Review Article

A Comprehensive Review of Treatment Options of OSMF Along With Future Developments

Abstract

In 600 B.C., Shushrutha, an ancient Indian Physician, in his book 'ShushruthaSamhita', reported an oro - pharyngeal condition called 'Vidari', which mimicked to Oral Submucous Fibrosis. It was first reported and described by J.Schwartz in 1952 in Indian women and described itas "Atropicaidiopathicamucosaeoris" and later by Jens J. Pindborg in 1966 as "an insidious, chronic disease that affects any part of the oral cavity and sometimes the pharynx .This article aims to review all the possible treatment options available for a patient suffering from osmfin a comprehensive yet simplified manner ranging from conservative approaches to radical surgical options.

Keywords: osmf, reduced mouth opening, interferon gamma, steroids, HBOT, pedicled flaps.

Introduction

Oral Submucous Fibrosis (OSMF) is a potentially malignant disorder which was described by Schwartz in 1952 as "Atropicaidiopathica mucosae oris" and later by Jens J. Pindborg in 1966 as "an insidious, chronic disease that affects any part of the oral cavity and sometimes the pharynx . Although occasionally preceded by, or associated with, the formation of vesicles, it is always associated with a juxtaepithelial inflammatory reaction followed by fibroelastic change of the lamina propria and epithelial atrophy that leads to stiffness of the oral mucosa and causes trismus and an inability to eat". [15]

In severe stage; hypomobility of soft palate & tongue, xerostomia, loss of gustatory sensations, fibrosis of pharyngeal & esophageal mucosa, hearing impairment, sunken cheeks, muscular dystrophy, hoarseness of voice, nasal twang and significant functional morbidity is noticed.

Progressive inability to open the mouth is due to loss of elasticity and development of vertical fibrous bands in labial and buccal tissues. The disease is seen in any age group, with prevalence being high in 18–35 years. It is a significant public health problem in India, and contributes significantly to mortality because of its high malignant transformation rate. There is compelling evidence to implicate the chewing of areca nut and its commercial preparations with the development of OSMF.The combined effect of alkaloids and tannins in areca nut forms the basis for fibrosis.The chewing of areca nut and its commercial preparations (gutkha, mawa, pan masala, flavored supari, etc.) is a regular and rampant practice in asian countries, irrespective of

age and sex .Once the process of uncontrolled fibrosis is initiated, the condition is not reversible at any stage of the disease process even after cessation of chewing areca nut or its substitute.

Pindborg JJ (1989)[1]separated OSMF into three stages based on clinical features:

Stage 1: Stomatitis includes erythematous mucousa, vesicles, mucosal ulcers, melanotic mucosal pigmentation and mucosal patechiae.

Stage 2: Fibrosis occurs in healing vesicles and ulcer, which is the hallmark of this stage. Early lesions demonstrate blanching of oral mucosa. Older lesion include vertical and circular palpable fibrous bands in the buccal mucosa and around the mouth opening or lips, resulting in a mottled marble like appearance of the mucosa because of the vertical thick, fibrous bands associated with balanced mucosa.
Specific finding include the following: Reduction of mouth opening (trismus)

- Stiff and small tongue
- Blanched and leathery floor of the mouth
- Fibrotic and depigmented gingival
- Rubbery soft palate with decrease mobility
- Blanched and atrophic tonsils
- Shrunken bud like uvula.
- Sinking of the cheeks, not commensurate with age

Stage 3: Sequelae of OSMF
• Leukoplakia is found in more than 25% of individuals with OSMF.
• Speech and hearing deficits may occur because of involvement of the Eustachian tubes.

Pindborg JJ and Sirsat SM (1966)[2]were the first to divide OSMF depending only on histopathological features alone are as follows:

Very early stage:Finely fibrillary collagen dispersed with marked edema. Plump young fibroblast containing abundant cytoplasm. Blood vessels are dilated and congested. Inflammatory cells, mainly polymorphonuclear leukocytes with occasionaleosinophils are found.

Early stage:Juxta-epithelial area shows early hyalinization. Collagen still in separate thick bundles. Moderate number of plump young fibroblasts is present. Dilated and congested blood vessels. Inflammatory cells are primarily lymphocytes, eosinophils and occasional plasma cells.

Moderately advanced stage Collagen is moderately hyalinized. Thickened collagen bundles are separated by slight residual edema. Fibroblastic response is less marked. Blood vessels are either normal or compressed. Inflammatory exudates consist of lymphocytes and plasma cells.

Advanced stage Collagen is completely hyalinized. No separate bundles of collagen are seen. Edema is absent. Hyalinized area is devoid of fibroblasts. Blood vessels are completely obliterated or narrowed. Inflammatory cells are lymphocytes and plasma cells.

Classification Based on Clinical and Histopathological Features:

Khanna JN and Andrade NN (1995)[3]developed a group classification system for the surgical management of OSMF:

Group I: **Very early cases** Common symptom is burning sensation in the mouth, acute ulceration and recurrent stomatitis and not associated with mouth opening limitation.

Histology: Fine fibrillar collagen network interspersed with mark edema, blood vessels dilated and congested, large aggregate of plump young fibroblasts present with abundant cytoplasm, inflammatory cells mainly consist of polymorhonuclear leukocytes with few eosinophils. The epithelium is normal.

Group II: Early cases Buccal mucosa appears mottled and marble like, wide spread sheets of fibrosis palpable, interincisal distance of 26 to35mm.
Histology: Juxta-epithelial hyalinization present, collagen present as thickened but separate bundles, blood vessels dilated and congested, young fibroblasts seen in moderate number, inflammatory cells mainly consist of polymorph nuclear leukocytes with feweosinophils and occasional plasma cells, flattening or shortening of epithelial rete-pegs evident with varying degree of keratinization.

Group III: Moderately advanced cases Trismus, interincisal distance of 15 to 25 mm, buccalmucosa appears pale firmly attached to underlying tissues, atrophy of vermilion border, vertical fibrous bands palpable at the soft palate, pterygomandibular raphe and anterior faucial pillars.

Histology: Juxta-epithelial hyalinization present, thickened collagen bundles, residual edema, constricted blood vessels, mature fibroblasts with scanty cytoplasm and spindle-shaped nuclei, inflammatory exudates which consists of lymphocytes and plasma cells, epithelium markedly atrophic with loss of rete pegs, muscle fibers seen with thickened and dense collagen fibers.

Group IVA: Advanced cases Severe trismus, interincisal distance of less than 15mm, thickened faucial pillars, shrunken uvula, restricted tongue movement, presence of circular band around entire lip and mouth.

Group IVB: Advanced cases Presence of hyperkeratotic leukoplakia and squamous cell carcinoma.

Histology: Collagen hyalinized smooth sheet, extensive fibrosis, obliterated the mucosal blood vessels, and eliminated melanocytes, absent fibroblasts within the hyalinized zones, total loss of epithelial rete pegs, presence of mild to moderate atypia and extensive degeneration of muscle fibers.

Several medical and surgical approaches have been tried for the management of OSF over the decades. The resultsof these treatments are not predictable and none has been consistently successful. Therefore it is suggested that a combination therapy including medicinal, adjuvants therapy and physiotherapy can provide the best results in terms of reducing morbidity and

improving quality of life of the patient thereby reducing the mortality associated with this precancerous condition.

This article reviews all the effective treatments modalities for osmf that were discovered over the years. This is an attempt to provide a clearer picture of most effective treatment modalities to clinicians and researchers.

Treatment options :

Conservative options :-
In vitro studies[4] performed on the effect of alcoholic extracts of turmeric (TE), turmeric oil (TO) and turmeric oleoresin (TOR), on the incidence of micronuclei (Mn) in lymphocytes from normal healthy subjects observed that all three treatment modalities decreased the number of micronucleated cells both in exfoliated oral mucosal cells and in circulating lymphocytes. Pratik r piplia et al(2016)l[5] found that Turmeric with black pepper and nigella sativa given every 15 days improved mouth opening, burning sensation, and serum superoxide dismutase SOD levels in the present OSMF study patients; however, further investigations are needed.Sarwaralam et al(2013)[6]in a group of 60 subjects receiving aloevera as an adjuvant found that it was effective as an adjuvant.
Earlier studies had identified nutritional deficiencies as a potential causative factor in OSMF[7] .Other reports have shown that many patients diagnosed with OSF had nutritional deficiencies, particularly in iron and B vitamins.[10] In view of these findings, several authors have attempted nutritional supplementation as a measure of adjunctive treatment for OSF. Among the supplements used, vitamins A, B complex, C, and E have been tried alone or in combination with other agents.
Recent work has shown that Manuka honey, an increasingly popular wound additive with potent antibacterial properties, also has anti-inflammatory properties[8] . The results indicate a cytotoxic limit of 3-5% v/v. The presence of 1% honey decreased superoxide release at 24 hours. The 0.5, 1, and 3% honey concentrations reduced chemotaxis and IκBα phosphorylation in a dose-dependent fashion. Suggesting that Manuka honey significantly reduces neutrophil recruitment and inflammatory behavior in the wound site in a dose-dependent fashion under the cytotoxic limit.

Medical management:-
Jksharma et al(1987)[9] showed that Conventional therapies, when combined with the peripheral vasodilator, increased the magnitude of remissions remarkably, reduced the treatment duration, dosages of associated drugs and frequency of relapses. In a series of treatment conducted by R M borle et al in 1991[10]three hundred twenty-six patients with oral submucous fibrosis were divided into two groups and treated either with conventional submucosal injections of steroids and hyaluronidase, or with topical vitamin A, steroid applications, and oral iron preparations. Jayachandtran et al[11] showed that pentoxifylline therapy results in significant improvement in clinical symptoms such as burning sensation, mouth opening,tongueprotrusion,relief from perioral fibrotic bands,difficulty in swallowing, speech and submucosal layer thickness and echogenicity using ultrasonography, both pre- and post-operatively.

Abhinav kumar et al(2007)[12] treated 56 patients of osmf with 16 gm lycopene biweekly and found that Mouth-opening values for the patients showed an average increase of 3.4 mm, 4.6 mm, and 0.0 mm for patients in groups A, B, and C, respectively. These values were statistically found to be highly significant. Suggesting that lycopene can and should be used as a first line treatment in initial management.Wanninayake et al(2016)[13]The degree of preinterventional mouth opening is the only feature we can rely on to select patients for treatment with corticosteroid injection. In the study, they injected corticosteroids to a group of selected patients who had 30 mm or a less of mouth opening at the preinterventional stage. Thus, an interincisal mouth opening of 30 mm or less can be regarded as a reference point for corticosteroid therapy. In a clinical trial by M F Haque et[14] using Interferon gamma reported its immuno-regulatory effect and has anti-fibrotic cytokine effect and hence its major role in altering collagen synthesis. In vivo studies of Intra-lesional injection of 0.01- 10.0U/ml 3 times a day for 6 months showed improvement of symptoms. There appears to be a key to the treatment of these patients, and intra-lesional injections of the cytokine may have a significant therapeutic effect on OSF. Steroids have their therapeutic effects due to anti- inflammatory and immune-suppressive action for prevention or suppression of the fibro productive inflammation seen in OSF, thus ameliorating the fibrocollagenous condition. It can be applied topically or intra-lesional injections depending upon the clinical stage of the disease. 4 mg/ml/biweekly injections of Betamethasone diluted in 1.0 ml of 2% xylocaine for 6 months given on buccal mucosa, bilaterally, using an insulin syringe, with a half dose on each side, was showed significant improvement of mouth opening and reduction in burning sensation in a stage II and stage III OSMF group ($p < 0.0001$), in comparison to a control group which received no treatment over two years.[16]

A Randomised control trial was performed by X Jiang et al using allicin and triamcinolone acetonide injected intralesionally weekly for 16 weeks in treatment of Stage 2 OSMF in a Chinese patient cohort and found that allicin as an adjunctive treatment improved mouth opening as well as oral-health related quality of life.[17]

Surgical approaches:-

Talsania JR et al (2009) conducted a prospective clinical study for 4 years(2002-2006) and suggested that Diode laser is a less expensive and alternative method in group III and group IVA cases in whom bilateral temporalis myotomy and coronoidectomy are considered to be the only solution.[18] Zainab C. includes a case series of 16 cases of moderate OSMF treated with Erbium Chromium Yttrium Scandium Gallium Garnet (ErCr:YSGG) laser fibrotomy under local anesthesia in combination with cessation of habits, topical steroids, lycopene and oral physiotherapy is presented. The mean increase in mouth opening achieved at 1 year was 17.5 mm.[19]

The pedicledbuccal fat pad has been widely used for the repair of oral defects. A new application of this flap in the treatment of patients suffering from trismus caused by oral submucous fibrosis is reported. The patients underwent incision of the fibrotic bands and coverage of the buccal defect with a pedicledbuccal fat pad flap. The results suggest that this is a logical, convenient, and reliable technique for omsf treatment.[20]

Aafiya et al (2021) in a series of patients showed that coronoidectomy as an adjunctive treatment in OSMF provides comparable treatment outcome in terms of MIO ; also offers a shorter operating time and less blood loss.[21]Utilizing a Platysma-based myocutaneous flap K rajkumar et al(2017) proved it to be durable and aesthetically acceptable for reconstruction of intraoral defects ; hence serving as a viable option for patients with severe OSMF.[22]
The use of the nasolabial flap for repair of orofacial defects is well established therefore the nasolabial flap is considered the most successful extraoral flap in the surgical treatment of osmf multiple articles suggest to use it as a donor site.[23][24][25][26] There is an added advantage of non-involvement of flap in the condition too.

PHYSIOTHERAPY

In a randomized control trial conducted by pravinkumar et al found that patients using the MED(mouth exercising device)showed reduction in burning sensation in the range of 64.8% to 71.1% and 27.8% to 30.9%, whereas in non users reduction in burning sensation ranged from 64.7% to 69.9% and from 29.3% to 38.6% after 6 months. The wo-way analysis of variance indicated statistically significant results in changes in initial VAS scores to 6-monthly VAS scores between MED users and non MEDusers.The MED helps to enhance the rate of reduction of mucosal burning sensation, in addition to the conventional ice-cream stick regimen, as an adjunct to local and surgical treatment.[28]Ultrasound therapy with 0.7–1.5 W/Cm^2 with thumb kneading physiotherapy for six days/ week for two consecutive weeks showed significant improvement in mouth opening ($p < 0.001$) and reduction of burning sensation.[27]

Patients who have undergone surgery along with active physiotherapy show good results. Thus post operative physiotherapy and cessation of habit are of equal importance for good prognosis in osmf patients.

Recent advances:-
HYPERBARIC OXYGEN THERAPY— A Novel Treatment Modality in Oral Submucous Fibrosis: Definition: The Committee on Hyperbaric Medicine defines HBOT therapy as “A mode of medical treatment during which the patient is entirely enclosed during a pressure chamber and breathes 100% oxygen at a pressure >1 atmosphere absolute (ATA).” ATA is the unit of pressure and 1 ATA is equal to 760 mm of mercury or pressure at sea level. Extensive fibrosis of the connective tissue causes reduction of vascularity, resulting in subsequent hypoxia in both fibroblasts and surface epithelia. Hypoxia causes atrophy and ulceration of the epithelium by inducing apoptosis. In addition, the over expression of hypoxia-induced factor-1a is seen in OSMF, which indicates changes in cell proliferation, maturation, and metabolic adaptation increasing the likelihood of malignant transformation.[29]
1.HBOT increases oxygen tension
2.Enhances the quantity of dissolved oxygen within the plasma, and
3.Raises oxygen delivery to the hypoxic areas.
4.HBOT improved ischemia via decreasing expression of HIF-1a..The anti-inflammatory effect of HBOT might occur through the relief of hypoxia and the down-regulation of HIF-1a
5.HBOT may have the potential to improve the vascular situation.Hyperbaric oxygen therapy (HBOT) involves inhalation of 100% oxygen at increased air pressure usually ranging between 2.0 and 2.5 atmospheres for periods between 60 and 120 m. [29]

Pirfenidone inhibits the progression of fibrotic lesions and prevent the formation of new lesions following tissue injuries. Pirfenidone has been tested in many in vivo and invitro fibrotic models which showed favourable results.[30]
While examining the inhibitory effect of TSN(Tanshinone) on progression of OSMF Zheng et al found that TSNs inhibits arecoline mediated proliferation of primary human oral mucosal fibroblast and reversed the promotive effects of arecoline on epithelial–mesenchymal transition (EMT) process. Oral mucosal tissues in OSMF have extremely low p53 when compared with normal tisues. Arecoline reacts with oral mucosal fibroblasts resulting in reduction of p53[6] and its related downstream molecules p21, Bax and p53 upregulated modulator of apoptosis.
Although there are very few studies conducted on effects of TSNs in OSMF till date, yet all of them have yielded positive results. Hence, TSNs appear to be promising in the management of OSMF.[31]
Mesenchymal Stem Cells (MSCs) are multipotent stromal cells present in adult and birth associated tissue . MSCs possess low immunogenicity as they lack MHC-II and low MHC-I expression making it a suitable candidate for allogeneic transplantation . MSCs can differentiate into various functional cell types and are capable of secreting immunomodulatory factors, proteins, and growth factors. Transplantation of MSCs is found to be effective in several systemic as well as tissue-specific.[32]
Employing MSCs which possess immunomodulatory, anti-fibrotic, anti-oxidative, and angiogenesis potential could aid in effectively halting the progression of the disease including its malignant potential. [32]

Conclusion

Although studied intensively over many decades, especially in South Asia, OSMF is still poorly understood across the globe. The incidence is rising with young individuals getting more affected. There has been significant improvements in the management modalities of osmf although no definitive treatment is effective on its own ; a combination therapy along with an early diagnosis can definitely improve treatment outcomes and improve quality of life of the patients.
OSMF being a potentially malignant disorder, intervention should be started early to improve outcomes, recognizing the stages early and treatment modalities which may be given to the patient will definitely benefit the patients.
Better integration of medical and dental services,will reduce patients' suffering and improve their life quality. All health care professions must work together in public education and primary prevention to then reduce the burden of OSMF.

References

1. Thakur N and Kumar V. An outline of existing clinical classification system for oral submucous fibrosis. J Res Adv Dent 2014;3(2):72-5.
2. More CB, Gupta S, Joshi J and Varma SN. Classification system for oral submucous fibrosis. J Indian Acad Oral Med Radiol 2012;24(1):24-9.

3. Khanna JN and Andrade NN. Oral submucous fibrosis: A new concept in surgical managementReport of 100 cases. Int J Oral MaxillofacSurg1995;24:433-9.
4. K Hastak, N Lubri, S.D Jakhi, C More, A John, S.D Ghaisas, S.V Bhide,Effect of turmeric oil and turmeric oleoresin on cytogenetic damage in patients suffering from oral submucous fibrosis,CancerLetters,Volume 116, Issue 2,1997,
5. Pipalia PR, Annigeri RG, Mehta R. Clinicobiochemical evaluation of turmeric with black pepper and nigella sativa in management of oral submucous fibrosis-a double-blind, randomized preliminary study. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016 Dec;122(6):705-712. doi: 10.1016/j.oooo.2016.07.023. Epub 2016 Aug 6. PMID: 27720650.
6. Alam S, Ali I, Giri KY, Gokkulakrishnan S, Natu SS, Faisal M, Agarwal A, Sharma H. Efficacy of aloe vera gel as an adjuvant treatment of oral submucous fibrosis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013 Dec;116(6):717-24. doi: 10.1016/j.oooo.2013.08.003. PMID: 24237724.
7. Maher R, Aga P, Johnson NW, Sankaranarayanan R, Warnakulasuriya S. Evaluation of multiple micronutrient supplementation in the management of oral submucous fibrosis in Karachi. Pakistan Nutr Cancer. 1997;27(1):41–7.
8. Minden-Birkenmaier B.A., Cherukuri K., Smith R.A., Radic M.Z., Bowlin G.L. Manuka honey modulates the inflammatory behavior of a dHL-60 neutrophil model under the cytotoxic limit. *Int. J. Biomater.* 2019;2019:6132581. doi: 10.1155/2019/6132581.
9. Sharma JK, Gupta AK, Mukhija RD, Nigam P. Clinical experience with the use of peripheral vasodilator in oral disorders. Int J Oral Maxillofac Surg. 1987 Dec;16(6):695-9. doi: 10.1016/s0901-5027(87)80055-3. PMID: 3125268.
10. Borle RM, Borle SR. Management of oral submucous fibrosis: A conservative approach. *J Oral Maxillofac Surg.*
11. Sadaksharam J, Mahalingam S. Evaluation of Oral Pentoxifylline in the Management of Oral Submucous Fibrosis - An Ultrasonographic Study. Contemp Clin Dent. 2017 Apr-Jun;8(2):200-204. doi: 10.4103/ccd.ccd_1192_16. PMID: 28839403; PMCID: PMC5551322.
12. Kumar A, Bagewadi A, Keluskar V, Singh M. Efficacy of lycopene in the management of oral submucous fibrosis. Oral Surg Oral Med Oral Pathol Oral RadiolEndod. 2007 Feb;103(2):207-13. doi: 10.1016/j.tripleo.2006.07.011. Epub 2006 Oct 24. PMID: 17234537.
13. Tilakaratne WM, Ekanayaka RP, Herath M, Jayasinghe RD, Sitheeque M, Amarasinghe H. Intralesional corticosteroids as a treatment for restricted mouth opening in oral submucous fibrosis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016 Aug;122(2):224-31. doi: 10.1016/j.oooo.2015.11.023. Epub 2016 Apr 19. PMID: 27422421.
14. Haque MF, Meghji S, Nazir R, Harris M. Interferon gamma (IFN-gamma) may reverse oral submucous fibrosis. J Oral Pathol Med. 2001

Jan;30(1):12-21. doi: 10.1034/j.1600-0714.2001.300103.x. PMID: 11140895.
15. Pindborg JJ, Sirsat SM. Oral submucous fibrosis. Oral Surg Oral Med Oral Pathol. 1966;22(6):764–79.
16. Goel S, Ahmed J. A comparative study on efficacy of different treatment modalities of oral submucous fibrosis evaluated by clinical staging in population of southern Rajasthan. J Cancer Res Ther. 2015;11(1):113–8.
17. Jiang X, Zhang Y, Li F, Zhu Y, Chen Y, Yang S, Sun G. Allicin as a possible adjunctive therapeutic drug for stage II oral submucous fibrosis: a preliminary clinical trial in a Chinese cohort. Int J Oral Maxillofac Surg. 2015 Dec;44(12):1540-6. doi: 10.1016/j.ijom.2015.06.015. Epub 2015 Jul 10. PMID: 26165773.
18. Talsania JR, Shah UB, Shah AI, Singh NK. Use of diode laser in oral submucous fibrosis with trismus: prospective clinical study. Indian J Otolaryngol Head Neck Surg. 2009 Jan;61(Suppl 1):22-5. doi: 10.1007/s12070-009-0012-x. Epub 2009 Mar 21. PMID: 23120664; PMCID: PMC3450091.
19. Chaudhry Z, Gupta SR, Oberoi SS. The Efficacy of ErCr:YSGG Laser Fibrotomy in Management of Moderate Oral Submucous Fibrosis: A Preliminary Study. J Maxillofac Oral Surg. 2014 Sep;13(3):286-94. doi: 10.1007/s12663-013-0511-x. Epub 2013 Apr 18. PMID: 25018602; PMCID: PMC4082553.
20. Sharma R, Thapliyal GK, Sinha R, Menon PS. Use of buccal fat pad in the treatment of oral submucous fibrosis. *J Oral Maxillofac Surg.* 2011.
21. Ambereen A, Bhutia O, Roychoudhury A, Yadav R, Khakhla DH, Vishwakarma K. Is Coronoidectomy Superior to Coronoidotomy for Improving Maximum Incisal Opening in Patients With Oral Submucous Fibrosis? J Oral Maxillofac Surg. 2021 Apr;79(4):863.e1-863.e7. doi: 10.1016/j.joms.2020.11.009. Epub 2020 Dec 11. PMID: 33345813.
22. K. Rajkumar, S.K. Roy Chowdhury, Vivek Saxena, Ramen Sinha,Superiorly based platysma myocutaneous flap for reconstruction of intra oral defect following fibrotomy in oral submucous fibrosis: Report of a case.
23. Chang Y-M, Tsai C-Y, Kildal M, Wei F-C. Importance of coronoidectomy and masticatory muscle myotomy in surgical release of trismus caused by submucous fibrosis. *PlastReconstr Surg.* 2004;113:1949–1954.
24. Girotra C, Padhye M, Desai R. Verastility of buccal fat pads in closure of oral defects. *Sci J.* 2008;8:1–3.
25. Krishna Prasad L, Chakravarthy PS, Sridhar M, Ramkumar S, Krishna S, Vivekanand SK. An evaluation of various treatment modalities in the management of oral submucous fibrosis. A clinical study. *J Orofac Sci.* 2009;1(2):17–20.
26. Cunha-Gomes D, Kavarana NM, Choudhari C, Rajendraprasad JS, Bhathena HM, Desai PB, et al. Total oral reconstruction for cancers associated with advanced oral submucous fibrosis. *Ann Plast Surg.* 2003;51(3):283–289. doi: 10.1097/01.SAP.0000063753.91476.05.

27. Vijayakumar M, Priya D. Physiotherapy for improving mouth opening & tongue protrusion in patients with Oral submucous fibrosis (OSMF) – case series. Int J Pharm Sci Health Care. 2013;3(2):50–8.
28. Patil PG, Hazarey V, Chaudhari R, Nimbalkar-Patil S. A randomized control trial measuring the effectiveness of a mouth-exercising device for mucosal burning in oral submucous fibrosis. Oral Surg Oral Med Oral Pathol Oral Radiol. 2016 Dec;122(6):713-718. doi: 10.1016/j.oooo.2016.07.026. Epub 2016 Aug 6. PMID: 27720659.
29. Kumar MA, Radhika B, Gollamudi N, Reddy SP, Yaga US. Hyperbaric Oxygen Therapy-A Novel Treatment Modality in Oral Submucous Fibrosis: A Review. J Clin Diagn Res. 2015 May;9(5):ZE01-4. doi: 10.7860/JCDR/2015/11500.5905. Epub 2015 May 1. PMID: 26155590; PMCID: PMC4484182.
30. More CB, Jatti Patil D, Rao NR. Medicinal management of oral submucous fibrosis in the past decade- A systematic review. J Oral Biol Craniofac Res. 2020 Oct-Dec;10(4):552-568. doi: 10.1016/j.jobcr.2020.08.004. Epub 2020 Aug 19. PMID: 32939334; PMCID: PMC7479289.
31. Zheng L, Guan ZJ, Pan WT, Du TF, Zhai YJ, Guo J. Tanshinone Suppresses Arecoline-Induced Epithelial-Mesenchymal Transition in Oral Submucous Fibrosis by Epigenetically Reactivating the p53 Pathway. Oncol Res. 2018 Apr 10;26(3):483-494. doi: 10.3727/096504017X14941825760362. Epub 2017 May 21. PMID: 28550687; PMCID: PMC7844836.
32. Suma GN, Arora MP, Lakhanpal M. Stem cell therapy: A novel treatment approach for oral mucosal lesions. J Pharm Bioallied Sci. 2015 Jan-Mar;7(1):2-8. doi: 10.4103/0975-7406.149809. PMID: 25709329; PMCID: PMC4333622.