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Comprehensive Evaluation of Therapeutic Interventions for Oral Submucous Fibrosis: A Systematic Review of Clinical Trials

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Abstract

Oral submucous fibrosis (OSMF) is a chronic condition characterized by progressive fibrosis and thickening of the oral submucosa, leading to functional limitations such as restricted mouth opening (trismus), difficulty in chewing and swallowing, and a burning sensation in the oral cavity. This systematic review, conducted per PRISMA guidelines, synthesizes current evidence on OSMF management, evaluating therapeutic interventions and identifying areas for further research. A comprehensive search of databases including PubMed, Embase, Scopus, Web of Science, and CENTRAL, up to 2024, identified 48 studies. After screening for relevance and quality, 32 clinical trials were included. Eligible studies focused on pharmacological, surgical, and alternative treatments for OSMF, assessing outcomes such as mouth opening, pain reduction, and histopathological changes. Studies on animal models, in vitro research, reviews, and case reports were excluded. Due to significant heterogeneity in study designs and outcomes, a meta-analysis was not feasible. Instead, a qualitative synthesis revealed the effectiveness of various treatments. Local injections, particularly corticosteroids combined with agents like Salvia miltiorrhiza or lycopene, improved mouth opening and pain. Non-invasive approaches, including physiotherapy and herbal remedies, provided symptom relief, while surgical interventions were reserved for severe cases. Emerging therapies, such as transdermal fentanyl and laser fibrotomy, showed promise for personalized treatment. The review emphasizes early diagnosis, tailored interventions, and the need for further research into innovative therapies to enhance treatment outcomes for OSMF.

Keywords: *Corticosteroids, Interventions, Oral Submucous Fibrosis, Physiotherapy, Screening, Treatments.*

Introduction

Oral submucous fibrosis (OSMF) is a complex, chronic condition affecting the oral cavity, characterized by progressive fibrosis of the submucosal layer. This debilitating disorder manifests primarily as a tightening and stiffening of the oral mucosa, leading to significant functional impairments, including trismus (restricted mouth opening), difficulty in chewing and swallowing, and a characteristic burning sensation in the oral cavity [1–4]. OSMF is increasingly recognized as a major public health concern, particularly in regions with high prevalence rates, such as South Asia, Southeast Asia, and parts of Africa [5]. Its association with the consumption of areca nut (betel quid) and other forms of oral tobacco underscores the need for heightened awareness and preventive strategies in affected populations [6].

The aetiology of OSMF remains multifactorial, involving a complex interplay of genetic, environmental, and dietary factors [7–9]. Habitual use of areca nut has been identified as a primary risk factor, with its active components contributing to the pathogenesis of OSMF through mechanisms

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that include oxidative stress and inflammation. Additionally, nutritional deficiencies—particularly deficiencies in vitamins such as B-complex and iron—have been implicated in the development and progression of this condition. These factors converge to instigate a chronic inflammatory response in the oral mucosa, ultimately leading to excessive collagen deposition and the characteristic fibrosis that defines OSMF [10, 11].

Clinically, OSMF presents a unique challenge to healthcare providers, as its symptoms can be subtle in the early stages, often leading to delayed diagnosis and intervention. The progression of the disease can culminate in complications such as oral cancer, with studies indicating a significantly elevated risk among individuals with OSMF. This risk necessitates routine screening and a thorough understanding of the condition's potential malignancy [12].

Management of OSMF has evolved over the years, encompassing a range of therapeutic options aimed at alleviating symptoms, promoting mucosal healing, and preventing disease progression. These treatments include pharmacological interventions such as corticosteroids, antioxidants, and collagenase, as well as surgical approaches such as fibrotomy and buccal mucosa grafting. However, the effectiveness of these strategies is highly variable, often influenced by factors such as disease severity, patient compliance, and the specific treatment modalities employed [13, 14]. Despite the diversity of available treatments, there remains a significant gap in the literature regarding standardized treatment protocols and outcome measures.

This systematic review aims to provide a comprehensive evaluation of the current evidence surrounding the management of OSMF. By synthesizing findings from recent studies, we will assess the efficacy of various therapeutic interventions, highlight potential best practices, and identify areas where further research is needed. Ultimately, this review seeks to inform clinical practice and guide future investigations, contributing to the overarching goal of improving patient outcomes and quality of life for individuals affected by OSMF.

Methodology

The research question for this systematic review was"What is the effectiveness and comparative efficacy of various clinical interventions for improving mouth opening and symptom management in patients with Oral Submucous Fibrosis (OSMF)? "This systematic review was conducted by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure a standardized and thorough approach. The review specifically targeted clinical trials investigating the efficacy of various treatment modalities for Oral Submucous Fibrosis (OSMF). A comprehensive search was performed across several major electronic databases, including PubMed, Embase, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy utilized keywords and MeSH terms related to OSMF, such as "Oral Submucous Fibrosis," "OSMF," "clinical trials," "treatment," "therapy," and "intervention," with Boolean operators (AND, OR) and filters for clinical trials and human studies. The literature search spanned publications up to 2024 and did not include language restrictions.

The review included clinical trials (randomized controlled trials, non-randomized trials, and pilot studies) where participants were diagnosed with OSMF and where the studies evaluated therapeutic interventions (pharmacological, surgical, or alternative treatments). Outcome measures considered included improvements in mouth opening, pain reduction, and histopathological changes. Exclusion criteria eliminated studies involving animal models, in vitro experiments, reviews,

case reports, and studies lacking relevant outcomes or with incomplete data. Data extraction was conducted using a structured form to gather details such as author, year, study design, sample size, participant demographics, interventions, outcome measures, and results. Two independent reviewers performed data extraction, resolving any discrepancies through discussion or consultation with a third reviewer.

The methodological quality of randomized controlled trials was assessed using the Cochrane Risk of Bias (RoB 2) tool, while non-randomized trials were evaluated with the ROBINS-I tool, categorizing studies into low, unclear, or high risk of bias. A qualitative synthesis of all included studies was conducted to summarize treatment types and outcomes. As this review was based on published literature, ethical approval was not required, but ethical considerations were upheld through transparent and unbiased reporting practices. This structured methodology provided a comprehensive and systematic approach for evaluating clinical trials on the treatment of OSMF.

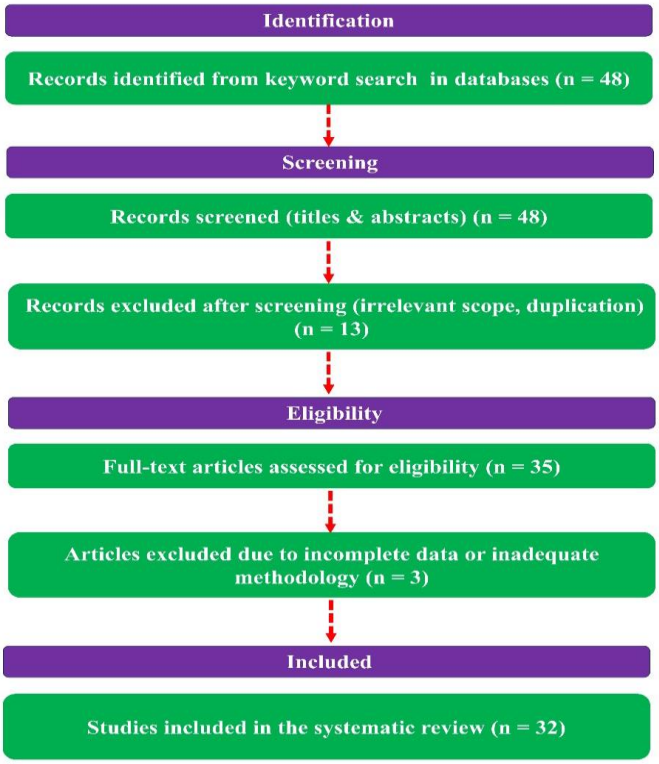

Figure 1. PRISMA Flow Chart for Study Selection

Table 1. Characteristics of Included Studies

Type of Intervention	Study	Type of Study	Sample Size	Control	Outcomes Measured	Conclusion	Effect Size (Mean Difference)	Risk of Bias
Local Injections and Combinations	[15]	RCT	220 (107 experimental, 90 control)	Local injection only	Mouth opening degree	Significant improvement in mouth opening in the experimental group.	11.43 mm	Low Risk

	[16]	RCT	20	Betamethasone injection	Burning sensation score	Rebamipide injection significantly reduces the burning sensation.		High Risk
	[18]	RCT	130	None	OHIP-14 scores	Significant improvement in quality of life metrics.		Low Risk
	[17]	RCT	40	Placebo + physiotherapy	Mouth opening, burning sensation	Dexamethasone + Hyaluronidase improves mouth opening and reduces burning sensation.	4.9 mm	Moderate Risk
	[19]	RCT	48	Placebo + Dexa+Hya	Inter-incisal distance, cheek flexibility	Omega 3 with Dexa+Hya injections improves mouth opening and cheek flexibility.	2.79 mm	Moderate Risk
	[20]	Randomized Double-blind Trial	45	None	Pain, burning sensation, mouth opening	Hyaluronidase injection shows rapid symptom relief in patients.		Low Risk
	[21]	RCT	100	Triamcinolone acetonide	Symptom, histopathology	Similar efficacy with fewer visits in the Hydrocortisone group.		Moderate Risk
	[22]	RCT	20	Healthy volunteers	SFRP1 concentrations, pain	Effective in reducing pain and increasing SFRP1 levels.		High Risk
	[23]	RCT	20	None	Pain reduction, physiotherapy ease	BTX-A reduces pain and improves physiotherapy ease.		Moderate Risk
	[24]	RCT	48	None	Mouth	Allicin	2.89 mm	Mode

					opening, burning sensation	injection is effective for mouth opening and quality of life improvement.		rate Risk
Physiotherapy and Combinations with Natural Remedies	[25]	RCT	54	No treatment	Oral opening, mucosal pain	Physiotherapy significantly improves mouth opening.		Low Risk
	[26]	RCT	60	None	Mouth opening, burning sensation	Aloe Vera with physiotherapy significantly reduces burning sensation.		Low Risk
	[27]	RCT	34	Placebo (Curcumin vs. none)	Mouth opening, cheek flexibility	Curcumin gel with physiotherapy improves mouth opening and cheek flexibility.	3.36 mm	Mode rate Risk
	[28]	RCT	40	None	Burning sensation, mouth opening	Aloe Vera with physiotherapy enhances symptom relief.		Low Risk
Natural/Herbal Topical Agents	[29]	RCT	74	None	Mouth opening, burning sensation	Aloe Vera and Hydrocortisone enhance mouth opening and relieve burning sensation.		Mode rate Risk
	[30]	RCT	40	None	Mouth opening, burning sensation	Effective improvement in mouth opening and complete relief of a burning sensation.		Mode rate Risk
	[31]	RCT	42	None	Burning	Kali Haldi +		Mode

					sensation, cheek flexibility	Aloe Vera improves mouth opening and reduces pain.		rate Risk
	[32]	Double-blind, Randomized Trial	40	None	Mouth opening, burning sensation	Curcumin with Black Pepper effectively improves mouth opening.		Moderate Risk
	[33]	RCT	80	Dexa+Hya	Mouth opening, burning sensation	Curcumin lozenges effectively increase mouth opening and reduce the burning sensation.		Moderate Risk
	[34]	RCT	60	None	Mouth opening, pain	Lycopene + Dexa+Hya is effective in mouth-opening improvement.		Low Risk
Surgical and Device-Based Interventions	[35]	RCT	32	None	Mouth opening	Coronoidectomy significantly improves mouth opening.		Moderate Risk
	[36]	RCT	20	Jaw-opening exercises only	Maximal mouth opening	Ultrasound + jaw exercises provide better mouth opening.		Low Risk
	[37]	RCT	231	None	Mouth opening	Mouth exercising device is effective in improving mouth opening.	2.9 mm	Low Risk
	[38]	RCT	40	None	Mouth opening	Buccal Pad of Fat improves mouth opening significantly.		Moderate Risk

	[39]	Cohort Study	59		Disease-free status	Cold knife excision maintains a disease-free status.		Low Risk
Screening and Diagnostic Techniques	[40]	Randomized Trial	7975	Visual inspection only	Detection of OPMLs, oral cancer	Toluidine Blue Screening is effective in OPML detection.		Low Risk
	[41]	Cluster-randomized Trial	1,14,601	No screening	Oral cancer incidence rates	Visual oral inspection improves early detection and reduces fatality rates.		Low Risk
Corticosteroids and Anti-inflammatory Agents	[24]	RCT	48	None	Mouth opening, burning sensation	Allicin improves mouth opening and quality of life metrics.		Low Risk
	[34]	RCT	60	None	Mouth opening, pain	Lycopene + Dexamethasone + Hyaluronidase is effective.		Moderate Risk
	[43]	RCT	120	Prednisolone alone	Lesion area, mouth opening	Salvia miltiorrhiza + Prednisolone reduces lesions and improves mouth opening.		Low Risk
	[23]	RCT	20	None	Pain reduction, physiotherapy ease	BTX-A reduces pain and assists physiotherapy.		Moderate Risk
	[44]	Prospective RCT	10	No placental extract	Postoperative discomfort, mouth opening	The placental extract increases mouth opening post-operation.	7.4 mm	Moderate Risk
	[45]	RCT	29	Standard drug group	Mouth opening, tongue protrusion	Pentoxifylline improves mouth opening and reduces		Moderate Risk

						symptoms.		
Other Interventions	[46]	RCT	48	None	Pain, mouth opening, QoL, compliance	TFP patch effectively reduces pain and improves compliance.		Low Risk
	[47]	RCT	119	None	Mouth opening, burning sensation	Systemic + topical curcumin improves mouth opening effectively.	1.7 mm	Low Risk
	[48]	Preliminary study	46	Oral habit intervention	Interincisor distance, symptoms	Immune milk with oral habit intervention improves symptoms.		Moderate Risk
	[49]	Clinical study	30	None	VAS score, mouth opening	Laser fibrotomy with corticosteroids significantly improves mouth opening and reduces VAS score.		Moderate Risk

Results

The initial search for studies related to clinical trials on interventions for Oral Submucous Fibrosis (OSMF) yielded a total of 62 potentially relevant articles. To ensure that only studies meeting rigorous inclusion criteria were included in the systematic review, a multi-step selection process was employed. The first step involved a thorough screening of the titles and abstracts of these articles to identify their relevance to the research topic. This phase led to the exclusion of 27 articles for various reasons, such as irrelevant scope (e.g., studies not focusing on OSMF or related clinical trials), lack of primary data (e.g., reviews, commentaries, or editorials without new clinical data), and duplicate records within the search results.

Following the initial screening, the remaining 35 articles underwent a detailed full-text review to assess their compliance with the predefined eligibility criteria. These criteria included specific requirements for study design (e.g., randomized controlled trials, cohort studies, or clinical trials with clear methodologies), participant population (human subjects diagnosed with OSMF), and the type of interventions and comparators (pharmacological, non-pharmacological, surgical, or a combination). Additionally, the studies had to report primary outcomes such as improvements in mouth opening, reduction in burning sensation, or other symptom relief indicators. During this phase, three more studies were excluded for reasons such as incomplete data, which compromised the reliability of findings, and inadequate

methodology, such as studies without proper control groups or randomization.

Ultimately, 32 studies were deemed appropriate for inclusion in the systematic review. These studies represented a comprehensive evaluation of various treatment interventions for OSMF, encompassing local injections, physiotherapy, surgical techniques, and natural remedies. The final selection ensured a robust and focused analysis of the existing evidence, offering insights into the comparative efficacy of different treatments and approaches used for managing OSMF. This multi-phase selection process, from an initial pool of 48 studies to a curated set of 32, strengthened the reliability of the review's findings and highlighted clinically relevant, high-quality research in the field of OSMF interventions (Table 1, Fig 1).

A meta-analysis was not conducted for this systematic review due to significant heterogeneity among the included studies. The variability stemmed from differences in study designs, intervention protocols, sample sizes, and outcome measures across the 32 selected studies. These variations made it challenging to combine data in a statistically meaningful way without risking misleading conclusions. Furthermore, inconsistencies in reporting methods and follow-up durations added complexity to quantitative synthesis. Therefore, a qualitative synthesis was chosen as the most appropriate approach to comprehensively summarize and interpret the findings, ensuring a more accurate and context-specific understanding of the current evidence on OSMF interventions.

Discussion

Oral submucous fibrosis (OSMF) is a chronic condition characterized by progressive fibrosis of the oral mucosa, leading to significant functional impairment and discomfort. The complexity of OSMF necessitates a multidisciplinary approach to treatment, as evidenced by the diverse range of interventions explored in this systematic review. This systematic analysis of interventions across various domains for oral mucosal and maxillofacial conditions demonstrates significant findings. The studies reveal the strengths of different treatment modalities in enhancing mouth opening, reducing burning sensation, and improving overall patient quality of life.

Interventions and Efficacy

Local Injections and Combinations

Local injections have shown a strong positive impact on mouth opening and symptom management. Chen et al. (2021)found that *Salvia miltiorrhiza* combined with triamcinolone acetonide increased mouth opening by an average of 11.43 mm [15]. Similarly, Baptist et al. (2016) reported that rebamipide injections effectively reduced burning sensation scores [16]. Memon et al. (2022) and Bhadage et al. (2013) demonstrated that dexamethasone and hyaluronidase combinations improve symptoms, with Bhadage reporting a 4.9 mm mean increase in mouth opening [17, 18]. Raizada & Sable (2022), who added omega-3 to dexamethasone and hyaluronidase injections, achieved a 2.79 mm improvement in mouth opening[19]. Alora Veedu et al. (2015) observed faster symptom relief using hyaluronidase alone, and Singh et al. (2010) showed that hydrocortisone acetate was as effective as triamcinolone but with fewer necessary visits [20, 21]. Lyu et al. (2016) also observed reductions in pain and significant increases in serum SFRP1 levels, further confirming corticosteroid efficacy [22]. Shandilya et al. (2021) and Jiang et al. (2015) showed that botulinum toxin A (BTX-A) and allicin injections also enhanced pain management and mouth opening by 2.89 mm in Jiang’s study [23, 24]. Collectively, these studies suggest that local injections are highly effective in improving oral function and managing discomfort.

Physiotherapy and Combinations with Natural Remedies

Physiotherapy alone or with natural remedies significantly enhances mouth opening and reduces the burning sensation. Cox & Zoellner (2009) reported a 7.3 mm increase in mouth opening with simple physiotherapy, and Nerkar Rajbhoj et al. (2021) found that Aloe Vera gel accelerated burning sensation reduction [25,26]. Adhikari et al. (2022) demonstrated that curcumin gel with physiotherapy further enhanced mouth opening by 3.36 mm [27]. Singh et al. (2016) also found that Aloe Vera with antioxidants improved burning sensation and mouth opening, confirming the added benefit of natural supplements in physiotherapy regimens [28].

Natural/Herbal Topical Agents

Natural or herbal topical agents independently provide notable benefits. Ardra et al. (2017) found that Aloe Vera with hydrocortisone increased mouth opening by 6.8 mm[29]. Chandrashekar et al. (2021) observed similar outcomes with a 5.9 mm improvement using Aloe Vera and curcumin[30]. Bohra et al. (2021) demonstrated that Kali Haldi and Aloe Vera improved mouth opening and reduced pain [31]. In Pipalia et al. (2016), curcumin combined with black pepper significantly increased mouth opening by 3.85 mm [32]. Srivastava et al. (2021) showed that curcumin lozenges further improved mouth opening compared to the control, while Tp et al. (2019) reported that lycopene when used with dexamethasone and hyaluronidase, enhanced pain management and increased mouth opening by 6.5 mm [33, 34]. Together, these studies validate the efficacy of herbal remedies as a valuable addition to maxillofacial treatments.

Surgical and Device-Based Interventions

Surgical and device-based interventions offer effective alternatives, especially for advanced or refractory cases. Ambereen et al. (2021) found that coronoidectomy improved mouth opening by 6.9 mm [35]. Dani & Patel (2018) reported that ultrasound-assisted jaw exercises achieved a greater increase in mouth opening than traditional exercises [36]. Patil et al. (2016) observed a 2.9 mm increase in mouth opening with a mouth-exercising device compared to standard methods [37]. Dasukil et al. (2022) reported significant gains in mouth opening with a buccal pad of fat interventions, while Pandey et al. (2001) demonstrated that cold knife surgical excision achieved a 74.8% disease-free status at three years [38, 39]. These results suggest that surgical and mechanical devices offer strong options for patients requiring significant interventions.

Screening and Diagnostic Techniques

Screening methods, while not directly therapeutic, play a vital role in early detection and intervention. Su et al. (2010) found that Toluidine Blue screening improved the detection of oral potentially malignant lesions (OPMLs) by 5%, and Sankaranarayanan et al. (2000) showed that visual inspection by trained health workers led to early cancer detection, with a significant reduction in case fatality [40, 41]. These findings highlight the importance of screening in improving survival rates and reducing progression risks.

Corticosteroids and Anti-inflammatory Agents

Corticosteroids and anti-inflammatory agents have been widely studied for their benefits in oral mucosal conditions. Jiang et al. (2013) showed that allicin increased mouth opening by 2.89 mm over triamcinolone acetonide [42]. TP et al. (2019) reported an improvement of 6.5 mm in mouth opening using lycopene combined with dexamethasone and hyaluronidase [34]. Wu et al. (2010) found

that *Salvia miltiorrhiza* with prednisolone effectively reduced lesion area and improved mouth opening, with lesion area decreasing from 10.37 cm^2 to 5.90 cm^2[43]. Shandilya et al. (2021) further observed pain reduction and ease in physiotherapy following BTX-A administration [23]. Thakur et al. (2015) reported that placental extract improved postoperative mouth opening by 7.4 mm over controls [44]. Rajendran et al. (2006) found that pentoxifylline improved mouth opening and symptom scores, confirming the value of anti-inflammatory agents in symptom relief and functional gains [45].

Other Interventions

Other interventions also provide meaningful therapeutic outcomes. Nihadha et al. (2022) reported that transdermal fentanyl patches reduced pain by 3.5 points and improved compliance, indicating its role in pain management [46]. Rai et al. (2019) showed that systemic and topical curcumin improved mouth opening, with Group III achieving an additional 1.7 mm increase over Group II [47]. Tai et al. (2001) observed that immune milk combined with oral habit interventions significantly improved inter-incisor distance and symptom relief, and Gupta et al. (2018) found that laser fibrotomy combined with corticosteroids reduced VAS pain scores and increased mouth opening by 7.7 mm [48, 49]. These findings underscore the therapeutic potential of alternative and complementary therapies in managing oral mucosal conditions.

Limitations and Future Directions

Despite the promising results, limitations such as small sample sizes, variability in study methodologies, and insufficient long-term follow-up data were identified. The heterogeneity of treatment approaches complicates the ability to draw definitive conclusions regarding the most effective interventions. Future research should focus on conducting large-scale, multicentric trials with standardized methodologies to validate the efficacy of various treatment options for OSMF and establish evidence-based guidelines.

Conclusion

This systematic review affirms the efficacy of a variety of treatment options for oral mucosal and maxillofacial conditions. Local injections and corticosteroids are highly effective in managing pain and improving mouth opening, especially when combined with agents like *Salvia miltiorrhiza*, omega-3, or lycopene. Physiotherapy and herbal remedies provide substantial non-invasive benefits, improving symptoms and function. Surgical and device-based approaches offer significant alternatives for severe or unresponsive cases. Screening remains crucial in detecting lesions early, improving survival rates and mitigating disease progression. The effectiveness of anti-inflammatory agents and other innovative therapies like transdermal fentanyl patches, immune milk, and laser fibrotomy adds further diversity to available treatment modalities, highlighting the potential of personalized therapy in enhancing patient outcomes.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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