Effectiveness of Antioxidants in Oral Submucous Fibrosis: A Retrospective Study

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Abstract

Background: Oral Submucous Fibrosis (OSMF) is defined as an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx. Although, occasionally preceded by and/or associated with vesicle formation, it is always associated with juxta epithelial inflammatory reaction followed by fibroelastic changes in lamina propria with epithelial atrophy leading to stiffness of oral mucosa causing trismus and difficulty in eating. It is a condition with increased oxidative stress leading to free radical release. Thus, the aim of the study is to assess the therapeutic effectiveness of antioxidants in oral submucous fibrosis.

Materials & Methods: Retrospective analyses of 52 clinically diagnosed OSMF patients were included in the study. The habit history was recorded. The patients were administered systemic antioxidants after habit cessation. Therapeutic effectiveness was assessed by analyzing the recorded inter incisal distance measurement and Visual Analog Scale (VAS) response at baseline, 15 days, 30 days and 45 days.

Results: OSMF were reported maximum in 31 to 40 years (28.8%) with a male predilection (94%). Predominant site was right and left buccal mucosa (88.4%). Clinical grade II (44.2%) and grade III (38.5%) of OSMF were more prevalent. A paired t test performed for assessing mouth opening and Visual Analog Scale (VAS) preoperatively and postoperatively revealed significance value of p<0.05 and p<0.01 respectively.

Conclusion: The study concludes that habit cessation with a combination of antioxidants, multivitamins and minerals rapidly decrease the burning sensation and a significant increase in mouth opening.

Keywords: Antioxidants; Habits; Mouth opening; Oral Submucous Fibrosis (OSMF); VAS

Introduction

OSMF is defined as an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx. Although occasionally preceded by and/or associated with vesicle formation, it is always associated with juxta epithelial inflammatory reaction followed by fibroelastic changes in lamina propria with epithelial atrophy leading to stiffness of oral mucosa causing trismus and difficulty in eating. [1] OSMF is also called as ‘diffuse oral submucous fibrosis’, ‘idiopathic palatal fibrosis’, ‘sclerosing stomatitis’, ‘juxta epithelial fibrosis’. [2] OSMF has multiple etiological agents [3,4] with areca nut use being the most predominant. [5] Arecodine, an active alkaloid found in betel nuts stimulates fibroblasts to increase production of collagen by 150%. [6] Studies have shown association of OSMF with HLA-DR antigens. [7] Antioxidants and cytokines, Glutathione S-transferase are part of the system. Increased association has been reported with GSTT1 and GSTM1, CYPIA phenotypes. [8] Others lesser known proposed risk factors are hot spicy food like chillies, [9] HLA-AIO, HLA-BT, HLA-DR3 alleles and iron deficiency. [10,11] They are more prevalent in Southeast Asian countries such as India, Bangladesh, Sri Lanka, Pakistan, and Taiwan. Prevalence rate in India is 0.2%-0.5%. [12] OPMD has high risk of malignant transformation. [13,14] Malignant transformation rate is 3%-7.6%. [15,16] Salivary micro RNA is used for early detection.
detection for OPMD.\textsuperscript{[17]} Biopsy is the gold standard diagnostic aid.\textsuperscript{[18]} Management of OSMF is by both medical and surgical measures.\textsuperscript{[19]} Medical measures include steroids, antioxidants,\textsuperscript{[20]} minerals,\textsuperscript{[21]} vitamins, placental extracts, interferon gamma. Surgical management includes coronoidectomy, nasolabial flap, oral stent, CO\textsubscript{2} laser, buccal pad fat,\textsuperscript{[22]} split thickness graft, therabite and excision upto anterior tonsillar pillar.\textsuperscript{[23]}

Mechanism of action of antioxidants on OSMF is by separating the free oxygen radicals from susceptible molecules and also they lyse and inactivate the free radicals, thus boosting the body’s multilevel defense system against them and also rapidly repair the damage caused by free radicals.\textsuperscript{[24-39]} Previously our team has a rich experience in working on various research projects across multiple disciplines. Thus, the aim of the study is to assess the therapeutic effectiveness of antioxidants in oral submucous fibrosis.

Materials and Methods

A retrospective study was conducted in the oral medicine department from June 2019-May 2020. The following inclusion and exclusion criteria were used to retrieve data from the institutional database. The research was approved by the institutional ethical committee and Scientific Review Board (SRB). The ethical approval number for the study is SDC/SIHEC/2020/DIASDATA/0619-0320.

Inclusion criteria

• All clinical stages of OSMF.
• Patients who have come at least for 3 reviews.
• Patients records with habit cessation and antioxidant management.

Exclusion criteria

Patients who were previously under any other treatment like intralesional steroids or other medical and surgical management. Patients who have been under any combined treatment modality with antioxidants.

In this study, 52 patients were included in final analysis. Sampling bias was minimized as all stages (I-IVa) of OSMF were included. All demographic details, habit history with type of tobacco and habit duration were included. Staging of OSMF, type of antioxidant prescribed, interincisal distance measurements and VAS score which was measured preoperatively and subsequently at 15 days, 30 days and 45 days were obtained. The antioxidant prescribed was a combination of alpha lipoic acid, lycopene and selenium (commercially marketed as SM-Fibro). Retrieved data were first documented in an excel sheet then they were transferred to SPSS importing. The qualitative variables were sex, OSMF stage, type of tobacco used, habit cessation, antioxidant. The quantitative variables were age, duration of habit, mouth opening distance and VAS.

SPSS version IBM 20 was used. The independent variables were age, sex, stages of OSMF, habits, antioxidants. Dependent variables were mouth opening (interincisal distance) and VAS score. Correlation and association was analyzed using a Chi-square test for age, sex, habit with stage of OSMF. A paired t test used for assessing the interincisal distance preoperatively and postoperatively (15, 30, 45 days) and for VAS assessment, both preoperatively and postoperatively (15, 30, 45 days).

Results and Discussion

In this retrospective study, 52 OSMF patients of all clinical stages and who were treated with systemic antioxidants were included. The age group and gender of the study population was 31 to 40 years 28.8%; 21 to 30 years 21.2%; 41 to 50 years 21.2%; 51 to 60 years 21.2% and 61 to 70 years 7.7% [Graph 1] and OSMF was predominant in males 94.23% when compared to female 5.77% [Graph 2].

Graph 1: This bar graph represents the age distribution of the study population where the X axis represents the age group in years and Y axis represents the frequency in numbers of OSMF patients. In this study, the maximum patients (n=15) belonged to age group of 31 to 48 years (28.85%).

Graph 2: This bar graph represents the sex distribution of the study population where the X axis represents the sex (F: Female and M: Male) and Y axis represents the frequency in numbers of OSMF patients. Graph 2 shows that males (94.23%) were predominantly affected than females (5.77%).

The most common type of tobacco product used and duration of habit reveals pan chewing in 38.46% followed by areca nut
36.5%, hans 15.4%, gutka 5.8%, mawa 3.8% and maximum duration reported was 34 years 1.9%, minimum duration was 3 years 3.8% and most frequently reported duration was 13 years 13.5% [Graph 3, Graph 4].

**Graph 3:** This bar graph represents the type of tobacco products used by the study population, where the X axis represents the tobacco products and Y axis represents the frequency of the number of OSMF patients. In this study, the maximum patients consumed pan (38.46%) followed by areca nut (36.54%).

**Graph 4:** This bar graph represents the duration of tobacco products consumed by the study population where the X axis represents the duration in years and Y axis represents the frequency in numbers of OSMF patients. In this study, the maximum duration of tobacco consumption habit was 13 years (13.46%).

Frequency distribution of site and clinical grading of OSMF reveals the right and left buccal mucosa 88.4% was the commonest site and maximum reported clinical grade was III 44.2% followed by grade II 38.5%, grade I 19.6%, grade IVa 7.7% [Graph 5, Graph 6].

**Graph 5:** This bar graph shows the site involvement in the study population where the X axis represents the oral mucosa sites and Y axis represents the frequency in numbers of OSMF patients. In this study the maximum involved site was both right and left buccal mucosa (88.46%).

**Graph 6:** This bar graph represents clinical grading of OSMF in our study population where the X axis represents the clinical grading a (Grade I: Burning, depapillation, blanching or leathery mucosa (disease triad) mouth opening >35 mm, Grade II: disease triad, mouth opening 20-35 mm, Grade III: Disease triad, mouth opening <20 mm, Grade IVa: Disease triad+Oral Potentially Malignant Disorder (OPMD) and Y axis represents the frequency in number of OSM patients. In this study, the maximum seen was Grade III (44.23%) followed by Grade II (38.46%).

Descriptive analysis for age and clinical grading of OSMF, sex and clinical grading using a chi square test revealed Grade II was more predominant in 31 to 40 years and 41 to 50 years, Grade III in 51 to 60 years with p<0.01 and Grade II and III more predominant in male gender; p>0.05 [Graph 7, Graph 8].
Graph 7: This bar graph represents the association of age and clinical grade where the X axis represents age group in years and Y axis represents the number of patients with different clinical grading of OSMF. Grade III was more commonly seen in 51 to 60 years and reticular Grade II was more frequently reported in 31 to 40 years and 41 to 50 years. Pearson chi square=2.801, p=0.004 (p<0.01) (chi-square test) denotes a significant association was found between age and clinical grading of OSMF.

Graph 8: This bar graph represents the association of gender and clinical grading where the X axis represents gender and Y axis represents the number of patients with different clinical grading of OSMF. Grade II and III were more common in males and grade III in females Pearson chi-square=4.014, p=0.260 (p value>0.05), chi-square test reveals gender and clinical grading of OSMF were not statistically significant.

Graph 9: This bar graph represents the association of type of tobacco product and clinical grading of OSMF where the X axis represents tobacco product and Y axis represents the number of patients with different clinical grading of OSMF. Pan chewing was more associated with grade III and areca nut with grade II. Pearson chi square=37.18, p=0.000 (p value<0.01), (chi-square test) reveals a statistical association between gender and clinical grading of OSMF.

Descriptive analysis used for habit and clinical grading revealed that Grade II more commonly reported in areca nut chewing and Grade III more common in pan chewing patients; p<0.01 [Graph 9].

Table 1: Showing mean difference of interincisal distance measured at baseline and first review (15 days), second review (30 days) and third review days (45 days) done using paired t test.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>First review (15 days)</th>
<th>Second review (30 days)</th>
<th>Third review (45 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean difference and Std dev</td>
<td>0</td>
<td>2.365 ± 24.892</td>
<td>-2.237 ± 1.368</td>
<td>-2.269 ± 1.402</td>
</tr>
<tr>
<td>p value</td>
<td>0</td>
<td>0.496</td>
<td>0</td>
<td>0</td>
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A paired t test used to assess the statistical difference of VAS preoperatively and first visit, first review and second review; second review and third review; preoperatively and postoperatively 45 days reveals a p<0.01 with a mean and standard deviation 3.538 ± 0.917; 0.750 ± 0.738; 0.577 ± 0.667 and 4.685 ± 1.205 respectively [Table 2]. Oral submucous
fibrosis was first reported in 1952 by Schwartz while examining 5 Indian women from Kenya and it was called as “A trophical diopathica Tropica Mucosae Oris”. [40] In 1956, Pindborg defined OSMF as an insidious chronic disease affecting any part of the oral cavity and sometimes pharynx. Although occasionally preceded by and or associated with vesicle formation, it is always associated with juxta epithelial inflammatory reaction followed by fibroelastic changes in lamina propria, with epithelial atrophy leading to stiffness of oral mucosa causing trismus and difficulty in eating. Altered keratinocyte and genomic instability have been reported to play an important role in malignant transformation. [41,42] Etiology of OSMF is multi-factorial [43] and areca nut plays a major role in the pathogenesis of OSMF.

Table 2: Showing mean difference of VAS score measured at baseline and first review (15 days), second review (30 days) and third review days (45 days) done using paired t test.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>First review (15 days)</th>
<th>Second review (30 days)</th>
<th>Third review (45 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean and Std dev</td>
<td>5.02 ± 1.093</td>
<td>1.48 ± 0.852</td>
<td>0.73 ± 0.598</td>
<td>0.15 ± 0.364</td>
</tr>
<tr>
<td>Mean difference and Std dev</td>
<td>0</td>
<td>3.538 ± 0.917</td>
<td>0.750 ± 0.738</td>
<td>0.577 ± 0.903</td>
</tr>
<tr>
<td>p value</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Areca nut and other tobacco products contain quinine/hydroquinone from which hydrogen peroxide and hydroxyl free radicals are released. [44] These hydroxyl free radicals lead to lipid peroxidation which in turn leads to release of many damaging aldehydes malondialdehyde, propanedial, 4-hydroxynonenal 4-HNE. [45] MDA causes crosslinking of collagen by providing its aldehyde group to lysine and helps in lysine to lysine bridging in presence of enzyme lysyl oxidase. This crosslinking of collagen leads to stiffening of tissue and reduces their function. To neutralize these free radicals antioxidants enzymes like glutathione peroxidase, catalase and superoxide dismutase were consumed by the body which in turn results in decrease in antioxidant enzyme levels in OSMF patients. [46-53]

In our study the minimum age reported was 22 years and maximum age was 69 years with a mean age of 42 years with a male predilection. These results were similar to a study conducted by Ali FM et al in 2013. Pan and areca nut chewing was a more common tobacco product used and the mean duration was 15 years which was similar to a study conducted by Cai X et al in 2019. [54] Grading of OSMF was done by using Warnakulasuriya criteria which revealed Grade III was more common and the studies were similar to study by Ali et al. Treatment which is most commonly used for OSMF is habit cessation, intralesional steroids, human placental extracts, antioxidants, vitamins, minerals, and circuminoids. [55] Antioxidants prevent free radicals formation and delay or nullify the malignant transformation. Post operatively mouth opening has increased 3 to 4 mm after habit cessation and antioxidant therapy similar to the results obtained by Karemore et al. [56] and was also statistically significant. VAS shows progressive reduction in pain and burning sensation and post operatively the patients are asymptomatic and results are in association with previous study conducted by Mehrotra et al. in 2013.

Limitations of study are reduced sample size, lack of histopathological correlation, short follow up period and progression of disease not being assessed. Future scope of the study is to assess the effectiveness of antioxidants with intralesional steroids which may lead to more reduction in the fibrosis, a greater increase in mouth opening, relief from burning sensation and prevent a possible malignant transformation. [57-59]

Conclusion

OSMF is an oral potentially malignant disorder with increased oxidative stress leading to free radical release. Free radical release can be carcinogenic. Treatment should be aimed to prevent release of free radicals and to minimize the injury caused by them. Studies conducted by previous authors proves Vitamin A, lycopene to be more beneficial in treating OSMF and our study concludes that habit cessation with a combination of antioxidants, multivitamins and minerals rapidly decreases the burning sensation and a significant increase in mouth opening over a time period of 45 days.

References

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