

Comparative Efficacy of Oxitard Capsules and Immusante Tablets in Early Stages of Oral Submucous Fibrosis – A Randomized Controlled Trial

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Abstract:

Objective: Oral submucous fibrosis (OSMF) is manifested by symptoms such as palpable fibrotic bands, ulceration, presence of stiffness in the mouth and lip, xerostomia, pigmentation in the oral mucosal layer, and burning sensation and drying of the mouth. It poses a challenge for researchers as there is no viable therapy for this gradually debilitating disorder with a high malignancy potential. Ayurveda is a traditional medicinal practice of the past and present times which can be useful in providing a viable cure. Thus, the current study was designed to assess and compare the effect of Oxitard capsule and Immusante tablet on the clinical and subjective symptoms of OSMF.

Material and Methods: The study included 36 patients with clinically diagnosed OSMF who were split evenly into two groups: Group A, the Oxitard group, and Group B, the Immusante group. For three months, Group A received two Oxitard capsules twice daily, while Group B received two Immusante tablets twice daily. At regular intervals, the clinical parameters were evaluated, and the data were analysed using repeated measures ANOVA and the Bonferroni post hoc test. P-value \leq 0.05 was regarded as statistically significant.

Results: On assessment of mouth opening, tongue protrusion, cheek flexibility and subjective symptoms there was significant improvement reported in both groups. In group comparison, the Oxitard and Immusante groups showed a

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significant difference in cheek flexibility at 3 months. There were no significant differences in subjective symptoms in either of the groups pre- and post-treatment.

Conclusion: Efficacy of both the drugs were equal was found to be similar when used as an adjunct to tobacco cessation counselling in the management of early stages of oral submucous fibrosis when used as an adjunct to behavioral management.

Keywords: antioxidants, ayurvedic, dentistry, immunomodulators, oral submucous fibrosis

Introduction

Oral submucous fibrosis is a premalignant condition characterized by an increase in the deposition of collagen fibers in the submucosa which leads to the formation of thick bands around the lips and in cheeks, including the para-oral tissues. The deposition increases the stiffness of the tissues and thus patients complain of difficulty in opening their mouth¹. According to the World Health Organization, these are lesions and conditions which have greater than normal potential to undergo malignant transformation and turn into oral squamous cell carcinoma. The symptoms reported by the patients include ulceration as the first symptom, followed by dry mouth, altered tone, difficulty in swallowing due to muscle stiffness, and pain and discomfort while opening the mouth, causing trismus. Clinically, tissue fibrosis frequently involves the buccal mucosa². The whole mucosa appears pale in colour with blanching.

Globally, oral submucous fibrosis accounts for more than 5 million patients, increasing the oral health burden in the community. The incidence differs with age and gender, among ethnic groups, different cultural practices, and adverse habits³. Worldwide, India ranks at the top in cases of oral submucous fibrosis (OSMF)⁴. The major reason for the development of OSMF is the habit of chewing areca nuts⁵. This condition possesses a high risk of malignant transformation. In India, around 7.6% of the diagnosed OSMF patients undergo malignant transformation to oral squamous cell carcinoma. The reason for the high mortality after malignant transformation is the late diagnosis

of these lesions and conditions⁶. The management of the condition is dependent on the clinical involvement and the degree of progression of the disease. More et al. classified OSMF into four stages; each stage denotes the degree of progression and the necessary treatment. In the early stages, the case is managed by cessation of tobacco chewing habit and incorporation of nutritional supplements in the diet^{7,8}. At the moderate stage, conservative treatments like intralesional injections along with medical therapy have proven to be beneficial, and in the advanced stage, surgical intervention is the only one left⁹. OSMF can be treated using Acharya Charaka's methods for managing unexplained diseases because it cannot precisely be compared to any Mukharogas in the classical Ayurvedic texts¹⁰. Ayurveda is a science of life that incorporates a comprehensive approach to healthcare. It is one of the world's oldest medical systems. It can cure terminal illnesses including cancer, diabetes, asthma, and arthritis. The word Ayurveda is derived from 'Ayu' meaning life and 'veda' meaning knowledge. According to the World Health Organization, around 70% to 80% of people worldwide rely on non conventional medicines, mostly herbal¹¹. The high degree of heterogeneity and sparse data in a systemic review published in 2020¹² suggest that the published studies do not provide credible evidence to support the efficacy herbal antioxidants despite the fact that several studies^{10,13} suggest that antioxidants and natural agents appear to be effective in managing OSMF.

Oxitard capsules and Immusante tablets were very recently introduced in the market of which Oxitard capsules is an antioxidant and Immusante tablets provide broad-spectrum immunotherapeutic support. Considering the properties of being antioxidant and immunotherapeutic, these medicines can be used in the initial stage of OSMF patients. Oxitard has been successfully tried among OSMF patients and has provided a beneficial effect. However, the evidence of the efficacy of both medications in treating is scarce. In light of this, the present randomized controlled trial was conducted to evaluate and compare the role of Oxitard and Immusante in the management of the initial stages of oral submucous fibrosis.

Material and Methods

The present prospective study was conducted in the Department of Oral Medicine and Radiology of Dr. D.Y. Patil Dental College and Hospital, Pune from January to October 2022. Ethical clearance was obtained from the institutional sub-ethics committee prior to the beginning of the trial. The trial was registered prospectively in the Clinical Trials Registry-India (ICMR-NIMS) [CTRI/2021/09/036499]. The sample size was calculated using the mean and standard deviation (S.D.) reported in a previous publication¹⁴ on Oxitard in improving mouth opening (primary endpoint). Considering the mean₁ of 21.6, mean₂ of 18.8, S.D.₁ of 2.6, and S.D.₂ of 1.8 as per the publication, 0.05 α error and 95% power of the study, the effect size obtained was 1.34. Based on this the sample size estimated for the present study was 32. The sample had to be increased from 32 to 36 considering 10% lost to follow up. Patients of either gender aged 18 years and above with OSMF were included in the study. A consecutive sampling technique was used to recruit patients with Stage I or Stage II of OSMF as classified by More et al. Those with any evidence of severe psychiatric, cardiac, gastrointestinal or metabolic disorders, edentulous patients and pregnant or lactating

women were excluded from the study. Detailed family and medical histories including a history of associated habits and the course of the disease were recorded. The chief investigator was trained prior to beginning the study. Inter-examiner reliability was assessed and was found to be 0.87 which showed perfect agreement. The random allocation of subjects to either of the groups was done using a computer software program that generated random sequences. These random numbers were followed for allocation of the different medications to the subjects. The medications with strips were packed into sequentially numbered opaque sealed envelopes thus offering allocation concealment. A third individual aware of the allocation of the subjects provided the medications and explained the usage to the participants. This was an open-labelled trial as these medications were not removed from their packaging in order to preserve the sterility of the drugs. The subjects were divided equally in 2 groups, Group A (Oxitard), (Himalaya Wellness Company, Bengaluru, Karnataka) and Group B (Immusante), (Himalaya Wellness Company, Bengaluru, Karnataka). Group A was told to take 2 Oxitard capsules twice daily and Group B was told to take 2 Immusante tablets twice daily. All the clinical parameters were thoroughly recorded. Mouth openings were measured by measuring the distance between the centre of the incisal edges of the maxillary central incisors and the mandibular central incisor at maximum opening of the mouth. Tongue protrusion was measured as the distance between the upper central incisor and the tip of the tongue on protrusion. Presence, absence or reduction of other subjective symptoms such as burning sensation, difficulty in eating and eating-related pain (these were secondary parameters which were recorded using visual analogue scale) was done at regular intervals at baseline, 1 month and 3 months. A gingival index and plaque index were recorded at baseline, 1 month and 3 months for all patients in both groups¹⁴. The data were collected and analysed using International Business Machines (IBM) Statistics Package

for Social Sciences Statistics for Windows version 20 (IBM Corp., Armonk, New York, United States of America). The results are presented as numbers and percentages. The Kolmogorov–Smirnov test was used to test the normality of the data. Since the data were normal, the Repeated Measures ANOVA and Bonferroni post hoc test were applied to test the hypothesis. A $p\text{-value} \leq 0.05$ was considered to indicate statistical significance.

Results

There were 31 males and 5 females with a mean age of 39 years out of which 83% consumed smokeless tobacco and 9% had the habit of consumption of both smoked and smokeless tobacco product and 8% consumed only the smoked tobacco products. Amongst the consumed tobacco products Pan was the most consumed variety i.e., 28%. Khaini was also significantly used with around 14%. Around 11% of them consumed mawa. 47% of them consumed other tobacco products like mishri, gul and cigarettes. Out of the 36 participants, 23 had consumed tobacco for 15 years or more. The means and standard deviations in both the groups for mouth opening, tongue protrusion, cheek flexibility, burning sensation, difficulty in speech, and difficulty in eating are presented in Figure 1. Intra-group comparisons showed statistically significant ($p\text{-value} \leq 0.05$) improvements in clinical parameters, i.e, mouth opening, tongue protrusion and cheek flexibility, plaque index and gingival index, in both groups when considered at the three different time points (Table 1). On post hoc analysis there was significant improvement ($p\text{-value} \leq 0.05$) in the clinical outcomes in both the Oxitard and the Immusante groups when compared between baseline versus 1 month and 1 month versus 3 months. The effect of taking the Oxitard capsules showed significant improvement in subjective symptoms of burning sensation, difficulty in speech and difficulty in eating ($p\text{-value} \leq 0.05$). On post hoc analysis, difficulty in speech showed improvement in baseline versus

3 months. Taking Immusante tablets showed improvement in difficulty in speech from baseline (0.66 ± 1.87) to 3 months (0.11 ± 0.32) but was statistically non-significant. In-between group comparisons showed improvement in mouth opening in the Oxitard group from 29.05 to 34.66 and in the Immusante tablet group from 30.16 to 35.77, but both were statistically non-significant (Table 2). In between group comparisons of Oxitard capsule and Immusante tablet showed a significant difference ($p\text{-value} \leq 0.05$) in cheek flexibility at 3 months. Subjective symptoms showed no significant differences in between group comparisons at three different time points (Table 3). Table 3 shows a decreased accumulation of plaque and improvement in gingival health but these findings were statistically non-significant. None of the patients reported any potential side effects. None of the patients withdrew from the study due to any reason.

Discussion

Oral submucous fibrosis is a disease that mostly affects people from South Asian and East Asian populations. However, the condition can also be found prevailing among the populations of Bangladesh, Sri Lanka, India, Pakistan, Nepal, China, Taiwan, the Pacific Islands, Melanesia, and Micronesia. The condition was formerly believed to be multifactorial and a number of potential causes were identified that included autoimmune disease, dietary deficiencies, genetic susceptibility, and local irritants like chillies. However, the current research provides conclusive evidence on the areca nut, which is commonly consumed by Asians, being the causative agent for OSMF¹⁵. The areca nut primarily consists of flavonoids and alkaloids. Due to the constant contact of areca nuts with the oral mucosa, the flavonoids and alkaloids undergo metabolism post-absorption from the mucosal cells and cause irritation and chronic inflammation of the mucosa on contact¹⁶. There has been, in recent years, a significant increase in the use of

areca nut among the people. A study reported 81.02% of school children consumed local brands of sweetened areca nut with the majority found among the government school children¹⁷. The habit was also reported at a very young age among 4- and 6-year-old pre-schoolers because of

some advantageous myths related to the use of areca nut¹⁸. The increase in the burden of OSMF in India and across the nations is evident from the increase in the reported publications which rose 66.26% from the year 1967 to 2016 with India contributing highest toward the increase¹⁹.

Table 1 Effect of Oxitard and Immusante on clinical parameters

Parameter	Oxitard		Immusante	
	Mean±S.D.	p-value	Mean±S.D.	p-value
Mouth opening				
Baseline	30.16±3.41	<0.0001*	29.05±1.76	<0.0001*
1 month	32.27±3.35		31.22±2.21	
3 months	35.77±2.66		34.66±3.25	
Tongue protrusion				
Baseline	21.77±6.18	<0.0001*	22.50±6.71	<0.0001*
1 month	24.44±6.41		24.55±6.73	
3 months	27.22±6.26		27.05±6.51	
Cheek flexibility				
Baseline	20.11±7.07	<0.0001*	22.50±5.72	<0.0001*
1 month	21.78±6.58		24.61±4.99	
3 months	23.52±6.82		27.55±4.84	
Burning sensation				
Baseline	4.05±1.79	<0.0001*	4.38±2.19	<0.0001*
1 month	2.33±1.72		2.61±1.46	
3 months	0.83±1.33		0.72±1.07	
Difficulty in speech				
Baseline	0.72±1.01	0.008*	0.66±1.87	0.116
1 month	0.33±0.59		0.33±0.97	
3 months	0.00±0.00		0.11±0.47	
Difficulty in eating				
Baseline	2.44±1.58	<0.0001*	2.88±2.63	<0.0001*
1 month	1.44±1.29		1.55±1.68	
3 months	0.38±1.14		0.11±0.32	
Plaque index				
Baseline	0.77±0.52	0.003*	0.85±0.46	<0.0001*
1 month	0.33±0.34		0.28±0.20	
3 months	0.43±0.43		0.27±0.16	
Gingival index				
Baseline	0.95±0.51	<0.0001*	1.15±0.49	0.002*
1 month	0.33±0.33		0.39±0.35	
3 months	0.37±0.35		0.49±0.67	

*Statistically significant, S.D.=standard deviation



Figure 1 Bar diagram representing mean and standard deviations in oxitard and immusante groups for mouth opening, tongue protrusion, cheek flexibility, burning sensation, difficulty in speech, and difficulty in eating

Table 2 Differences in the mean clinical parameters in OSMF patients at different time intervals using a post hoc Bonferroni test

Parameter	Baseline vs 1 month	p-value	Baseline vs 3 months	p-value	1 month vs 3 months	p-value
Mouth opening						
Immusante	2.11	<0.0001*	5.61	<0.0001*	3.50	<0.0001*
Oxitard	2.16	0.001*	5.61	<0.0001*	4.44	<0.0001*
Tongue protrusion						
Immusante	2.05	<0.0001*	4.55	<0.0001*	2.50	<0.0001*
Oxitard	2.66	0.026*	5.44	<0.0001*	2.77	<0.0001*
Cheek flexibility						
Immusante	2.11	0.015*	5.05	<0.0001*	2.94	<0.0001*
Oxitard	1.67	0.002*	3.41	<0.0001*	1.73	<0.0001*
Burning sensation						
Immusante	1.77	<0.0001*	3.66	<0.0001*	1.88	<0.0001*
Oxitard	1.50	<0.0001*	3.22	<0.0001*	1.72	<0.0001*
Difficulty in speech						
Immusante	0.33	0.48	0.55	0.34	0.22	0.31
Oxitard	0.38	0.09	0.72	0.024*	0.333	0.088
Difficulty in eating						
Immusante	1.33	0.005*	2.77	0.001*	1.44	0.005*
Oxitard	1.00	0.001*	2.05	<0.0001*	1.05	<0.0001*
Plaque index						
Immusante	0.56	<0.0001*	0.58	<0.0001*	0.01	1.000
Oxitard	0.44	0.002*	0.339	0.009*	0.106	1.00
Gingival index						
Immusante	0.75	<0.0001*	0.65	0.007*	0.10	1.000
Oxitard	0.617	<0.0001*	0.572	0.001*	0.044	1.00

*Statistically significant, OSMF=oral submucous fibrosis

Table 3 Mean differences in clinical parameters between Immusante and Oxitard OSMF patients at different time intervals

Parameter	Baseline	p-value	1 month	p-value	3 months	p-value
Mouth opening						
Immusante	30.16	1.11	32.27	1.05	35.77	0.27
Oxitard	29.05		31.22		34.66	
Tongue protrusion						
Immusante	22.50	0.72	24.55	0.96	27.05	0.93
Oxitard	21.77		24.44		27.22	
Cheek flexibility						
Immusante	22.50	0.27	24.61	0.15	27.55	0.04*
Oxitard	20.11		21.78		23.52	
Burning sensation						
Immusante	4.38	0.62	2.61	0.91	0.72	0.78
Oxitard	4.05		2.55		0.83	
Difficulty in speech						
Immusante	0.66	0.91	0.33	1	0.11	0.32
Oxitard	0.72		0.33		0.00	

Table 3 (continued)

Parameter	Baseline	p-value	1 month	p-value	3 months	p-value
Difficulty in eating						
Immusante	2.88	0.54	1.55	0.82	0.11	0.32
Oxitard	2.44		1.44		0.38	
Plaque index						
Immusante	0.85	0.64	0.28	0.64	0.27	0.14
Oxitard	0.77		0.33		0.43	
Gingival index						
Immusante	1.15	0.24	0.39	0.60	0.49	0.52
Oxitard	0.95		0.33		0.37	

*Statistically significant, OSMF=oral submucous fibrosis

The treatment of OSMF has been modified from time to time. The role of drugs in the management of OSMF was discussed in a review by Jiang and Hu and Fedorowicz et al. A review by Jiang and Hu demonstrated no satisfactory results of the use of drugs on the OSMF condition²⁰. The use of alternative therapies for the management of OSMF, such as aloe vera, turmeric, tulsi, spirulina, turmeric with black pepper, Ksheerabala Taila, kavala (gargling), nigella sativa, Madhupippalyadi Yoga, and Oxitard, has been the subject of several research studies in recent years²¹.

In the present randomized controlled trial the role of Oxitard was compared with Immusante in the management of the initial stages of oral submucous fibrosis. Though Oxitard has been in use for a long time, studies on its effectiveness are scarce in the literature. Moreover, the other medication, Immusante, is a new drug that has not yet been evaluated. Considering this, the results of the present study are compared with the available Oxitard literature and other herbal products used for OSMF. When Oxitard and Immusante were compared at different time intervals, baseline, 1 month, and 3 months, both the therapies proved to be significantly effective in increasing the mouth opening, tongue protrusion, cheek flexibility, reducing the burning sensation, limiting the difficulty in speech, and difficulty in eating. The effects of the therapy were also commendable for the gingival condition with a significant reduction in

plaque and gingival index. The results of the present study were in accordance with a study reported by Patil et al. wherein the effectiveness of Oxitard was evaluated at baseline, 1 month, 2 months, and 3 months. Oxitard demonstrated significant clinical improvement in mouth opening and tongue protrusion from baseline values of 19.1 and 10.1 mm to 3 months values of 21.5 mm and 24.5 mm, respectively. The subjective symptoms also showed a noteworthy improvement with significant reductions in burning sensation and difficulty in speech. At baseline a burning sensation and difficulty in speech were reported by 60% and 56% of the patients, which was reduced to 3% and 10% at 3 months²².

The results of the present study also agreed with a few more studies. A study by Patil et al. evaluated changes in the clinical and symptomatic parameters in patients with OSMF at baseline, 1 month, 2 months, and 3 months. Like the present study, significant improvements were observed in patients who were treated with Oxitard. At 3 months, the mouth opening had improved from 19.1 mm to 31.5 mm and tongue protrusion from 10.1 mm to 24.5 mm. Before starting the treatment, 56% reported difficulty in speech which significantly dropped down to only 10% of the patients. Likewise, difficulty in swallowing was present among 57% of the patients that was reduced and was reported by only 7% of the patients at 3 months of treatment¹². The same author

conducted extensive research on the use of Oxitard as an antioxidant in OSMF patients. Another study with a similar design evaluating the effectiveness of Oxitard at baseline, 1 month, 2 months, and 3 months found results similar to the present study. The mouth opening improved from 19.1 mm to 31.5 mm and tongue protrusion from 10.1 mm to 24.5 mm from baseline to 3 months, respectively. Difficulty in speech was also significantly reduced with initial reports in 56% of the patients and after 3 months in only 10% of the patients. Burning sensation was also reduced among a significant number of the patients with an initial count of 60% and after 3 months of treatment with Oxitard to 3%. Improvements were also found in the plaque index and gingival index with significant reductions in their scores from 2.32 and 2.18 to 2.30 and 2.16, respectively, from baseline to 3 months²³. Difficulty in mouth opening was significantly reduced following 3 months of Oxitard treatment in a study by Singh et al.²⁴.

One systematic review has been conducted on understanding the role of antioxidants in management of clinical and symptomatic parameters of oral submucous fibrosis patients, but it failed to provide any conclusive statements. Various studies included in the review did state that antioxidants were effective in managing OSMF, but the heterogeneity across the studies and the limited number of studies reported in the literature does not permit firm conclusions¹². In contrast, another systematic review and network meta-analysis reported that Oxitard was the most effective compared to all other interventions in improving mouth opening among OSMF patients²⁵. Though Oxitard has been shown to be effective in various studies, it also has some associated side effects. Two studies by Patil et al. reported abdominal discomfort among the included patients. Both studies reported this side effect in 13% of the patients^{14,23}. However, none of the participants from either group reported any potential side effects during this study. The role of immunomodulatory drugs in the management

of OSMF has shown similar results with that of the present study. Immusante, an immunomodulator used in the present study, is a new drug and lacks evidence thus the results of the present study are compared with other immunomodulators used in the literature. A prospective randomized controlled trial demonstrated significant improvement in the objective criteria like mouth opening, tongue protrusion, and relief from perioral fibrotic bands. Further, subjective criteria like a burning sensation in the mouth and difficulty in speech also recorded significant improvements²⁵.

When both of these drugs were compared in the present study, it was observed that there was no significant difference between the groups, indicating that both treatments were equally effective in reducing a burning sensation, difficulty in speech and difficulty in eating, while increasing mouth opening, tongue protrusion, and cheek flexibility. The two drugs also showed comparable effects in reducing the plaque and gingival index scores and improving the gingival health except for cheek flexibility which was significantly higher in Group A compared to Group B at 3 months. However, the management of OSMF cannot be accomplished with a single form of therapy. The triple treatment used concurrently is more effective. The potential for managing precancer OSMF using naturally occurring herbal remedies is enormous. Particularly in individuals with compromised health, they can be used for a longer period without causing any side effects²⁷. Additionally, some recently introduced compounds have been demonstrated to have a significant influence on the oral environment²⁸. The use of lysate²⁹ and postbiotics³⁰ can modify certain clinical and microbiological parameters in periodontal patients, so these products should also be considered in future clinical trials, as adjuvants and in combination with Oxitard capsules and Immusante tablets for oral submucous fibrosis management.

With the advantages of these drugs, it is also important to assess the side effects and weigh the benefits against the risks involved. One study reported that the drugs given as capsules had more associated side effects compared to the tablet form due to slower drug delivery³¹. Nevertheless, capsules demonstrate rapid action when taken orally. For high treatment success rates and to prevent adverse drug responses, proper medication usage is crucial. When taking these medications, patients should adhere to strict guidelines that include taking the proper dosage at the right time for the right duration of time. While swallowing, the particles of the drugs may stick to the oesophagus and reduce the bioavailability of the active drug³².

Limitations

The present study had certain limitations. Firstly, the follow-up period of the study was short at only 3 months; thus, further studies with longer follow-up periods are recommended. Secondly, the sample size of the study was small (36 patients with OSMF), thus future studies with larger sample sizes are recommended. Thirdly, the present study did not document adverse effects associated with the two drugs, thus further studies are essential to understand the safety aspect of these drugs in OSMF patients.

Conclusion

The study concludes that both the tested drugs were equally effective in the management of early stages of oral submucous fibrosis. Quitting of the habit along with the intervention had a significant effect on the symptoms of OSMF. Antioxidants and immunomodulating agents have proven to be a boon for improving the clinical outcomes of submucous fibrosis. Strict laws should be put in place to curb the menace of tobacco. Not much difference has been reported in terms of the two study medications with clinical parameters but the new drug Immusante showed considerably significant results considering the

cost effectiveness of the drug. To reach a more certain conclusion on the effectiveness of both medications in the treatment of OSMF, multicentre prospective studies for assessing the effects of both medicines are recommended.

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