



Comparative Analysis of Rebamipide and Betamethasone in managing stomatopyrosis in Oral Submucous Fibrosis Patients

Jay Doshi¹, Dharti N Gajjar², Foram Patel³, Bhoosha Ambani⁴, Piyush Pujara⁵, Shrikant Patel⁶

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¹MDS, Reader, Department of Oral and Maxillofacial Surgery, Pacific Dental College, Udaipur, Rajasthan

²MDS, Assistant Professor, Department of Dentistry, Vedantaa institute of medical sciences, Dahanu, Maharashtra

³Master of Health Administration, Department of Health Sciences and Kinesiology; Georgia Southern University

⁴BDS, Faculty of Dental Science, Dharmsinh Desai University, Nadiad, Gujarat

⁵Reader, Department of Public Health Dentistry, Pacific Dental College, Udaipur, Rajasthan

⁶Reader, Department of Oral and Pathology, Pacific Dental College, Udaipur, Rajasthan

Corresponding Author: Dr Jay Doshi, E-mail address: jaydoshi512@gmail.com

Abstract

Background and Aim: Oral submucous fibrosis (OSMF) is an irreversible condition and the management strategies are aimed at alleviating the symptoms. Present study was done with an aim to evaluate the efficacy of rebamipide to reduce the oral burning sensation associated with OSMF as compared to conventional Betamethasone intralesional injection. **Material and Methods:** This prospective clinical study was undertaken among OSMF patients reporting to the OPD of Tertiary care institute for the period of one year in 50 patients. After providing information about the study and obtaining consent, these individuals were divided into two groups of 25 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 25 patients (group II) were given SOC, intralesional betamethasone injection 4 mg/mL once a week for 4 weeks. 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. **Results:** Patients who were in rebamipide group the burning sensation reduced from 4.65 to 0.71 on day 30. The burning sensation Patients in betamethasone group, reduced from 5.24 to 1.57 on day 30. (Table 1) The VAS score was significantly different between the rebamipide and betamethasone group ($p \leq 0.05$) in Third, Fourth and Fifth visit. **Conclusion:** Rebamipide was equally efficacious if not better than the Betamethasone intralesional injections. Patients treated with rebamipide shows better compliance and lack of iatrogenic fibrosis that commonly caused by repeated mucosal injections make rebamipide a painless alternative to alleviate burning sensation in patients with OSMF.

Key Words: Betamethasone, Oral submucous fibrosis, Rebamipide, Visual analog scale

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Introduction

Oral submucous fibrosis (OSMF) is a chronic and subtle oral potentially malignant disorder (OPMD) affecting the oral cavity and oropharynx, in mainly the South-Asian populations.¹ Clinically, signs and symptoms of

OSMF include but are not limited to, trismus, restricted tongue protrusion, burning mouth, marble-like appearance of the oral mucosa, xerostomia, recurrent ulceration, tongue papillae atrophy, and presence of palpable fibrous bands.² These oral complications are



fundamentally due to a juxtaepithelial inflammatory reactions leading to fibroelastic changes of the lamina propria, and subsequently to the stiffness of the oral mucosa, which significantly affects patients' quality of life by reducing their ability to eat and speak.

The malignant transformation rates vary from 3 to 19%.³⁻⁵ 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. Chronic inflammation, oxidative stress, and cytokine production are caused by the injuries due to the continuous local irritation by paan masala, gutkha, or areca nut. Oxidative stress and subsequent reactive oxygen species (ROS) generation can induce cell proliferation, cell senescence, or apoptosis, depending upon the amount of ROS produced. Such events can lead to preneoplastic lesions in the oral cavity that can subsequently transform into malignancy.⁶ 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. It affects the oral cavity and in severe forms can involve the pharynx. The characteristic symptoms of burning sensation and stiffness of the oral mucosa. It is estimated that 33% of men and 18% of women use smokeless forms of tobacco in India.⁷ Carcinogenesis occurs by the generation of ROS, which acts by initiating lipid peroxidase. In OSF, lipid peroxidase was found to increase according to the severity of the disease. Rebamipide 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.⁸

Present study was done with an aim to evaluate the efficacy of rebamipide [2-(4-chlorobenzoyl) amino]-3-(2-oxo-1Hquinolin-4-yl) propanoic acid], essentially a mucosal protective agent, to reduce the oral burning sensation associated with OSMF as compared to conventional Betamethasone intralesional injection.

Material and Methods

This prospective clinical study was undertaken among OSMF patients reporting to the OPD of Tertiary care institute for the period of one year in 50 patients.

All clinically diagnosed immune-competent OSMF patients complaining of burning sensation in the mouth were included in the study. Patients who were already taken treatment for OSMF, pregnant or nursing mothers, and those with known systemic illnesses or history of drug allergies were excluded from the study.

Ethical approval was taken from the institutional ethical committee and written informed consent was taken from all the participants.

After providing information about the study and obtaining consent, these individuals were divided into two groups of 25 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 25 patients (group II) were given SOC, intralesional betamethasone injection 4 mg/mL once a week for 4 weeks. 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.



Statistical analysis

The recorded data was compiled and entered in a spreadsheet computer program (Microsoft Excel 2007) and then exported to data editor page of SPSS version 15 (SPSS Inc., Chicago, Illinois, USA). For all tests, confidence level and level of significance were set at 95% and 5% respectively.

Results

The age range of the study population was 18 to 70 years, with a mean age of the study population being 34.5 ± 05.12 years. The rebamipide group had 13 males and 2 females,

and the SOC (betamethasone) group had 14 males and 1 female. The VAS scores were evaluated for both the groups on 1st, 7th, 14th, 21st, and 30th day.

Patients who were in rebamipide group the burning sensation reduced from 4.65 to 0.71 on day 30. The burning sensation Patients in betamethasone group, reduced from 5.24 to 1.57 on day 30. (Table 1) The improvement in the VAS score in each visit was significant in the 1st, 2nd, 3rd, and 4th visit. The VAS score was significantly different between the rebamipide and betamethasone group ($p \leq 0.05$) in Third, Fourth and Fifth visit.

Table 1: Mean VAS scores for burning sensation

Visit	Rebamipide (gp-1 of 15) Mean \pm SD3	Betamethasone (gp-11 of 15) Mean \pm SD	P value
First	4.65 \pm 1.92	5.24 \pm 1.64	0.45
Second	3.15 \pm 1.60	3.89 \pm 1.45	0.34
Third	1.78 \pm 1.15	3.20 \pm 1.34	0.04*
Fourth	0.75 \pm 0.32	2.22 \pm 1.40	0.003*
Fifth	0.71 \pm 0.20	1.57 \pm 1.23	0.001*

*indicates statistically significance at $p \leq 0.05$

Discussion

Oral submucous fibrosis is a premalignant condition of the oral cavity and oropharynx seen predominantly in the Indian subcontinent and Southeast Asian countries. The pathophysiology of this condition is complex, and various factors such as, ingestion of spicy food, genetic susceptibility, nutritional deficiencies, altered salivary constituents, autoimmunity and collagen disorders are thought to be involved in the pathogenesis. The fibrotic potential of arecanut alkaloids and tannin have been proved to have an effect in the etiology of this chronic inflammatory mucosal disease.⁹ In the treatment of OSMF, various categories of drugs have been used, but their effectiveness leaves much to be desired and definitive cure has not been afforded by any treatment.¹⁰ Increased potential for side

effects is high while oral administration as it limits the concentration of drugs in lesional tissue and significant mechanical injury and noncompliance on the patient's part is high with intralesional injections due to the accompanying discomfort and pain.¹¹ The health of the consumers has been compromised immensely by the use of arecanut in different forms with or without tobacco as it has unfortunately permeated the ordinary household. The major fatal sequel to their usage is the onset of OSMF and cancer of the oral cavity and India is the globally leading country in this.

Several studies in humans have confirmed the cancer preventive nature of antioxidants. Lycopene also up-regulates the lymphocyte resistance to stress and suppresses the inflammatory response.¹² The unifying



mechanism, which underlies these diseases is cumulative oxidative damage. Hence, antioxidants can influence or prevent seemingly unrelated conditions. It is clear from this that a long term maintenance treatment is necessary, if there has to be an impact on oral cancer incidence. Another point in favor of the use of lycopene for the prevention of OSMF is that it is relatively non-toxic and can be easily supplemented in the diet.¹³

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.¹¹⁻¹³ The Complete cure of the disease has not been possible till date. Intralesional 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. Rebamipide work by reduces or blocking the ability of human mast cells to release an inflammatory mediator cyclic adenosine monophosphate phosphodiesterase, it also blocks proinflammatory substances and the production of substances that cause inflammatory reactions.¹⁴ 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.¹⁵⁻¹⁷

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. Our finding are consistent with study conducted by Joanna B et al (2016). In OSMF Patients stomatopyrosis and trismus are the major cause for inability to eat. The use of newer adjunctive modalities, such as rebamipide will ease patients suffering and also encourage them to consume food.

Results of clinical studies show that there is clear scope for investigating the preventive and therapeutic effects of antioxidants in betel nut chewers and patients with OSMF through well-designed, large, controlled studies.

Conclusion

Rebamipide was equally efficacious if not better than the Betamethasone intralesional injections. Patients treated with rebamipide shows better compliance and lack of iatrogenic fibrosis that commonly caused by repeated mucosal injections make rebamipide a painless alternative to alleviate burning sensation in patients with OSMF.

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