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Comparative Study of Rebamipide & Betamethasone in Managing Stomatopyrosis in Oral Submucous Fibrosis (OSMF) Patients

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Original Article

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ABSTRACT

Background: 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 forms of tobacco products. The malignant transformation rates vary from 3 to 19%. The standard of care (SOC) in managing OSF includes habit cessation, intralesional steroid and hyaluronidase injections, and mouth opening exercises.

Objectives: To evaluate the efficacy of rebamipide to reduce the oral burning sensation associated with OSMF as compared to coventional Betamethasone intralesional injection.

Materials and Methods: After providing information about the study and obtaining consent, these individuals were divided into two groups of 15 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 15 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: 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 ($p>0.05$). The VAS score was significantly different between the rebamipide and betamethasone group ($p > 0.05$) in the third & fourth visits.

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Conclusion: Our results showed that rebamipide was equally efficacious if not better than the betamethasone intralesional injections.

Keywords: Betamethasone, Management, Oral Submucous Fibrosis, Rebamipide.

Introduction

The incidence of oral submucous fibrosis (OSF) is commonly seen in the Indian subcontinent. It affects individuals of all age groups. It is a potentially malignant disorder caused almost exclusively by the use of smokeless forms of tobacco products. The malignant transformation rates vary from 3 to 19%.[1-3] 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.[4] 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.[5] 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.[6] Rebamipide's 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.[7]

Aim & Objective

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 coventional Betamethasone intralesional injection.

Materials & Methods

After obtaining the institution's ethical committee approval, this prospective clinical study was undertaken among OSMF patients reporting to the OPD of the Department of Oral Medicine & Radiology.

Inclusion & Exclusion Criteria

The inclusion criteria included all clinically diagnosed immune-competent OSMF patients complaining of burning sensations in the mouth.

Patients who were already taken treatment for OSMF, pregnant or nursing mothers and those with known systemic illnesses or a history of drug allergies were excluded from the study.

Methodology

After providing information about the study and obtaining consent, these individuals were divided into two groups of 15 each using a 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 15 patients (group II) were given SOC, intralesional betamethasone injection 4 mg/mL once a week for 4 weeks. Visual analog scale (VAS) with

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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, a number of tablets remaining was evaluated to ensure compliance to therapy.

Results

The mean & standard deviation of the evaluation of burning sensation by VAS score was calculated and a comparison between the rebamipide and betamethasone group was done by using paired t-test. (Graph pad method). The age range of the study population was 19 to 65 years, with the mean age of the study population being 32.2 ± 10.09 years. The rebamipide group had 13 males and 2females, and the SOC (betamethasone) group had 14 males and 1 female. The VAS scores were evaluated for both the groups on the 1st, 7th, 14th, 21st, and 30th days.

Table 1 summarizes the mean VAS scores of burning sensation in both groups during their weekly follow-up visit. In patients who were in the rebamipide group the burning sensation reduced from 4.7 to 0.8 on day 30. The burning sensation Patients in the betamethasone group, reduced from 5.3 to 1.6 on day 30.

Type of treatment	Visit	VAS Mean	Std .deviation
Rebamipide (gp-1 of 15)	First	4.7	1.94
	Second	3.2	1.68
	Third	1.8	1.68
	Fourth	0.8	0.91
	Fifth	0.8	0.91
Betamethasone (gp-11 of 15)	First	5.3	1.70
	Second	3.9	1.37
	Third	3.1	1.28
	Fourth	2.1	1.52
	Fifth	1.6	1.07

Table 1: Mean VAS scores for burning sensation

The improvement in the VAS score in each visit was significant ($p < 0.05$) in the 1st, 2nd, 3rd, and 4th visits. The VAS score between the 4th and 5th visit failed to reach a statistically significant level ($p > 0.05$). The VAS score was significantly different between the rebamipide and betamethasone groups ($p > 0.05$) in the third & fourth visits **(Table 2)**

Visits	t value	df value	P-value
First	t=0.90	df=28	P=0.3753
Second	t=1.25	df=28	**P=0.2214**
third	t=2.38	df=28	**P=0.0242**
Fourth	t=2.84	df=28	**P=0.0083**
Fifth	t=2.38	df=28	**P=0.024**

Table 2: Statistical comparative analysis between group1 & group 11

Discussion: 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.[8-12] The Complete cure of the disease has not been possible to 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 pro-inflammatory substances and the production of substances that cause inflammatory reactions.[13] 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.[14-15] Rebamipide has been used effectively in managing aphthous stomatitis and Behcet's disease.[16]

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. A 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 findings are consistant with the study conducted by joanna. b et al(2016). It is further suggestated that a similar study with a large sample size should be carried out to prove the authenticity of the efficacy of this drug in managing stomatopyrosis in OSMF. In OSMF Patients stomatopyrosis and trismus are the major cause of the inability to eat. The use of newer adjunctive modalities, such as rebamipide will ease patient's suffering and also encourage them to consume food.[17]

Conclusion: Our results showed that Rebamipide was equally efficacious if not better than the Betamethasone intralesional injections. Patients treated with rebamipide show better compliance and lack of iatrogenic fibrosis that is commonly caused by repeated mucosal injections make rabamipide a painless alternative to alleviate burning sensation in patients with OSMF. More studies with large subjects should be carried out for more authenticity of findings and scientific basis of its clinical implications.

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