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ORAL SUBMUCOUS FIBROSIS;

STUDY OF CASES REPORTED AT DOW INTERNATIONAL MEDICAL COLLEGE HOSPITAL IN KARACHI, PAKISTAN.

Abdul Hafeez Shaikh[1], Shaheen Ahmed[2], Sadia Siddique[3], Noureen Iqbal[4], Syed Mohd. Umer Hasan[5], Syed Jaffar Abbas Zaidi[6], Anwar Ali[7]

1. BDS, MPhil, FCPS
Assistant Professor
Department of Oral Surgery
Dow International Dental College,
Dow University of Health Sciences,
Karachi.
2. BDS, FCPS
Associate Professor
Department of Oral Surgery
Dow International Dental College,
Dow University of Health Sciences,
Karachi.
3. BDS, PG Trainee
Department of Oral Surgery
Dr. Ishrat ul Ebad Khan Institute of Oral
Health Sciences, Dow University of Health
Sciences, Karachi.
4. BDS, FCPS
Assistant Professor
Department of Oral Surgery
Dr. Ishrat ul Ebad Khan Institute of Oral
Health Sciences, Dow University of Health
Sciences, Karachi.
5. BDS, MCPS
Associate Professor
Department of Oral Diagnosis & Oral
Medicine, Dow International Dental
College, Dow University of Health
Sciences, Karachi.
6. MD, MSc. (Oral Biology), MFDS RCPSG,
MFD RCSI,
Assistant Professor
Department of Oral Biology
Dow International Dental College
Dow University of Health Sciences.
7. BDS, FDS
Professor
Department of Oral Surgery
Dr. Ishrat ul Ebad Khan Institute of Oral
Health Sciences, Dow University of Health
Sciences, Karachi.

Correspondence Address:
Dr. Syed Jaffar Abbas Zaidi
House No. FL 1/11, Block No.3,
Gulshan-e-Iqbal, Karachi.
jaffar.zaidi@duhs.edu.pk

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ABSTRACT… Objectives: Oral Submucous Fibrosis is a chronic, high risk, debilitating, pre-cancerous oral condition that is prevalent in Southeast Asian consumers of areca nut. This study was conducted to determine gender specificity with relation to stages of OSF and medical & surgical treatment modalities. **Setting:** OSF patients treated at Oral Surgery clinics of Dow International Medical College, Dow University of Health Sciences. **Period:** From January 2016 to November 2017. **Design of Study:** Cross-sectional Hospital based study. **Materials & Methods:** Patients were divided into four groups based on their clinical presentations according to Khanna JN and Andrade NN classification. Two groups were divided based on treatment modalities. First group comprised of patients treated conservatively with medications and physiotherapy while the second group comprised of patients treated surgically. **Results:** Out of 225 patients treated with OSF, 88% of them were males while 12% were females with male to female ratio of 7:1. As per Khanna & Andrade classification, 9.7% belonged to group II, while 34.6% belonged to III and 55.5% of OSF patients belonged to IV-A. 56.8% of patients were treated conservatively while 43.1% were treated surgically. In the group of patients treated surgically, majority 84.6% of patients were treated with buccal fat pad while only 15.4% has nasolabial flap surgery performed. **Conclusion:** Statistical significant difference in male preponderance in OSF disease severity was observed as compared to women in this sample of Pakistani population reporting to tertiary care hospital. A holistic approach should be undertaken with public health policies in place to discourage the use of areca nut products with or without tobacco to lower the burden of OSF in the general population.

Key words: Oral Submucous Fibrosis, Nasio-labial Flap Surgery, Areca Nut.

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INTRODUCTION

Oral submucous fibrosis is a complex, debilitating insidious and precancerous disease of the oral cavity.[1] The identifying characteristics of oral submucous fibrosis is presence of fibrous bands in cheeks, lips and palate due to underlying submucosal fibrosis that initiates in the oral cavity and progresses to the oropharynx and upper third of the esophagus. It is always associated with juxta epithelial inflammation and progressive fibrosis of the lamina propria.[2] Clinical features include blanching, numerous fibrous bands in oral mucous membrane of cheek and oropharyngeal region, progressive inability to open mouth i.e. trismus, altered gustatory sensation, difficulty in swallowing, nasal voice and burning sensation affecting the oral, oropharyngeal and sometimes the esophageal mucosa.[3] Amongst these symptoms the most common presenting symptoms reported by patients is progressive inability to open mouth. Even after surgery it leaves the affected individual with inability to open mouth appropriately.

The disease is seen mostly in India, Bangladesh, Sri Lanka, Pakistan, Nepal, Taiwan, China, Pacific Islands and sporadic cases among other Asians.[4] There are several case series and case reports of OSF amongst Southeast Asians including Pakistani immigrants in South Africa and the UK.

In histopathological sections of OSF, there is loss of rete pegs, flat epithelium connective tissue interface, atrophy of epithelium, decreased vascularity, chronic inflammatory infiltrate and subepithelial hyalinization.[5] Etiology is multifactorial which includes habitual chewing of Areca nut, Nutritional deficiencies, autoimmunity, collagen defects, altered salivary composition and chilies consumption but habitual consumption of areca nut with or without the use of tobacco is said to be the main etiological factor.[6] The frequency, duration of habitual chewing of areca nut either with tobacco or without has strong dose dependent relationship with the development of OSF and its potential for malignancy.[7] Commercially prepared freeze dried areca nut products such as pan masala contains tobacco with areca nut while Gutkha and Mawa contains areca nut in combination with lime and both of these products have higher concentrations of areca nut per chew as compared to homemade or self-prepared conventional betel quid.[8]

Based on strong body of evidence from in vitro experimental studies and epidemiological data compiled by International Agency for Research on Cancer (IARC) have suggested areca nut to be one of the major etiological factors of oral submucous fibrosis in Southeast Asians.[9]

In Pakistan, there are variations in the areca nut compositions in the products available locally. The predominant areca nut product used in Pakistan is betel quid that contains leaf, slaked lime or tobacco followed by Pan Masala and Gutkha. Pan Masala also known scientifically as Areca quid contains areca nut, catechu, lime, flavors and spices as constituents. Whereas Gutkha contains tobacco as an added ingredient besides all the components of Pan Masala. Gutkha is popular in Pakistan amongst the young generation belonging to urban and rural areas and has local substitutes popularly known as Kharra or Mawa. Both Gutkha and Pan masala are commercial products for which both local and imported variants exist. Gutkha is more strongly associated with the development of OSF owing to its highest relative risk.[10] Although exact financial reports for the Pakistani market for Gutkha and Pan Masala are still lacking but reports for Indian market of Gutkha and Pan Masala are worth approximately 500 million US Dollars.[11,12]

OSF is considered a public health issue in Pakistan as oral cancer is one of the most common malignancies in Pakistan with malignant transformation rate of OSF being 7.6% over a median observation rate of 10 years in Indian, Chinese and Malaysian studies.[8,13-16]

In Pakistan there is a federal as well as provincial ban on the sale, purchase, distribution and use of Pan masala and Gutkha at all public and private institutions and public places. Recently the prices of betel nut have quadrupled as a consequence of global taxation rise on unhealthy food to discourage their use, but the current Government has not subsidized healthy food items and even life-threatening medicines.

Chaudhuri SR et al20, demonstrated a genetic component that shows enhanced risk of OSF with polymorphisms in CYP1A1 and CYP2E1.[6] Areca nut which is usually present in betel quid is regarded as the fourth most common psychotropic and addictive material in the world after alcohol, nicotine and caffeine and is used by about 10–20% of the world's population.[17] Different components of Areca Nut are involved in the biological pathways that leads to the development of OSF.[18] The alkaloids are an inherent component of the areca nut and are responsible for stimulation of fibroblast growth that results in increased production of insoluble collagen with subsequent decrease in collagen breakdown.[18] The tannins and the catechins in the areca nut are involved in forming a more stable and hence insoluble collagen by inhibiting an enzyme named collagenase.[19] 3 to 108 mg/g of copper is present in various products of Areca nut which increases production of highly crosslinked of collagen by upregulation of lysl oxidase pathway.[2] OSF is essentially a collagen metabolic disorder due to the imbalance in the formation and degradation of extracellular matrix that includes collagen as a constituent. Transforming growth factor-beta has significant role in the production and deposition of extracellular matrix

by acting as a potent stimulator and is expressed in OSF tissue samples along with connective tissue growth factor.[20,21] The normal integrity of the connective tissue is maintained by balanced collagen metabolism depicted by equilibrium by the two enzymes MMPs and TIMPs. In OSF, this balance is disturbed resulting in increased deposition of ECM.

Various therapeutic interventions have been proposed that work against the different mechanisms of pathogenesis of OSF.[1] There has been considerable work in finding diagnostic and prognostic salivary biomarkers for early minimally invasive detection of Oral Submucous fibrosis in high risk patients. Advances in salivary proteomics and metabolomics has indicated significantly lower expression levels of MMP-2, MMP-9 and salivary Statherin in saliva of patients with Oral Submucous Fibrosis and have potential for early detection of malignant change in OSF.[22,24] Limited or restricted mouth opening in OSF patients can be attributed to loss of some ECM molecules namely elastin and their subsequent replacement of muscle tissues by collagen type I.[25]

MATERIALS & METHODS

A Hospital-based cross-sectional study was conducted from January 2016 to November 2017 in the Department of Oral Maxillofacial Surgery at Dow International Medical and Dental College, Ojha campus. Informed consent was taken from all the patients, advantages and disadvantages regarding treatment options were conveyed to the patient in an unambiguous manner. Inclusion criteria for this study was all patients 18 years old or older presenting with unilateral or bilateral OSF. Exclusion criteria for this study included those patients who were not willing to participate in this study and those patients with OSF who has histologically confirmed reports of malignant transformation and those follow up patients of OSF who had been treated previously.

Patients were evaluated clinically for the presence of fibrous bands in the oral cavity & their demographic data and history was recorded. Patients were classified according to Khanna JN and Andrade NN classification for oral submucous fibrosis (1995).

Clinical presentations of OSF were regarded for staging purposes without any reliance on histological grading based on biopsy.

Group I: Earliest stage without mouth opening limitations i.e. ≥ 35mm
Group II: Interincisal mouth opening 26-35mm
Group III: Interincisal mouth opening 15-25mm, Fibrotic bands visible at soft palate, pterygomandibular raphe and anterior pillars of fauces
Group IV A: Interincisal mouth opening less than 15mm and extensive fibrosis of all oral mucosa
Group IV B: Disease is most advanced with premalignant and malignant changes in oral mucosa.
Patients were divided into two groups according to the treatment modality given:

Group 1

No Surgical Intervention was given
Discontinuation of Habit and counselling
Muscle stretch or mouth opening exercises with the use of sticks of tongue depressors
Intralesional Injections biweekly for 8 to 10 weeks comprising of
- Injection Chymotrypsin 5000 IU
- Injection Dexamethasone 4mg

Group 2

Surgical Intervention was given
-Buccal Fat Pad
-Nasolabial Flap

RESULTS

In the section of Tables.

Gender	Number (N)	Percentage
Male	198	88%
Female	27	12%

Table-I. Gender distribution of OSF patients

Stage	Number (N)	Percentage
I	0	0
II	22	9.7%
III	78	34.6%
IV-A	125	55.5%

Table-II. Stage distribution of OSF patients

Treatment	Number (N)	Percentage
Non-Surgical	128	56.8%
Surgical	97	43.1%

Table-III. Distribution based on treatment

Treatment	Number (N)	Percentage
Buccal Fat Pad	82	84.5%
Nasolabial Flap	15	15.4%

Table-IV. Distribution based on type of surgical intervention

DISCUSSION

Cancer of mouth and throat is the second most common cancer in children and adults of Pakistan as per reports from tertiary care hospitals in Pakistan as there is no official oral cancer registry in Pakistan.[15,26] OSF is a significant health concern particularly in men and women belonging to low socio-economic status and should be regarded as a major public health issue.[6] It is a chronic, progressive disease resulting in loss of fibro elasticity and hardening of the oral mucosa and restriction in opening of the mouth with a significant cancerous potential.[6] Malignant potential of OSF has a conversion rate of 2-8%.[6]

All the participants of this study were long term consumers of area nut and betel quid. Currently in Pakistan, there are around 122 brands of areca nut; mistakenly known as betel nut but is popular amongst the masses as Chalia or Sweet Supari.

Due to sweetening and artificial coloring of areca nut, it is popular in the younger generation due to its addictive nature. Owing to its sweet and addictive taste, it is regarded as “Sweet Poison” amongst the dental professionals and WHO also considers areca nut as a potential carcinogen.

Areca nut is not grown in Pakistan and areca nut supplies in Pakistan are dependent solely on import of Areca nut and its products. Although areca nut comes under the domain of Food Ordinance 1960 and Pure Food rules of 1965 that restricts the manufacture, sale and purchase of substances injurious to human health but as this law has not been enforced properly and areca nut is still being imported and sold in Pakistan.

Banning of areca nut and its products in Pakistan has not been effective in eradicating areca nut or its products as it is still being imported and even smuggled as there is huge demand of it. A practical means of tackling the growing menace of areca nut consumption is imposing heavy taxes on areca nut and tobacco and raising revenues for providing subsidies to health food items. Globally increased taxes on alcohol and tobacco reduced consumption of targeted products while generating revenues for achieving sustainable health objectives, distributing the burden of tax across all socio-economic groups in an equitable and efficient manner; thereby making it more politically sustainable.[27]

Clinical criteria for the diagnosis of OSF has been established by consensus of histo-pathologists and oral maxillofacial surgeons in a workshop in Malaysia.[28] This clinical criterion includes presence of leathery mucosal texture, fibrous bands that are palpable manually, loss of appearance of tongue papillae, burning sensation to spicy food in all clinical cases, rigidity of the tongue and blanching of mucosa. These clinical criteria are present in varying degrees in all cases of OSF.

In this study although Khanna JN and Andrade NN classification has been followed for grading purposes, but all the four groups had varying degrees of these clinical criteria but the hallmark feature of OSF is progressive limitation of mouth opening due to the presence of vertical fibrous bands.

Oral Submucous Fibrosis has been classified in stages and groups of severity by various classification schemes based on either clinical criteria or histopathological features. Amongst all these schemes, mouth opening is considered to be an important treatment criterion as well as treatment outcome for grading the severity of OSF. Moderate to severe disease has been associated with mouth opening that has been restricted to 35 mm or less. The interincisal opening as measure of severity of OSF has been reported by Maher et al.[29] and confirmed that interincisal opening has been associated well with the extent of OSF disease severity in the oral cavity. As study

has focused on treatment outcomes of OSF, interincisal opening as an integral component of Khanna JN and Andrade NN classification has been used for grading the severity of OSF cases. Latest staging of OSF has at World Workshop on Oral Medicine and it includes a mixture of clinical and histopathological features.[20] Due to the inherent financial and ethical issues associated with biopsy of early lesions, this staging of OSF has not been used in our context.

Majority of patients treated with OSF belonged to group IV-A, which is in sharp contrast to other studies that have reported majority of patients that belonged to Group III-A.[13-15] This highlights the increased importance for increased awareness and early referral.

Although many medical and surgical treatment modalities have been assessed for the treating OSF, but as of yet no gold standard exists due to lack of reliability and reproducibility of these interventions. None of these suggested treatment modalities have reliably and repeatedly resulted in increased inter-incisal mouth opening or significant clinical improvement in OSF cases.[31] Wide range of medical interventions that include nutritional supplements, antioxidants, biogenic stimulants, enzymes, fibrinolytic agents, intralesional injections of dexamethasone, hyaluronidase, triamcinolone, placental extracts and oral pentoxifylline have shown some improvements in the clinical signs and symptoms of OMFS.[31]

In our study, majority of the patients were male compared to females making a ratio of 7:1. Our results were approximately same as those concluded by Hasmukhbhai et al in Gujarat India in 2016 i.e. 7.33:1 and Pakistani studies[31-33] although some studies have quoted higher female predilection.[9,10,34]

Tillakaratne WM et al used intralesional injections of corticosteroids in his patients and observed an increase in their mouth opening in a period of 12 months.[35] Nonsurgical group of our study who were given combination of intralesional injections of dexamethasone and chymotrypsin and had undergone stick exercise or physiotherapy also showed significant improvement in their mouth opening. The use of physiotherapy either in combination therapy or as a standalone medical therapy has been explored in a few studies to augment already existing medical and surgical therapies.[30]

K. Saravanan in his study in 2012 showed significant improvements in mouth opening of OSF patients when treated with buccal Fat pad.[36] The results of our patients who were surgically treated with buccal fat pad were consistent with the above mentioned study.

SM Balaji in 2016 checked the versatility of nasolabial flaps in patients with severe trismus due to oral submucous fibrosis and concluded that trismus of those patients was significantly reduced after the surgery.[37] Results of our patients who underwent Nasolabial Surgery were consistent with his findings.

Long term evaluation of surgical modality is needed to assess which surgical modality results in improved inter-incisal mouth opening.

Immediate outcomes represented by improved inter-incisal mouth openings has been associated with surgical interventions although in certain cases relapses in mouth opening have also been reported.[18] There is a dearth of studies that explore the impact of habit cessation on medical and surgical interventions.

CONCLUSION

Based on the findings of this study, it can thus be concluded that there is a notable difference in the frequency and disease severity in men as compared to women and that majority of patients treated at tertiary hospitals belong to advanced level of severity due to lack of awareness. With the emerging prevalence of OSF, urgent public health policies are warranted coupled with increased awareness and early referral of OSF affected individuals to curb and lower the burden of this menace of “Sweet Poison”.

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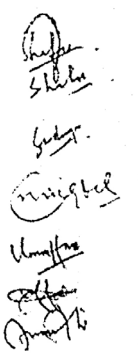
AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Abdul Hafeez Shaikh	Literature search	
2	Shaheen Ahmed	Conceptualization of study design.	
3	Sadia Siddique	Write up	
4	Noureen Iqbal	Proof reading	
5	Syed Mohd. Umer Hasan	Data analysis	
6	Syed Jaffar Abbas Zaidi	Data interpretation	
7	Anwar Ali	Endnote referencing	