Open Access Journal
Indian Journal of Medical Research and Pharmaceutical Sciences
July 2016; 3(7) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.58937 Impact Factor: 3.052

EFFICACY AND SAFETY ASSESSMENT OF OXITARD, A HERBAL ANTIOXIDANT IN ORAL SUBMUCOUS FIBROSIS- AN OBSERVATIONAL CLINICAL STUDY

Shwetha V, MDS*, Yashoda Devi B K, MDS
*Assistant professor, Department of Oral medicine and Radiology, Faculty of Dental Sciences, MSRUAS, Bangalore
Senior Professor, Department of Oral medicine and Radiology, Faculty of Dental Sciences, MSRUAS, Bangalore

Keywords:
Oral submucous fibrosis, oxitard capsules, mouth opening, burning sensation.

Abstract

Objectives: Oral submucous fibrosis (OSMF) is a potentially malignant condition characterized by inflammation, formation of fibrotic bands due to collagen deposition which limit mouth opening. Till date no definitive therapy is available for the management of OSMF. This study was carried out to determine the safety and efficacy of oxitard in the treatment of OSMF.
Methods: 60 subjects with clinically and histopathologically diagnosed OSMF were included in the study. Capsule Oxitard was administered to all patients at a dose of 2 capsules twice daily for a period of 3 months. During every clinical visit the mouth opening was measured and symptoms associated with the lesions were graded on VAS. Results were analysed using ANOVA and student t test.
Results: Clinical improvement in mouth opening and symptoms of burning sensation as measured by the VAS scale following oxitard therapy was significant.
Conclusion: Oxitard proves to be relatively safe, noninvasive and efficacious in bringing about significant clinical improvement in symptoms like mouth opening, reduction in burning sensation in patients with oral submucous fibrosis.

Introduction

Oral submucous fibrosis is a chronic insidious disease and a well recognized potentially malignant condition of the oral cavity characterized by inflammation and a progressive fibrosis of the lamina propria and deeper connective tissues. Although occasionally preceded by vesicle formation, it is always associated with juxtaepithelial inflammatory reaction followed by a fibroelastic change of lamina propria with epithelial atrophy leading to stiffness of oral mucosa, causing trismus and inability to eat[1].

The main etiological agent causing the disease is confirmed as arecoline in arecanut[2]. Pan masala and gutkha users are more severely affected due to their fine particulate nature, with more particle adhesion to the traumatized mucosa, which leads to morphological changes and membrane damage[1].
This continuous local irritation by pan 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, according to the level of ROS production. These events can lead to preneoplastic lesions in the oral cavity and subsequent to malignancy in chronic use[1]. The malignant transformation rate of OSF has been reported to be around 7.6% over a 17-year period[3].

Pathogenesis The pathogenesis of OSF is not well established, although a number of possible mechanisms have been suggested. Pathogenesis is believed to involve juxta-epithelial inflammatory reaction and fibrosis in the oral mucosa, probably due to increased cross-linking of collagen through up-regulation of lysyl oxidase activity. Fibrosis, or the buildup of collagen, results from the effects of arecanut, which increases collagen production (e.g., stimulated by arecoline, an alkaloid) and decreases collagen degradation. Thus, OSF is now considered a collagen metabolic disorder[4].

Indian Journal of Medical Research and Pharmaceutical Sciences
July 2016; 3(7) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.58937 Impact Factor: 3.052

Various treatment modalities have been tried to treat patients suffering from this disease. Medical interventions include dietary supplementation with vitamins, antioxidants, corticosteroid therapy, proteolytic agents such as hyalronidase and placental extracts and anticytokines[5]. Severe trismus and refractory cases are treated by surgical excision of fibrous bands[1].

ROS is found to play a significant role in both pathogenesis and malignant transformation. Therefore antioxidants should have significant therapeutic benefits in managing the disease and preventing carcinogenesis in the background of fibrosis[2]. In this regard lycopene has been studied extensively and its therapeutic efficacy has been proven. This study was planned to evaluate the efficacy of Oxitard, a polyherbal formulation in the management of Oral submucous fibrosis.

Materials and Methods

This study was conducted in the Department of Oral Medicine and Radiology, Faculty of Dental Sciences, M S Ramaiah University of Applied Sciences, Bengaluru. The study population comprised of 60 adult patients of either sex aged between 18-60 years diagnosed clinically and histopathologically with oral submucous fibrosis with difficulty in mouth opening and pain. Ethical clearance was obtained from the institutional review board. Prior to conducting the study, the subjects were explained the need for the study and a written consent was taken from them. Patients who were not taking any medications for OSMF previously were included in the study.

Patients with known systemic diseases such as bleeding and clotting disorders, cardiac disorders, diabetes mellitus, renal or hepatic disorders, collagen diseases like scleroderma, thromboembolic disorders, patients with known history of allergy to similar pharmaceutical products, its components or ingredients, pregnant and lactating women were excluded from the study.

A thorough case history was elicited, which included a detailed medical and habit history. Clinical examination of the oral cavity was performed for all the subjects. VAS scale was used to record the severity of symptoms viz burning sensation in the patients, with the severity of symptoms extending from a numerical 0 (no pain or discomfort) to 10 (severe most pain /discomfort). Patients' maximum mouth opening was measured using vernier calipers and a clinical staging was done based on criteria given by Khanna. Mouth opening was measured by measuring the distance between the centre of incisal edges of maxillary central incisors and mandibular central incisor at maximum opened mouth position. In edentulous patients, the interalveolar distance along the midline was measured. The subjects were counselled to quit the habit during the study period. Capsule Oxitard was administered to all patients at a dose of 2 capsules twice daily for a period of 3 months. During every clinical evaluation the mouth opening was measured and symptoms associated with the lesions were graded on VAS.
Baseline liver function tests, serum urea and creatinine were done for these patients to rule out any existing hepatic pathology and the tests were repeated once every month during the study period and one month following cessation of treatment. Patients were asked to report any adverse reactions or constitutional symptoms immediately. At monthly follow up visits, mouth opening and VAS scale were recorded.

Statistical Analysis:-
Descriptive and inferential statistical analysis was carried out and results on continuous measurement are presented on Mean ±SD (Min- Max) and results on categorical measurements are presented in number(%). Significance is assessed at 5% level of significance. Analysis of Variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients, Student t test(two tailed , independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Levenes test for homogeneity of variance has been performed to assess the homogeneity of variance and Student t test(two tailed, dependent) has been used to find the significance of study parameters on continuous scale within each group ($p \leq 0.01$ was considered strongly significant, $0.01<p\leq.05$ was considered moderately significant). The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

Indian Journal of Medical Research and Pharmaceutical Sciences
July 2016; 3(7) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.58937 Impact Factor: 3.052

Results

All subjects included in the present study were assessed for improvement in the mouth opening and reduction in burning sensation which was recorded in terms of VAS. All the data was recorded at 3 different visits for 3 months following oxitard therapy.

Among 60 subjects, 40 (66.7%) were male patients and 20 (33.3%) were females (Table 4). All the subjects were smokeless tobacco users. None of them were smokers or snuff dippers. Clinical improvement in mouth opening and symptoms of burning sensation as measured by the VAS scale following oxitard therapy was significant (Table 1). The differences in mouth opening at baseline visit and consecutive visits was significant (Table 2). Comparative evaluation of VAS score from baseline visit to other visits was also significant (Table 3).

Discussion

Oral submucous fibrosis (OSMF) is a potentially malignant disorder of the oral mucosa, mainly associated with the practice of chewing gutka and betel quid[6]. It has been reported in the Indian literature since the time of Sushruta as 'Vidari'. In 1952, Schwartz was the first to report a case of this type and in 1956, Paymaster identified its precancerous nature. In 1966, Pindborg and Sirsat defined OSF as, "an insidious chronic disease affecting any part of the oral cavity and sometimes the pharynx. Although occasionally preceeded by and /or associated with vescicle formation, it is always associated with juxtaepithelial inflammatory reaction followed by fibroelastic changes in the lamina propria, with epithelial atrophy leading to stiffness of the oral mucosa causing trismus and inability to eat" [7]. Paymaster first described the malignant potential of OSF in 1956, the rate of which has been estimated to be 7- 13% recently. Pindborg in 1972 put forward five criterias to prove that the disease is precancerous. They included, high occurrence of OSF in oral cancer patients, higher incidence of SCC in patients with OSF, histological diagnosis of cancer without any clinical suspicion in OSF, high frequency of epithelial dysplasia and higher prevalence of leukoplakia among OSF cases[8]. Recently it has been proposed that oral cancers arising in OSF constitute a clinicopathologically distinct disease, the differences of which are believed to arise from differential mechanisms of arecanut carcinogenesis[2].

The pathogenesis of oral submucous fibrosis is obscure, and till date, no definitive therapy is available for the management of OSMF[6]. Various treatment modalities have been advocated for the management of oral submucous fibrosis but have not been successful so far. The first step of preventive measure should be in advising the patient to discontinue the habit which can be encouraged through education, counseling and advocacy. Medical treatment includes steroids steroids, placental extracts, IFNγ, lycopene, pentoxifylline, surgical excision, laser removal etc [9].

Oxitard is a polyherbal formulation containing extracts of Mangiferaindica, Withaniasomnifera, Daucuscarota, Glycyrrhizaglabra, Vitisvinifera, powders of Emblica officinalis and Yashadabhasma; and oils of Triticumsativum. Each oxitard capsule contains

Extracts	Mangifera Indica	94mg
	Withania Somnifera	71mg
	Daucus Carota	47mg
	Glycyrrhiza glabra	29mg
	Vitis Vinifera	12mg
Powders	Emblica officinalis	141mg
	Sygium aromaticum	29mg
	Yashada bhasma	2.5mg
Oil	Triticum sativum	6.5mg

Mangifera Indica is shown to have antioxidant and immunomodulatory effect[10], Withania Somnifera (Ashwagandha,WS) possesses anti-inflammatory, antitumour, antistress, antioxidant, immunomodulatory, hemopoietic and rejuvenating properties[11]. Daucus carota possesses anti-inflammatory properties[12] and Vitis Vinifera possesses antioxidative, anti-inflammatory and antimicrobial properties[13]. Glycyrrhiza glabra has immunomodulatory and anti-inflammatory properties. Emblica officinalis is a rich source of vitamin C and is a potent antibiotic. Yashada bhasma contains zinc which plays a significant role in protein synthesis, cell division and wound healing. Triticum sativum is a rich source of minerals and has an antioxidant property[9].

Indian Journal of Medical Research and Pharmaceutical Sciences
July 2016; 3(7) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.58937 Impact Factor: 3.052

Different management protocols have been tried in the management of symptoms in OSMF. The ingredients of arecanut induce excessive reactive oxygen species which damages the cell structures, including lipids and membranes, proteins and nucleic acids. Moreover vitamin deficiency, iron deficiency anemia and malnutrition can derange the repair of the inflamed oral mucosa, leading to defective healing and the resulting atrophic oral mucosa is more susceptible to the effects of arecanut. Here comes the role of antioxidant vitamins that stabilize and deactivate the free radicals before they attack cells [14].

In our study 66.7% were males while 33.3% were females indicating a male predominance of the condition. 33.3% of the patients fell into the age group of 20-29 years which was similar to the findings of Selvam et al [14] (Table 5) . None of the patients reported any adverse reaction to the administered drug. Singh et al showed a significant improvement in mouth opening with oxitard capsules [15]. The present study showed significant improvement (p=0.001) in mouth opening and burning associated with the lesion as measured by VAS scale.
Sudarshan et al. showed an improvement of 80% in burning sensation in the aloe vera group whereas 65.7% patients in the antioxidant group showed improvement in burning sensation [6]. A comparative study of efficacy of oxitard and aloe vera in OSMF by Santosh et al showed significant improvement in mouth opening(p=0.0005), tongue protrusion(p=0.0005), pain associated with the lesion(p=0.0003), difficulty in swallowing(0.0000) and speech (p=0.0001) in the oxitard group when compared to the aloe vera group [9]. However the improvements in burning sensation were not statistically significant (p=0.002). However in our study a significant improvement in burning sensation (p value <0.001**) compared to baseline values were observed.
Treatment with injection of steroids, placental extracts and hyaluronidase though may be palliative is invasive and may in turn result in rebound fibrosis and patient discomfort. A multi disciplinary palliative care approach is the need of the hour for patients with this chronic fibroblastic scarring disease developing severe trismus refractory to conventional therapies. So being a noninvasive and safe mode of treatment oxitard can be considered to be an effective management protocol for oral submucous fibrosis. However further elaborate studies with large sample size are needed to ascertain the role of these antioxidants.

References

1) Devesh T, Sunil D, Tripathi YC. Oral Submucous fibrosisi(OSMF): Premalignant threat to humanity with special reference to India. SMU Medical Journal.2015;2(1):281-290.
2) Ekanayaka RP, Tilakaratne WM. Oral Submucous Fibrosis: Review on mechanisms of pathogenesis and malignant transformation. J Carcinogene Mutagene.2013;1-11.(S5:002.doi:10.4172/2157-2518.S5-002)
3) PC Anila N. Cystatin C: Its role in pathogenesis of OSMF. J Oral Biology and Craniofacial Research.2014;4:42-46.
4) Ajit A, Miriam PR, Lewei Z, Sumanth KN. Oral submucous fibrosis, a clinically benign but potentially malignant disease: Report of 3 cases and review of literature. JCDA 2008;74(8):735-740.
5) Fareedi MA, Prasant MC, Ashok P, Vinit A, Safiya T, Rashmi D. Oral submucous fibrosis: medical management. GJMEDPH 2012;1(1): 12-19.
6) Ramachandran S, Rajeshwari GA, Vijayabala GS. Aloe vera in the treatment for oral submucous fibrosis- a preliminary study. J Oral Pathol Med 2012;41:755-761.
7) Yoithapprabhunath TR, Maheshwaran T, Dineshshankar J, Anusushanth A, Sindhuja P, Sitra G. Pathogenesis and therapeutic intervention of oral submucous fibrosis. J Pharm Bioall Sci 2013;5(1): 85-88.
8) Gupta MK, Shubhangi M, Raju R, Imtiyaz. Oral submucous fibrosis- current concepts in etiopathogenesis. People's Journal of Scientific Research 2008;1:39-44.
9) Santosh P, Vishal H, Sneha M, Santosh BS. Comparative study of efficacy of herbal antioxidants oxitard and aloe vera in the treatment of oral submucous fibrosis. J Clin Exp Dent 2014;6(3):e265-70.
10) Shah KA, Patel MB, Patel RJ, Parmar PK. Mangifera Indica (Mango). Pharmacogn Rev. 2010; 4(7): 42–48.
11) Lakshmi-Chandra M, Betsy BS, Simon D. Scientific basis for therapeutic use of Withania somnifera (Ashwagandha): a review. Alt Med Rev 2000;5(4): 334-346.
12) Mani V, Kumar KG, Milind P. Antinociceptive and anti-inflammatory properties of Daucus carota seeds extract. Journal of Health Science 2006; 52(5): 598-606.

Indian Journal of Medical Research and Pharmaceutical Sciences
July 2016; 3(7) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.58937 Impact Factor: 3.052

13) Marjan N, Hossein H. Review of the pharmacological effects of *Vitis vinifera* (Grape) and its bioactive compounds. Phytotherapy Research 2009;23(9): 1197-1204.
14) Niranzena PS, Arjun AD. Lycopene in the management of oral submucous fibrosis. Asian J Pharm Clin Res 2013;6(3):58-61.
15) Singh BP, Neelam M, Vishal S, Palani. Evaluation of the role of oxitard capsules in the treatment of oral submucous fibrosis. The Antiseptic 2009;106(10):503-507.

	Mouth opening	Burning Sensation
Baseline	19.13±2.04	7.43±1.49
Visit 1	22.43±4.04	5.85±1.47
Visit 2	24.29±4.08	4.08±1.52
Visit 3	25.77±4.70	2.42±1.63

Table1. Effect of oxitard in improving mouth opening and symptoms of burning sensation (Mean values in mm)

Mouth opening	**Baseline**	**Visit 1**	**Visit 2**	**Visit 3**
Min-Max	14.00-24.00	14.00-34.00	17.00-34.00	17.00-36.00
Mean ± SD	19.13±2.04	22.43±4.04	24.29±4.08	25.77±4.70

Table 2: Mouth opening at different visits P value <0.001‡ compared to baseline values

VAS Score	**Baseline**	**Visit 1**	**Visit 2**	**Visit 3**
Min-Max	4.00-10.00	2.00-9.00	0.00-7.00	0.00-6.00
Mean ± SD	7.80±1.90	5.85±1.47	4.08±1.52	2.42±1.63

Table 3. Comparative evaluation of VAS score at baseline, Visit 1, Visit 2 and Visit 3 P value <0.001‡ compared to baseline values

Significant figures
*Suggestive significance (P value: 0.05<P<0.10)
† Moderately significant (P value:0.01<P ≤ 0.05)

‡ Strongly significant (P value : P≤0.001)

Gender	**No. of patients**	**%**
Male	40	66.7
Female	20	33.3
Total	60	100.0

Table 4. Gender distribution of patients studied

Indian Journal of Medical Research and Pharmaceutical Sciences
July 2016; 3(7) ISSN: ISSN: 2349-5340
DOI: 10.5281/zenodo.58937 Impact Factor: 3.052

Age in years	No. of patients	%
20-29 yrs	20	33.3
30-39 yrs	11	18.3
40-49 yrs	17	28.3
50-59 yrs	10	16.7
60+ yrs	2	3.3
Total	60	100.0

Table 5. Age distribution of patients studied