"ROLE OF PENTOXIFYLLINE IN ORAL SUBMUCOUS FIBROSIS"

By

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DISSERTATION SUBMITTED TO

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IN

OTORHINOLARYNGOLOGY

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Under my guidance and supervision

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ABSTRACT

Background and objectives

Oral submucous fibrosis (OSMF) is a pre-cursor of oral malignancy and is a distressing disease endemic to the Indian sub-continent. The Incidence of oral malignancy in India is among the highest in the world. Overall prevalence of OSMF in India is about 0.5%. The anti-inflammatory and immunomodulatory actions of pentoxifylline appear to have therapeutic advantages in the management of OSMF. In this study the role of pentoxifylline therapy as an adjunct in the treatment of OSMF is evaluated.

Materials and methods

Patients diagnosed with oral submucous fibrosis in the Department of Otorhinolaryngology, R.L. Jalappa Hospital & Research centre, Sri Devaraj Urs Medical College, Kolar, from Oct 2008 to March 2010 were included in this study. The study design adopted was a randomized controlled double-blind study, where patients are randomly chosen to form a group called experimental drug group (EDG) and a control group called standard drug group (SDG). Both groups had a comparable degree of the disease and share common demographic features. The EDG were administered 400 milligrams of pentoxifylline (Trental 400 mg) tablets thrice daily for six months whereas the SDG were given a vitamin B complex with zinc (Becozinc capsules) for the same duration. Other measures such as local hot fomentation and forceful mouth opening exercises were practiced uniformly by both groups of patients. The study variables were grouped as objective and subjective criteria. The physically variable objective criterion was inter-incisal distance and tongue protrusion

distance. The subjective criterion was burning sensation in the mouth, intolerance to spicy food and digitally palpable fibrotic bands in the oral cavity. The treatment period was six months and follow-up period was also six months.

Observations and results

This study comprises of a prospective clinical analysis of 80 randomly selected patients with OSMF. The EDG consisted of 35 patients and SDG had 45 patients. During the six months treatment period of our study, significant improvement was observed in the subjective criteria (burning sensation in the mouth and intolerance to spicy food) among patients of EDG (91.4%) when compared to the SDG (45-60%). The objective criteria did not show any significant improvement in both groups of patients during the six months period. During the follow-up period it was observed that both subjective and objective study variables deteriorated. This observation was statistically highly significant which indicates pentoxifylline has significance in halting the progression of disease.

Conclusion

Pentoxifylline appears to have a significant role in preventing the progression of OSMF. A longer duration of treatment can possibly improve the signs and symptoms of this disease.

Key words

Oral submucous fibrosis; Sub epithelial fibrosis; Pentoxifylline.

LIST OF ABBREVATIONS USED

OSMF	Oral submucous fibrosis
EDG	Experimental drug group
SDG	Standard drug group
COX	Cyclo oxygenase
MMPs	Matrix metalloproteinases
TGF	Tumour growth factor
TNF	Tumour necrosis factor
IFN	Interferon
H&E	Haematoxylin & Eosin
HLA	Human leucocytes antigen
ELISA	Enzyme linked immune sorbent assay
PDGF	Platelet derived growth factor
FGF	Fibroblast growth factor
CTLA	Cytotoxic T- lymphocyte associated antigen
Na	Sodium
K	Potassium
Cl	Chlorine
HCO_3^-	Bicarbonate
IU	International units
ECM	Extra cellular matrix
Mrna	Messenger ribonucleic acid
Col	Collagen
TC	Total leukocyte count
DC	Differential count
Hb	Haemoglobin
PC	Platelet count
CT	Clotting time
BT	Bleeding time
N	Number
BP	Blood pressure
CVS	Central nervous system
CNS	Cardio vascular system
RS	Respiratory system
RBS	Random blood sugar
IIT	Inter-incisal distance
BS	Burning sensation
TP	Tongue protrusion
DPPFB	Digital palpation of palpable fibrotic bands
ITSF	Intolerance to spicy food

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INTRODUCTION

'The chances of habit are too weak to be felt till they are too strong to be broken'

Dr. Samuel jones.

Half a century ago Schwartz described Oral submucous fibrosis (OSMF) in the tobacco chewing women of Indian origin in Kenya.[1,2,3,4.] Since then this condition evoked an intense enthusiasm among many researchers in India and throughout the world. Various authors have investigated the condition thoroughly and proposed several factors that play a role in the etiopathogenesis of this condition.[1,5.] Current evidence suggests that arecoline in the areca nut is the key factor in initiating this disease process.[6,7,8.]

The Incidence of oral malignancy in India is among the highest in the world.[7] The incidence of OSMF is on the rise in the younger age group in India.[3] OSMF is silently spreading like wild-fire throughout India, as pan masala and gutkha are available in most parts of the country even to young children at price less than 50 paise.[3,6.]

In our country this habit is widely prevalent in teenagers and young adults. In this fast-growing century, people are subjected to varying degrees of stress.[3,6] Most of them fall into the so-called "stress-relieving" habits like smoking, pan, tobacco, betal quid chewing and alcohol. OSMF is the result of one such addictive "stress-relieving" habits.[3]

Indian medical experts warned that millions of people addicted to pan masala and gutkha will be affected by OSMF.[9,10.] The close association between betal nut chewing, OSMF and malignancy demands the need for a preventive approach through health education and increased awareness among public.[5,6,8.]

Oral submucous fibrosis is a well-documented pre-cursor of oral malignancy and is a distressing disease endemic to the Indian subcontinent.[6,7,11.] Both oral malignancy and oral submucous fibrosis are frequently encountered diseases in R.L.Jalappa Hospital. Most of the Patients are from poor socio-economic background.

The aetiopathogenesis of oral submucous fibrosis is still inconclusive and so is the treatment. A variety of empirical treatments both medical and surgical are in use with limited success.[12] Hence the need for newer therapeutic measures especially newer non-invasive and inexpensive measures. In a pilot study, pentoxifylline has been tried as a newer adjunct with promising results. However, further trails with larger sample size are needed to establish the therapeutic value of pentoxifylline.[12] In this study an attempt is made towards this objective.

AIMS & OBJECTIVES

To evaluate the role of pentoxifylline therapy as a newer adjunct in the treatment of oral submucous fibrosis.

REVIEW OF LITERATURE

A condition resembling Oral submucous fibrosis (OSMF) was described as early as "600" BC by Sushruta and it was named as "VIDARI" having features of progressive narrowing of mouth, depigmentation of oral mucosa and pain on taking food.[9,13]

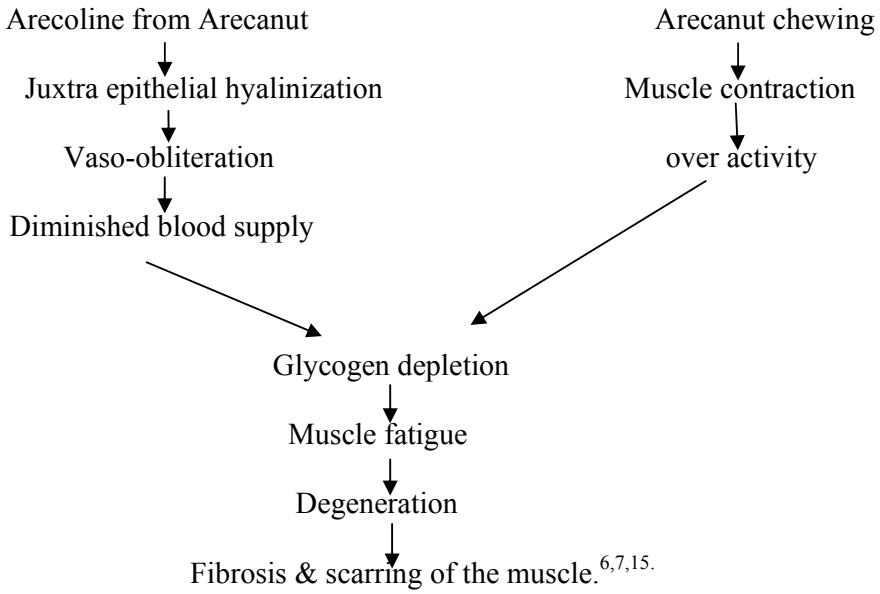
In 1952, Schwartz described five Indian women in Kenya with a condition of the oral mucosa including the palate and pillars of the fauces, which he called "atrophia idiopathica mucosae oris".[1,2,3,4,14,15,16.]

In India, in 1953, Joshi SG was the first to describe the condition and he called the condition as "submucosal fibrosis of the palate and pillars".[2,3,4,5,13,,16.]

In 1965 Pindborg et al defined this condition as "an insidious disease primarily affecting buccal mucosa, soft palate and floor of the mouth. Burning sensation on eating spicy foods, superficial mucoceles (vesicles) and pale mucosa are some of the early signs. Bands of fibrosis appear which gradually widen to form sheets of fibrosis producing trismus which is progressive and irreversible".[3,8,14.]

Pillai et al in their review concluded that the etiology is unknown but is probably multifactoral. Main contributing factor is the use of pan which typically consists of areca nut, tobacco and crude lime wrapped in betal leaf.[8]

Role of arecanut in pathogenesis of OSMF:



Oral submucous fibrosis is a precancerous lesion occurring mainly in India and Pakistan, and rarely among North Americans or Europeans.[11] Recent epidemiological data indicates that the number of cases of OSMF has risen rapidly in India from an estimated 2,50,000 cases in 1980 to two million cases in 1993.[6] The reasons for the rapid increase of the disease are reportedly due to an upsurge in the popularity of commercially prepared areca nut preparations (pan masala) in India and an increased uptake of this habit by young people due to easy access, effective price changes and marketing strategies.[6]

Oral submucous fibrosis is a condition in which due to limited opening of the oral cavity, the patient is neither able to consume a normal diet nor maintain proper oral hygiene.[17]

Reports of the sex ratio vary majority demonstrating female predominance. The largest number of cases occur between the age of 20-40 years.[14,18.]

Pindborg et al in 1972 analyzed 220 biopsies from patients with OSMF for pre malignant changes. Epithelial atypia was found in 13.2% of the biopsies. They

suggested that OSMF is a precancerous condition of the oral cavity. Overall prevalence of OSMF in India is about 0.5% with a range of 0.2 -1.2% in different regions of country. [9,19.]

Oral submucous fibrosis is a well-recognized, potentially pre malignant condition. Malignant transformation rates are as high as 7.6% have been reported from the Indian sub continent over a 17 year period.[20]

Oral submucous fibrosis is diagnosed on clinical criteria including mucosal blanching, burning sensation, hardening, and the presence of characteristic fibrous bands, and is associated with gradual inability to open the mouth. Mouth opening is an objectively verifiable criterion by which severity of the disease can be assessed. The oral mucosa becomes stiff and opaque.[21,22,23.]

Histological features include epithelial atrophy with loss of rete ridges, epithelial atypia, and pigment incontinence. Lamina propria shows fibrous and hyalinization with a chronic inflammatory infiltrate.[14]

Conservative treatment with local steroids, hyaluronidase injections and physiotherapy are not beneficial in advanced cases and high incidence of relapse.[24,25.] Injection of an aqueous extract of human placenta (Placentrex) at weekly intervals has shown significant benefit but larger trials are required. The action of placenta extract is essentially biogenic stimulation and use is based on the tissue therapy method. The extract when implanted or injected into the body after resistance of pathogenic factors stimulates metabolic or regenerative process thereby favouring recovery.[19]

Oral zinc therapy proved to be beneficial in the treatment of early disease. [25] Vitamin A 50,000 IU chewable tablets, if given once daily could cause symptomatic improvement, but trismus did not improve with this treatment.[10]

Mahar et al evaluated the role of multiple micronutrients consisting of retinol, vitamin E, vitamin D, vitamin B complex and some minerals in the management of OSMF. But no conclusive statement was available regarding aetiological correlation of any specific micro nutrient and hence their usefulness of administration in management of OSMF.[27]

Excision of fibrous band and skin grafting to cover the raw areas has been disappointing due to the high incidence of shrinkage, contracture, and rejection of the graft and recurrence of symptoms. Tongue flaps were found to be bulky, and require additional surgery for detachment. Bilateral tongue flaps cause severe dysphagia and disarticulation and carry the risk of post operative aspiration. Nasolabial flaps cannot be extended adequately to cover the raw areas.[15] The use of an oral stent as an adjunct to surgery has been tried. However patients have to wear an oral stent for a prolonged period of time (6 months).[26]

The treatments proposed for OSMF have been palliative rather than curative. They are aimed to improving the patient's ability to open the mouth, which becomes restricted when more scar tissue is formed as the disease progresses. The treatment includes the following: the conservative approach of topical application of vitamin A, steroids (betamethasone), and oral iron applications (ferrous fumarate ointment) for mild cases. Local submucosal injection of steroids (dexamethasone), hyaluronidase, and chymotripsin. Intralesional injection of aquesous extract of healthy human placenta, excision of the fibrotic bands with submucosal placement of human placental grafts, surgery with split-thickness skin graft, combined with temporalis myotomy or coronoidectomy and bilateral full thickness nasolabial flaps for severe trismus cases. Relapse is a common complication that occurs after surgical release of the oral trismus caused by OSMF.[27]

The property of pentoxifylline that may have far reaching effect in the management of oral submucous fibrosis is perhaps due to its effect on the fibroblast and the role it assumes in fibrinolysis. [12] Fibroblasts cultured in the presence of pentoxifylline produce twice as much collagenase activity and decreased amount of collagen, glycosaminoglycans and fibronectins.[28] Pentoxifylline blocked tumour necrosis factor-α induced synthesis of fibroblast collagen, glycosaminoglycans and collagenolytic activity.[29]

Pentoxifylline decreases red cell and platelet aggregation, granulocyte adhesion, fibrinogen levels, and whole blood viscosity. Recent work has delineated pentoxifylline ability to decrease production of tumour necrosis factor alpha and reduce some of the systemic toxicities mediated by interleukin-2.[28,29,30.]

Pentoxifylline has proved effective in treating intermittent claudication caused by chronic peripheral arterial occlusion, it also be effective in treating OSMF, having a putative association with mucosal ischemia and resultant epithelial atrophy. This drug has the property of suppressing leucocyte function while altering fibroblast physiology and stimulating fibrinolysis. [28]

The anti inflammatory and immunomodulatory actions of pentoxifylline seems to have definitive therapeutic advantages in the management of OSMF.[29]

Although primary or adjunctive therapy with pentoxifylline has been suggested for a multitude of disorders that include cases of pathological fibrosis, there are few controlled clinical trials to confirm its efficacy. It is hoped that future double blind placebo controlled clinical studies that use pentoxifylline and its derivatives will determine if the many beneficial pharmacokinetic properties of pentoxifylline are effective in treating this enigmatic human disease of OSMF.[12]

01. Traditional betal quid chewing ingredients and the commercial examples of betal quid chewing substitutes, pan masala and gutkha.

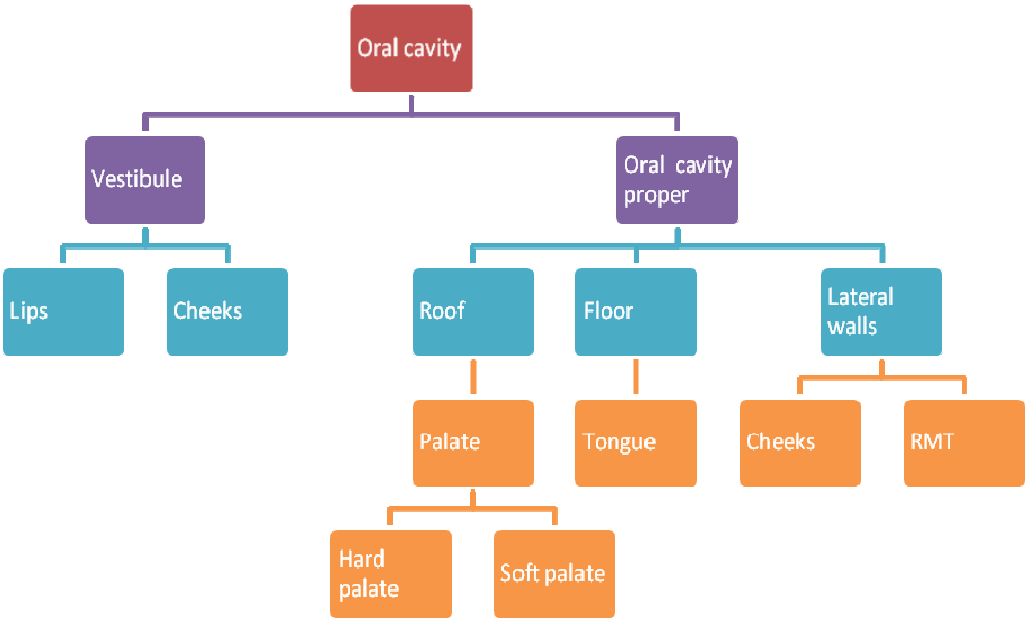
ANATOMY OF ORAL CAVITY

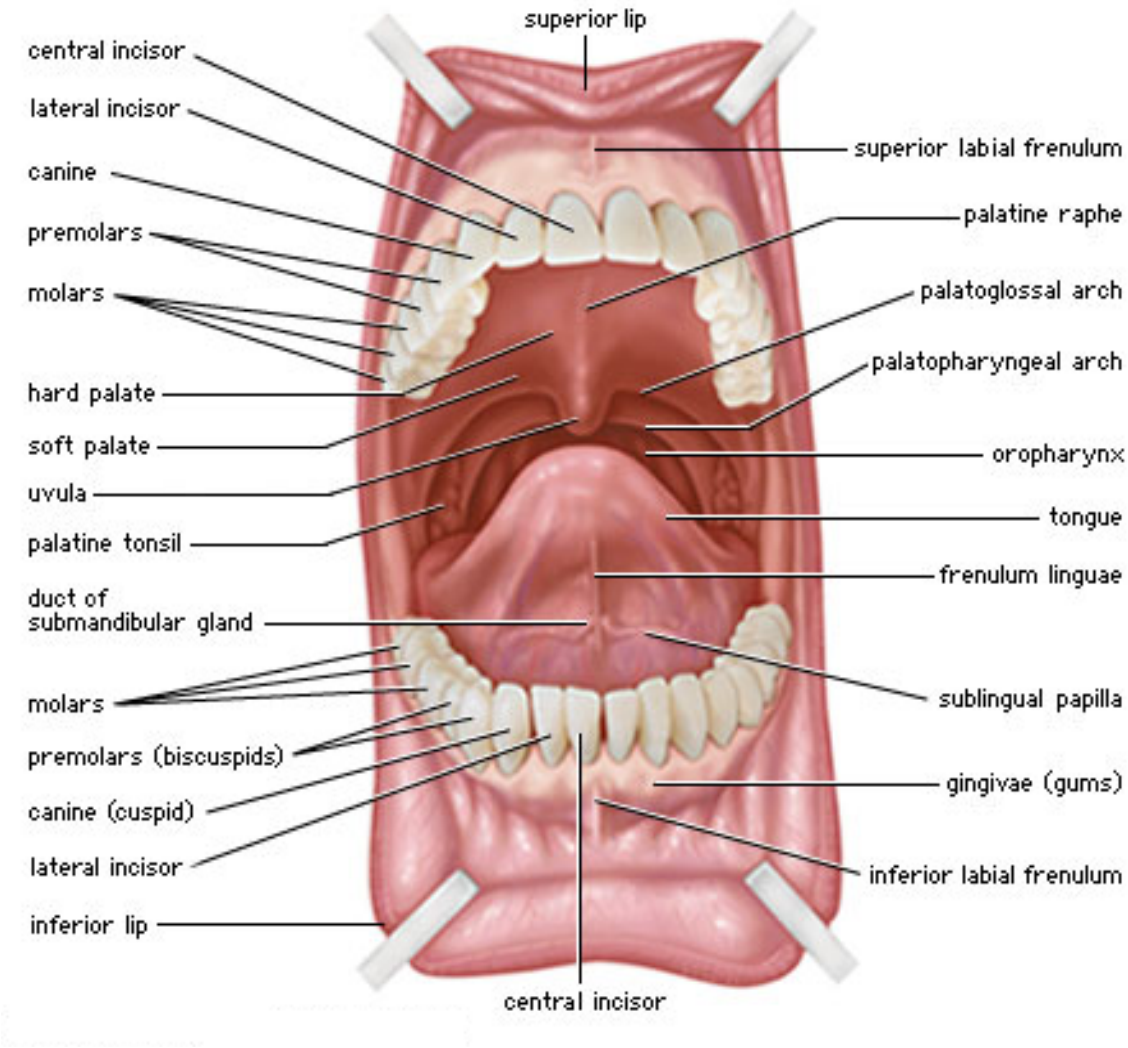
EMBRYOLOGY

The primitive oral cavity or stomatodeum forms a portion of both the nasal and mouth cavities. During the formation of the boundaries of the oral cavity, fusion occur which involve the fronto-nasal process, as well as the maxillary and mandibular processes of both sides.[31]

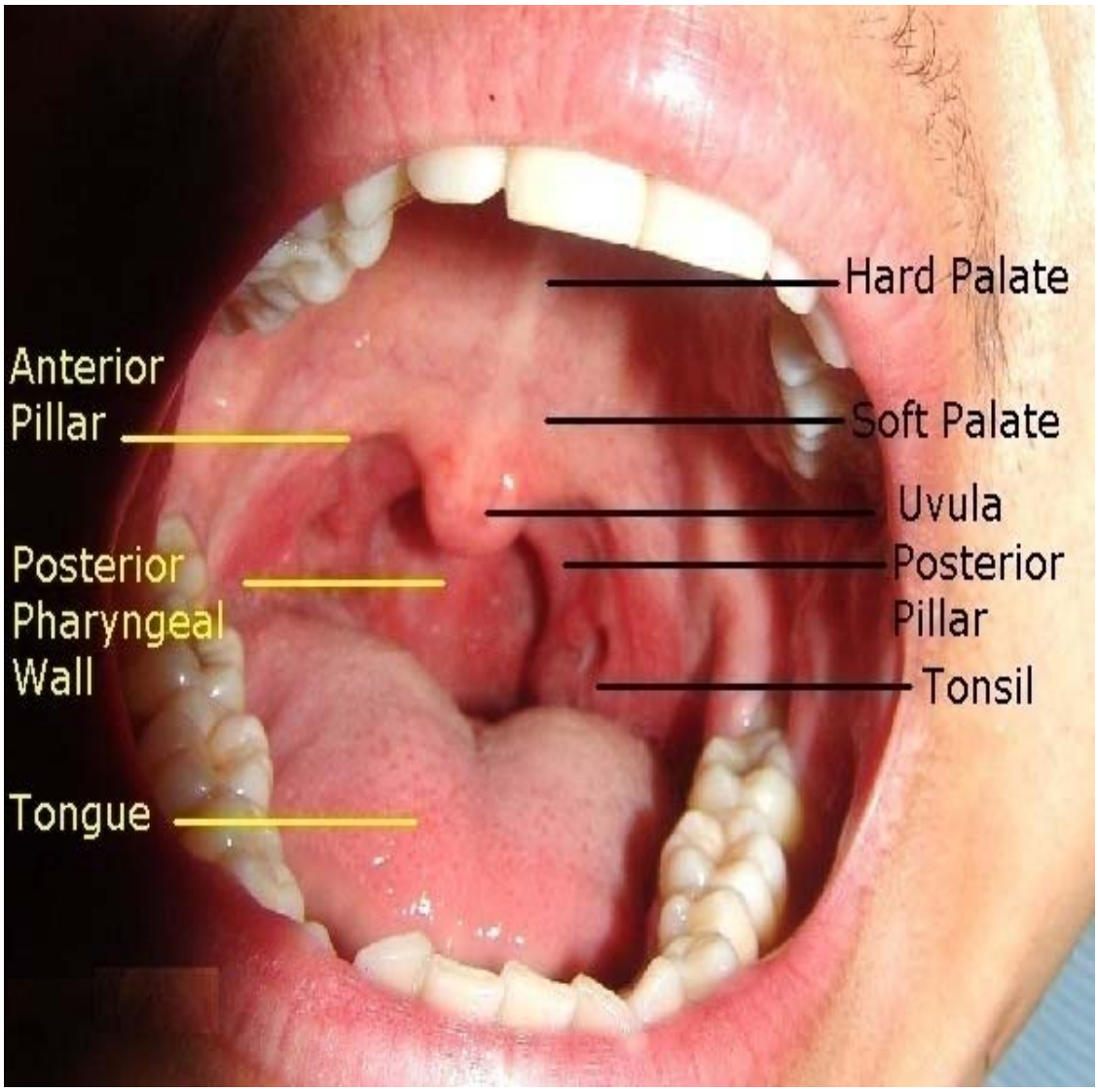
ANATOMY

The oral cavity can be sub divided in to the vestibule (external to the teeth) and the oral cavity proper (internal to the teeth). The oral cavity extends from the lips and cheeks externally to the anterior pillers of the faucies (palatoglossal arches) internally, where it continues to the oropharynx. The roof of the mouth is the palate and seperates the oral and nasal cavities. The floor of the mouth is formed by the mylohyoid muscles and is occupied mainly by the tongue. The lateral walls of the oral cavity are defined by the cheeks and retromolar regions.[32]





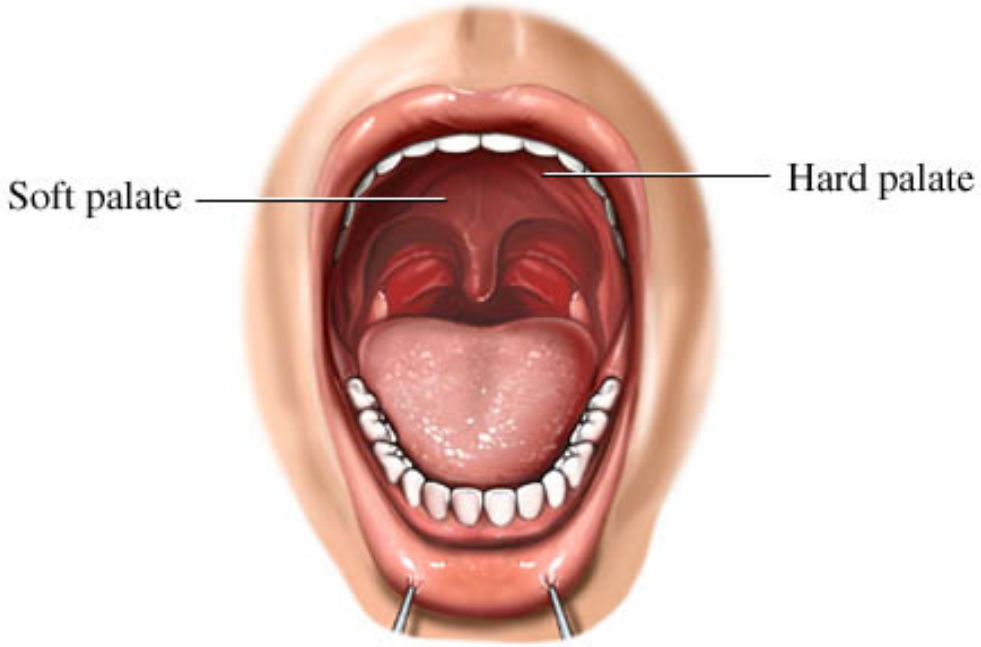
02.Diagramatic representation of anatomy of the oral cavity



03. Anatomy of the Oral cavity

PALATE

The palate is divisible into two regions: the hard palate in front and soft palate behind.[32]



04. Divisions of the palate

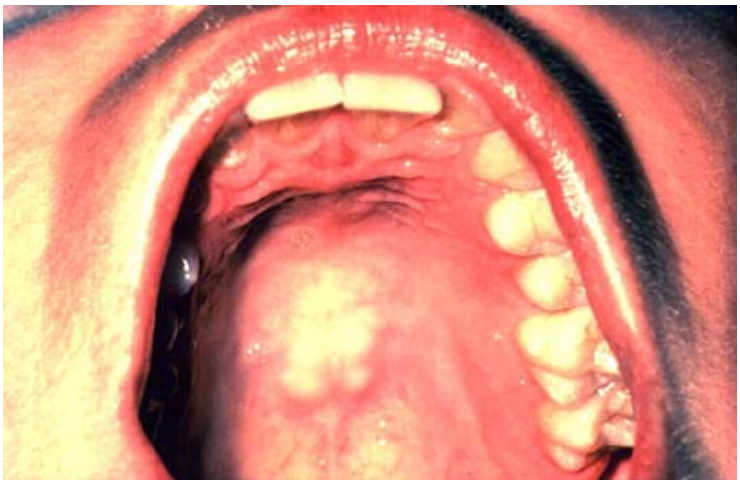
HARD PALATE

The skeleton of the hard palate is formed by the palatine processes of the maxilla and the horizontal plates of the palatine bones. The oral mucosa is bound tightly to the underlying periosteum.[32]

The periphery of the hard palate surrounding the necks of the teeth is termed the gingiva and a zone similarly lacking submucosa runs anteroposteriorly in the mid line as a narrow, low ridge, the palatine raphe.[32]

The submucosa in the posterior half of the hard palate contains minor mucous salivary glands. The upper nasal surface of the hard palate is the floor of the nasal

cavity and is covered by ciliated respiratory epithelium. The lower oral masticatory surface is covered by keratinized squamous epithelium.[32]



05. Intra oral photograph of the Hard palate

SOFT PALATE

The soft palate is a mobile flap suspended from the back of the hard palate, sloaping down between the oral and nasal parts of the pharynx. The boundary between the hard and soft palate may be distinguished by a change in colour, the soft palate being a darker red with a yellowish tint. In its relaxed and pendant position, its anterior (oral) surface is concave, with a median raphe. Its posterior aspect is convex and continuous with the nasal floor. A median conical process, the uvula, projects downwards from its posterior border.[32]

A thin, fibrous palatine aponeurosis is attached to the posterior border of the hard palate. It represents the expanded tendons of the tensor veli palatine muscles and provides the fibrous skeleton of the soft palate that supports the palatine musculature.[32]

CHEEKS

The cheeks are covered externally by skin and internally by mucous membrane (buccal mucosa) and have a muscular skeleton, the buccinators. Internally, the pink mucosa of the cheek adhers firmly to the buccinator muscle.[32]

Between the lips or cheeks and the teeth lies a slit-like space, the oral vestibule. Where the mucosa covering the alveolus of the jaw is reflected onto the lips and cheeks, a trough or sulcus is formed which is called the fornix vestibule.[32]

FLOOR OF THE MOUTH

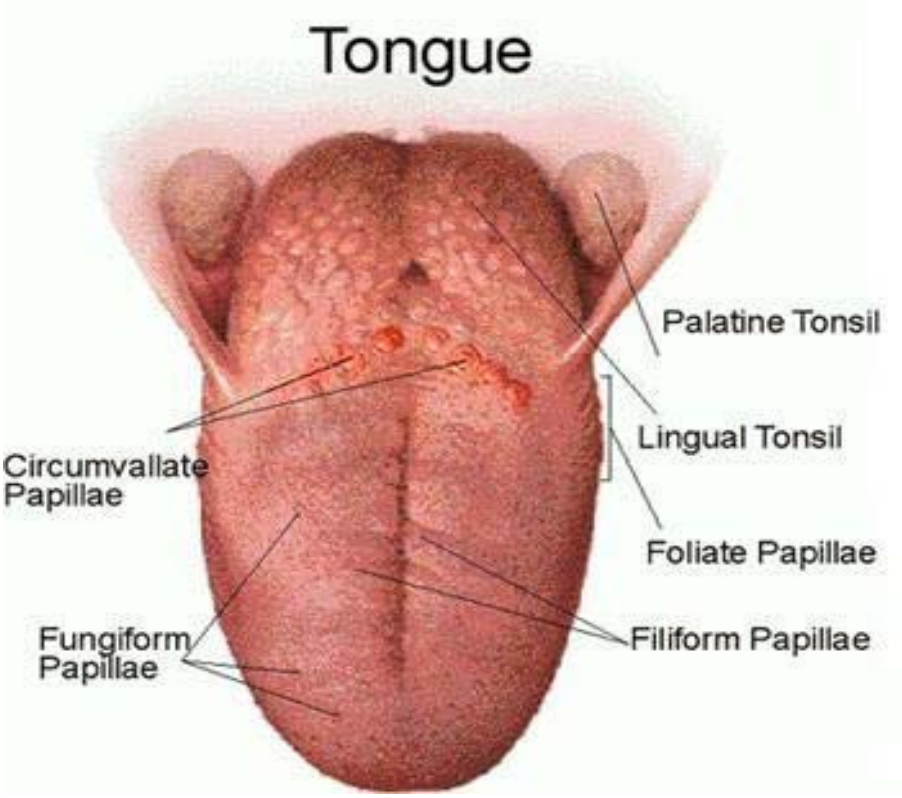
This comprises a small horseshoe-shaped region beneath the tongue. Near the base of the tongue in the midline, a fold of tissue called the lingual frenum is seen to extend onto the inferior surface of the tongue. Sublingual papilla is a conspicuous centrally positioned protuberance at the base of the tongue. The muscle forming the floor of the mouth is the mylohyoid muscle.[32]

TONGUE

The tongue is partly oral and partly pharyngeal in position. It has dorsal and ventral surfaces and a root and an apex. The curved dorsum of the tongue shows an anterior, oral part facing upwards and a posterior, pharyngeal part facing posteriorly, the two being separated by a V-shaped groove, the sulcus terminalis.[32]

The anterior two-thirds of the tongue anterior to the sulcus terminalis is related to the hard and soft palates above and has a tapered tip or apex touching the incisor teeth, and a margin in contact with the gums and teeth. On each side, in front of the palatoglossal arch, are four or five vertical folds, the foliate papillae. The dorsum has a longitudinal median sulcus and is papillated, the three remaining types of papillae

representing the filiform, fungiform and circumvallate papillae. Of the papillae, all except the filiform papillae bear taste buds.[32]



06. Tongue anatomy

ORAL MUCOSA

The lining of the mouth, the oral mucosa, is continuous with the skin at the vermilion of the lip and with the pharyngeal mucosa at the oropharyngeal isthmus. It varies in structure, appearance and function in different regions of the oral cavity. It can be classified into masticatory, lining and specialized mucosae.[32]

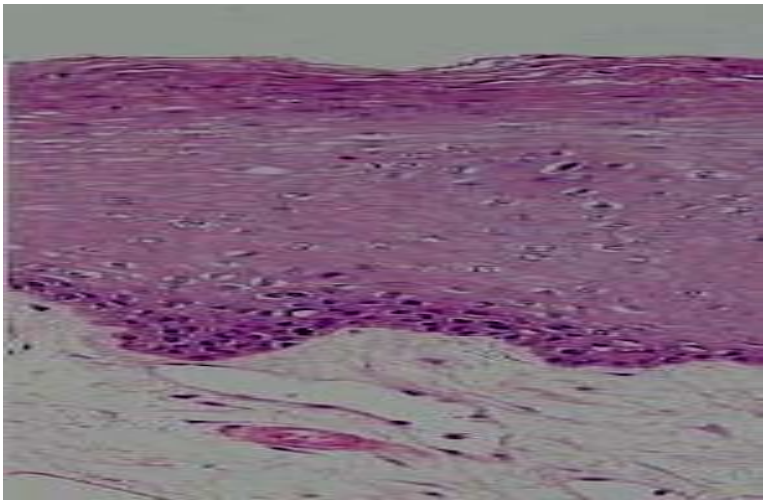
Masticatory mucosa covers the gingivae [gums] and hard palate. Its epithelium is keratinized and has a dense fibrous lamina propria. It is pink in colour. A sub mucosa is absent from the gingivae and the midline palatine raphe,but is present over the rest of the hard palate.[32]

Lining mucosa covers the internal surface of the lips and cheeks, floor of the mouth, soft palate, ventral surface of the tongue and the alveolar processes. It is red in colour, having a non-keratinized stratified squamous epithelium overlying a loosely fibrous and elastic lamina propria, and the submucosa contains some fat deposits and collections of minor mucous glands.[32]

Gustatory mucosa covers the anterior two-thirds of the dorsum of the tongue. It shares features of both lining and masticatory mucosa.[32]

HISTOLOGY

The entire oral cavity is lined by a protective mucous membrane, the oral mucosa, which contains many sensory receptors, including the taste receptors of the tongue. The epithelium of oral mucosa is of the stratified squamous type which tends to be keratinized in areas subject to considerable friction such as the palate. The oral epithelium is supported by dense collagen tissue, the lamina propria. In highly mobile areas such as the soft palate and floor of the mouth, the lamina propria is connected to the underlying muscle by loose submucosal supporting tissue. [33,34.]



07. Microphotograph showing histology of normal oral mucosa (haematoxylin-eosin, original magnification X150)

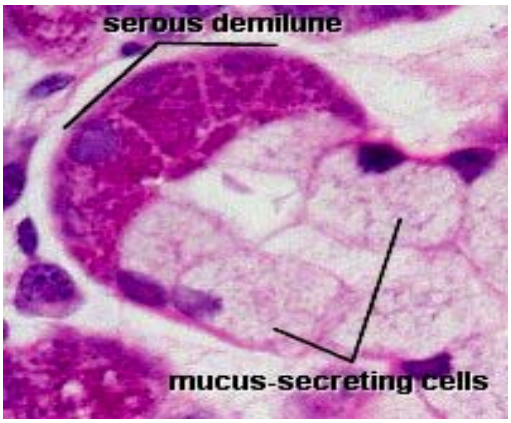
In contrast, in areas where the oral mucosa overlies bone, such as the hard palate and tooth-bearing ridges, the lamina propria is tightly bound to the periosteum by a relatively dense fibrous submucosa. Throughout the oral mucosa, numerous small accessory salivary glands of both serous and mucous types are distributed in the sub mucosa.[33,34.]

PALATAL MUCOSA

The palate is covered by a thick stratified sqamous epithelium supported by a tough, densely collagenous lamina propria. To assist mastication, the palatal mucosa is thrown up into transverse folds or rugae.[33,34.]

SALIVARY GLANDS

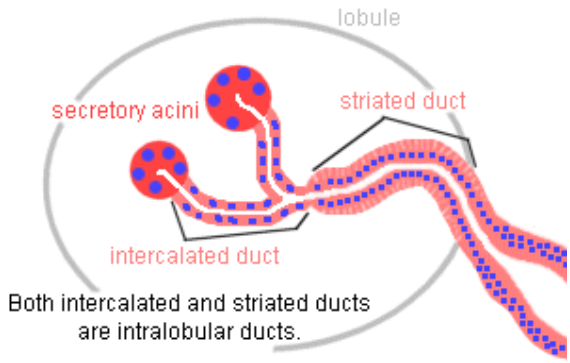
Saliva is a hypotonic watery secretion containing variable amounts of mucus, enzymes (principally amylase and the antibacterial enzyme lysozyme), antibodies and inorganic ions. Two types of secretory cells are found in the salivary glands: serous cells and mucous cells.[33,34.]



08. Secretory cells of salivary gland

SALIVARY SECRETORY UNIT

The salivary secretory unit consists of a terminal branched tubulo-acinnar structure composed exclusively of either serous or mucous secretory cells or a mixture of both types.[33]



09. Salivary secretory unit

The terminal secretory units merge to form small intercalated ducts which are also lined by secretory cells. They drain into larger ducts called striated ducts. The striations result from the presence of numerous inter digitations of the basal cytoplsmic processes of adjacent columnar lining cells.[33]

PHYSIOLOGY.

Swallowing is a complex physiologic act where by food or liquids passes from the mouth to the stomach. Chewing begins the digestive process; it breaks the food in to particles of a size that can be swallowed, lubricates it by mixing it with saliva, and mixes starch containing food with salivary amylase.[35,36,37,38,39,40.] It is a highly coordinated muscular sequence initiated by a voluntary movement of the tongue and completed by a series of reflexes in the pharynx and oesophagus. The afferent side of this reflex arc involves fibres in the trigeminal (V), glossopharyngeal (IX), vagus (X) cranial nerves.[38]

A swallowing or deglutition centre is present in the medulla. Under the coordinatation of this center, impulses pass outward in a flawlessly timed sequence via the trigeminal (V), glossopharyngeal (IX), vagus (X), and hypoglossal (XII) cranial nerves to the muscles of the tongue, pharynx, larynx, and oesophagus.[39]

During the oral phase of swallowing, a mouthful of chewed, called bolus is thrown backward against the posterior wall of the pharynx by a voluntary movement of the tongue. The impact of the bolus against the pharynx is the stimulus that sets off the reflex movements of swallowing.[39]

The mouth and oropharynx are responsible for chopping food into small pieces, lubricating it, initiating carbohydrate and fat digestion, and propelling the food in to the oesophagus.[37]

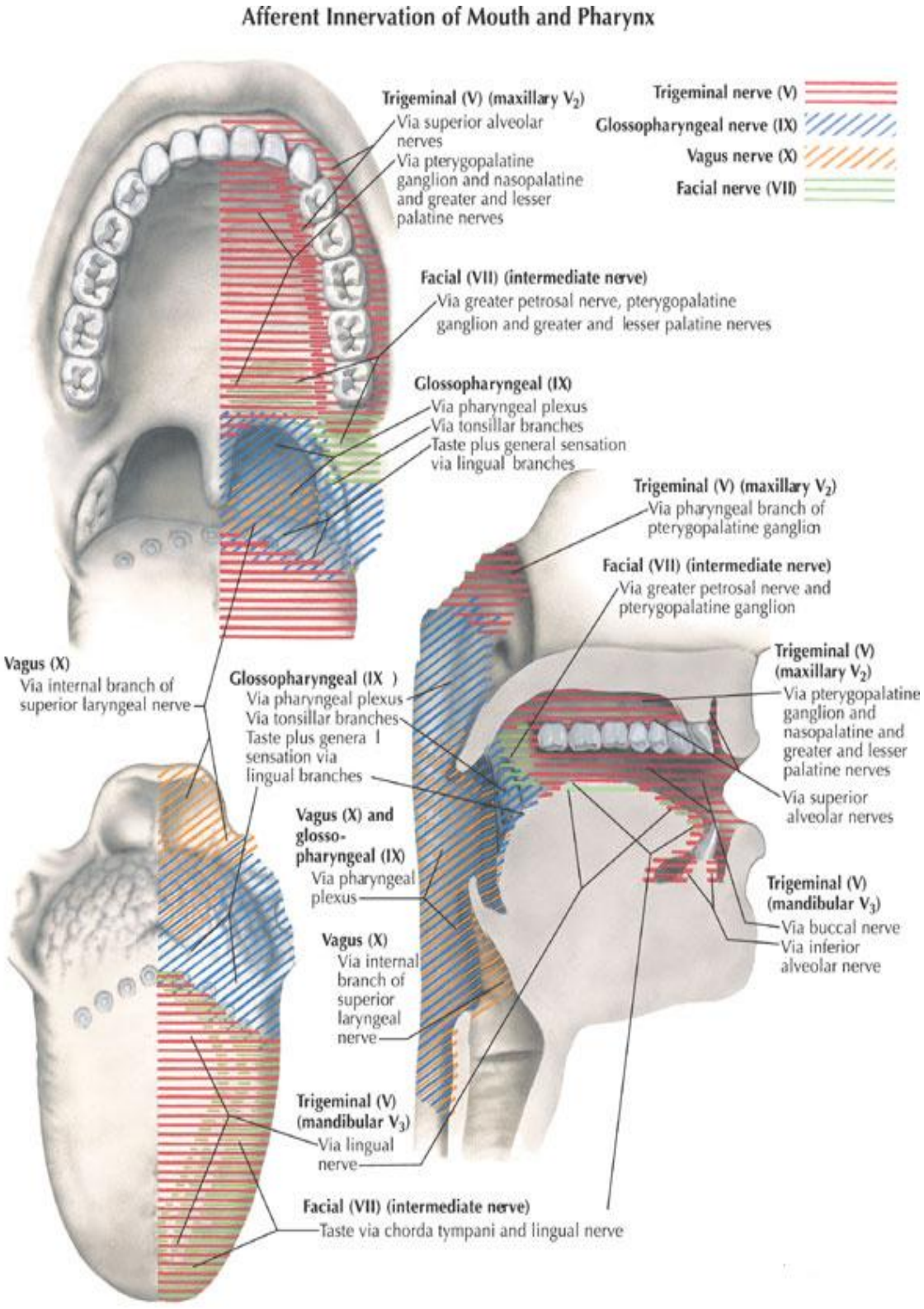
Chewing process is caused by a chewing reflux, which may be explained as, the presence of a bolus of food in the mouth at first initiates' reflex inhibition of the nucleus of mastication, which allows the lower jaw to drop. The drop in turn initiates

a stretch reflex of the jaw muscles that leads to rebound contraction. This automatically raises the jaw to cause closure of the teeth, but it also compresses the bolus again against the linings of the mouth, which inhibits the jaw muscles once again, allowing the jaw to drop and rebound another time; this is repeated again and again. Chewing is important for digestion of all foods.[36,39.]

There are two varieties of salivary secretion: spontaneous and stimulated. Spontaneous secretion occurs all time, without any known stimulus and it is this secretion which keeps our mouth moist all the time. Stimulated secretion of saliva occurs after a known stimulus. It may be psychological, visual, taste, and others like vomiting.[35,40]

In 24 hours, between 1 to 1.5 litres of saliva is secreted by an average healthy person. Saliva is a watery secretion; pH is about 6.0. 99.5% of saliva is water, rest is solid. Solids are of two kinds: inorganic (Na^+, K^+, Cl^- and HCO_3^- –electrolytes) and organic (alpha amylase or ptyline – the salivary enzyme, mucus, glycoprotein, lysozyme, lingual lipase and epidermal growth factor.)Usually the saliva is hypotonic. Lysozyme is a bactericidal agent.[35]

Major functions of saliva are digestive, protective and lubricative. Saliva contains enzymes, salivary amylase and lingual lipase, which help in the digestion. Saliva contains lysozymes, which kills bacteria. Mucin of the saliva lubricates the food, helps the swallowing of the food. Saliva keeps the mouth cavity moist and lubricated so that speech becomes possible.[35]



10. Afferent innervations of mouth and pharynx

ORAL SUBMUCOUS FIBROSIS

It is an insidious disease primarily affecting buccal mucosa, soft palate, and floor of the mouth. Burning sensation on eating spicy foods, superficial mucoceles and pale mucosa are some of the early signs. Bands of fibrosis appear which gradually widen to form sheets of fibrosis producing trismus which is progressive and irreversible.[1,3,14,22.]

Synonyms:

Vidari (Sushruta, 600 BC)[9,13,16.]

Atrophia idiopathica mucosae oris (Schwartz, 1952)[1,2.]

Submucous fibrosis of the palate and pillers (Joshi, 1952)[1,2,4,9.]

Diffuse oral submucous fibrosis (Lal, 1953)[1,2.]

Idiopathic scleroderma of mouth (Su, 1953)[18]

Submucous fibrosis of the palate (Sirsat and Khanolkar, 1957, 1960, 1962)[5]

Submucous fibrosis of palate and cheek (Desa, 1957)[1,18]

Idiopathic palatal fibrosis (Rao, 1962)[18]

Oral submucous fibrosis (Pindborg and Sirsat, 1966)[5,14,18.]

Subepithelial fibrosis (Goleria, 1970)[18]

Idiopathic oral fibrosis (Krishna murthy, 1970)[18]

INCIDENCE:

Oral submucous fibrosis is an insidious disease, considered to be a pre cancerous condition and chiefly occurring in the Indian subcontinent.[41,42] The incidence varies from 0.2 to 0.5% in India with a higher percentage being found in

southern areas.[9,19] The disease is predominantly seen in India, Bangladesh, Srilanka, Pakistan, Taiwan, Southern China, Polynesia and Micronesia. Several case-series are reported among Asian immigrants to the UK, South and East Africa.[11]

EPIDEMIOLOGICAL STUDIES:

A community based epidemiological survey in three areas of India recorded a prevalence of 0.36% in Ernakulam, Kerala, and 0.04% in Srikakulam district of Andhra Pradesh, and 0.16% in Bhavnagar, Gujarat. Among Indian villagers based on baseline data recorded a prevalence of 0.2% in Gujarat, 0.4% in Kerala, 0.04% in Andhra Pradesh, and 0.07% in Bihar.[1,4.]

ETIOLOGY:

The etiology of oral submucous fibrosis is still uncertain as no conclusive etiological factor has been identified though plenty of data has been generated on various aspects of the disease.

Following factors have been mentioned by various investigators such as

(i) Hereditary

(ii) Prolonged local irritation by pan, tobacco, chilli.

(iii) Deficiency diseases – nutritional deficiency of vitamin B, vitamin A, iron

(iv) Localized collagen diseases

(v) Immunological diseases

(vi) Autoimmune basis

(vii) Reaction to bacterial infection – Klebsiella rhinoscleromatosis, Streptococcal toxicity[4]

Betal nut chewing:

Lal DC in his study observed that all cases of OSMF gave a history of chewing supari. Supari is the Hindi word for betal nut, which is the fruit of areca catechu palm, which is widely available in India and in the Far East. Sirsat SM and Khanolkar VR stated that arecoline an active ingradient of betal nut was thought to be an aetiological factor.[7]

The commercially freeze dried products such as pan masala, Gutkha and mawa (areca and lime) have high concentrates of areca nut per chew and appear to cause oral submucous fibrosis more rapidly than by self prepared conventional betal quid which contain smaller amounts of areca nut.[3,6,7,15.]

OSMF as an autoimmune disorder:

Autoimmunity as an aetiological factor for OSMF has been examined. The reasons for investigating an autoimmune basis, included, slight female predilection and occurrence in the middle age reported in some studies, the presence of circulating immune complexes, their immunoglobin contents and the detection of various auto antibodies in patients' sera. The presence of various auto antibodies at varying titres was reported in several studies suggesting the possibility of an autoimmune basis to the disease. The first report on this concept came in 1986 showing 65% of the sample being positive for at least one of the auto antibodies tested. The frequencies of HLA A10, DR3, AND DR7 proved to be significantly different compared with an ethnically, regionally and age matched control group.[4]

PATHOLOGY

Structural and micro structural changes:

The epithelial changes in the different stages of OSMF are predominantly hyperplasia (early) and atrophy (advanced), associated with increased tendency for keratinizing metaplasia. The epithelial atrophy reported by Pindborg et al (1966) is the marked epithelial changes seen in advanced OSMF, which contrasts with the predominantly hyper plastic epithelium of early OSMF. Lesions' involving the palate shows predominantly orthokeratosis and those of the buccal mucosa, parakeratosis. The high mitotic count in parakeratotic epithelium, which is more common with the OSMF and the association with parakeratotic leukoplakia and atrophic epithelial changes, predisposes OSMF to malignancy.[4]

Subepithelial changes:

On the basis of the histopathological appearance of stained (H&E) sections, OSMF can be grouped into four clearly definable stages; very early, early, moderately advanced and advanced.[43] These stages are based not only on the amount and nature of the sub epithelial collagen but also on the following criteria taken together.[4]

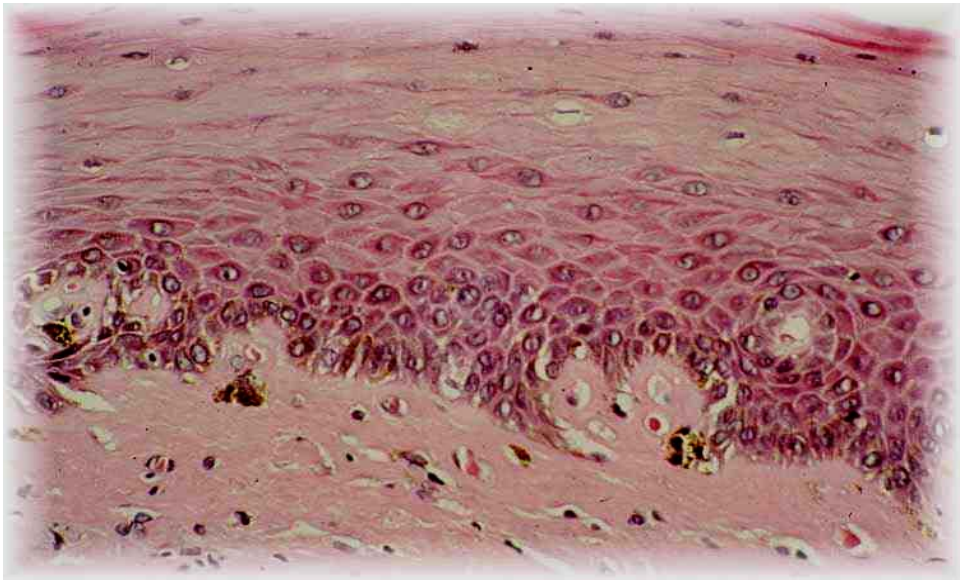
(a) Presence or absence of oedema

(b) Physical state of the mucosal collagen

(c) Overall fibroblastic response

(d) State of the blood vessels and

(e) Predominant cell type in the inflammatory exudates.



11. Classical oral submucosis fibrosis (OSMF) showing thin atrophic epithelium with chronic inflammation and dense fibrosis in the submucosa (haematoxylin-eosin, original magnification X200).

A vascular response due to inflammation, apart from the connective tissue repair process, has been very commonly found in OSMF. Many dilated and constricted blood vessels are often seen in combination, in the same section. Apparent narrowing of the smaller vessels appear first in the upper mucosa and spreads gradually to the larger, deeper vessels. Persistent dilation has also been seen in the moderately advanced and advanced biopsies. A rise in mast cells occurs in the earlier stages of the tissue reaction but in advanced stages the counts are less in number.[4]

The inflammatory cells seen are mainly lymphocytes and plasma cells. The connective tissue in advanced stages is characterized by submucosal deposition of extremely dense and avascular collagenous tissues with variable numbers of the inflammatory cells. Epithelial dysplasia without carcinoma is found in 10 to 15% of cases submitted for biopsy and carcinoma is found in at least 5 percent of sampled cases. The excessive fibrosis in the mucosa seems to be the primary pathology in OSMF with atrophic cells in the epithelium as a secondary feature.[4]

Relevance of epithelial - mesenchymal interactions in OSMF

The epithelium depends on the underlying connective tissue for its nutritive supply; with changes such as inflammation in the connective tissue, the epithelial cells seem to respond in a characteristic manner. The pathogenic mechanism generally in OSMF starts in the connective tissue, the epithelium responding secondarily. A persistent juxtaepithelial inflammatory response is characteristically seen in OSMF. The hyperplastic epithelial response, noticed during the early and moderately advanced stages of OSMF, may be a reaction to this.[4]

An alternative explanation for the epithelial hyperplasia is an adaptive response to local irritants to provide a greater degree of protection to the tissues. However, a hyperplastic oral epithelium resulting from mild mechanical abrasion or chemical treatment has shown increased permeability to water or horse radish peroxidise. This reduced barrier function of the hyperplastic epithelium may be related to an increased widening of the intercellular spaces and an increased turnover rate of this tissue.[4]

Serum-derived antibodies provide a further basis for an increase in mucosal permeability. Although serum-derived IgG retards the penetration of its corresponding antigen, it nevertheless can cause impairment of the mucosal barrier through immune complex formation or an increased absorption of antigen into epithelial cells. Ultra structural studies of small intestinal mucosa have indicated increased antigen absorption into epithelial cells after parenteral immunization.[4]

Thus, the epithelial response in OSMF is secondary to progressive changes in the connective tissue. The epithelial response and later atrophy probably reduces the barrier function of the mucosa to local irritants. Circulating immune complexes and

serum antibodies in OSMF probably help to accentuate the already existing pathological change in the oral mucosa.[4]

PATHOGENESIS

The role of the constituents of areca nut in the pathogenesis of OSMF is apparent that fibrosis and hyalinization of sub epithelial tissues account for most of the clinical features encountered in this condition. It is logical to hypothesise that the increased collagen synthesis or reduced collagen degradation as possible mechanisms in the development of the disease.[6]

Areca alkaloids causing fibroblast proliferation and increased collagen synthesis

Alkaloids from areca nut are the most important chemical constituents biologically. Four alkaloids identified in biochemical studies, arecoline, guvacine, guvacoline, of which arecoline is the main agent.[6]

Hydrolysis of arecoline produces arecaidine that has pronounced effects on fibroblasts. Arecoline in high doses is cytotoxic and cells showed detachment from the culture surface. It was evident that the correlation between the hydrolysis rates of different esters and the extent to which they stimulate collagen synthesis, suggest that hydrolysis of arecoline into arecaidine is necessary before fibroblast stimulation can occur. This suggests that arecaidine is the active metabolite in fibroblast stimulation.[6]

Stabilization of collagen structure by tannins

One of the mechanisms that can lead to increased fibrosis is by reduced degradation of collagen by forming a more stable collagen structure. The ability of large quantities of tannin present in areca nut reduce collagen degradation by inhibiting collagenases and proposed the basis for fibrosis as the combined effect of

tannin and arecoline by reducing degradation and increased production of collagen respectively.[6]

Collagenase activity was measured with soluble 14C-glycine-labeled collagen as a substrate and showed reduced activity in fibroblasts from OSMF compared with controls. The cleavage pattern of the collagen is similar to that of typical mammalian collagen. The reason for high level of collagen production in OSMF because these fibroblasts are a subset with increased potential for proliferation among heterogenetic fibroblasts.[6]

Copper in areca nut and fibrosis

The copper content of areca nut is high and the levels of soluble copper in saliva may rise in volunteers who chew areca quid. The same group showed that the oral mucosa of areca nut chewers had significantly raised levels of copper. The association between copper and OSMF has been linked on the basis that excess copper is found in tissues of other fibrotic disorders: Wilson's disease, Indian childhood cirrhosis and primary biliary cirrhosis.[6]

The enzyme lysyl oxidase is found is found to be up regulated in OSMF. This is a copper dependent enzyme and plays a key role in collagen synthesis and its cross linkage. The possible role of copper as a mediator of fibrosis is supported by the demonstration of up regulation of this enzyme in OSMF biopsies and in OSMF fibroblasts compared to normal fibroblasts grown in culture. The fibroblasts in OSMF have not only increased lysyl oxidase activities but also specific growth characteristics.[6]

Upregulation of cyclo-oxygenase (COX-2)

It is known that OSMF is associated with inflammatory changes in at least some stages of the disease. Prostaglandin is one of the main inflammatory mediators and its production is controlled by various enzymes such as cyclooxygenase.[6]

Fibrogenic cytokines

Endothelial and TGF beta-1 estimated by radioimmunoassay and ELISA respectively were increased in OSMF fibroblasts of normal individuals. External stimuli such as areca nut may induce the development of the disease by increased levels of cytokinins in the lamina propria. Increased levels of pro inflammatory cytokinins and reduced anti-fibrotic IFN-gamma in patients with the disease.[6]

Increased expression of fibrogenic cytokinins namely TGF-beta, platelet derived growth factor (PDGF) and basic fibroblast growth factor (bFGF) in OSMF tissues compared to normal. The disease process in OSMF may be an altered version of wound healing as our recent findings show that the expression of various ECM molecules are similar to those seen in maturation of granulation tissue.[6]

Genetic polymorphisms predisposing to OSMF

Polymorphisms of the genes coding for TNF-alpha is a significant risk factor for OSMF. TNF-alpha is known to stimulate fibroblastic in vitro providing evidence for an active role for TNF-alpha in the pathogenesis of OSMF. Some genotypes of cytotoxic T- lymphocyte associated antigen (CTLA-4), a negative regulator of T-lymphocyte activation seems to have susceptibility for various autoimmune diseases. The G allele at position +49 of exon 1 was found to be significantly associated with OSMF compared with controls.[6]

Inhibition of collagen phagocytosis

Degradation of collagen by fibroblast phagocytosis is an important pathway of physiological remodelling of the extracellular matrix (ECM) in connective tissue. The reduction of phagocytic cells was strongly related to the arecoline levels in fibroblast culture. There was a dose–dependent enhancement of phagocytic cells when the cultures were treated with corticosteroids.[6]

Stabilization of extracellular matrix

Increased and continuous deposition of extracellular matrix may take place as a result of disruption of the equilibrium between matrix metalloproteinase's (MMPs) and tissue inhibitors of MMPs subjected to arecoline and arecadine in culture, OSMF fibroblasts produced more TIMP-1 protein than normal fibroblasts; mRNA expression of TIMP-1in OSMF fibroblasts was also higher.[6]

TIMP-1 expression is increased at transcriptional level. It was apparent that the expression of tenascin disappeared when the lesion advanced from early to intermediate phase. Heparin sulphate proteoglycans, fibronectin, type III collagen and elastin appeared in the early and intermediate phases but there was complete replacement by collagen type I when the lesion progressed to an advanced phase. The pattern of expression of most of these molecules followed a similar pattern to the organization of granulation tissue.[6]

Collagen – related genes

Collagen related genes play an important role in the homeostasis of collagen in the body. As OSMF is a disease with deregulation of collagen metabolism, it is important to identify the enzymes and various other molecules that may contribute to genetic modulation during the progression of the disease.[6]

Different enzymes such as collagenases and lysyl oxidase together with cytokines, namely TGF- beta. There is evidence to suggest that collagen –related genes are altered due to ingredients in the quid. The genes CoL1a2, CoL3A1, CoL6A1, CoL6A3, and CoL7A1 have been identified as definite TGF-beta targets and induced in fibroblasts at early stages of the disease. The transcriptional activation of procollagen genes by TGF-beta suggests that it may contribute to increased collagen levels in OSMF.[6]

The genotypes associated with highest OSMF risk for collagen 1A1, collagen 1A2, collagenase-1, TGF-beta1, lysal oxidase and cystanin C were CC, AA, CC, AA, and AA, respectively in the low-exposure group whilst TT, BB, AA, CC, GG, and AA, respectively for the high-exposure group.[6]

Precancerous nature and malignant transformation

The precancerous nature of OSMF was first described by Paymaster in 1956 when he observed slow growing squamous cell carcinoma in one third of the patients with the disease. This was confirmed by various groups and Pindborg in 1972 put forward five criteria to prove that the disease is precancerous. They included high occurrence of OSMF in oral cancer patients, higher incidence of SCC in patients with OSMF, histological diagnosis of cancer without any clinical suspicion, high frequency of epithelial dysplasia and higher prevalence of leukoplakia among OSMF cases. [45,46]

Most of the earlier studies have focussed on the prevalence of epithelial dysplasia in OSMF. It has so far been the most reliable indicator for predicting potential malignant transformation of an oral precancerous lesion though new markers are emerging. Epithelial dysplasia in tissues appeared to vary from 7 to 26% depending on the study population.[6,45.]

However according to the current awareness of the disease and some refined criteria for grading dysplasia, it is reasonable to assume that the prevalence of dysplasia is more towards the midway of the reported range. Malignant transformation rate of OSMF was found to be in the range of 7-13%. According to long term follow-up studies a biotransformation rate of 7.6% over a period of 17 years was reported.[6,45.]

Recently, the carcinogenicity of areca nut without tobacco was identified, and the second IARC monograph on betal quid has classified areca nut as a group one carcinogen based on epidemiologic and laboratory studies. The strong association of areca nut with OSMF, its dose-dependant effects and the confirmation of OSF as a potentially malignant disease leading to oral cancer provided further evidence for this assertion.[6]

The dense fibrosis and less vascularity of the corium, in the presence of an altered cytokine activity creates a unique environment for carcinogens from both tobacco and areca nut on the epithelium.[6]

It could be assumed that carcinogens from areca nut accumulate over a long period of time either on or immediately below the epithelium allowing the carcinogens to act for a longer duration before it diffuses into deeper tissues. Less vascularity may deny the quick absorption of carcinogens into the systemic circulation.[6]

CLINICAL FEATURES

The commonly observed features of OSMF are ; presence of burning sensation in oral cavity upon taking spicy food, restricted mouth opening, inability to protrude the tongue, changes in the colour of mucosa, presence of palpable fibrous bands in oral cavity, excessive salivation.[47,48,49.]

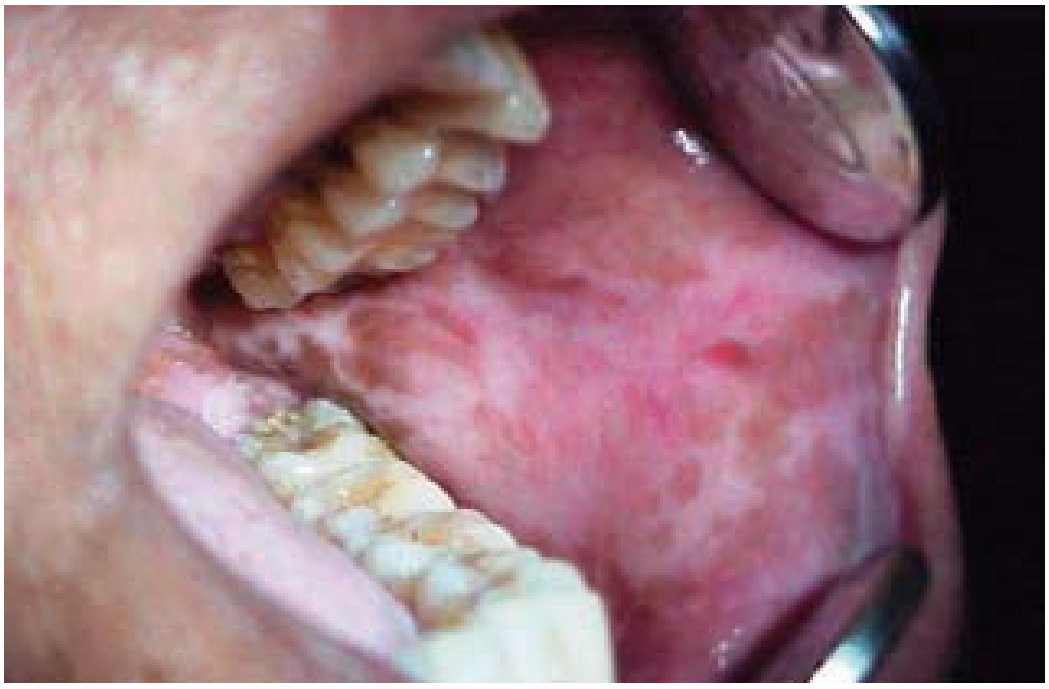
STAGING

Clinical stage:

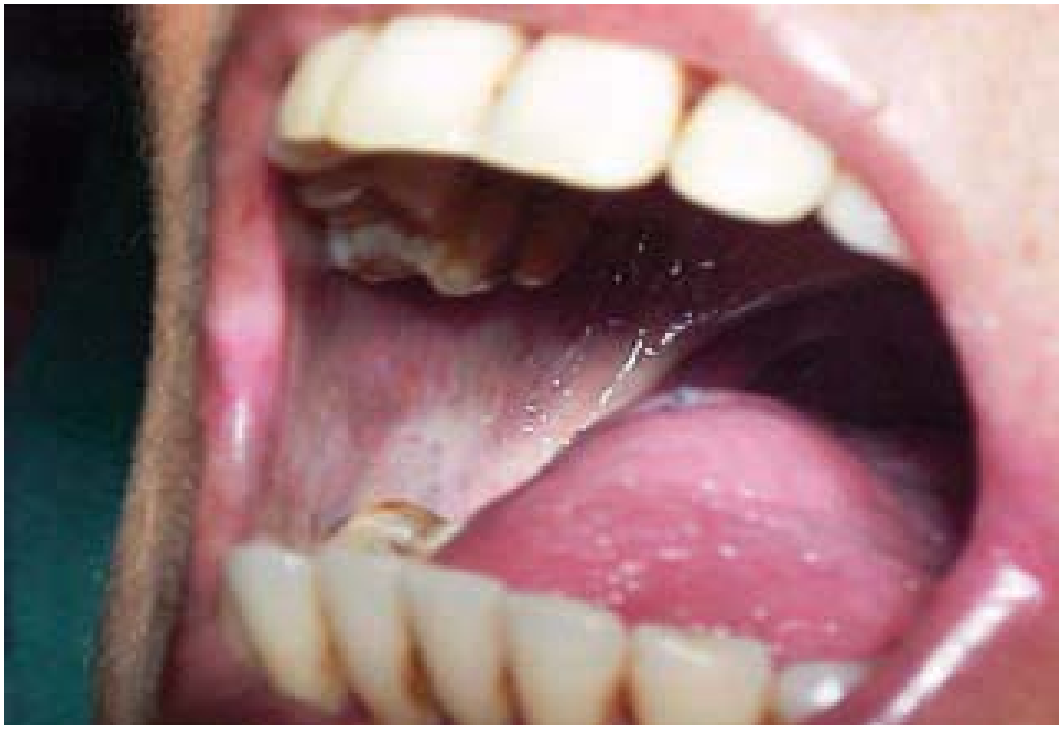
1. Faucial bands only
2. Faucial and buccal bands
3. Faucial, buccal, and labial bands.

Functional stage:

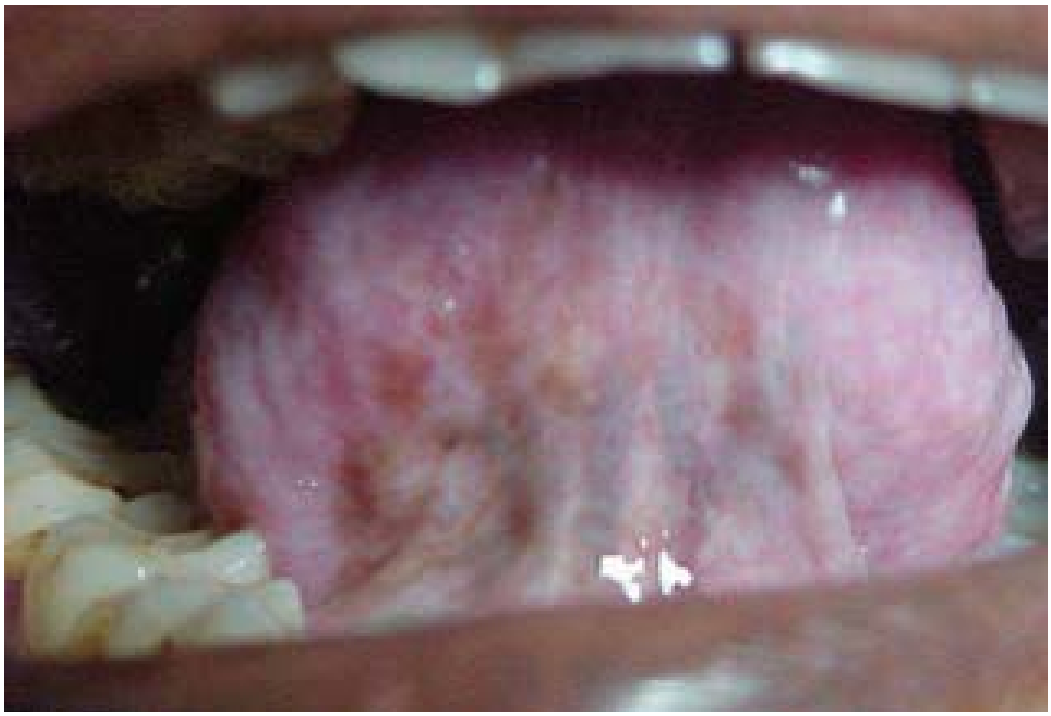
1. Mouth opening > 20 mm
2. Mouth opening 11-19 mm
3. Mouth opening < 10 mm



12. Intra oral photograph of the buccal mucosa showing blanched oral mucosa with erosions in the initial stages of OSMF.



13. Intra oral photograph showing blanched fibrosed oral mucosa and restricted mouth opening.



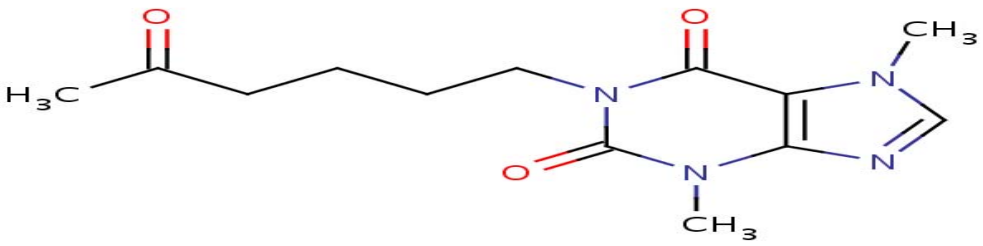
14.Intra oral photograph showing extensive blanching and fibrosis of the ventral surface of the tongue.

15. Intra oral photograph showing fibrosis and trismus.

PENTOXIFYLLINE

INTRODUCTION

Pentoxifylline is a Dimethyl-1-(5-oxyhexyl) xanthine.[50] Its structure consists of isolated molecules connected by Vander walls forces. The bond lengths and angles of the caffeine moiety are similar to those found in other caffeine derivatives. The xanthine ring system is planar. The dihedral angle between the pyrimidine and imidazole rings is $0.5(4)^0$. The conformation of the side chain is gauche-trans-trans-trans.[51]



16.Molecular structure of pentoxyifylline

Molecular structure: $C_{13}H_{18}N_4O_3$=278.[50]

MECHANISM OF ACTION

Tablet pentoxifylline inhibits erythrocyte phosphodiesterase, resulting in an increase in erythrocyte cAMP activity. Subsequently, the erythrocyte membrane becomes more resistant to deformity. Along with erythrocyte activity, pentoxifylline also decreases blood viscosity by reducing plasma fibrinogen concentrations and

increasing fibrinolytic activity. Pentoxifylline inhibits production of tumour necrosis factor alpha, a cytokine that is implicated in the pathogenesis of many diseases.[13,14,30,52,53.]

PHARMACOPOEIAL DESCRIPTION

It is a white or almost white crystalline powder. Soluble in water; sparingly soluble in alcohol; freely soluble in dichloromethane; very slightly soluble in ether. Protect from light.[50]

PHARMACOKINETICS

Pentoxifylline is readily absorbed from the gastrointestinal tract but undergoes first-pass hepatic metabolism. Some metabolites are active. The apparent plasma half life is reported to be 0.4 to 0.8 hours; that of the metabolites varies from 1.0 to 1.6 hours. In 24 hours most of a dose is excreted in the urine mainly as metabolites and less than 4% is recovered in the faeces. Elimination is decreased in elderly patients with hepatic disease. Pentoxifylline and its metabolites are distributed into breast milk.[50]

USES AND ADMINISTRATION

Pentoxifylline is a xanthine derivative used as a vasodilator in the treatment of peripheral and cerebral vascular disorders. It also reduces blood viscosity probably by effects on erythrocyte deformability, platelet adhesion, and platelet aggregation. It increases blood flow in ischemic tissues and improve tissue oxygenation in patients with peripheral vascular disease and to increase oxygen tension in the cerebral cortex and in the cerebrospinal fluid. It inhibits production of the cytokinine, tumour necrosis factor alpha.[50]

The usual dose of pentoxifylline is 400 mg three times daily by mouth in a modified-release formulation, reducing to 400 mg twice daily if adverse effects are troublesome. Doses should be taken with meals to reduce gastrointestinal disturbances. Beneficial effects may not be evident until after 2 to 6 weeks of treatment.[50]

ADVERSE EFFECTS

Pentoxifylline can cause nausea, gastrointestinal disturbances, dizziness, and headache. Flushing angina, palpitations, cardiac arrhythmias, and hypersensitivity reactions may also occur. Bleeding is rare, usually in association with bleeding risk factors. Over dosage with pentoxifylline may be associated with fever, faintness, flushing, hypotension, drowsiness, agitation, and seizures.[50,52.]

PRECAUTIONS

Pentoxifylline should be avoided in cerebral haemorrhage, extensive retinal haemorrhage, and acute myocardial infarction. It should be used with caution in patients with ischemic heart diseases or hypo tension. The dose of pentoxifylline may need to be adjusted in patients with impaired renal function or severe liver impairment.[50,52.]

INTERACTIONS

Pentoxifylline may potentiate the effect of antihypertensive. High parenteral doses may enhance the hypoglycaemic action of insulin in diabetic patients. It should not be given concomitantly with ketorolac as there is increased risk of bleeding or prolongation of the prothrombin time. There may also be an increased risk of bleeding during concomitant use with meloxicam. Serum levels of theophylline may be raised by pentoxifylline.[50]

MATERIALS AND METHODS

Source of Data

All patients diagnosed with Oral submucous fibrosis (OSMF) in the Outpatient Department of Otorhinolaryngology, R.L. Jalappa Hospital & Research Centre, Kolar, from Oct 2008 to July 2010 were included in the study. The study compromised a prospective double-blind clinical analysis of 80 randomly selected OSMF patients. All the patients recruited to the study were of comparable disease progression and share the common demographic features of ethnicity, geographic location and socioeconomic status and all of them were habitual chewers of betal quid or pan masala of similar durations.

The patients stock was fragmented into Experimental drug group (EDG, n=35) where the active treatment option was pentoxifylline (Trental 400 mg tablets, thrice daily) and the standard drug group (SDG) was managed with multi-vitamin capsules (Becozinc) once daily. Local hot fomentation and forceful mouth opening was practiced uniformly by both the group of patients.

The EDG before administration of pentoxifylline underwent clinical and laboratory tests to rule out systemic aliments such as hypertension, diabetes mellitus, cardiac diseases, malignant oral ulcers, acid- peptic disease and bleeding diathesis. The haematological work up comprised recording of total leukocyte count (TC), differential count (DC), haemoglobin values (Hb), platelet count (PC), clotting and bleeding times (CT,BT), recordings of blood pressure and pulse characters of the patients.

Inclusion Criteria

Presence of Burning Sensation in oral cavity upon taking spicy food, restricted mouth opening (inter incisal distance < 4 cms) and presence of palpable fibrous bands in the oral mucosa.

Exclusion Criteria

1) Patients with concurrent oral pathology such as lichinus planus, leukoplakia, erythroplakia or malignancy.
2) Patients treated for OSMF surgically in the past.
3) Patients on long term pentoxifylline therapy for OSMF or other indications**.**

METHODS

The drug pentoxifylline was administered as an inductive regime for the initial 30 days at a reduced dosage of two tablets daily and at the end of the period, all the test cases underwent routine blood and systemic examinations to record untoward adverse effects, if any. The dose was hiked to three tablets daily for all the patients in the EDG. The drop out figure recorded was zero and the clinical symptoms reported were mild gastritis and gastric irritation that could be managed easily. No other reportable complications or side effects were recorded from any of the patients included in this study and the clinical trial was carried further for five more months (total of six months).

Clinical follow up and review of all the patients included in the EDG and SDG was carried out at 30 days intervals for the whole trial period of six months. During each visit, recordings to evaluate the objective and subjective improvement from disease of both the groups were assessed and entered in a specially designed 'proforma' drawn for the purpose. To prevent bias due to interpersonal variability, the same investigator measured all the patients during each visit. Furthermore, this

investigator was unaware as to the patient's group (EDG or SDG), and so were the patients themselves (double-blind).

Study variables

The clinical recordings were made under two headings during each visit.

A. Objective:

1. Improvement in mouth opening (measurement of inter-incisal distance in millimetres)
2. Tongue protrusion beyond the free margins of the upper central incisors.

B. Subjective:

1. Relief from burning sensation.
2. Relief from Intolerance to spicy food.
3. Relief from fibrous bands (digital palpation).

Statistical comparison of EDG and SDG at each visit with respect to each other and to base-line values (pre treatment measures) was done using paired student't' test and Chi-square test.

Follow up period

All patients included in this study were followed-up for 6 months after cessation of active medication, however, the base line therapy of hot fomentation and forceful mouth opening exercises continued during the six months follow-up period.

OBSERVATIONS AND RESULTS

The present study involved a total of 80 cases comprising 35 cases in the experimental drug group and 45 cases in the standard drug group.

Table 1: Number of cases in each group

	EDG group	SDG group	Total
No. Of cases	35	45	80

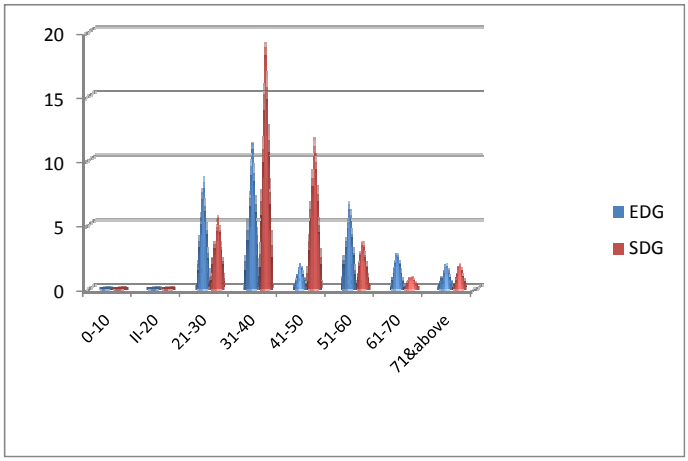
Age Distribution

The age distribution of our patients is shown in table 2. The youngest patient was 25 years old and the oldest patient was 80 years old. In EDG group the mean age was 45.28 years and in SDG group mean age was 41.75 years, overall mean age was 43.29 years. Out of 80 patients studied 32 patients (40%) belonged to the age group of 31-40 years [12 patients (34.28%) in EDG group and 20 patients (44.45%) in EDG group]. This was the most populous group. This was followed by 15 patients (18.75%) [9 patients (25.71%) in EDG group and 6 patients (13.33%) in SDG group] in the age group of 21-30 years. Fourteen patients (17.5%) [2 patients (5.71%) in EDG group and 12 patients (26.67%) in SDG group] belonged to the age group of 41-50 years. There were 11 patients (13.75%) [7 patients (20%) in EDG group and 4 patients (8.89%) in SDG group] belonged to the age group of 51-60 years and 4 patients each in the age group of 61-70 years and above 70 years of age.

Table 2: Age distribution

Age in years	EDG Group n=35		SDG Group n=45		Total =80	
	No.	Percentage	No.	Percentage	No.	Percentage
0-10	0	0	0	0	0	0
11-20	0	0	0	0	0	0
21-30	9	25.71	6	13.33	15	18.75
31-40	12	34.28	20	44.45	32	40
41-50	2	5.71	12	26.67	14	17.5
51-60	7	20	4	8.89	11	13.75
61-70	3	8.57	1	2.22	4	5
71 and above	2	5.71	2	4.44	4	5
Mean age in Years	45.28		41.75		43.29	

Chart 3: Bar diagram showing age distribution



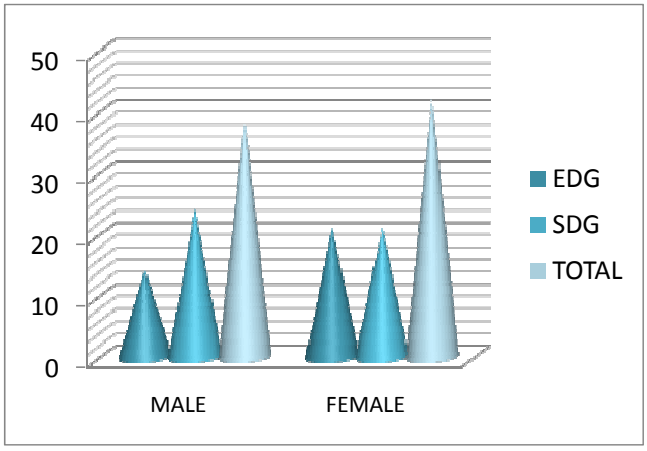
SEX DISTRIBUTION

There were 38 male patients (47.5%) [14 patients (40%) in EDG group and 24 patients (53.33%) in SDG group) and 42 female patients [21 patients (60%) in EDG group and 21 patients (46.67%) in SDG group].

TABLE 3: Sex distribution

Sex	EDG group		SDG group		Total	
	No	Percentage	No	Percentage	No	Percentage
Male	14	40	24	53.33	38	47.5
Female	21	60	21	46.67	42	52.5

Chart 4: Bar diagram showing sex distribution



I. Assessment of objective criteria

1) Inter-incisal distance

The maximum distance between upper and lower central incisor teeth of all patients was measured in millimetres before starting treatment, then at the end of six months of treatment and again at the end of the follow-up period. The maximum, minimum and mean inter-incisal distances at the above mentioned three stages of this study are shown below in tables 4 to 6.

Table 4: Inter-incisal distance at the start of treatment

	EDG	SDG
Maximum IID	32	32
Minimum IID	18	19
Average IID	25.65	25.82

Chart 5: Bar diagram showing Inter-incisal distance at the start of treatment

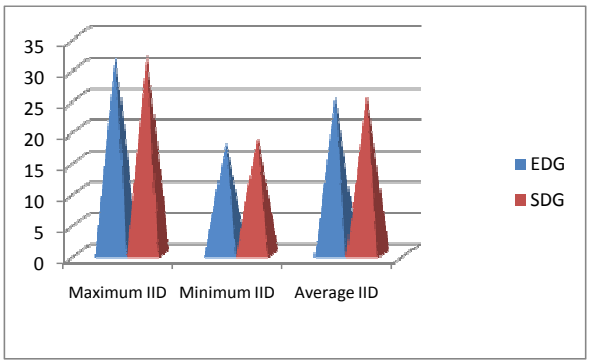


Table 5: Inter-incisal distance at the end of six months of treatment

	EDG	SDG
Maximum IID	32	33
Minimum IID	18	18
Average IID	25.71	25.84

Chart 6: Bar diagram showing inter-incisal distance at the end of 6 months of treatment

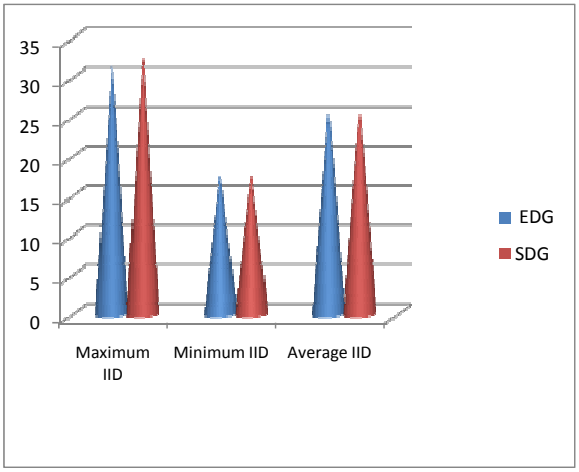
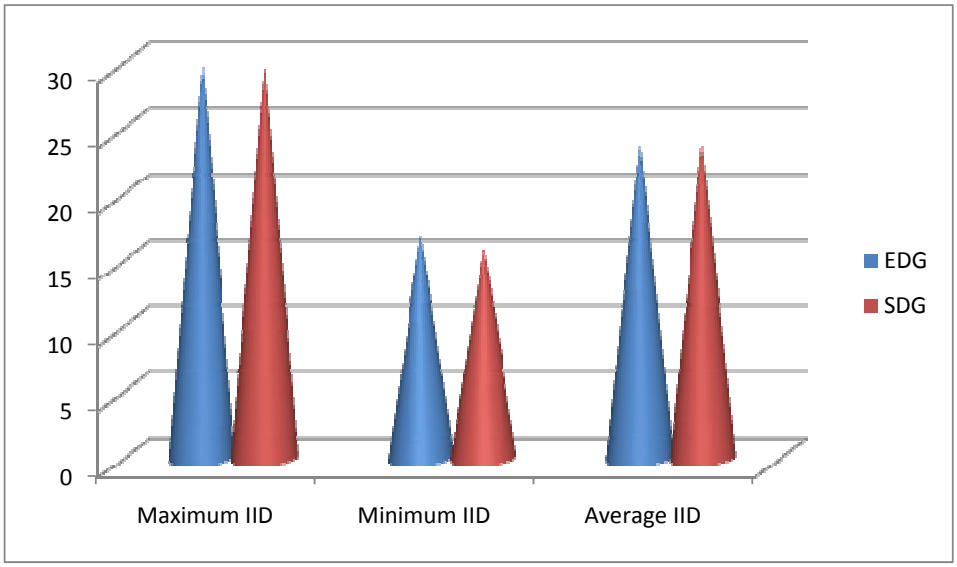


Table 6: Inter-incisal distance after a follow-up period of six months

	EDG	SDG
Maximum IID	30	30
Minimum IID	17	16
Average IID	23.94	24.08

Chart 7: Bar diagram showing inter-incisal distance after 6 months follow-up period



It was observed that the average inter-incisal distance at the start of treatment was similar in both groups; 25.65 mm in EDG and 25.82 mm in SDG. At the end of six months of treatment the average inter-incisal distance did not vary significantly in either group [25.71 mm in EDG and 25.84 mm in SDG]. However, the average inter-incisal distance when measured at the end of six months follow-up period, revealed a significant decline [23.94 mm in EDG and 24.08 mm in SDG].

Statistical analysis of inter-incisal distance

The results showed that the decreases in average inter-incisal distances after cessation of treatment were highly significant during the follow-up period.

Table 7: Statistical analysis of inter-incisal distance

		Paired differences mean	Standard deviation	Standard error mean	95% Confidence interval of the difference		't'	Degrees of freedom	'p' value	Significance
					Lower	Upper				
V_1-V_6	EDG	-.0571	.68354	.11554	-.2919	.1777	-.495	34	.624	Not significant
	SDG	.0833	.76997	.12833	-.1772	.3439	.649	35	.520	Not significant
V_7-V_{12}	EDG	1.6000	1.00587	.17002	1.2545	1.9455	9.411	34	.001	Highly significant
	SDG	1.3333	1.30931	.21822	.8903	1.7763	6.110	35	.001	Highly significant
V_1-V_{12}	EDG	1.5429	1.19663	.20227	1.1318	1.9539	7.628	34	.001	Highly significant
	SDG	1.4167	1.74642	.29107	.8258	2.0076	4.867	35	.001	Highly significant

V_1-V_6 = The period of drug trial

V_7-V_{12} = Follow-up period

V_7-V_{12} =1st Visit of the patient to end of the follow-up period

2. Tongue protrusion distance

The maximum distance between the tip of the tongue and the free margins of the upper incisor teeth was recorded in millimetres of all the patients before starting treatment, at the end of six months and at the end of the follow-up period. The maximum, minimum and mean values are shown in tables 8- 10.

Table 8: Tongue protrusion distance at the start of treatment

	EDG	SDG
Maximum tongue protrusion	31	29
Minimum tongue protrusion	18	19
Average tongue protrusion	24.77	23.08

Chart 8: Bar diagram showing Tongue protrusion distance at the start of treatment

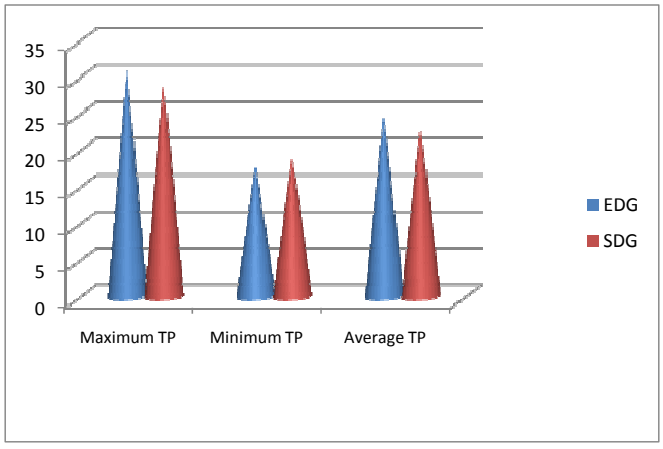


Table 9: Tongue protrusion distance at the end of six months of treatment

	EDG	SDG
Maximum tongue protrusion	32	29
Minimum tongue protrusion	20	20
Average tongue protrusion	24.8	23.51

Chart 9: Bar diagram showing tongue protrusion distance at the end of six months of treatment

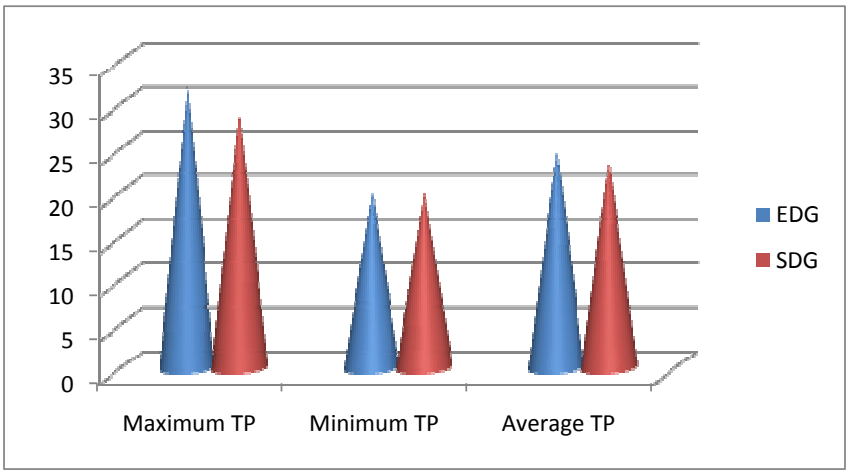
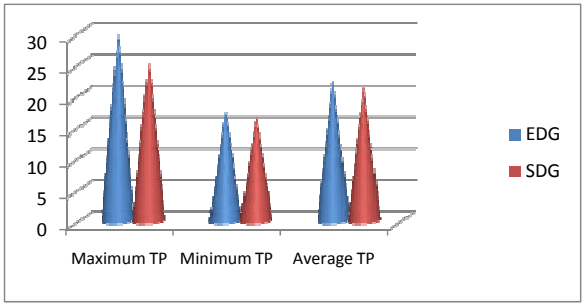


Table 10: Tongue protrusion distance after a follow-up period of six months

	EDG	SDG
Maximum tongue protrusion	30	26
Minimum tongue protrusion	18	17
Average tongue protrusion	22.74	21.68

Chart 10: Bar diagram showing tongue protrusion distance after six months follow-up period



It was observed that the average tongue protrusion at the start of treatment was 24.77 mm in EDG and 23.08 mm in SDG. At the end of six months of treatment the average tongue protrusion distance did not vary significantly. [EDG=24.8 mm and SDG=23.51]. As observed with the inter-incisal distance during follow-up period, the tongue protrusion distance significantly decreased during the six months after cessation of treatment [EDG=22.74 mm and SDG=21.68].

Statistical analysis of tongue protrusion distance

The results showed that the decreases in average inter- incisal distances after cessation of treatment were highly significant during the follow-up period.

Table 11: Statistical analysis of tongue protrusion distance

		Paired differences mean	Standard deviation	Standard error mean	95% Confidence interval of the difference		't'	Degrees of freedom	'p' value	Significance
					Lower	Upper				
V_1-V_6	EDG	-.0268	1.09774	.18555	-.4057	.3485	-.154	34	.879	Not significant
	SDG	-.3243	1.02886	.16914	-.6674	.0187	-1.917	36	.063	Not significant
V_7-V_{12}	EDG	2.0571	1.02736	.17366	1.7042	2.4101	11.846	34	.001	Highly significant
	SDG	2.0811	.95389	.15682	1.7630	2.3991	13.271	36	.001	Highly significant
V_1-V_{12}	EDG	2.0286	1.20014	.20286	1.6163	2.4408	10.000	34	.001	Highly significant
	SDG	1.7568	1.06472	.17504	1.4018	2.1118	10.036	36	.001	Highly significant

V_1-V_6 = The period of drug trial

V_7-V_{12} = Follow-up period

V_7-V_{12} =1st Visit of the patient to end of the follow-up period

II. Assessment of subjective criteria

1) Burning sensation in the mouth

It was observed that out of 35 patients in the EDG 32 patients (91.4%) reported a significant improvement of burning sensation in the mouth after six months of treatment. Among the 45 patients in the SDG 20 patients (44.4%) reported relief from burning sensation in the mouth (table 12). However, all patients of both the groups complained of recurrence of their symptoms at the end of the follow-up period. These observations when statistically analysed using the chi-square test as shown in the table 13 was found to be highly significant.

Table 12: Burning sensation in the mouth

	EDG (n=35)	SDG (n=45)
At the start of treatment	35	45
At the end of 6 months of treatment	03	25
After 6 months follow-up period	35	45

Chart 11: Bar diagram showing burning sensation in the mouth

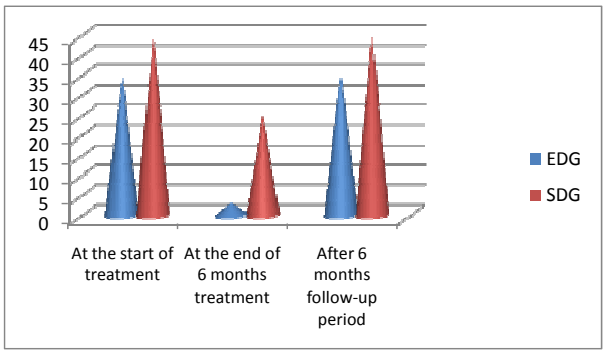


Table 13: Statistical analysis of burning sensation

	Chi-square value	'p'value	Significance
V_1-V_6	9.926	0.00163	Highly significant

V_1-V_6 = The period of drug trial

2) Intolerance to spicy food

Based on the patients' feed back as recorded at each monthly visit during the treatment period, only three patients (8.5%) out of 35 patients in EDG complained of persisting intolerance to spicy food [Burning sensation when attempting to eat spicy food]. Whereas 18 patients (40%) in the SDG complained of intolerance to spicy food even after six months of treatment. However all patients of both groups complained of intolerance to spicy food at the end of the six months follow-up period (table 14). The severity of this symptom was comparable to pre-treatment levels. These observations were statistically highly significant as shown in table 15.

Table 14: Intolerance to spicy food

	EDG (n=35)	SDG (n=45)
At the start of treatment	35	45
At the end of 6 months of treatment	03	18
After 6 months follow-up period	35	45

Chart 12: Bar diagram showing intolerance to spicy food

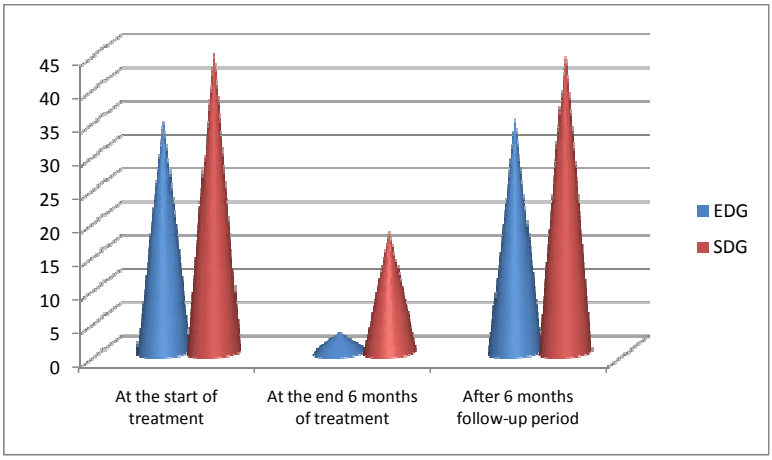


Table 15: Statistical analysis of intolerance to spicy food

	Chi-square value	'p'value	Significance
V_1-V_6	6.153	0.013	Highly significant

V_1-V_6 = The period of drug trial

3) Digital palpation of fibrotic bands in the oral cavity

Out of the 35 patients in the EDG only one patient (2.85%) had a significant improvement in the condition of his palpable fibrotic bands. This patient happens to be the youngest patient (age-25 years) in this study. None of the patients belonging to the SDG showed an improvement in the palpatory findings (table-16).

Table 16: Digital palpation of fibrotic bands in the oral cavity

	EDG (n=35)	SDG (n=45)
At the start of treatment	35	45
At the end of 6 months of treatment	34	45
After 6 months follow-up period	35	45

Chart 13: Bar diagram showing digital palpation of fibrotic bands in the oral cavity

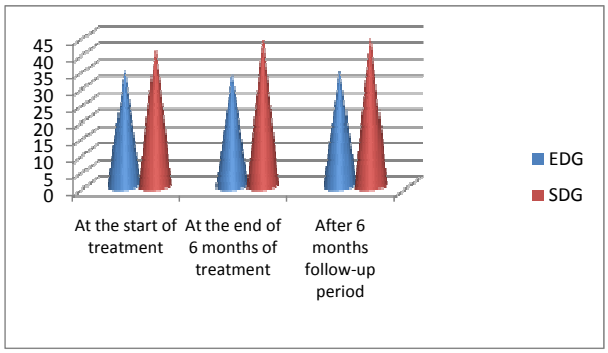


Table 17: Statistical analysis digital palpation of fibrotic bands in the oral cavity

	Chi-square value	'p'value	Significance
V_1-V_6	0.092	0.7612	Not significant

V_1-V_6 =The period of drug trial

Summary of statistical significance

The assessment of objective and subjective criteria is summarized in table-18. Out of the 80 patients studied 52 (65%) patients [32(EDG), 20(SDG)] had a statistically significant improvement in their signs and symptoms during the period of treatment. However, all the 80 patients [EDG (35) and SDG (45)] when evaluated during and at the end of the follow-up period had worsening of their signs and symptoms, which was statistically highly significant.

Table 18: Summary of statistical significance

		EDG		SDG	
		'p' value	**Significance**	**'p' value**	**Significance**
Inter-incisal distance	V_1-V_6	0.624	Not significant	0.520	Not significant
	V_6-V_{12}	0.000	Highly significant	0.000	Highly significant
	V_1-V_{12}	0.000	Highly significant	0.000	Highly significant
Tongue protrusion	V_1-V_6	0.879	Not significant	0.630	Not significant
	V_6-V_{12}	0.001	Highly significant	0.001	Highly significant
	V_1-V_{12}	0.001	Highly significant	0.001	Highly significant

	'p' value	Significance
Burning sensation	0.00163	Highly significant
Intolerance to spicy food	0.013	Highly significant
Digital palpation of fibrotic bands	0.7612	Not significant

V_1-V_6 = The period of drug trial; V_7-V_{12} = Follow-up period

V_7-V_{12} =1st Visit of the patient to end of the follow-up period

DISCUSSION

Oral submucous fibrosis is a precancerous lesion occurring mainly in India and Pakistan.[11] Malignant transformation rates are as high as 7.6%.[20] The Incidence of oral malignancy in India is among the highest in the world.[7] Indian medical experts warned that millions of people addicted to pan masala and gutkha will be affected.[9,10.] Recent epidemiological data indicates that the number of cases of OSMF has risen rapidly in India from an estimated 2,50,000 cases in 1980 to 2 million cases in 1993. The reasons for the rapid increase of the disease are reportedly due to an upsurge in the popularity of commercially prepared areca nut preparations (pan masala) in India and an increased uptake of this habit by young people due to easy access, effective price changes and marketing strategies.[6]

Oral submucous fibrosis is a distressing condition in which due to limited opening of the oral cavity, the patient is neither able to consume a normal diet nor maintain proper oral hygiene. Overall prevalence of OSMF in India is about 0.5% with a range of 0.2 -1.2% in different regions of country.[9,19]

Oral submucous fibrosis is diagnosed on clinical criteria including mucosal blanching, burning sensation, hardening, and the presence of characteristic fibrotic bands, and is associated with gradual inability to open the mouth. Mouth opening and protrusion of tongue is an objectively verifiable criterion by which severity of the disease can be assessed. The oral mucosa becomes stiff and opaque.[21,22,23.] The treatments proposed for OSMF have been palliative rather than curative. They are aimed to improving the patient's ability to open the mouth, which becomes restricted when more scar tissue is formed as the disease progresses. The treatment includes the conservative measures such as topical application of vitamin A, steroids

(betamethasone), and oral iron applications (ferrous fumarate ointment) for mild cases. Local submucosal injection of steroids (dexamethasone), hyaluronidase, and chymotripsin. Intralesional injection of aquesous extract of healthy human placenta, excision of the fibrotic bands with submucosal placement of human placental grafts, surgery with split-thickness skin graft, combined with temporalis myotomy or coronoidectomy and bilateral full thickness nasolabial flaps for severe trismus cases. Relapse is a common complication that occurs after surgical release of the oral trismus.[27]

Pentoxifylline is a tri-substituted methylxanthine derivative, the biologic activities of which are numerous. This includes increasing red cell deformability, leukocyte chemotaxis, antithrombin and anti- plasmin activities, and more importantly to the present context, its fibrinolytic activity. Pentoxifylline decreases red cell and platelet aggregation, granulocyte adhesion, fibrinogen levels, and whole blood viscocity.[54] Recent work has delineated pentoxifylline ability to decrease production of tumour necrosis factor alpha and reduce some of the systemic toxicities mediated by interleukin-2.[55,56,57.] These two cytokines are important mediators of the inflammatory response. In addition, pentoxifylline has been shown to increase the production of PGE2 and PGI2 by vascular epithelium, important in maintaining cellular integrity and homeostasis after acute injury.[58,59,60.] Since this drug has proved effective in treating intermittent claudication caused by chronic peripheral arterial occlusion, we surmised that it might also be effective in treating OSMF, having a putative association with mucosal ischemia and resultant epithelial atrophy. The sub-mucosal fibrosis, which is the hallmark of the disorder, is envisaged to be the result of a defective inflammatory reparative response culminating in fibrotic healing.[61]

The degree of vascularity of the diseased mucosa in OSMF has always been a matter of dispute. While good case control studies on the integrity and patency of microvasculature of the mucosa in OSMF are still lacking, histological evidence goes against the concept of decreased vascularity in this disease.[62] An evidence in support of this was the recent demonstration of the status of vascular patency in OSF, by image analysis, that the mean vascular luminal diameter recorded an increasing trend as the disease progresses. This was a significant conceptual deviation from the common wisdom, as regards to the pathogenesis of this disease. Against this backdrop the concept of ischemic atrophy was disputed. The usual tissue reaction resultant to ischemia / hypoxia does not seem to operate in this disease; which is preconditioned by significant stromal changes as part of the disease process. A mean vascular dilatation, instead of a generalized vasoconstriction, which assumed to be an adaptive response to tissue ischemia due to the physical effects of pathological fibrosis. It is speculative therefore to evaluate the role of a peripheral vasodilator pentoxifylline, in the treatment of OSMF. The beneficial effect recorded by pentoxifylline in managing advanced OSMF, prompt us to explore further with the biological effects of this drug, and also to elucidate the effectiveness of this drug in dealing with this rather prototype of pathologic fibrosis.[63]

As OSMF is a chronic mucosal inflammatory disease (persistent stomatitis and glossitis), control of the inflammation or the factors influencing the inflammatory process should form the basis of definitive management. Primary immunologic abnormalities have been reported with OSMF and that these immune abnormalities probably mediate local tissue damage and that they appear to be the final common pathway in the pathogenesis of OSMF. But there is no unifying explanation for this immunological basis of OSMF.[63]

The drug pentoxifylline is said to have the property of suppressing leucocyte function while altering fibroblast physiology and stimulating fibrinolysis. Its immuno-modulating actions include increasing leucocyte adhesion. It also causes neutrophil degranulation and the release of peroxides, promotes natural killer cell activity and the production of tumour necrosis factor, and inhibits T and B cell activation.[64] The subjective improvement in clinical outcome recorded in this study may probably be attributed to these pharmacological effects of the drug.

The anti inflammatory and immunomodulatory actions of 'Trental' seems to have definite therapeutic advantages in the management of OSMF but the long term effects of which is difficult to speculate now. Some of our patients are being followed up for a period of more than 12 months and the beneficial effects seemed to be holding, is regarded as a desirable effect of the drug.

The property of pentoxifylline that may be far-reaching in the management of OSMF is perhaps its effect on the fibroblast and the role it assumed in fibrinolysis. There are some features exclusive to skin and the subcutaneous tissue that may also be important in the oral mucosal sites, particularly in the context of wound healing and connective tissue diseases in general. Berman and Duncan (1989) showed that fibroblasts cultured in the presence of pentoxifylline produce twice as much collagenase activity and decreased amount of collagen, glycosaminoglycans and fibronectins.[28] IL-1 induced fibroblast proliferation was inhibited by the addition of pentoxifylline. In another series by Berman et al (1992) pentoxifylline blocked TNF-a induced synthesis of fibroblast collagen, glycosaminoglycans and collagenolytic activity.[29] It was determined that these selective inhibitory effects occurred without altering TNF-a receptor mRNA, the number of cell receptors, or affinity for TNF-a receptors compared with untreated controls. These results suggest that the inhibitory

activities of pentoxifylline on fibroblasts are mediated at a locus other than TNF-a receptors.

The central nervous system and gastro-intestinal side effects of pentoxifylline are dose related and are therefore minimized by dose reduction. How ever, the adverse side effects which warrant cessation of therapy did not occur in patients samplified for this study.

This study constitutes 80 patients. We included the patients diagnosed with OSMF in the Department of Otorhinolaryngology, R.L. Jalappa Hospital & Research centre, Kolar, from Oct 2008 to Mar 2010. The study design adopted was a prospective randomized controlled double blind study, where patients are randomly chosen to form a group called experimental drug group (EDG) and a control group called standard drug group (SDG).

Both groups had a comparable degree of the disease and share common demographic features. The EDG were administered pentoxifylline (Trental 400 mg) tablets twice or thrice daily whereas the SDG were given a multivitamin capsule (Becozinc). Other measures such as local hot fomentation and forceful mouth opening exercises were practice uniformly by both groups of patients.

An extensive search of the English language literature was carried out. The websites visited were Pubmed, Science direct, World science.org, Elsevier science, Google scholar, Ovid. The key words used for the search were; Oral submucous fibrosis, submucous fibrosis, Pentoxifylline in submucous fibrosis. There is a paucity of controlled studies.

In a pilot study by Rajendran et al, there were a total of 29 patients, of which 14 patients belonged to the experimental drug group and 15 were in the standard drug group. Pentoxifylline was given orally in the dose of 400 mg tablets daily to patients in the experimental drug group. The mean age in both groups centred around 40 years. Males outnumbered females in the ratio of 9:5.

The inter-incisal distance during the treatment period of seven months showed statistically highly significant values for all the monthly evaluations in favour of the experimental drug group. Tongue protrusion distance showed an overall improvement after 5-6 months of treatment in patients belonging to both groups. The comparison between the EDG and SDG was statistically insignificant. Relief from fibrotic bands was observed in all of their patients belonging to EDG which was in strake contrast to the patients of the SDG were none showed improvement.

With regard to evaluation of subjective criteria, their study concluded that relief from intolerance to spicy food and burning sensation in the mouth improved in all their patients belonging to the experimental drug group. Whereas in the SDG about 55% of their patients reported relief from intolerance to spicy food and about 33% reported relief from burning sensation in the mouth.

Their study also concluded other subjective criteria such as salivation, rigidity of mucosa, de-papillation of dorsum of tongue and tinnitus, difficulty in swallowing and difficulty in speech. The effect of pentoxifylline on salivation, rigidity of mucosa and de-papillation of tongue could not be assessed and the result was inconclusive. However, improvement in tinnitus, difficulty in swallowing and speech was highly significant in the experimental drug group. The observations of this study by Rajendran et al summarized in table 19.[12]

TABLE 19: Results of Rajendran et al study

	'p' value	Significance
Improvement in mouth opening	0.000023	Highly significant
Improvement in tongue protrusion	0.049	Not significant
Relief from fibrotic bands	0.0001554	Highly significant
Relief from intolerance to spicy food	0.0063218	Highly significant
Relief from burning sensation in mouth	0.0005797	Highly significant
Improvement in salivation, rigidity of mucosa, and de-papillation of dorsum tongue	-	Inconclusive
Improvement from tinnitus	-	Highly significant
Improvement from difficulty in swallowing, speech	-	Highly significant

In our study, out of a total of 80 patients, 35 patients were in the EDG, 45 in the SDG. All were treated for a period of six months. The mean age of both groups was around 43 years. Sex ratio was 1:1.

During the six months period of our study, a significant improvement was observed in the subjective criteria (Burning sensation in the mouth and intolerance to spicy food) among patients of the EDG (91.4%) when compared to the SDG (45-60%). These findings are similar to observations made in the study by Rajendran et al. However, there was no difference in the palpable fibrotic bands in patients of both drug groups. With regard to digitally palpable fibrotic bands in the oral cavity, our study observed no significant improvement in either the EDG or SDG. This was in contrast to observations made in the study by Rajendran et al where all patients of the EDG (100%) showed improvement while none improved in the SDG.

The all important objective criteria of inter-incisal distance and tongue protrusion distance did not show any significant improvement in either drug group during our six months treatment period. This observation was not in tandem with

observations of Rajendran et al where the improvement in inter-incisal distance was statistically highly significant in the EDG when compared to the SDG, and the tongue protrusion distance improved in both groups of their patients.

Table 20: study comparison of our study and Rajendran et al study

OBSERVATIONS	RAJENDRAN ET AL STUDY	OUR STUDY
Total no. Of patients	29	80
EDG	14	35
SDG	15	45
Average age	40	43.29
Sex ratio	9:5	1:1
Statistical significance		
Inter-incisal distance	Highly significant	Not significant
Tongue protrusion distance	Not significant	Not significant
Burning sensation in the mouth	Highly significant	Highly significant
Intolerance to spicy food	Highly significant	Highly significant
Digital palpation of fibrotic bands	Highly significant	Not significant

We made a significant observation during the follow-up period where in, after cessation of treatment all patients of both groups showed a gradual deterioration in both subjective criteria as well as objective criteria. This observation indicates a highly significant influence of pentoxifylline as well as multivitamins in halting the progress of the disease during the treatment period. Although objective criteria did not improve in our patients, the progression of disease was clearly checked. This finding could not be compared with that of Rajendran et al study since their patients were in various stages of follow-up at the time of their study publication.

In a study by Lai et al medical treatment in which B complex was given in combination with bufflomedial hydrochloride and topical triancinalone acetonide was found to be satisfactory in those patients with early disease where in the inter-incisal distance was more than 20 mm. In the long term their patients had only symptomatic relief.

Kumar et al assessed the efficacy of zinc in OSMF; they evaluated the role of zinc as a standalone as well as in combination with vitamin A and local hydrocortisone injections. They concluded that a 12 week therapy with zinc showed a significant improvement in severity of disease. The addition of zinc to their treatment of local hydrocortisone injections significantly improved the condition and observed that there was no recurrence during a 15 month follow-up period.[25]

In a study by Maher et al the role of several micronutrients including vitamin B complex and zinc was evaluated. They were unable to establish an etiological correlation between any specific micronutrient and hence their usefulness in treatment of OSMF.[27]

From the observations of the above studies it appears that the role of multivitamins including B complex and minerals such as zinc is either minimally beneficial or inconclusive. Probably a longer duration of treatment may reveal a more significant role of pentoxifylline in improving the clinical features of OSMF. The possibility of drug synergy between pentoxifylline and multi vitamin also needs to be studied as both these medications when given separately were equally effective in halting the progress of disease in this study.

CONCLUSION

Oral submucous fibrosis is a disease that remains to be fully understood. Treatment options are numerous but un-established. Controlled and blinded studies involving large samples with long term follow-up periods is lacking in medical literature.

In our study patients had a statistically significant improvement in the subjective criteria. Burning sensation in the mouth and intolerance to spicy food were alleviated in more number of patients when treated with pentoxifylline as compared to those treated with B complex and zinc. With regard to objective criteria such as inter-incisal distance and tongue protrusion distance. We did not record an improvement in either group of patients. However, these features did not deteriorate during the treatment period but gradually worsened after withdrawal of treatment. This observation was statistically highly significant which indicates that pentoxifylline and B complex with zinc have a significant influence on the progression of this disease. We opine that longer duration of treatment may yield a more significant role of pentoxifylline in not only halting the progress of disease but possibly improving the signs and symptoms of oral submucous fibrosis.

SUMMARY

Oral submucous fibrosis is a chronic disease which is commonly seen in india characterized by burning sensation in oral cavity on taking spicy food, restricted mouth opening, palpable fibrous bands, decreased tongue protrusion, mucosal rigidity, depapillation of the tongue, excessive salivation. The precise cause is unknown but chewing of betal quid as well as other areca nut containing products and, pan masala, excessive use of chillies and spices, poor nutrition and vitamin and iron deficiency have been suggested.

Medical treatment includes iron and multivitamin supplements, intralesional injection of steroids, hyaluronidase, human placenta extracts, chemotrypsin, pentoxifylline and collagenase.

This study is a prospective randomized double-blind study which evaluates two groups of patients with OSMF, one experimental drug group and other standard drug group.

Eighty patients were randomized into two groups. The EDG consisted of 35 patients and SDG had 45 cases. The EDG underwent treatment with pentoxifylline 400 mg tablets thrice daily and the SDG was given B complex with zinc (Becozinc capsules) for a period of six months. Both groups were practised hot fomentation and mouth opening exercises.

The maximum number of cases belonged to the age group of 31-40 years. Males and females were more or less equally affected. The study variables were grouped as objective and subjective criteria. The physically verifiable objective criterion was inter-incisal distance and tongue protrusion distance. The subjective

criteria was burning sensation in the mouth, intolerance to spicy food, digitally palpable fibrotic bands in the oral cavity. The treatment period was six months and follow-up period was also six months.

The key observations made during this were that patients of both groups showed a statistically significant improvement in their subjective criteria more so in patients treated with pentoxifylline. Palpable fibrotic bands in the oral cavity did not appear to improve.

In the objective criteria neither the inter-incisal distance nor the tongue protrusion distances improve during the treatment period. However, after cessation of treatment with pentoxifylline and vitamin B complex with zinc in the respective groups of patients; it was observed that both groups of patients had a gradual deterioration in their subjective and objective criteria. This observation when subjected to statistical analysis was found to be highly significant indicating that pentoxifylline has a significant influence in halting the progress of OSMF. Although the objective criteria did not improve in our patients, the progression of disease clearly checked.

A longer duration of treatment may provide a more significant role of pentoxifylline in not only halting the progress of disease but possibly improving the signs and symptoms of OSMF.

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PROFORMA

Name of the patient:

Age:

Sex:

Occupation:

Address:

Hospital no.:

Date:

Chief complaints: Yes/No Since

Presence of burning sensation in oral cavity upon taking spicy food:

Restricted mouth opening:

History of presenting illness: Yes/No Since

Presence of burning sensation in oral cavity upon taking spicy food:

Restricted mouth opening:

Able to insert 1/2/3 fingers into the mouth:

Difficulty in speaking:

Halitosis:

Excessive salivation:

Difficulty in swallowing:

Weight loss:
Generalised weakness:
Loss of appetite:

Past history: Yes/No Since

HTN:

DM:

PTB:

Acid peptic disease:

Treatment history: Yes/No

Contributory:

Non contributory:

Personal history:

Sleep,bowel,bladder habbits:

Appetite:

Yes/No Since

Areca/betal quid:

Tobacco chewing:

Smoking: Number/day Since

Bidi:

Cigarette:

Pan masala:

Alcohol Duration:
Frequency:
Quantity:

General physical examination:

Built: Cyanosis: Pulse:

Nourishment: Clubbing: Temperature:

Pallor: Oedema: BP:

Icterus: Weight:

Local examination:

Oral cavity:

Lips:

Mouth opening: Trismus : +/-

Inter incisal distance :

Oro-dental hygiene:

Nicotine Stains:

Mucosal Blanching:

Tongue Protrusion:

Lingual de – papillation:

Palpable fibrous bands in:

Anterior fauces:

Buccal mucosa:

Lateral regions:

Dental arcades:

Alveolar arches:

Oral vestibule:

Anterior 2/3rd of tongue:

Hard palate:

Floor of mouth:

RMT:

Oropharynx:

Palatine arch:

Soft palate:

Uvula:

Anterior faucial pillars:

Posterior faucial pillars:

Tonsils:

Base of tongue:

Tonsillo-lingual sulcus:

Vallecula:

Posterior pharyngeal wall:

Lateral pharyngeal wall:

Examination of the nose:

Examination of the ear:

Examination of neck:

Systemic examination:

CVS:

RS:

Per abdomen:

CNS:

Clinical diagnosis:

Investigations:

HB:	TC:	DC:
Platelet count:	BT:	CT:
ESR:	RBS:	Urine routine:

ECG:

Treatment:

KEY TO MASTER CHART

Sl.No	Serial Number
H.No	Hospital number
M	Male
F	Female
IID	Inter-incisal distance
TP	Tongue protrusion
DPFB	Digital palpation of fibrotic bands
BS	Burning sensation
ITSF	Intolerance to spicy food
1	First visit of the patient
2	At the end of the six months treatment period
3	At the end of six months follow-up period