



Comparative evaluation of the efficacy of systemic levamisole and antioxidant in the management of oral submucous fibrosis – A randomized control trial

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Abstract

Background: Oral submucous fibrosis (OSF) is a chronic, disabling disease involving the entire oral mucosa, mainly reported in Indian population. A number of treatment modalities have been tried, but none of these have been completely therapeutic. Levamisole, an immunomodulator, has been reported to be beneficial in oral mucosal lesions, but there are hardly any studies reported in literature for OSF patients, and hence, the study was taken up.

Aim: This study aims to compare the efficacy of levamisole with antioxidant for the assessment of burning sensation and mouth opening in OSF patients.

Materials and Methods: A total of 60 patients clinically diagnosed of OSF were selected for the study. We assessed patients for burning sensation and mouth opening. Patients were divided into four groups according to staging of OSF (More *et al.*, classification), then randomly subdivided into three groups to dispense medicines. Group I patients received levamisole, 150 mg once daily for 3 alternate weeks, Group II patients received antioxidant BID for 6 weeks, and Group III patients received levamisole and antioxidant both. The patients were followed up for 2 months.

Results and Conclusion: The results proved that levamisole, antioxidant, and the combination of both showed significant improvement in mouth opening and reduction in burning sensation.

Introduction

In today's century mostly, the prevalence of cancer is linked to our diet and lifestyles. Tobacco and diet are the major reasons accounting for nearly two-thirds of all cancers we see worldwide; most of these are preventable. The recent decades have seen a massive global increase in tobacco use.^[1] The Indian scenario is far worse because of the prevalence of the tobacco chewing habit, which covers a wide spectrum of socioeconomic and ethnic groups.^[1]

Oral submucous fibrosis (OSF) defined as an "insidious, chronic disease affecting any part of the oral cavity and sometimes the pharynx. Occasionally, it is preceded by and/or associated with vesicle formation and is always associated with a juxta-epithelial inflammatory reaction followed by progressive hyalinization of the lamina propria and further subepithelial and

submucosal myofibrosis, leading to blanching and stiffness of the oral mucosa and deeper tissues with progressive limitation in opening of the mouth and protrusion of the tongue, thus causing difficulty in eating, swallowing, and phonation."^[2]

It is also known as idiopathic scleroderma of the mouth, idiopathic palatal fibrosis, sclerosing stomatitis, diffuse OSF, and submucous fibrosis of the palate and pillars.^[3]

OSF is a chronic condition almost exclusively occurring among Indians and to a lesser extent in other Asiatic people.^[4] Recent epidemiological data indicate that the number of cases of OSF estimated of 5 million in India.^[5] The prevalence rate in India increased over the past 4 decades from 0.03% to 6.42%.^[6]

Observations from animal studies and epidemiologic investigations provide the biologic basis of chemoprevention of cancer. Epidemiologic studies have proved the protective role of diets rich in fruits and vegetables in oral carcinogenesis

and reduced risk of oral cancer with high intake of various vitamins, minerals such as Vitamins A, C, and E, and carotenoids. Retinoids, carotenoids, and Vitamin E and the combination of the above with other vitamins and minerals have been shown to block chemically induced oral carcinogenesis in animal studies and to result in the regression of hamster buccal pouch cancers.^[7]

Several medicinal approaches have been tried such as corticosteroids, nutritional supplements, antioxidants, intralesional injections of placental extracts, hyaluronidase, and chymotrypsin. Furthermore, surgical modality has been used such as excision of fibrotic bands and coronoidectomy.

Levamisole acts as an immunomodulator has been used in the treatment of recurrent aphthous stomatitis, oral lichen planus, and herpes labialis. Very few authors have evaluated the clinical efficacy of levamisole in OSF patients. Hence, this present study was conducted to compare the efficacy of systemic ingestion of levamisole with antioxidants in OSF patients among Navi Mumbai population. The objectives of the study were to evaluate the efficacy of tablet Levamisole 150 mg and tablet Antioxidant in OSF patients. The efficacy of both the medicines was compared according to the four stages of OSF.

Materials and Methods

The present study was conducted in the Department of Oral Medicine and Radiology, Y. M. T. Dental College and Hospital, Navi Mumbai. Patients attending the OPD were screened randomly for habits of gutka and areca nut chewing. A total of 60 subjects of either gender were enrolled in the study who were having OSF. Diagnosis of OSF was made on the basis of a history of characteristics of habits and clinical features which included the presence of burning sensation in the mouth, intolerance to spicy food, blanching and loss of suppleness of oral mucosa, presence of palpable fibrous bands, and decreased mouth opening. Patients were categorized into different stages according to More *et al.*^[8] classification of OSF.

Clinical staging

- Stage 1 (S1): Stomatitis and/or blanching of oral mucosa.
- Stage 2 (S2): Presence of palpable fibrous bands in buccal mucosa and/or oropharynx, with/without stomatitis.
- Stage 3 (S3): Presence of palpable fibrous bands in buccal mucosa and/or oropharynx, and in any other parts of oral cavity, with/without stomatitis.
- Stage 4 (S4) as follows:
 - a) Any one of the above stage along with other potentially malignant disorders, for example, oral leukoplakia, oral erythroplakia, etc.
 - b) Any one of the above stage along with oral carcinoma.

Functional staging

- M 1: Interincisal mouth opening up to or >35 mm.
- M 2: Interincisal mouth opening between 25 and 35 mm.
- M 3: Interincisal mouth opening between 15 and 25 mm.

- M 4: Interincisal mouth opening <15 mm.

Subjects who were chewing gutka and/or areca nut at least for 1 year, who satisfied the characteristic clinical features of OSF and had burning sensation and those who were not taking any medication for their disease condition also, patients who were willing for follow-up visits were included in the study. Patients who gave the history of systemic diseases or suffering from acute or chronic infection and patients with a known allergy or contraindication to the study drugs were excluded from the study.

The drugs used in the study were tab. levamisole 150 mg (brand name Vermisol) and antioxidant capsules (brand name Antoxid, contains beta-carotene – 10 mg, zinc sulfate monohydrate – 27.5 mg, selenium dioxide – 75 mg, manganese – 2 mg, and copper – 1 mg).

The methodology of the study was described to the patient in his/her language and the consent to participate in the study was taken. Based on inclusion and exclusion criteria, 60 were selected for the study. Patients were divided into four groups according to staging of OSF [according to More *et al.* classification (2012)] and then randomly subdivided into three groups according to medicines.

- Group-I: 15 subjects – Stage 1 OSF
- Group-II: 15 subjects – Stage 2 OSF
- Group-III: 15 subjects – Stage 3 OSF
- Group-IV: 15 subjects – Stage 4 OSF.

These groups were subdivided into three groups.

- Group A – Tab. Levamisole
- Group B – Tab. Antoxid
- Group C – Combination of both tablets.

All patients received their first treatment dose on the 1st day of appointment. Patients were recalled at weekly intervals for 6 weeks and then at an interval of 30 days for the next 2 months. At each visit, patients were evaluated for burning sensation and mouth opening and administered the subsequent dose of respective medicine. Group IA, IIA, IIIA, and IVA patients received tablet levamisole 150 mg once in a day for 3 consecutive days in a week for the next 3 alternate weeks. Group IB, IIB, IIIB, and IVB patients received the capsule Antoxid 2 times daily for 6 weeks. Group IC, IIC, IIIC, and IVC patients received one tablet of levamisole 150 mg, 1 time daily for 3 consecutive days in a week for 3 alternate weeks and one capsule of Antoxid 2 times daily for 6 weeks.

We recorded the decrease in burning sensation and increased in mouth opening on every appointment day. We compare and correlate the responses of burning sensation and mouth opening on the day of 1st appointment to the 1st month and 2nd month responses. Post-treatment follow-up involved the evaluation of the patient every week for 30 days and over a period of the next 60 days.

Interincisal mouth opening was measured using divider and scale from the mesioincisal angle of upper central incisor to the mesioincisal angle of lower central incisor and recorded in millimeters. The intensity of burning sensation was determined using a visual analog scale (VAS) of 0–10, where 0 was no

burning sensation and 10 was the worst possible burning sensation. Patients were asked to mark the VAS at a point which best represented the burning sensation at their respective visit.

Statistical analysis

Descriptive statistics were used to summarize patient’s demographics and study responses. Paired *t*-test was used for intragroup comparison and unpaired *t*-test was used for intergroup comparison using the SPSS package where *P* < 0.05 was considered to be statistically significant. The study was of randomized controlled trial.

Results

None of the patients in the present study reported any side effects due to the study drugs.

Of 60 patients, 51 (85%) were male and 9 (15%) female who fell in the age range of 41.12 years. The male-to-female ratio was found to be 8:1.4.

At the end of the 1st month, the reduction in burning sensation [Table 1] among patients treated with levamisole Stage 1 OSF was 44%, in Stage 2 OSF 48%, in Stage 3 52%, and in Stage 4 OSF 20%. At the end of the 2-month follow-up period, the reduction in burning sensation in Stage 1 OSF was 54%, in Stage 2 OSF 64%, and in Stage 3 OSF 54%. In Stage 4 OSF, the improvement remained the same, i.e., 20%. We observed the maximum reduction in burning sensation in Stage 3 OSF (52%) at the end of the 1st month follow-up and in Stage 2 (64%) at the end of the 2nd month follow-up.

Patients treated with cap. antioxidants showed 28% reduction in burning sensation in Stage 1, 28% in Stage 2 OSF, 30% in Stage 3, and 10% in Stage 4 at the end of the 1st month recall while further reduction in burning sensation was noted in different stages during the 2nd month recall, i.e., 32% in Stage 1, 34% in Stage 2, 32% in Stage 3, and 15% in Stage 4 OSF as shown in Table 1.

On comparing individual medicines with combination, we found that maximum reduction in burning sensation was seen in combination groups for Stage 1 and 2 OSF (66%) [Table 1 and Graph 1].

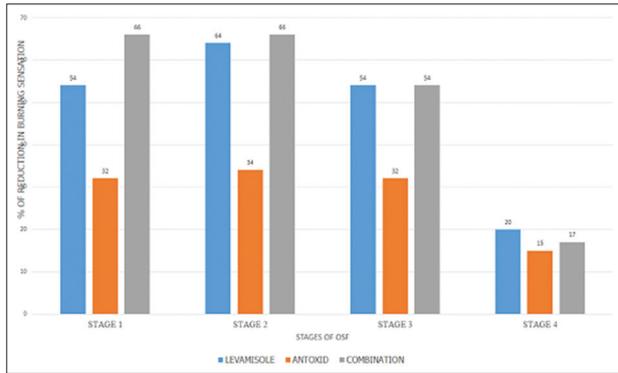
Statistically highly significant reduction in burning sensation was seen in all the three groups. Intergroup comparisons did not reveal statistically significant differences [Table 2].

On statistical evaluation, significant improvement in mouth opening was seen in all the three groups among all the stages of OSF and the improvement was better in the levamisole and Antoxid combination group at the end of the 2nd month follow-up, i.e., 22% (Group C) in Stage 2 when compared to other groups. The response was not statistically significant between all groups of Stage 4 OSF, remaining groups showed statistically significant result. Whereas in Stage 4 OSF, the improvement remained the same, i.e., 5% [Table 3 and Graph 2]. Intergroup comparisons did not reveal statistically significant differences [Table 4].

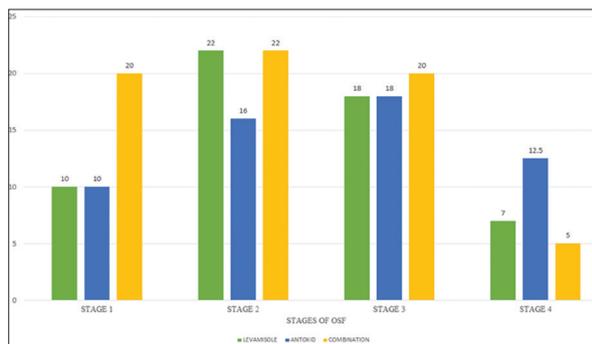
Table 1: Comparison of reduction in burning sensation (using VAS) in all groups

Stages of OSF	Drugs used						P value			Significance
	Tab. Levamisole		Cap. Antoxid		Combination		Levamisole	Antoxid	Combination	
	End of the 1 st month (%)	End of the 2 nd month (%)	End of the 1 st month (%)	End of the 2 nd month (%)	End of the 1 st month (%)	End of the 2 nd month (%)				
Stage 1	44	54	28	32	50	66	0.000*	0.005*	0.001*	Highly significant
Stage 2	48	64	28	34	60	66	0.005*	0.004*	0.004*	
Stage 3	52	54	30	32	52	54	0.002*	0.001*	0.001*	
Stage 4	20	20	10	15	15	17	0.01*	0.013*	0.016*	

**P*<0.05. VAS: Visual analog scale, OSF: Oral submucous fibrosis



Graph 1: Comparison of reduction in burning sensation (using visual analog scale) in all groups at the end of the 2nd month follow-up



Graph 2: Comparison of increase in mouth opening in all groups at the end of the 2nd month follow-up

Table 2: Burning sensation (using VAS) before and after treatment (intergroup comparison)

Difference between groups	Stage 1	Stage 2	Stage 3	Stage 4
A-B	0.08 Not	0.75 Not	0.03 Not	0.35 Not
A-C	0.06 Not	0.80 Not	0.00* YES	1 Not
B-C	0.04* YES	0.65 Not	0.01* YES	0.35 Not

*P<0.05. VAS: Visual analog scale

Discussion

OSF is one of the poorly understood and unsatisfactorily treated precancerous diseases of the oral cavity. An estimated 5 million people suffer from the disease in India. Only symptomatic treatment is available for OSF to reduce its early symptoms such as burning sensation, xerostomia, stomatitis, and vesicle formation. A modality for complete treatment is still under research. This is mainly due to the fact that the etiology of the disease is not fully understood and the disease is progressive in nature. Younger the age, more rapid the progression of the disease, and more likely the recurrence of symptoms. A wide range of treatments, such as local injections of steroids, hyaluronidase, human placental extracts, chymotrypsin, multivitamin therapy, and physiotherapy, have been proposed

Table 3: Comparison of increase in mouth opening in all groups

Stages of OSF	Drugs used				P value		Significance
	Tab. Levamisole		Tab. Antioxid		Levamisole	Antioxid	
	End of the 1 st month (%)	End of the 2 nd month (%)	End of the 1 st month (%)	End of the 2 nd month (%)			
Stage 1	4	10	6	10	0.034*	0.089*	Significant
Stage 2	16	22	12	16	0.004*	0.002*	Significant
Stage 3	12	18	14	18	0.000*	0.008*	Significant
Stage 4	5	7	5	12.5	0.057	0.141	Not significant

*P<0.05

Table 4: Comparison of increase in mouth opening in all groups (intergroup comparison)

Difference between groups	Stage 1		Stage 2		Stage 3		Stage 4	
A-B	0.92	Not	0.36	Not	0.54	Not	0.35	Not
A-C	1.00	Not	0.44	Not	0.28	Not	0.35	Not
B-C	0.91	Not	0.92	Not	0.44	Not	0.64	Not

* $P < 0.05$

for OSF, but none have proved curative or have reduced the morbidity significantly.^[9]

Levamisole, an immunomodulator, has been reported to be beneficial in oral mucosal lesions, but there are hardly any studies reported in literature for OSF patients, and hence, the study was undertaken.

Levamisole is a synthetic phenylimidothiazole salt grouped under antihelminthic drug, a compound that possesses a wide variety of immunological effects both *in vivo* and *in vitro*. Since levamisole acts apparently as an immunosuppressant at prolonged dosages, and as an immunopotentiator at lower dosages or on intermittent administration, it has been designated as an immunomodulator.^[10] On the other hand, the anti-inflammatory action is by the inhibition of TNF-alpha (tumor necrosis factor) and interleukin. Levamisole also acts as antineoplastic agent by two ways; first, through its apoptotic action causing cell cycle inhibition and increased endothelial cell adhesion and the second action is through its antiangiogenic property.^[11]

Levamisole, an immunomodulator, has been reported to be beneficial in oral mucosal lesions, but its effects in OSF are not known. Antioxidant formulation that contains beta-carotene, zinc, copper, manganese, and selenium. It has been found that these micronutrients have antioxidant properties and enhance cellular immunity.^[12]

In the present study, we found highly significant improvement in burning sensation which was seen in all the three groups but were better in combination of levamisole and Antoxide group in Stage 1 and Stage 2 OSF (66%) at the end of the 2nd month follow-up. Comparing both the drugs individually, we found that levamisole was more effective in improvement of burning sensation for all the stages of OSF, but the differences among the groups were not statistically significant. We also noticed that at the end of follow-up, the mouth opening continued to improve in patients who had taken levamisole and antioxidants 22% in Stage 2. When we compared the improvement of mouth opening separately, we found that levamisole gave better result in Stage 2 (22%) and Stage 3 (18%), while antioxidants gave better result in Stage 3 (18%) and Stage 4 (12.5%), but the differences among the groups were not statistically significant.

Many studies have documented the effect of various medical therapies in OSF, but till now, only one published study has evaluated the clinical efficacy of levamisole in OSF patients; hence, the findings associated with levamisole cannot

be directly compared with many other studies. Jirge *et al.*^[12] reported significant improvement in the levamisole and Antoxid combination group, i.e., 8% (Group III) when compared to 7.1% in the levamisole (Group I) and 6.7% in the Antoxid (Group II) groups were noticed at the end of the 1st month, but at the end of follow-up period, levamisole group continued to improve the mouth opening till 10.7% and other groups remain static. Authors also reported the decrease in burning sensation in levamisole group (98.6%), Antoxid group (86.7%), and combination of both drugs (96.7%). Hence, authors reported that the levamisole is better than Antoxid in improving mouth opening and decreasing burning sensation and levamisole alone may be given to patients with OSF. The results are partially consistent with our study where we found that combination of levamisole and Antoxid is better in Stage 1, Stage 2, and Stage 3 OSF. Individually, levamisole gives better results in Stage 1, Stage 2, and Stage 3 OSF where antioxidants give better results in Stage 4 OSF.

Many studies have been done using antioxidant supplements and have shown similar results like our study. Gupta *et al.*,^[13] 2004, conducted a study in OSF patients and reported that plasma beta-carotene and Vitamin E levels were found to be decreased significantly in patients. Authors reported that, after 6 weeks of oral administration of beta-carotene and Vitamin E, patients showed increase in plasma level of these two antioxidants along with decrease in MDA level associated with clinical improvement.^[12]

Maheer *et al.*^[7] evaluated the role of multiple and some minerals in the management of OSF and reported they found the clinical improvement in patients. However, they did not give any correlation of etiological factor of OSF and mechanism of the action of any specific micronutrient.^[6]

As zinc is one of the major constituents of Antoxid, few studies reported the positive effect of zinc in OSF patients. Kumar *et al.* reported that oral zinc therapy either alone or in combination with pharmacological doses of oral Vitamin A proved to be significantly better for the treatment of Grade I and II patients.^[14]

Although intralesional injections with different drugs have shown better improvement in mouth opening, they are associated with significant discomfort, pain and infection at the injection site, and reduction in mouth opening over a longer follow-up period.^[11] Hence, our treatment modality is safer. However, the long-term prognosis was not assessed in the present study.

Better patient compliance and consequently better results were expected in our treatment modality, due to its non-invasive nature and absence of side effects compared to other treatment modalities such as intralesional injections. Reduction in burning sensation was there in all groups and levamisole appeared to be more effective than antioxidants; however, statistical significance was not found. The anti-inflammatory action of levamisole can be contributed to the relief of burning sensation.

Conclusion

Based on the results and statistical analysis, we concluded that combination of levamisole and antioxidants gives better results in the treatment of OSF. Overall assessment of the results and statistical analysis depicted that combination of levamisole and antioxidants group showed a better treatment response in Stage 1, Stage 2, and Stage 3 OSF compared to the individual group. It reduces the burning sensation and improves mouth opening, thereby enhancing the patients' compliance. However, when we compared both drugs individually, we found that levamisole is more effective in case of reducing burning sensation in Stage 1 and Stage 2 OSF, whereas antioxidants are more effective in improvement of mouth opening in Stage 3 and Stage 4 OSF. However, the data are not statistically significant. Furthermore, it proves to be a relatively safe, can be taken systemically, easily available, economical, non-invasive, and efficacious in the treatment for OSF.

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