gutkha, a smokeless tobacco product gone global: is there more to the toxicity than nicotine? *Int J Environ Res Public Health* 2014 Jan;11(1):919-933.
6. Jeng JH, Wang YJ, Chang WH, Wu HL, Li CH, Uang BJ, Kang JJ, Lee JJ, Hahn LJ, Lin BR, et al. Reactive oxygen species are crucial for hydroxychavicol toxicity toward KB epithelial cells. *Cell Mol Life Sci* 2004 Jan;61(1):83-96.
7. Gupta S, Reddy MV, Harinath BC. Role of oxidative stress and antioxidants in aetiopathogenesis and management of oral submucous fibrosis. *Indian J Clin Biochem* 2004 Jan;19(1):138-141.
8. Kim H, Seo JY, Kim KH. Inhibition of lipid peroxidation, NF-kB activation and IL-8 production by rebamipide in *Helicobacter pylori*-stimulated gastric epithelial cells. *Dig Dis Sci* 2000 Mar;45(3):621-628.
9. Lai DR, Chen HR, Lin LM, Huang YL, Tsai CC. Clinical evaluation of different treatment methods for oral submucous fibrosis. A 10-year experience with 150 cases. *J Oral Pathol Med* 1995 Oct;24(9):402-406.
10. Rajendra R, Rani V, Shaikh S. Pentoxifylline therapy: a new adjunct in the treatment of oral submucous fibrosis. *Indian J Dent Res* 2006 Oct-Dec;17(4):190-198.
11. Kumar A, Bagewadi A, Keluskar V, Singh M. Efficacy of lycopene in the management of oral submucous fibrosis. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007 Feb;103(2):207-213.
12. Lin HJ, Lin JC. Treatment of oral submucous fibrosis by collagenase: effects on oral opening and eating function. *Oral Dis* 2007 Aug;13(4):407-413.

13. Kakar PK, Puri RK, Venkatachalam VP. Oral submucous fibrosis-treatment with hyalase. *J Laryngol Otol* 1985 Jan;99(1): 57-59.
14. Shimoyama T, Fukuda S, Liu Q, Fukuda Y, Nakaji S, Sugawara K. Characteristics of attenuating effects of rebamipide, an anti-ulcer agent, on oxidative bursts of human neutrophils. *J Pharmacol Sci* 2003 Feb;91(2):153-157.
15. Iijima K, Ichikawa T, Okada S, Ogawa M, Koike T, Ohara S, Shimosegawa T. Rebamipide, a cytoprotective drug, increases gastric mucus secretion in human: evaluations with endoscopic gastrin test. *Dig Dis Sci* 2009 Jul;54(7):1500-1507.
16. Naito Y, Kuroda M, Mizushima K, Takagi T, Handa O, Kokura S, Yoshida N, Ichikawa H, Yoshikawa T. Transcriptome analysis for cytoprotective actions of rebamipide against indomethacin-induced gastric mucosal injury in rats. *J Clin Biochem Nutr* 2007 Nov;41(3):202-210.
17. Matsuda T, Ohno S, Hirohata S, Miyanaga Y, Ujihara H, Inaba G, Nakamura S, Tanaka S, Kogure M, Mizushima Y. Efficacy of rebamipide as adjunctive therapy in the treatment of recurrent oral aphthous ulcers in patients with Behçet's disease: a randomised, double-blind, placebo-controlled study. *Drug R D* 2003;4(1):19-28.