Rebamipide to Manage Stomatopyrosis in Oral Submucous Fibrosis

Joanna Baptist, Shrijana Shakya, 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.

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%.1,2

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.3

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,4 which involves chewing of betel-quin or “paan” (combination of betel nut, tobacco, slaked lime, and flavoring/coloring agents hand-rolled in betel leaf) and gutkha or paan masala5 (substitute for betel-quin), which is marketed in small single-use sachets widely consumed by young adults.

Source of support: Nil

Conflict of interest: None
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.

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.

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.

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

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. Rebamipide has been used effectively in managing aphthous stomatitis and Behcet's disease.

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**