https://doi.org/10.48047/AFJBS.6.Si4.2024.4731-4770

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

CRITICAL REVIEW OF TOPICAL, INTRALESIONAL AND SYSTEMIC STEROIDS IN MANAGEMENT OF ORAL SUBMUCOUS FIBROSIS

Dr.Amna Rehman[1], Dr.Noor hayat khan[2], Dr.Samreen Malik[3], Dr.Samir Azeem[4], Dr.Hijab Farid Khan[5], Prof.Dr.Navid Rashid Qureshi[6]

[1]Assistant professor Oral and Maxillofacial Surgery, Liaquat college of medicine and dentistry, Karachi
[2]Senior Registarar otolaryngology(ENT), Mardan medical complex, Mardan
[3]Assistant Professor Oral Medicine , Liaquat college of medicine and dentistry, Karachi
[4]Assistant Professor Oral Medicine, Liaquat college of medicine and dentistry, Karachi
[5]Assistant professor Oral Medicine, Liaquat college of medicine and dentistry, Karachi
[6]Head of Department, Oral and Maxillofacial Surgery, Liaquat college of medicine and dentistry, Karachi

Corresponding author: Dr.Amna Rehman (ramna8282@gmail.com)

Volume 6, Issue Si4, Aug 2024

Received: 09 June 2024

Accepted: 19 July 2024

Published: 08 Aug 2024

doi: 10.48047/AFJBS.6.Si4.2024.4731-4770

INTRODUCTION:

Oral submucous fibrosis (OSMF) is a long-lasting and debilitating condition affecting the mouth. It was initially identified by Schwartz in 1952 and referred to as "Atropica idiopathica mucosae oris". (1) In 1953, Joshi in India introduced the term "Submucous fibrosis of palate and faucial pillars." Additional names proposed in literature include "diffuse oral submucous fibrosis", “idiopathic palatal fibrosis", "idiopathic scleroderma of the mouth", and "sclerosing stomatitis” (2). The condition known as oral submucous fibrosis is currently referred to as a "potentially malignant disorder". The condition is marked by the whitening and painful sensation of the lining of the mouth, discoloration of teeth, limited ability to open the mouth, and a significant likelihood of developing into cancer (3).

It is predominantly prevalent among populations in the Asian subcontinent and the Far East. However, due to population transmigration, there has been a rise in the number of cases observed in America and other populations. The prevalence of it varies based on geographical regions and countries. An epidemiological study conducted in India documented the occurrence of oral submucous fibrosis (OSF) in a patient as young as 11 years old. The study also observed that the number of males using guthka, a chewing tobacco product, was three times higher than females. However, it is worth noting that the opposite male-female ratio has been reported in Pakistan and South Africa. According to Zhang (2007), the rate of betel quid chewing in China is highest in the Hunan (64.5% to 82.7%) and Hainan provinces. Additionally, 0.9% to 4.7% of the population in these regions show symptoms of OSF. The age group most typically affected by OSF is between 30 to 49 years. A survey conducted in Taiwan revealed comparable statistics, indicating that as many as 69.5% of the participants habitually consume betel/areca quid on a regular basis (4).

OSF is distinguished by its complex and varied causes. The variables most frequently recognized are the habit of chewing Areca Nut (AN), issues related to diet, and a hereditary predisposition. They function independently or in a cooperative manner in the formation of OSF (1). The areca nut is a subtropical food that contains flavonoids, alkaloids, copper, and other components. AN contains four alkaloids: arecaidine, guvacine, arecoline, and guvacoline. Among these, arecoline is the most potent agent that affects the development of OSF by causing an aberrant increase in collagen formation. The majority of current clinical and epidemiological investigations indicate that chewing areca nut is the primary causative factor in OSF. According to the paper, the likelihood of developing OSF in those who chew AN was found to be 109-287 times more than in those who do not chew. Furthermore, this risk increased with the frequency and length of daily AN chewing. The risk may also be closely linked to the method of chewing AN and the composition of AN products. For instance, research revealed that the risk escalated when individuals consumed AN items that included betel inflorescence, a substance widely consumed in China (6). AN is associated with adverse consequences such as physical and chemical irritations. While chewing, the presence of coarse fibers will activate the oral mucosa, leading to the occurrence of small-scale injuries. The alkaloid and flavonoid chemical components present in AN will penetrate the submucosal tissue, causing the autologous tissue to transform into autoantigen. This transformation triggers an autoimmune reaction, resulting in the infiltration of inflammatory cells such as activated T cells and macrophages. Additionally, it stimulates the synthesis of cytokines like tumor necrosis factor (TNF), interleukin 6 (IL-6), and interferon α (IF-α), as well as growth factors like transforming growth factor-beta (TGF-β) (6). Specifically, TGF-β is the primary growth factor that significantly affects OSF through two distinct mechanisms: enhancing collagen synthesis and inhibiting collagen breakdown, ultimately resulting in the development of OSF (7).

Recent investigations have indicated that the onset and progression of OSF are controlled by the regulation of genes related to collagen correlation, human leukocyte antigen (HLA), and detoxifying enzymes. The study revealed an increase in the prevalence of HLA-B76 phenotype, HLA-B48/Cw7, HLA-B51/Cw7, and HLA-B62/Cw7 haploid type in individuals with OSF, which suggests an elevated susceptibility to OSF. Following the exposure of specific collagen genes, including as TGF-β1, COL1A2, COL1A1, LOX, collagenase-1, and cystatin C, to AN chewing products, there was an increase in high-risk alleles, which subsequently led to an increase in the prevalence of OSF (8). In addition, the levels of cytochrome P450 (CYP) subtype genes, which are a type of enzymes involved in detoxification, such as CYP2B6, CYP2C18, CYP2F1, and CYP3A5 genes, were shown to be reduced at various stages of OSF. This reduction increases the likelihood of OSF progression. There is an association between the development of OSMF and nutritional deficiencies such as vitamins, protein, selenium, zinc, iron, and anemia. The lack of iron affects

the structure and permeability of the oral epithelium, hence compromising its ability to provide barrier protection. Decreasing selenium levels enhances the accumulation of harmful chemicals, resulting in the development of fibrosis.

Multiple staging/grading categorization schemes have been recorded in medical literature by different writers in the past. Certain components of the staging system are commonly utilized in clinical practice to facilitate prompt diagnosis and treatment.

Stage 1/Early OSMF	Stage II/ Moderate OSMF	Stage 1II/ Severe OSMF
Stomatitis and vesiculation: Stomatitis include erythaematous mucosa, vesicles, mucosal ulcers, melanotic ,mucosal pigmentation, mucosal Petechia	Fibrosis: Blenching of oral mucosa, vertical and circular palpable fibrous bands in buccal mucosa and lips, mottled marble like appearance of mucosa. Reduction of mouth opening. Fibrotic and depigmented gingiva, rubbery soft palate with reduced mobility, atrophic and blanched tonsils, shrunken cheeks and bud like uvula not commensurate with age or nutritional status	Sequelae of OSMF: Leukoplakia, Erythroplakia is present in 25% of cases. Speech and hearing difficulties may occur because of the involvement of tongue and Eustachian tube

Functional staging/classification: Based on mouth opening between upper and lower central incisors

Grading/ Staging	**Maximum Interincisal Opening**
Stage 1	Maximum Interincisal opening up to > 35mm
Stage 1I	Maximum Interincisal opening between 25 to 35mmm
Stage 1II	Maximum Interincisal opening between 15 to 25mmm
Stage 1V	Maximum Interincisal opening between 5 to 15mmm
Stage V	Maximum Interincisal opening up to < 5mm or nil

The clinician faces a considerable challenge in managing OSMF due to the lack of a treatment regimen that is supported by evidence. The primary goals in managing OSMF are to alleviate the indications and

symptoms, halt the advancement of the disease, and diminish the susceptibility to malignant transformation (9). The treatment of OSMF involves a variety of medications, including dietary supplements, anti-inflammatory drugs, substances that break down proteins, drugs that widen blood vessels, substances that affect the immune system, and drugs that counteract cytokines. These modalities can be delivered orally, topically, or through submucosal injection. Surgical procedures are necessary for advanced cases of Oral Submucous Fibrosis (OSMF).Physical therapy can be used in conjunction with other treatment methods or as a standalone approach to manage patients with OSMF. In recent years, some natural herbal substances like as Tulsi, Aloe Vera, and Turmeric have emerged as potential treatments for OSMF (5). Despite the existence of numerous therapies, there is a scarcity of evidence-based literature regarding their usefulness in managing OSF. The adrenal cortex releases corticosteroids, which include prednisone, hydrocortisone, dexamethasone, clobetasol, triamcinolone, and mometasone. Glucocorticoids exert an impact on the metabolism of lipids, carbohydrates, proteins, calcium, and electrolytes. The physiological and metabolic impacts of corticosteroids are numerous, but their pharmaceutical value mostly stems from their anti-inflammatory and immunosuppressive properties. Glucocorticoids inhibit all forms of inflammation and allergy responses. Glucocorticoids achieve these effects by suppressing the function of white blood cells, stabilizing the membrane of lysozyme, inhibiting the activation of plasminogen, and decreasing the production of inflammatory mediators such prostaglandins and leukotrienes (6). The use of various forms of corticosteroids is a commonly used medical intervention nowadays. It is the primary therapeutic choice for patients with noticeable fibrous bands at many medical institutes (10). The primary method by which corticosteroids work is through immunological regulation. It inhibits inflammation and subsequent fibrosis, and additionally, it enhances the activation of immune-mediated fibrolytic pathways (11). OSF is linked to notable morbidity, including malnutrition. The rate of change of oral submucous fibrosis cases into oral cancer is less than 7%, as indicated by mortality rates. Previous evaluations of OSMF treatment have been conducted, such as a Cochrane review by Fedorowicz et al in 2009, a narrative review by Jiang and Hu, and a systematic review by Kerr et al. in 2011. However, there is a scarcity of dependable evidence regarding the efficacy of any of these treatments in managing OSF (4). Due to the growing occurrence of OSMF and its related health issues, it is necessary to conduct a thorough study to evaluate the effectiveness of current treatment methods and propose successful approaches for future research. Hence, this research aims to establish dependable clinical or investigative measures to determine the appropriateness and efficacy of corticosteroid as a therapeutic method for patients with OSMF. The objective of the review is to compile the existing literature from 1971 to 2021 and commence a discourse on the potential application of various corticosteroids in the treatment of OSMF. The research inquiry was: "What is the subsequent course of corticosteroid usage in the treatment of oral submucous fibrosis?" This review aimed to evaluate the effectiveness of corticosteroids in treating oral submucous fibrosis.

MATERIAL AND METHODS:

Study design:

The current systematic review was conducted using the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (12).

Search strategy:

The articles covering the management of OSF from 1971-2021 were searched on major scientific platforms such as ScienceDirect, PubMed, and Google Scholar. The search for papers was conducted using the phrases "steroids," "Oral sub mucous fibrosis," AND "Effectiveness" in all fields. According to the search method, all the pertinent papers were identified.

Eligibility criteria:

The inclusion criteria encompassed all complete articles that employed steroids in individuals with OSF. The exclusion criteria encompassed animal research, metaanalysis, case series, case reports, editorial, review articles, and communication. In addition, the studies with incomplete data were also removed. There were no limitations on the date or language of publication, as long as English translations were available. The utilized result measure encompassed mouth opening, ulceration, and discomfort or burning feelings.

Study selection:

The selection process of the studies started after defining a clear eligibility criterion with mutual consent of all the investigators. Initially one hundred and twenty six articles were separated and screened. Thirty two were selected according to eligibility criteria in screening. Out of which twenty seven articles were separated and finally after last screening seventeen articles included in the review after removal of duplicates.

Data extraction:

The investigators (AR and HF) independently documented the titles of all the publications discovered during online research on Excel spreadsheets. The sheets were subsequently examined for resemblance by the third investigator (NH). If an article was discovered to be absent from any sheet, another author (SA) conducted the search and made necessary corrections as needed. The investigators (AR and SM) independently examined the title and abstracts of all the articles in the sheet to choose which ones should be included or eliminated. They prepared two distinct computerized lists, one for the included articles and one for the excluded papers. The rationales for exclusion were documented in the event that the articles failed to satisfy the eligibility criteria. (NH) compared these listings. If there was a debate over the inclusion or exclusion of research, the viewpoint of the senior investigator (NR) was sought, and his

determination was regarded as definitive. (AR and SM) also examined the reference lists of the papers that were included.

All supplementary papers that met the eligibility requirements were included in the reference list. (SA) created a predetermined Excel spreadsheet with predefined columns for recording the data. The provided Excel spreadsheet was utilized by three investigators (AR, NH, HF) individually to extract data from the enclosed papers. NR subsequently compared these three sheets. If there were any inconsistencies in the extracted data between the sheets, (AR) examined and rectified the data to create a final sheet. The ultimate roster was thereafter forwarded to the three preceding investigators for their assessment. If there was a disagreement among the investigators on the data that should be included, the discrepancies were resolved through discussion. The ultimate extracted data sheet was sanctioned unanimously by all the authors.

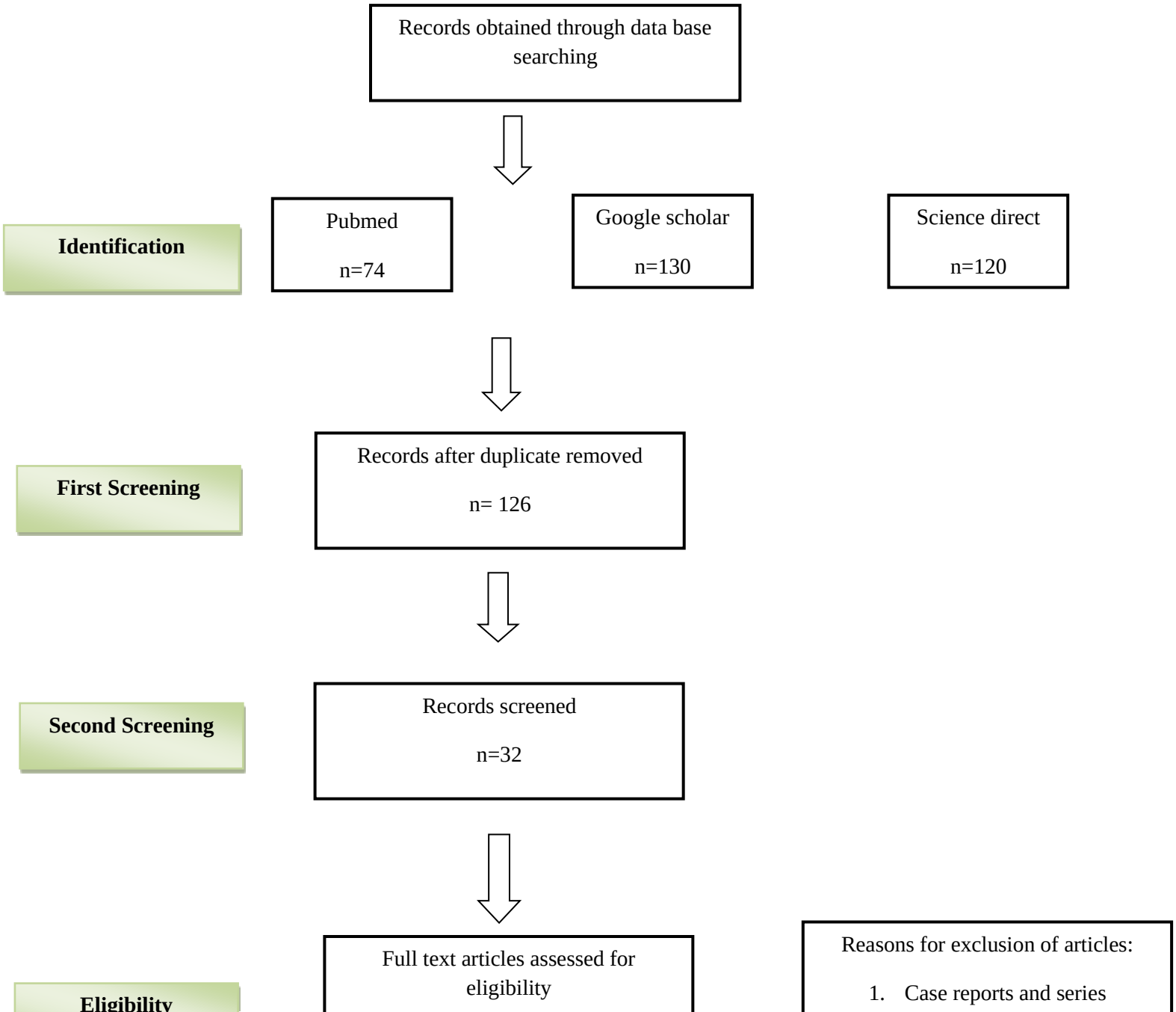
Data analysis:

Data extraction revealed considerable heterogeneity of the included studies. Data were pooled into a table and a descriptive summary was generated to report on study characteristics and outcomes.

Risk of Bias Assessment:

The risk of bias was assessed based on the following criteria: studies reporting 1 to 3 items were categorized as having a high risk of bias, studies reporting 4 to 6 items were categorized as having a medium risk of bias, and studies reporting 7 or 8 items were categorized as having a low risk of bias. AR provided the investigators with a pre-existing excel sheet consisting of 8 questions to assess the likelihood of bias in each study. The appraisal of the included studies considered the following criteria: presence of a control group, time of assessment, sample size, randomization, sufficient details of interventions (if not standard/established or in case of herbal), blinding of the observer, unbiased reporting, and grading of OSMF. Each item was assigned the letter "Y" to indicate that it was reported, and the letter "N" to indicate that it was not reported. Following the completion of rating by each investigator, a discussion session was conducted to resolve any discrepancies.

SEARCH STRATEGY



Included

Study	One group assigned as control	Sample size	Time of assessment	Blinding of observer	Sufficient details of interventions if not standard/not established or herbal	randomization	Proper and unbiased Reporting of outcome related to main objective	Grading of osf	Risk of Bias
Kakar et al.(1985)	N	Y	Y	N	Y	N	Y	Y	Medium Risk
Gupta et al. (1988)	N	Y	Y	N	Y	N	Y	Y	Medium Risk
Borle et al(1991)	Y	Y	Y	N	Y	N	Y	N	Medium Risk
Lai et al (1995)	N	Y	Y	N	Y	N	Y	Y	Medium Risk
Kumar et al. (2007)	Y	Y	Y	Y	Y	Y	Y	Y	Low Risk
Mangal et al (2010)	N	Y	Y	Y	Y	Y	Y	Y	Low Risk

Jiang et al(2013)	N	Y	Y	N	Y	Y	Y	Y	Medium Risk
Monu Yadav(2014)	N	Y	Y	N	Y	Y	Y	Y	Medium Risk
Panigrahi et al. 2014	N	Y	Y	Y	Y	Y	Y	Y	Low Risk
R.P. Ekanayaka et al(2015)	N	Y	Y	N	Y	N	Y	Y	Medium Risk
Rajitha et al(2015)	N	Y	Y	Y	Y	Y	Y	Y	Low Risk
Leena James et al (2015)	N	Y	Y	N	Y	N	Y	Y	Medium Risk
Veedu et al.(2015)	N	Y	Y	Y	Y	Y	Y	Y	Low Risk
Pravinkumar et al (2016)	N	Y	Y	N	Y	Y	Y	Y	Medium Risk
Warnakulasuriya (2016)	N	Y	Y	N	Y	N	Y	Y	Medium Risk
Paolo J. Fantozzi et al (2019)	N	Y	Y	N	Y	N	Y	Y	Medium Risk

RESULTS"

S. NO	STUDY	TREATMENT	MODE	DURATION	NO. OF PATIENTS	IMPROVEMENT IN MO/ULCERATION/BURNING

1	**Gupta et al. (1988) Clinical trial** (13)	**Biweekly submucosal injections of following drugs:** **1. Dexamethasone(4mg)** **2. Hyaluronidase(1500IU)** **3. Placental extract (2 mL)** **4. Chymotrypsin (5000 IU)** **5. Dexamethasone+Hyaluronidase** **6. Chymotrypsin + dexamethasone** **7. Hyaluronidase + chymotrypsin + dexamethasone** **8. Placental extract + dexamethasone**	**Submucosal injections**	**10 weeks**	**1. 25** **2. 25** **3. 25** **4. 25** **5. 25** **6. 25** **7. 25** **8. 25**	**94% relief of limited mouth opening**	**50%**	**82%**

2	**Veedu et al. 2015 A Randomized Double-Blind, Multiple Arm Trial** (14)	**G1-biweekly submucosal injections of hyaluronidase 1500 IU × 5 weeks G2-biweekly submucosal injections of Dexamethasone 2 Ml G3-biweekly submucosal injections of a combination of dexamethasone 1 ml (4 mg/ml) (Dexona) and one part of hyaluronidase (750 I.U)**	**Submucosal injection**	**3 months**	**45**	**_G2-reduction in mean score of BS 3.20 ± 1.52 but not statistically significant. G3-statistically significant reduction in pain upon opening with a total reduction in mean score of 1.93 ± 2.15. The maximum improvement in tightness of the mucosa Occurred in G1 with a reduction in mean score of 3.73 ± 1.67. For MO no significant difference observed between groups (p = 0.068).**		
3	**Lai et al (1995) Clinical trial** (15)	**Biweekly submucosal injections of Dexamethasone (4mh/ml) And two part of hyaluronidase (200 u.s.p. unit/ml) diluted in 1.0 ml of 2% xylocaine**	**Submucosal injection**	**4 weeks**	**25**	**83%**	**94%**	**89%**
4	**Kakar et al. (1985) Clinical trial** (16)	**Dexamethasone Hyaluronidase Combination of dexamethasone + hyaluronidase**	**intralesional injections**	**3 months to 2 years**	**96**	**Patients receiving hyaluronidase alone showed quicker improvement in symptoms. Combination with dexamethasone gave somewhat better longer-term results**		

5	**Kumar et al. (2007) RCT** (17)	**Lycopene 16 mg along with biweekly intralesional steroid Injections**	**Submucosal injection**	**Evaluated weekly for 2 months**	**19**	**4.6mm**	**–**	**100 %**
6	**Pentapati Kalyana Chakravarthy (2016) A randomized double-blind, multiple-arm trial** (18)	**Hyaluronidase(1500IU) mixed with Dexamethasone(4mg/ml) sub mucosal injection** **Hyaluronidase(1500IU)** **Dexamethasone(4mg/ml)**	**Submucosal injection**	**Weekly 8 weeks**	**50 stage2 with grade 2 and 3 trismus**	**88%**	**–**	**100 %**
7	**Goel et al.** (19)	**G1- 2 mg of capsule lycopene BD for 6 months** **G2-ILI of betamethasone 4 mg/ml biweekly for 6 months** **G3-Contrls -no treatment**	**Intralesional injections**	**8 weeks**	**270**	**<u>Mean±SD)</u>** **S1=3.00±1.11** **S2=6.07±2.00** **S3=6.53±1.45** **S1=3.30±1.51** **S2=9.47±2.47** **S3=3.27±1.36** **S1=0.00±0.00** **S2=0.00±0.00** **S3=0.00±0.00**	**<u>P value</u>** **S1= >0.05 (non-significant)** **S2= <0.0001 (highly significant)** **S3= <0.0001 (highly significant)**	

8	**Pravin kumar et al (2016) RCT** (20)	**Subgroup A1 (n=35) Local (No additional treatment)** **Subgroup A2 (n=30) Injections (1ml Depomedrol+1 ml Local Anesthesia: Once a week)** **Subgroup A3 (n=10) Band removal Surgery** **Subgroup B1 (n=35) Local (No additional treatment)** **Subgroup B2 (n=30) Injections (1ml Depomedrol+1 ml Local Anesthesia: Once a week)** **Subgroup B3 (n=10) Band removal Surgery**	**intra-lesional injections**	**Weekly 6 weeks**	**30**	**8.4 mm** (p<0.01) **9.3mm** (p<0.01) **9.6mm** (p<0.01) **5.5 mm** (p<0.01) **5.1 mm** (p<0.01) **4.8mm** (p<0.01)	**(SD) 1.7174** **1.6329** **1.3853** **1.4376** **1.4057** **1.3671**	**100%**

9	**Rajitha et al(2015) Randomized double blind multiple trial** (21)	**1. biweekly submucosal injections of hyaluronidase 1500 I.U. not more than 0.2 mL solution per site, on bilateral buccal mucosa for a period of 5 weeks** **2. biweekly submucosal injections of dexamethasone 2 mL (4 mg/mL) with 1 mL of 2% lignocaine with adrenaline (1:80000) not more than 0.2 mL solution per site, on bilateral buccal mucosa** **3. biweekly submucosal injections of a combination of dexamethasone 1 mL (4 mg/mL) and one part of hyaluronidase (750 I.U) diluted with 1 mL of 2% lignocaine with adrenaline (1:80000) and 1 mL of water for injection not more than 0.2 mL solution per site, on bilateral buccal mucosa for a period**	**submucosal injections**	**Weekly 5 weeks**	**45**	**6.67 ± 3.74mm** **4.27 ± 1.58 mm** **5.8 ± 2.60 mm;**	**Minimum** **Moderate** **Maximum**	**Minimum** **Maximum** **Moderate**

10	**Mangal et al (2010) randomized single blinded outcome based study** (8)	**1: Patients of group 'A' (n=50) were treated by a combination of hydrocortisone acetate (1.5 ml 25 mg/ml) and hyaluronidase (1500 IU) at** **2: Patients of group B, combination of triamcinolone acetonide, 10 mg/ml and hyaluronidase (1500 IU) Injection in all patients were given submucosally in retromolar trigone and adjacent soft palate and cheek, half dose on each side by one observer and response to treatment was assessed by another observer.**	**submucosal injections**	**Weekly for 22 weeks** **15 days interval, 22 weeks**	**100**	**(Data are mean ± SD)** **170.42 ± 16.27** **165.89 ± 15.11**	**(Data are mean ± SD) 35.61 ± 7.24** **33.94 ± 8.41**	**(Data are mean ± SD) 294.48 ± 15.76** **291.04 ± 16.41**
			submucosal injections			**Total improvement in group 'A' and 'B' was 9.67+1.72 and 10.23+2.05 respectively**		

11	**Jiang et al (2013) RCT** (5)	**intralesional injection after 5 minutes of local anesthetic cream application (20% Topcaine; 1: Group A received Triamcinolone acetonide (2 mg) intralesionally. 2:** **2: Group B received Salvianolic acid B (4mg, 99% high-performance liquid chromatography, intralesionally,** **3: Group C received Triamcinolone acetonide (2 mg) and Salvianolic acid B(4 mg) by intralesional injection.**	**intralesional injection**	**Weekly for 20 weeks**	**44**	**3.88 + -1.42 mm** **5.51 _ +1.76 mm** **6.76 _ +1.36mm**	**80.9% patient complained tenderness at retromolar area**	**On VAS** **5.41+ _ 1.13** **3.82+ _ 1.14** **5.88 +_ 0.95**
12	**R.P. Ekanayaka et al (2015) Original article** (7)	**intralesional injections of 40mg methylprednisolone at the buccal mucosa, 20 mg on each side on every visit on monthly bases**	**intralesional injection**	**Monthly intervals for six consecutive months**	**116**	**(59.5%) +5mm (21.6%) More than 5mm but less than 10 mm (19%) more than 10mm**		

13	**Paolo J. Fantozzi et al (2019) retrospective single-center study** (22)	**51 (54.8%) were already being managed with topical steroids, 26 (27.9%) with a combination of topical and systemic steroids, and 7 (7.5%) with systemic steroids only. 1 intralesional injection of triamcinolone acetonide (TA) 40 mg/ml and returned for at least 1 follow-up visit. Injections with triamcinolone acetonide were administered by using a disposable 1-cc syringe at the periphery of the ulcer. Only 1 injection per single lesion was performed at each visit.**	**Topical+ systemic+ intralesional injection**		**93**	**Patients with traumatic ulcers had a higher resolution rate [86.8%]compared with patients with OLP/ autoimmune[73.2 %]Patients with traumatic ulcers required a median of 2 injections (range 1_5 injections) and the median time to resolution was 69 days (range 21_305 days) whereas patients OLP/autoimmune had an overall median resolution time of 140 days (range 21_357 days).**		
14	**R.M. BORLE, (1991) Clinical trial** (23)	**1) Biweekly submucosal injection of triamcinolone and hyaluronidase** **2) Topical vitamin A, ferrous fumarate, and topical betamethasone**	**submucosal injection**	**4weeks** **3weeks**	**1)160** **2) 166**	**No** **No**	**95.78%** **84.61%**	**%86.84** **96.15%**
15	**Leena James et al (2015) Retrospective study** (24)	**The patients were administered hyaluronidase 1500 IU mixed in 1.5 ml of dexamethasone and 0.5 ml of lignocaine HCL injected intralesionally biweekly**	**Intralesional injection**	**4 weeks**	**28**	**92.8 %**	**89.28 %**	**78.57 %**

16	**Monu Yadav (2014) A randomized open label, interventional study** (25)	**1)Given weekly submucosal intralesional injections of Dexamethasone (Inj Decadran 4 mg/ml, 1500 International units of Hyaluronidase along with 0.5 ml of 2% (1:80,000) Lignocaine Hydrochloride. The selection of the sites of injection was based on clinical judgment.Injections were given at multiple sites with a 26 guage Needle 2) Given oral administration of 2 tablets of Turmix (Film coated tablet containing C. longa 300 mg, Piperine 5 mg, given once daily**	**intralesional injections**	**Weekly 3 Months** **Daily 3 Months**	**40**	**22.4(4.3)mm** **24.5 (3.3)mm** **P value= 0.1153**	**15.6** **0**	**22.4 (8.7)a** **63.5 (24.7) P value <0.0001**
17	**Panigrahi et al. 2014 Prospective randomized double blind study** (26)	**G1- Intralesional injection of triamcinolone accetonide (10 mg/ml) and hyaluronidase (1500IU) once in 2 weeks** **G2- Intralesional injection of triamcinolone acetonide (10 mg/ml) once in 2 weeks**	**intralesional injections**	**16 weeks**	**20**	**(Mean+-SD) 11.47±2.16** **P value= 0.0001** **5.82±0.76** **(p value= 0.0032)**	**(Mean+-SD) 6.8±1.14 (P value= 0.0001)** **6.1±1.20 (P value = 0.0001)**	**(Mean+-SD) 5.6±1.58 (P value= 0.0001)** **2.6±0.97 (P value= 0.0041)**

Results:

Study selection:

The initial search across all databases yielded a combined total of 324 articles, with 74 from PubMed, 130 from Google Scholar, and 120 from Science Direct. After removing duplicate entries, there were 32 articles remaining. These papers underwent scrutiny based on the specified criteria for inclusion and exclusion. After conducting a comprehensive initial evaluation of the titles and abstracts of these papers, the search results were narrowed down to 27.Upon reviewing the complete text of these 27 investigations, 10 studies were deemed ineligible due to their classification as case series, letter to editors, duplicates, or conference proceedings. Out of the total number of studies, 17 were identified as meeting the qualifying criteria (5,7,8,12,13,14,15,16,17,18,19,20,21,22,23,24,25) (Table 1). The agreement among reviewers was evaluated using the ƙ statistic (52), which indicated a substantial level of agreement (0.75) among the reviewers. The table presents the overall features of the research considered in this evaluation. The systematic review encompassed a total of 17 papers, all of which were published between the years 1980 and 2021. Out of all these investigations, there were 8 clinical trials, 4 randomized controlled trials, one randomized double-blind multiple trial, one randomized single-blinded outcome-based study, two retrospective studies, and one randomized open-label interventional research. The total sample size throughout these trials was 1,547 patients. The participants' age spanned from 11 to 63 years, with an average age. The mean period of intervention in the trials that were considered ranged from 3 to 4 months. The duration of the follow-up period ranged from 4 to 6 months among the 11 completed research. All the investigations included in this evaluation were done in hospitals or institutes. Demographic data, including age and gender, was incorporated in 16 research. The prevalence of areca nut consumption was documented in 15 investigations. Eleven of the studies documented the consumption of tobacco and alcohol. The predominant habits observed in patients with OSMF were Gutkha, pan masala, and areca nut, listed in descending order. None of the studies provided any analysis or discussion of the nutritional status or dietary assessment. Three studies highlighted the hematologic evaluation conducted through laboratory tests before to treatment. The diagnosis of OSMF was mostly determined by the examination of clinical characteristics in the majority of the investigations. Four investigations employed histological examination to validate the diagnosis. The patients enrolled in the trials exhibited varying stages of oral submucous fibrosis (OSMF), ranging from early to advanced. However, the bulk of the study population was classified as being in stage II and III. Eight research emphasized the categorization of the study population into groups according to OSMF staging.9 research were assessed based on the degree of mouth opening. The subsequent classifications were as follows: (Khanna and Andrade, 1995), (Singh et al., 2010), (Bailoor and Nagesh, 2005), (Ranganath et al., 2001),

and (More et al., 2012). The tongue protrusion and cheek flexibility were categorized based on the classifications provided by Ranganath et al. (2001) and Mathur and Jha (1993).

Outcomes of the Included studies:

Sixteen studies used two treatment interventions and one triple therapeutic modalities. Outcomes that were assessed in the included studies were as follows: Mouth opening, mucosal ulceration, Pain and burning sensations.

Author	Year	Country	Sample size	Interventions	Mode of usage	Method of assessment	Duration	Main Outcome
Gupta et al	1986	India	200	Dexamethasone(4mg),Hyluronidase(1500IU),Placental extract(2ml),Chymotrypsin(5000IU),Dexamethasone+hyluronidase,Chymotrypsin+dexamethasone,Hyluronidase+chymotrypsin+dexamethasone,Placental extract+dexamethasone	biweekly submucosal injections	MO with vernier caliper, ulceration and burning with clinical signs	10 weeks	94% relief of limited mouth opening, 50% relief in ulceration and 82% relief in burning
Veedu et al	2015	India	45	Hyluronidase 1500 IU*5weeeks,Dexamethasone 2 MI, Dexamethasone 1ml (4mg/ml) and one part of hyluronidase(750I.U)	biweekly submucosal injections	MO with vernier caliper, ulceration and burning with clinical signs	3 months	G2-reduction in mean of BS 3.20 ± 1.52 but not statistically significant,G3-statistically significant reduction in pain upon opening with a total reduction in mean score of 1.93+-2.15, maximum improvement in tightness of mucosa occurred in GI with mean score of 3.73+-1.67. For MO no significant difference observed between groups (p+0.068)

Lai et al	1995	China	25	Dexamethasone (4mh/ml) and two part of hyluronidase(200u.s.p unit?ml) diluted in 1.0 ml of 2% xylocaine	biweekly submucosal injections	MO with vernier caliper, ulceration and burning with clinical signs	4weeks	83% improvement in MO, 94% relief in ulceration and 89% relief in burning
Kakar et al	1985	India	96	Dexamethasone , Hyluronidase Combination of dexamethasone+hyluronidase	biweekly submucosal injections	MO with vernier caliper, ulceration and burning with clinical signs	3 months to 2 years	Patients receiving hyaluronidase alone showed quicker improvement in symptoms.Combination with dexamethasone gave somewhat better long-term results
Kumar et al	2007	India	19	Lycopene 16 mg along with steroids	biweekly intralesional injections	MO with vernier caliper, ulceration and burning with clinical signs	Evaluated weekly for 2 months	4.6mm improvement in MO, 100% relief in burning
Mishra et al	2021	India	50(stage2 with grade 2 and 3 trismus)	Hyaluronidase(1500IU) mixed with Triamcinolone(40mg/ml)	submucosal injections	MO with vernier caliper, ulceration and burning with clinical	8 weeks (weekly)	

						signs		
Warnakulasuriya	2016	Srilanka	190	Betamethasone, triamcinolone acetonide, hydrocortisone, methylprednisolone(20mg/0.5ml),triamcinolone diacetate	Topical and intralesional injections	MO with vernier caliper, ulceration and burning with clinical signs	After 7 days	Topical steroids may relieve the early symptoms of inflammation and mucositis in OSF but have not shown any efficacy in reversing fibrosis better results derived by intra-lesional injections, although it is alleged that repeated needle-stick trauma may cause additional scar tissue formation(2)
Pravin Kumar	2016	India	30	1ml Depomedrol+1 ml Local Anesthesia	intralesional injections	MO with vernier caliper, ulceration and burning with clinical signs	6 weeks (weekly)	9.3mm improvement in MO,84% relief in ulceration and 100% relief in burning
Rajitha et al	2015	India	45	Hyluronidase 1500I.U on bilateal mucosa, dexamethasone 2ml with 1 ml of 2% lignocaine with adrenaline(1:80000) bilaterally, combination of dexamethasone1ml and one part of Hyluronidase(750I.U) diluted with 1ml of 2% lignocaine with adrenaline(1:80000) and 1 ml of water for injection	biweekly submucosal injections	MO with vernier caliper, ulceration and burning with clinical signs	5 weeks (weekly)	6.67+-3.74mm improvement in MO with minimum relief in ulceration and burning withhyluronidase injections, 4.27+-1.58mm improvement in MO with moderate to maximum relief in ulceration and burning withdexamethasone injections, 5.8+-2.60mm improvement

								in MO along with maximum to moderate releif in ulceration and burning with combination therapy
Mangal et al	2010	India	100	Patients of group 'A' (n=50) were treated by a combination of hydrocortisone acetate (1.5 ml 25 mg/ml) and Hyluronidase (1500IU)) Patients of group B,combination of triamcinolone acetonide, 10 mg/ml and hyaluronidase (1500 IU) Injection in all patients were given submucosally in retromolar trigone and adjacent soft palate, cheek, half dose on each side by one observer and response of treatment by another observer	submucosal and intralesional	MO with vernier caliper, ulceration and burning with clinical signs	weekly for 22 weeks and 15 days interval, 22 weeks	170.42+-16.27 (MO), 124.89+-15.24(ulceration),294.48+-15.76 (Burning),Total improvement in group 'A' and 'B' was 9.67+1.72 and 10.23+2.05 respectively
Jiang at al	2013	China	44	Group A received Triamcinolone acetonide (2 mg) intralesionally. 2: 2: Group B received Salvianolic acid B (4mg, 99% high-performance liquid chromatography, intralesionally, 3: Group C received Triamcinolone acetonide (2 mg) and Salvianolic acid B(4 mg) by intralesional injection	intralesional injection	MO with vernier caliper, ulceration and burning with clinical signs	20 weeks(weekly)	3.88+-1.42mm (MO) in group A, 5.51+-1.76mm in groupB, 6.76+-1.36mm in group C, 80.9% patient complained tenderness at retromolar area,3.05+-0.76(b) in group A, 4.96+-0.97 in group B,6.11+-0.93 in group C
R.P Ekanayaka et al	2013	Sirilanka	116	40mg methyl predinsolone at buccal mucosa, 20mg per side	intralesional injections	MO with vernier caliper, ulceration and burning with clinical signs	monthly interval for 6 consecutive months	(59.5%) +5mm,(21.6%) More than 5mm but less than 10 mm,(19%) more than 10mm
Paolo J. Fantozzi et al	2019		93	topical steroids, systemic steroids, inj: Triamcinolone acetonide in 1cc syringe	topical, systemical and intralesional	MO with vernier caliper, ulce	not mentioned	Patients with traumatic ulcers had a higher resolution rate [86.8%]compared with

						ration and burning with clinical signs		patients withOLP/autoimmune[73.2%] Patients with traumatic ulcers required a median of 2 injections (range 1_5 injections) and the median time to resolution was 69 days(range 21_305 days) whereas patients OLP/autoimmune had an overall
R.M.BORLE	2011	India	160 for triamcinolone inj and 166 for for topical vitamin A	triamcinolone and hyluronidase inj and vitamin A, ferrous fumararte and betamethasone(topical)	biweekly submucosal injection and topical application	MO with vernier caliper, ulceration and burning with clinical signs	4 weeks for inj and 3 weeks for topical agents	no improvement in MO, 95.78% and 84.61% improvement in ulceration and burning in with triamcinilone inj respectively, 86.84% and 96.15% improvement in ulceration and burning with topical agents respectively
Leena James et al	2015	China	28	hyluronidase 1500IU mixed in 1.5 ml of dexamethasone and 0.5ml of lignocaine HCL	biweekly intralesional injection	MO with vernier caliper, ulceration and burning with clinical signs	4 weeks	92.8% improvement in MO, 89.28% in ulceration and 78.57% improvement in burning
Monu Yadav	2014	India	40	group 1 Dexamethasone 4mg/ml,1500 IU of hyluronidase along with 0.5ml of 2% lignocaine hcl with 26 guage needle, group 2 :2 tablets of Turmix(film coated tablet containing C.longs 300mg, piperine 5 mg, once)	oral,submucosal and intralesional injection	MO with vernier caliper, ulceration and	weekly 3 months gor group 1 and daily 3 mont	Group A (1.5MO),(15.6 ulceration),(0.9 burning) Group B (0.82 MO, 0 ulceration, 0.23 burning)

						burning with clinical signs	hs for group 2	
Panigrahi et al	2014	India	20	triamcenolone accetonide (10mg/ml) and haluronidase(1500IU) once in 2 weeks in group a, triamcinolone acetonide (10mg/ml) once in 2 weeks in group 2	intralesional injections	MO with vernier caliper, ulceration and burning with clinical signs	16 weeks	1:11.47mm, 2:5.82mm (MO), burnng and ulceration improved

(Gupta & Sharma, 1988)	Relief of Symptoms/Signs(%)			
	Painful Ulceration	Burning sensations	Blenching of oral mucosa	Limited opening
Dexamethasone (4 mg)	50%	82%	56%	72%
Hyaluronidase (Hyalase, Rallis India) 1500 IU	48%	82%	58%	74%
Chymotrypsin (Chymar, Walter Bushnell, India) 5000 IU	50%	84%	56%	76%
Placental Extract (2 mL)				
Hyalase + Dexamethasone	46%	51%	48%	65%
Chymar + Dexamethasone				
Hyalase + Chymar + Dexamethasone	62.5%	86.7%	66%	84%
Placental extract + Dexamethasone	61.8%	94%	66%	83%
Placental graft placement	74%	100%	79.5%	94%
	54%	86%	60%	72%
	86%	94%	82%	96%
(Kakar, Puri, & Venkatachalam, 1985)	The response to treatment was evaluated, subjectively on the basis of improvement in Symptoms and, objectively, by recording changes in the oral mucosa. The patients were The patients were followed up for periods varying from 3 months to 2 years.			

	Painful ulceration	Burning sensations	Intolerance to chilies	Trismus	Blanching of the oral mucosa	Improvement in Fibrous Suppleness	Bands
Local dexamethasone, 4mg bi-weekly	41.25%	50%	91.66%	66.6%	66.6%	66.6%	50%
local hyaluronidase 1,500 I.U. dissolved in 1 c.c. of 2 per cent lignocaine. bi-weekly;	54.16%	100%	100%	91.66%	58.33%	83.66%	66.6%
combination of hyaluronidase 1.500 I.U. dissolved in 4 mg of dexamethasone locally bi-weekly	62.5%	75%	100%	100%	79.16%	91.66%	75%
combination of hyaluronidase 1.500 I.U. dissolved in 4 mg of dexamethasone locally bi-weekly	50%	75%	87.5%	50%	45.83%	70.83%	41.25%

(Alora Veedu, Balan, & Sankar S, 2015)	Relief of Symptoms/Signs (Reduction in mean score)		
	Burning sensations	Mouth opening	Cheek Flaxibility
G1-biweekly submucosal injections of hyaluronidase 1500 IU × 5 weeks	Not significant	For MO no significant difference observed between groups (p = 0.068).	3.73 ±1.67. ⇩
G2-biweekly submucosal injections of Dexamethasone 2 ml	3.20 ± 1.52 ⇩ not statistically significant		
G3-biweekly submucosal injections of a combination of dexamethasone 1 ml (4 mg/ml) (Dexona) and one part of hyaluronidase (750 I.U)	1.93 ± 2.15. ⇩ statistically significant		

(Lai et al., 1995)	**Improvement in symptoms**				
	Painful Ulcerationn	Burning Sensations	Blanching	Trismus	Decrease of interincisal distance in the range of 3-5mm after 2 years follow-up
Oral administration of vitamin B-complex. buflomedial hydrochloride, and topical triamcinolone acetonide 0.1%	95%	88%	No	No	No
Biweekly submucosal injections of dexamethasone and hyaluronidase	94%	89%	71%	83%	69%
l)+2)	96%	91%	81%	86%	66%

(Kumar, Bagewadi, Keluskar, & Singh, 2007)	**Improvement in symptoms** (*P* value was set at .05 and was considered very significant at <.01 and highly significant at <.001			
	Burning Sensations	Mouth opening	Improvement of areas	
A, n =21) were given 16 mg of lycopene daily in 2 equally divided Doses.	complete relief	Average improvement in Group A was 3.4mm A vs B, *P* =1.91	37.5% improvement	
B, n=19) were given 16 mg of lycopene daily in 2 equally divided doses and were given intralesional injections of betamethasone (1-mL) ampules of 4 mg each) twice weekly.	complete relief	Average improvement in Group B was 4.6 mm. B vs C, *P* =1.61;	38.89% improvement	
C, n=18) were given placebo capsules.	Only one patient got relief	No improvement A vs C, *P* =1.81).	6.25% improvement	

(Pentapati, Gadicherla, & Smriti, 2016)	**Improvement in symptoms**		
	Mouth Opening	Ulceration	Burning Sensations

Hyaluronidase(1500IU) mixed with Dexamethasone(4mg/ml) sub mucosal injection	88%	37%	100%	
Hyaluronidase(1500IU) sub mucosal injection	56%	22%	87%	
Dexamethasone(4mg/ml) sub mucosal injection	69%	15%	92%	
(Singh, Niranjan, Mehrotra, Sharma, & Gupta, 2010)	**Improvement in symptoms** (Data are mean ± SD)			
	Mouth Opening	Ulceration	Burning Sensation	
1: Patients of group 'A' (n=50) were treated by a combination of hydrocortisone acetate (1.5 ml 25 mg/ml) and hyaluronidase (1500 IU)	170.42 ± 16.27	35.61 ± 7.24	294.48 ± 15.76	Total improvement in group 'A' and 'B' was 9.67+1.72 and 10.23+2.05 respectively
2: Patients of group B, combination of triamcinolone acetonide, 10 mg/ ml and hyaluronidase (1500 IU)	165.89 ± 15.11	33.94 ± 8.41	291.04 ± 16.41	
(Patil, Hazarey, Chaudhari, & Nimbalkar-Patil, 2016)	**Improvement in symptoms (**The significance level was set at α = 0.05.)			
	Mouth Opening	Ulceration	Burning sensation	
Subgroup A1 (n=35) Local (No additional treatment)	8.4 mm	(SD) 1.7174	87%	
Subgroup A2 (n=30) Injections (1ml Depomedrol+1 ml Local Anesthesia: Once a week)	9.3mm	1.6329	100%	
Subgroup A3 (n=10) Band removal Surgery	9.6mm	1.3853	91%	
Subgroup B1 (n=35) Local (No additional treatment)	5.5 mm	1.4376	77%	
Subgroup B2 (n=30) Injections (1ml Depomedrol+1 ml Local Anesthesia: Once a week)	5.1 mm	1.4057	98%	
Subgroup B3 (n=10)				

Band removal Surgery	4.8mm	1.3671	83%	
(Jiang et al., 2013)	**Improvement in symptoms after 20 weeks Data (mean +_ SD)**			
	Mouth Opening	Burning Sensations		
Intralesional injection after 5 minutes of local anesthetic cream application (20% Topcaine;		On VAS scale		
1: Group A received Triamcinolone acetonide (2 mg) intralesionally. 2:	3.88+ _ 1.42 mm	5.41+ _ 1.13		
2: Group B received Salvianolic acid B (4mg, 99% high-performance liquid chromatography, intralesionally,	5.51 1.76 mm	3.82+ _ 1.14,		
3: Group C received Triamcinolone acetonide (2 mg) and Salvianolic acid B(4 mg) by intralesional injection.	6.76 +_ 1.36 mm	5.88 +_ 0.95		
(Tilakaratne et al., 2016)	**Improvement in symptoms**			
	Mouth Opening	Restricted Tongue movement		
Intralesional injections of 40mg methylprednisolone at the buccal mucosa, 20 mg on each side on every visit on monthly bases.		P value 0.126 ($\chi 2$ 2= 7.201)		In this paired comparison, statistically significant difference (t= -8.78, Df = 115, P<0.001) was observed in mouth opening over a period of 12 months, in the patients who had corticosteroid injections.
Group 1: 20 to 30 years	6 (23.1%)			
Group 2: 31 to 40 years	3 (7.5%)			
Group 3: 41 to 50 years	8 (28.6%)			

Group 4: 51 to 60 years Group 5: more than 61 years	4(25.0%) 1 (16.7%)			
(Fantozzi, Treister, Shekar, Woo, & Villa, 2019)	**<u>Improvement in symptoms (Median pain score on VAS and median size of ulceer</u>** Ulceration	Pain	Complete Resolution	
G1- Topical Clobetasol 0.05% gel Dexamethasone 0.1 mg/mL solution Fluocinonide 0.05% gel Desonide 0.05% ointment Triamcinolone acetonide 0.1% ointment G2- Topical+ Systemic G3-Systemic 1 intralesional injection of triamcinolone acetonide (TA) 40 mg/ml and returned for at least 1 follow-up visit. Injections with triamcinolone acetonide were administered by using a disposable 1-cc syringe at the periphery of the ulcer. Only 1 injection per single lesion was performed at each visit.	The median size of the ulcer at the initial visit was 1 cm (range 0.1-5 cm), which, after the first IST, reduced to 0.3 cm (range 02 cm; P < .001) When the number of injections was considered over time, the median size of the ulcer was 0.5 cm (range 0.2 to 5 cm) in patients who received a single treatment, compared with 1 cm (range 0.24 cm) in patients who received greater than 1 injection (P < .001)	The median pain score reduced from 5 (range 1-10) to 1 (range 0-10) after the first IST (P < .0001)	54.8% Patients 27.9% Patients <u>7.5%</u> Patients	Patients with traumatic ulcers had a higher resolution rate [86.8%]compared with patients with OLP/ autoimmune[73.2%] Patients with traumatic ulcers required a median of 2 injections (range 1_5 injections) and the median time to resolution was 69 days (range 21_305 days) whereas patients OLP/autoimmune had an overall median resolution time of 140 days (range 21_357 days). Ulcers persisted in 3 patients (3.2%) despite IST (median of 4 injections; range 2-6 injections) and required further treatment (e.g., high-dose prednisone, hydroxychloroquine, and topical steroids)

(Borle & Borle, 1991)	**Improvement in signs/symptoms**				
	Mouth Opening	Ulceration	Burning Sensation	Blanching	
1) Biweekly submucosal injection of triamcinolone and hyaluronidase					
A- 15-20 Years	No	95.78%	86.84%	No	
B- 20-25	No	96.0%	95.74	No	
C- 25-35	No	91.30%	91.30%	No	
D- 35+	No	96.42%	85.71%	No	
2) Topical vitamin A, ferrous fumarate, and topical betamethasone					
A- 15-20 Years		96.1%	84.61%	No	
B- 20-25		96.29%	85.18%	No	
C- 25-35		91.84%	87.75%	No	
D- 35+		97.16%	95.12%	No	
(James, Shetty, Rishi, & Abraham, 2015)	**Improvement in signs/symptoms(%)**				
	Mouth Opening	Ulceration	Burning Sensations	Blenching	
The patients were administered hyaluronidase 1500 IU mixed in 1.5 ml of dexamethasone and 0.5 ml of lignocaine HCL injected	92.85% (26/28)	78.57% (22/28)	89.28% (25/28)	71.42% (20/28)	

intralesionally biweekly					
(Yadav et al., 2014)	**Improvement in signs/symptoms(%) Mean (SD); P* - Repeated measures ANOVA**				
	Interincisal Distance(mm)	Burning Sensations	Tongue Protrusion(mm)		
1) Given weekly submucosal intralesional injections of Dexamethasone (Inj Decadran 4 mg/ml, 1500 International units of Hyaluronidase along with 0.5 ml of 2% (1:80,000) Lignocaine Hydrochloride. The selection of the sites of injection was based on clinical judgment. Injections were given at multiple sites with a 26 guage Needle	22.4(4.3)mm	22.4 (8.7)a	18.7 (2.5)		
2) Given oral administration of 2 tablets of Turmix (Film coated tablet containing C. longa 300 mg, Piperine 5 mg, given once daily	24.5 (3.3)mm P value=0.1153	63.5 (24.7) P value <0.0001	18.7 (2.5) P value= 0.9999		
(Goel & Ahmed, 2015)	**Improvement in signs/symptoms (Data Mean±SD)**				
	Mouth Opening	P value			
G1- 2 mg of capsule lycopene BD for 6 months	S1=3.00±1.11 S2=6.07±2.00 S3=6.53±1.45	S1= >0.05 (non-significant)	G1 showed better improvement in mouth opening in stage 1 &2 (3.30 ± 1.51 mmvs3.00 ± 1.11 mm), (9.47 ± 2.47 vs 6.07 ± 2.00 mm).respectively.		
G2-ILI of betamethasone 4 mg/ ml biweekly for 6 months	S1=3.30±1.51 S2=9.47±2.47 S3=3.27±1.36	S2= <0.0001 (highly significant)	In Stage 3 Cap Lycopene group showed significant improvement in MO 6.53 ± 1.45 mm > 3.27 ± 1.36		
G3-Contrls -no	S1=0.00±0.00 S2=0.00±0.00 S3=0.00±0.00	S3= <0.0001 (highly significant)			

treatment				
(Pharmaceutical & Sciences, 2014)	**Improvement in signs/symptoms(Data Mean+- SD)** Mouth Opening	Burning Sensations	Fibrosis	
G1- Intralesional injection of triamcinolone acetonide (10 mg/ml) and hyaluronidase (1500IU) once in 2 weeks	11.47±2.16 P value= 0.0001	6.8±1.14 (P value= 0.0001)	5.6±1.58 (P value= 0.0001)	In G1, the MO improved by 11.47 mm with a relatively more reduction in symptom score and fibrosis. In group 2 the MO improved by 5.82 mm with a relatively less reduction in symptom score and fibrosis.
G2- Intralesional injection of triamcinolone acetonide (10 mg/ml) once in 2 weeks	5.82±0.76 (p value= 0.0032)	6.1±1.20 (P value= 0.0001)	2.6±0.97 (P value= 0.0041)	

Discussion

The OSMF, as defined by Pindborg and Sirsat, is a chronic disease that affects various parts of the oral cavity and occasionally the pharynx (4, 27) This condition is characterized by an inflammatory reaction in the epithelium, which is then followed by alterations in the fibroelastic tissue in the layer beneath, known as the lamina propria. Additionally, there is a loss of epithelial cells, leading to a stiffening of the oral mucosa and resulting in difficulty in opening the mouth, a condition known as trismus (28, 29). The care is contingent upon the severity of symptoms and the classification or evaluation of the disease. Given that OSMF is a chronic inflammatory disease, the primary goal of final treatment should be to effectively manage the factors that contribute to inflammation or the advancement of inflammation. If recognized in the initial stages prior to the onset of trismus, it can be managed by enhancing nutritional status, discontinuing harmful habits, and minimizing any other factors that contribute to persistent inflammation. However, once trismus or fibrosis occurs, it becomes challenging to reverse the processes. Management's primary objective is to preserve the quality of life by ensuring the maintenance of oral function and minimizing the advancement of disease (30, 31)

In literature, the management is categorized into conservative and surgical alternatives. Scientific literature has documented the use of various drugs to manage conservative means, such as steroids, fibrinolytic enzymes, anti-ischemic vasodilators, anti-oxidants, nutritional supplements, anti-fibrotic agents, and biogenic stimulants. However, the effectiveness of these drugs has been inconsistent (32). Corticosteroids efficiently alleviated the symptoms, specifically the burning sensation, ulceration, and

pain. It functions by reducing the inflammatory response and breaking down the byproducts of inflammation. Corticosteroids alleviate fibrosis by augmenting the function of phagocytic cells, hence facilitating the phagocytosis of collagen damaged by OSMF. Following the administration of corticosteroids to the fibroblast cultures, Tsai et al. noticed an increase in the number of phagocytic cells that was directly proportional to the dosage (24,33) Topical or intralesional preparations are frequently employed for the administration of corticosteroids. Betamethasone and triamcinolone acetonide are frequently employed as topical agents. Hydrocortisone, Methylprednisolone, Dexamethasone, and triamcinolone diacetate are administered using intralesional injections. The combination of Corticosteroids with hyaluronidase yields improved outcomes as hyaluronidase facilitates the deeper infiltration of the steroid. Hyaluronidase breaks down the hyaluronic acid matrix, reduces the thickness of intracellular cement-like compounds, and triggers certain plasma mechanisms. The disadvantages encompass the experience of pain during injection, the production of scars resulting from needle puncture, and an increased likelihood of relapse (34)(35). In their study, Veedu et al. examined the effects of two traditional treatments: submucosal injections of hyaluronidase (1500 I.U), dexamethasone (8 mg), or a combination of both (750 I.U and 4 mg). The treatments were administered for a period of 5 weeks. The study determined that hyaluronidase had superior efficacy in reducing the assessed symptoms. In their prospective study, Panigrahi et al. evaluated the effectiveness of combining intralesional triamcinolone acetonide and hyaluronidase with triamcinolone acetonide alone. They found that the intralesional injection of the combination of triamcinolone acetonide and hyaluronidase is more effective than triamcinolone alone in improving symptoms and providing convenience for patients. The primary constraint of Corticosteroids is the puncture caused by the needle.(3) Gupta et al conducted a study where they compared the impact of administering Dexamethasone (4mg), Hyaluronidase (1500IU), Placental extract (2 ml), and Chymotrypsin (5000 IU) individually and in combination. They discovered that the combination of dexamethasone and hyaluronidase, when administered through intralesional injections, resulted in a significant reduction in burning sensation and improved mouth opening. The study lacked a randomized controlled trial design and had incomplete data with missing follow-ups, which compromised the study's validity.(13) Kakar et al administered intralesional injections of Dexamethasone, Hyaluronidase, and a combination of both substances. According to his report, patients who were just administered hyaluronidase exhibited a faster alleviation of symptoms. The use of dexamethasone resulted in moderately improved long-term outcomes. However, it lacked a randomized controlled trial design and contained incomplete data.(16) Rajitha et al administered submucosal injections of Dexamethasone, Hyaluronidase, and a combination of both every two weeks. The study was a randomized, double-blind, multiple trial that found significant improvement in several symptoms, including mouth opening, swallowing, tongue protrusion, alleviation from fibrotic bands, tinnitus,

intolerance to spicy food, and burning sensation, throughout monthly follow-up and evaluation. The combination of dexamethasone and Hyaluronidase leads to enhanced salivation, increased rigidity of the mucosal tissue, and reduction in the presence of papillae on the tongue.(14) In a randomized control trial conducted by Kumar et al. (2007), three groups were employed. The first group received a daily oral dose of 16 mg lycopene, the second group received a daily oral dose of 16 mg lycopene together with twice weekly intralesional injections of 8 mg betamethasone, and the third group received placebo capsules. After conducting regular follow-up and reviewing the progress on a weekly basis, he observed an increase in the distance between the upper and lower incisors (measured in millimeters) and an improvement in the extent to which the tongue protrudes (measured in units of 5 millimeters). Additionally, he noticed the presence of palpable fibrous bands in the lining of the cheeks (buccal mucosa). Is there a complete elimination of the burning feeling (present/persisting/absent)?Indicated that the severity of additional discoveries was evaluated using a 3-point scale, but the specific details were not provided.(17) Lai et al conducted a clinical experiment where they administered biweekly submucosal injections of Dexamethasone and hyaluronidase. The study documented a substantial enhancement in the healing of mucosal ulcers during the monthly monitoring period. (15) In their investigation, Pravinkumar et al determined that the utilization of the MED (mouth opening exercise device) is beneficial in enhancing oral opening in individuals with OSMF (Oral Submucous Fibrosis) when used with local injection.(20) Jiang et al conducted a comparison research and observed a substantial increase in mouth opening following intralesional injections. (5) In their study, R.P. Ekanayaka et al. found that intralesional corticosteroid injections are commonly used to treat OSF, especially in individuals with noticeable fibrous bands. The study provides evidence supporting the use of corticosteroids in enhancing mouth opening.(7) In his clinical experiment, R.M. Borle separated three hundred twenty-six patients with oral submucous fibrosis into two groups. One group received traditional submucosal injections of steroids and hyaluronidase, while the other group was treated with topical vitamin A, steroid applications, and oral iron preparations. (23) The findings were compared and he concluded that the traditional method of treatment involving injections was deemed risky, while the more cautious approach was considered to be secure. Both interventions were solely aimed at providing relief from symptoms. Leena James and her colleagues discovered that the administration of hyaluronidase along with dexamethasone is a successful approach for treating Grade III OSMF and has the potential to remove the negative health effects associated with surgical treatment.(24) Panigrahi et al revealed that the intralesional administration of a combination of triamcinolone acetonide and hyaluronidase is more effective than triamcinolone alone in terms of symptom relief and patient convenience. (3) In the Rajendran 2006 trial, the investigators reported the occurrence of mild gastritis, gastric irritation, and peripheral flushing as side effects. However, they did not provide specific details regarding the number of participants affected, the treatment

group they belonged to, or the severity and duration of these side effects. The investigators only mentioned that these side effects were managed through unspecified dietary changes. The other trial (Kumar 2007) did not identify any negative effects associated with the medication.

The studies included in this review revealed that the use of topical and intralesional corticosteroids effectively reduced burning sensations and improved oral ulceration. However, there is no conclusive evidence to suggest that weather management options, which involve therapeutic interventions with anti-inflammatory or antifibrotic properties, would be the most effective approach. The combined use of intralesional steroid injections and lycopene, both known for their anti-inflammatory properties, likely made it difficult to accurately assess the effectiveness of lycopene used alone. Additionally, the evidence provided for the effectiveness of pentoxifylline, which acts as both an anti-inflammatory and fibrinolytic agent, was inconclusive. All the studies reached the consensus that the findings suggested that these interventions were safe, seemed to be effective in reducing symptoms, and could potentially be advantageous in the therapeutic management of oral submucous fibrosis. However, due to the uncertain dependability of the limited data currently available, it does not seem to provide substantial support for these claims.

The utilization of anti-inflammatory and immunomodulatory agents has been found to be efficacious in the initial symptoms or phases. As an illness progresses, its effectiveness diminishes. Incorporating either stratified randomization or minimization techniques in studies is recommended to allocate participants to interventions in a way that minimizes variations in the distribution of known or suspected characteristics that may affect the result. The included trials encountered challenges such as the characteristics of the intervention and control, the complexity of blinding participants and investigators, the likelihood of biased outcomes assessment, and significant losses to follow up. While the interincisal distance is commonly used as the primary measure, the quality and dependability of the test are demonstrated by its sensitivity and ability to detect even small changes, especially when those changes are measured in millimeters, as was observed in the two trials included in the study.

This evaluation assessed the scientific literature of the included studies and determined that none of them examined the efficacy of outcomes based on the staging or grading of the condition. In the future, it will be necessary to conduct trustworthy randomized control trials with large sample sizes and compare the efficacy based on the disease's stage in order to make any credible statements. If it is not possible to blind either the participants or the trialists to an intervention or the assessment of outcomes, then it is important to make strong steps to ensure that the data analyzers are blinded. When assessing the effectiveness of interventions, it is important to employ validated pain scales to measure pain outcomes. Investigators should additionally investigate strategies that might effectively address withdrawals and losses to ensure proper follow-up in future trials. While acknowledging the limited resources in developing countries, it is

advisable to explore the adoption of more advanced measurement techniques. Future trials could potentially incorporate various tools for image analysis, such as photography or digital morphometry, in combination with cephalometric digital radiography and extraoral imaging systems.

Conclusion:

Despite the existence of numerous steroids, there is a scarcity of evidence-based literature regarding their usefulness in treating OSF. Additionally, no specific approach has been discovered thus far that can fully cure the disease.

Steroids have been used with several medications, including hyaluronidase, human placenta extracts, chymotrypsin, collagenase, pentoxifylline, nylidrin hydrochloride, iron, and multivitamin supplements including lycopene. However, the absence of high-quality research investigating the efficacy of steroids in the treatment of OSF is disheartening. Prior evaluations have indicated a dearth of dependable evidence regarding the efficacy of any particular method of administering steroids for the treatment of OSMF. Additionally, it is challenging to objectively evaluate or merge the results of these studies in a meaningful manner. A recent systematic review has also discovered a limited amount of evidence to support the use of steroids in the treatment of OSMF. Nevertheless, this review made a valuable contribution by identifying opportunities for future research. Specifically, it provided recommendations regarding the populations that should be studied, the interventions that are necessary, the outcomes that should be measured, the study designs that are required, and the infrastructure that is needed to conduct such studies. Therefore, further clinical research is still necessary to gather the evidence that would allow doctors to make unbiased judgments regarding the efficacy of the therapy alternatives currently available. Moreover, implementing educational programs that raise awareness about the detrimental consequences of areca nut consumption and enforcing stricter regulations to hinder the promotion of areca nut products could help tackle this public health concern.

References:

1. More CB, Jatti Patil D, Rao NR. Medicinal management of oral submucous fibrosis in the past decade- A systematic review. J Oral Biol Craniofacial Res [Internet]. 2020;10(4):552–68. Available from: https://doi.org/10.1016/j.jobcr.2020.08.004
2. Khan S, Sinha A, Kumar S, Iqbal H. Oral submucous fibrosis: Current concepts on aetiology and management - A review. J Indian Acad Oral Med Radiol. 2018;30(4):407–11.
3. Peng Q, Li H, Chen J, Wang Y, Tang Z. Oral submucous fibrosis in Asian countries. J Oral Pathol Med. 2020;49(4):294–304.
4. Fedorowicz Z, Chan Shih-Yen E, Dorri M, Nasser M, Newton T, Shi L. Interventions for the management of oral submucous fibrosis. Cochrane Database Syst Rev. 2008;(2).
5. Jiang XW, Zhang Y, Yang SK, Zhang H, Lu K, Sun GL. Efficacy of salvianolic acid B combined with triamcinolone acetonide in the treatment of oral submucous fibrosis. Oral Surg Oral Med Oral

Pathol Oral Radiol. 2013;115(3):339–44.
6. M Shashi Kiran 1, S Vidya 2, Gunjan Singh Aswal 3, Vinod Kumar 3 VR 3. No TitleSystemic and Topical Steroids in the Management of Oral Mucosal Lesions. J Pharm Bioallied Sci. 2017;suppl 1(1–3).
7. 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 [Internet]. 2016;122(2):224–31. Available from: http://dx.doi.org/10.1016/j.oooo.2015.11.023
8. Singh M, Niranjan HS, Mehrotra R, Sharma D, Gupta SC. Efficacy of hydrocortisone acetate/hyaluronidase vs triamcinolone acetonide/hyaluronidase in the treatment of oral submucous fibrosis. Indian J Med Res. 2010;131(5):665–9.
9. Mohiuddin S, Fatima N, Hosein S, Hosein M. High risk of malignant transformation of oral submucous fibrosis in Pakistani females: A potential national disaster. J Pak Med Assoc. 2016;66(11):1362–6.
10. 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;122(2).
11. Mishra S. A comparative study on the use of antioxidants and intralesional steroid infiltration in oral submucous fibrosis. MRIMS J Heal Sci. 2021;9(1):1.
12. Gondivkar SM, Gadbail AR, Sarode SC, Gondivkar RS, Patil S, Gaikwad RN, et al. Clinical efficacy of mouth exercising devices in oral submucous fibrosis: A systematic review. J Oral Biol Craniofacial Res [Internet]. 2020;10(4):315–20. Available from: https://doi.org/10.1016/j.jobcr.2020.06.010
13. Gupta D, Sharma SC. Oral submucous fibrosis-A new treatment regimen. J Oral Maxillofac Surg. 1988;46(10):830–3.
14. Alora Veedu R, Balan A, Sankar S P. A randomized double-blind, multiple-arm trial comparing the efficacy of submucosal injections of hyaluronidase, dexamethasone, and combination of dexamethasone and hyaluronidase in the management of oral submucous fibrosis. Oral Surg Oral Med Oral Pathol Oral Radiol [Internet]. 2015;120(5):588-593.e1. Available from: http://dx.doi.org/10.1016/j.oooo.2015.07.003
15. Lai DR, Chen HR, Lin LM, Huang YL, Tsai CC, Lai D -R. Clinical evaluation of different treatment methods for oral submucous fibrosis. A 10-year experience with 150 cases. J Oral Pathol Med. 1995;24(9):402–6.
16. Kakar PK, Puri RK, Venkatachalam VP. Oral submucous fibrosis—treatment with hyalase. J Laryngol Otol. 1985;99(1):57–60.
17. Kumar A, Bagewadi A, Keluskar V, Singh M. Efficacy of lycopene in the management of oral submucous fibrosis. Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology. 2007;103(2):207–13.
18. Pentapati KC, Gadicherla S, Smriti K. "A randomized double-blind, multiple-arm trial comparing the efficacy of submucosal injections of hyaluronidase, dexamethasone, and combination of dexamethasone and hyaluronidase in the management of oral submucous fibrosis"—a commentary. Oral Surg Oral Med Oral Pathol Oral Radiol [Internet]. 2016;122(6):784. Available from: http://dx.doi.org/10.1016/j.oooo.2016.06.098
19. 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.
20. Patil P, Hazarey V, Chaudhari R, Nimbalkar-Patil S. Clinical efficacy of a mouth-exercising device adjunct to local ointment, intra-lesional injections and surgical treatment for oral submucous fibrosis: A randomized controlled trial. Asian Pacific J Cancer Prev. 2016;17(3):1255–9.
21. Alora Veedu R, Balan A, Sankar S P. A randomized double-blind, multiple-arm trial comparing

the efficacy of submucosal injections of hyaluronidase, dexamethasone, and combination of dexamethasone and hyaluronidase in the management of oral submucous fibrosis. Oral Surg Oral Med Oral Pathol Oral Radiol [Internet]. 2015;120(5):588-593.e1. Available from: http://dx.doi.org/10.1016/j.oooo.2015.07.003

22. Fantozzi PJ, Treister N, Shekar R, Woo S Bin, Villa A. Intralesional triamcinolone acetonide therapy for inflammatory oral ulcers. Oral Surg Oral Med Oral Pathol Oral Radiol [Internet]. 2019;128(5):485–90. Available from: https://doi.org/10.1016/j.oooo.2019.07.024
23. Borle RM, Borle SR. Management of oral submucous fibrosis: A conservative approach. J Oral Maxillofac Surg. 1991;49(8):788–91.
24. James L, Shetty A, Rishi D, Abraham M. Management of Oral Submucous Fibrosis with Injection of Hyaluronidase and Dexamethasone in Grade III Oral Submucous Fibrosis: A Retrospective Study. J Int oral Heal JIOH [Internet]. 2015;7(8):82–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26464545%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4588796
25. Yadav M, Aravinda K, Saxena VS, Srinivas K, Ratnakar P, Gupta J, et al. Comparison of curcumin with intralesional steroid injections in Oral Submucous Fibrosis - A randomized, open-label interventional study. J Oral Biol Craniofacial Res [Internet]. 2014;4(3):169–73. Available from: http://dx.doi.org/10.1016/j.jobcr.2014.11.003
26. Pharmaceutical JOOF, Sciences B. J OURNAL OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES. 2014;04(04):365–70.
27. Richa, Vibha, Swain N. Medical management of oral submucous fibrosis: An update. J Oral Maxillofac Surgery, Med Pathol. 2013;25(2):151–6.
28. Chole RH, Gondivkar SM, Gadbail AR, Balsaraf S, Chaudhary S, Dhore S V, et al. Review of drug treatment of oral submucous fibrosis. Oral Oncol [Internet]. 2012;48(5):393–8. Available from: http://dx.doi.org/10.1016/j.oraloncology.2011.11.021
29. Maher R, Aga P, Johnson NW, Sankaranarayanan R, Maher R, Aga P, et al. Evaluation of multiple micronutrient supplementation in the management of oral submucous fibrosis in Karachi , Pakistan Evaluation of Multiple Micronutrient Supplementation in the Management of Oral Submucous Fibrosis in Karachi , Pakistan. (January 2015):37–41.
30. Aziz SR. Coming to America betel nut and oral submucous fibrosis. J Am Dent Assoc [Internet]. 2010;141(4):423–8. Available from: http://dx.doi.org/10.14219/jada.archive.2010.0194
31. Shen YW, Shih YH, Fuh LJ, Shieh TM. Oral submucous fibrosis: A review on biomarkers, pathogenic mechanisms, and treatments. Int J Mol Sci. 2020;21(19):1–19.
32. Xie H, Guo J, Tan B, Wu H. Efficacy of Salvia miltiorrhiza injection combined with steroids in the treatment of oral submucous fibrosis. Medicine (Baltimore). 2019;98(27):e16339.
33. Sabharwal R, Gupta S, Kapoor K, Puri A, Rajpal K. Review Article : Oral Submucous Fibrosis- A Review. J Adv Med Dent Scie. 2013;1(1):29–37.
34. Warnakulasuriya S, Kerr AR. Oral submucous fibrosis: a review of the current management and possible directions for novel therapies. Oral Surg Oral Med Oral Pathol Oral Radiol [Internet]. 2016;122(2):232–41. Available from: http://dx.doi.org/10.1016/j.oooo.2016.02.020
35. Hu J, Angadi P V. Drug treatment for oral submucous fibrosis. Evid Based Dent. 2010;11(2):56.