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# Efficacy and safety of different interpositional flaps and grafts for closing fibrotomy wound in patients of oral submucosal fibrosis: A systematic review with meta-analysis

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**General Note**

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## ABSTRACT

*Background:* Oral Submucous Fibrosis (OSMF) is a chronic pre-malignant condition characterized by progressive fibrosis of oral cavity. *Objective:* The objective of this systematic review and meta-analysis is to assess the efficacy and safety of different interpositional flaps and grafts for closing fibrotomy wound in patients of OSMF. *Methods:* We followed the methodology in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. *Results:* We identified 195 reports and included seven studies in quantitative synthesis. Existing evidence indicates that after one month; mouth opening was better with Buccal Fad Pad (BFP) as compared to tongue flap (MD1.24, 95%CI -0.36 to 2.84mm), split skin graft (MD0.52, 95%CI -1.12 to 2.16mm) and collagen sheet (MD0.63, 95%CI -2.87 to 4.13mm). However; after two years mouth opening was better with split skin graft (MD-0.68, 95%CI -2.41 to 1.05mm) as well as nasolabial flap (MD -1.08, 95%CI -2.73 to 0.57mm). Application of placental extract provides additional benefit to BFP in mouth opening. Risk of hair growth and extra-oral scars seems to be lesser with BFP. We did not find any data on relapse, malignant transformations, quality of life and costs estimates.

**Keywords**: Oral submucosal fibrosis, precancerous conditions, Surgical Procedures, fibrotomy, surgical flaps, systematic review, meta-analysis

## 1. BACKGROUND

Oral Submucous Fibrosis (OSMF) is a chronic premalignant condition characterized by progressive submucosal fibrosis of the oral cavity, oropharynx and rarely the upper third of esophageal mucosa (Hande A et al., 2019). People affected by this disease mostly live in South Asia, South Africa, and Middle-East regions but, as a consequence of migration of these populations, an increasing number of OSMF cases are being seen in other countries like United States, Europe, Canada, Germany and other countries may present with OSMF (VanWyk, 1997; Reichart and Philipsen, 2006; Auluck et al., 2008; Ali et al., 2014; Wollina et al., 2015; Tilakaratne et al., 2016). World Health Organization estimates that more than five million people are suffering from OSMF globally (Shih et al., 2019). Also Oral submucous fibrosis has a high potential for transformation in oral squamous cell carcinoma. (Gadbail A.R, 2017)

The aetiology of OSMF is considered to be multifactorial including habit of betel quid chewing, excessive consumption of chillies and spices in diet, poor nutrition, autoimmunity, human papilloma virus (HPV) infection, genetic mutations and deficiency of vitamins and iron (Arakeri et al., 2017; Bari et al., 2017; Shih et al., 2019, Hande A et al,2018). Epidemiological studies have shown that betel quid chewing is one of the most significant risk factors for OSMF (Tilakaratne et al., 2016). Certain studies also reported that habits such as chewing and smoking tobacco and drinking alcohol increase the risk of OSMF (Aishwarya et al., 2017; Arakeri et al., 2017).

Diagnosis of OSMF is based on clinical symptoms and confirmation by histopathology. Clinical findings depend on the severity and staging of the disease. Stomatitis and mucosal ulcers tend to occur at an early stage, which later develop into fibrous bands in soft tissues of oral cavity, blanched gums and mucosa, rubbery deformed soft palate, and leathery floor of the mouth. The characteristic feature of the disease is fibrosis of submucosal oral soft tissues, that begins over the palate and then progressively involves buccal mucosa, labial mucosa, floor of mouth, tongue, palate glossal arches and the oropharynx (Mahomed, 2012; Sharma et al., 2017). The condition can cause problems in oral hygiene, and impairment of speech, mastication, and swallowing (Ali et al., 2014; Haider et al., 2000). Fibrosis of soft tissues of oral cavity may sometimes block the eustachian tubes and thereby may impair



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hearing (Haider et al., 2000). Fibrous bands in lip leads to its thickening and causes difficult in retracting or everting the lips, which gives an elliptical shape to mouth (Wollina et al., 2015). Hypovascularity due to fibrosis of tongue and mouth causes depapillation and lightening of mucosa (Haider et al., 2000; Wollina et al., 2015). OSMF also presents with dysplastic features in the atrophic epithelium and can lead to malignant transformation. (Gadbail A.R, 2018, Sarode S.C, 2018, Tekade S.A, 2017, Alka H.H, 2017). In advanced cases, disuse of jaw resulting from restricted mandibular movements may alter the morphologic features of the jaw bones (Panchbhai, 2019). Considering OSMF as an over healing wound, a more grave complication of OSMF is the high risk of malignant transformation (7-30%) to oral squamous cell carcinoma (OSCC), thereby presenting a global burden for public health (Arora et al., 2014; Bari et al., 2017; Peng et al., 2019). OSMF is deceptive in origin and not reversible at any stage of the disease (VanWyk, 1997). It may remain either stationary or may progress, leaving the patient challenged physically as well as psychologically (Bari et al., 2017). Due to colossal efforts dedicated to OSMF, there have been sizeable developments of medicinal and surgical approaches targeting the same. Prime medicinal therapy include anti-fibrotic drugs, anti-inflammatory drugs, anti-oxidants, immune modulators, and drugs to enhance the blood flow (Warnakulasuriya and Kerr, 2016; Wollina et al., 2015). In most cases, combined drug treatment is prescribed (Wollina et al., 2015).

Surgery may be required in advanced cases of OSMF where there is restriction of mouth opening (Wollina et al., 2015) which includes excision of the oral fibrotic bands (by scalpel or laser) followed by interpositional flaps or grafts to retain the mouth opening (Kamath, 2015). Masticatory muscle myotomies or coronoidectomy with split-thickness skin-grafting techniques have been tried in more advanced cases (Kamath, 2015). Use of interpositional flaps and grafts (like buccal fat pad, nasolabial flap, temporalis fascia flap, platysma flaps, tongue flaps, split skin graft, collagen membranes, artificial dermis, human placenta and amnion) in areas of band excision have been adopted as part of surgical intervention for OSMF and have been used with varying success rates (Kamath, 2015). Over the decade surgery has been the mainstay treatment of OSMF. However; there is no definite protocol for adoption of a particular therapeutic intervention for OSMF (Kamath, 2015). The oral health-related quality of life has also been assessed for Oral Submucous fibrosis patient using OHRQoL-OSF instrument (Gondivkar S.M, 2019, Gondivkar S.M, 2019, Gondivkar S.M, 2019, Gondivkar S.M, 2018, Gondivka, S.M, 2018, Gondivkar S.M, 2018). There is a need for critical evaluation of the available literature and to generate sufficient evidence regarding different surgical interventions for this condition so as to ascertain the best treatment option. Hence, we undertook this systematic review and meta-analysis to assess the efficacy and safety of different interpositional flaps and grafts used for closing fibrotomy wound in patients of OSMF. It will help not only to assess the effectiveness of current and newly evolving therapies but can also be utilized for making recommendations for future research.

## 2. METHODS

This systematic review and meta-analysis has been conducted in accordance with the methodology in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The protocol of this systematic review is registered with PROSPERO (Registration No: CRD42017057386) (Borle et al., 2017).

**Eligibility criteria for considering studies**

We included observational and randomized controlled trials (RCTs) that examined the efficacy of different surgical interventions in adult patients of OSMF irrespective of gender, ethnicity, stage of OSMF, primary cause of OSMF, type of OSMF and presence of other co-morbidities. We included studies that used any type of interpositional flaps and grafts for closing fibrotomy wound either singly or in combination with other additional therapies. We permitted the inclusion of studies that used concomitant interventions as long as they were provided in both the intervention and the control group. We did not restrict study eligibility by language or publication status.

**We undertook following comparisons for our review:**

1. One surgical intervention versus the other surgical intervention
   - Buccal Fat Pad versus Non-Buccal Fat Pad
   - Nasolabial Fold versus Non-Nasolabial Fold
   - Buccal Fat Pad versus Nasolabial Fold
2. One surgical intervention with additional intervention versus the same surgical intervention without the additional intervention (like aloe vera or placental extracts, physiotherapy)



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**We considered following outcomes in this review:**

**Primary outcomes:**

1. Mouth opening measured as the inter-incisal distance in mm
2. Relapse
3. Malignant transformations to oral carcinoma

**Secondary outcomes:**

1. Adverse events / complications (like post-operative pain, post-operative swelling, extra-oral scars, hair growth, commissural distortion; etc.) as a result of intervention
2. Quality of Life (QoL): As assessed by any validated questionnaire
3. Costs: Costs of medicines, hospital stay and any costs for surgical intervention

Reporting of any of these outcome measures did not form part of criteria for including studies in this review.

**Search methods for identification of studies**

We identified studies through systematic searches of the following bibliographic databases in July 2017 and further updated the search in February 2019:

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library (Issue 1 of 12, January 2019)
- The Cochrane Oral Health Group's Trial Register (to February 2019)
- MEDLINE (R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) (Ovid, 1946 to February 2019)

We used text word terms and Medical Subject Headings (MeSH) and tailored the search to individual databases. We used synonyms and keywords to sensitize the search and adapted the preliminary search strategy for PubMed for use in the other databases. The search strategy is provided in the Supplementary Material (File 1). We searched all databases from their inception to the present. We did not levy any restriction on language and status of publication. We conducted a search of clinical trials registers via ClinicalTrials.gov (www.ClinicalTrials.gov) and the WHO International Clinical Trials Registry Platform (ICTRP) Search Portal (http://apps.who.int/trialsearch/). We searched the Indian medical literature via the Indian Council of Medical Research (http://www.icmr.nic.in/) from 1913 to February 2019. We carried out hand-searches for journals as well as abstract publications of conferences in the field of oral and maxillofacial surgery. We checked the reference lists of all primary studies and review articles for additional references and contacted experts in this field to procure the data of any ongoing and/or unpublished studies on surgical interventions for OSMF.

**Screening of studies for inclusion**

Two authors (PN, PH) independently screened titles and abstracts of all the potential studies identified as a result of the electronic and manual searches. We used the Rayyan online screening tool for screening the studies (Ouzzani et al., 2016). We resolved disagreements (on inclusion of studies) amongst the primary reviewers by consulting a third author (RB). Two review authors (PN, PH) then independently screened the full-texts of potentially relevant studies sorted in primary screening, categorized the studies for inclusion, and recorded the reasons for exclusion of ineligible studies. Third reviewer (RB) resolved disagreement through consultation. We recorded the selection process in detail and presented the same in PRISMA flow diagram.

**Data extraction and management**

Two review authors (PN, PH) abstracted the data from studies that met the inclusion criteria using a piloted data extraction form and presented the details in Characteristics of Studies Table. We contacted the authors for seeking additional information if required.

We extracted the following study details from the included studies:

1. Methodological/trial design: Study design; duration of study
2. Participants: Number of participants allocated to each treatment group; mean age/age range; gender distribution; severity of disease, inclusion and exclusion criteria.
3. Interventions: Total number of intervention groups with number of participants in each group; type of intervention
4. Outcomes: Primary and secondary outcomes assessed in the study



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**Assessment of risk of bias in included studies**

Two review authors (MNK, PN) independently assessed the risk of bias (RoB) for each study using the 'Cochrane risk of bias tool' criteria charted in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011) and resolved discrepancies by consultation with third reviewer (RB). We judged the risk of bias according to the following domains: Random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other bias. We did not assess blinding of participants and personnel, as it is not possible to blind the participants because of the type of intervention. Also we feel that our outcomes are not likely to be influenced by lack of blinding. We graded each potential source of bias as 'high', 'low' or 'unclear' and summarized the risk of bias judgments across different studies for each of the domains listed. 'High' risk of bias meant that plausible bias have weakened our confidence in the results seriously, 'moderate' risk of bias meant that plausible bias has raised some doubts about the results, and 'Low' risk of bias meant that plausible bias is unlikely to alter the results seriously.

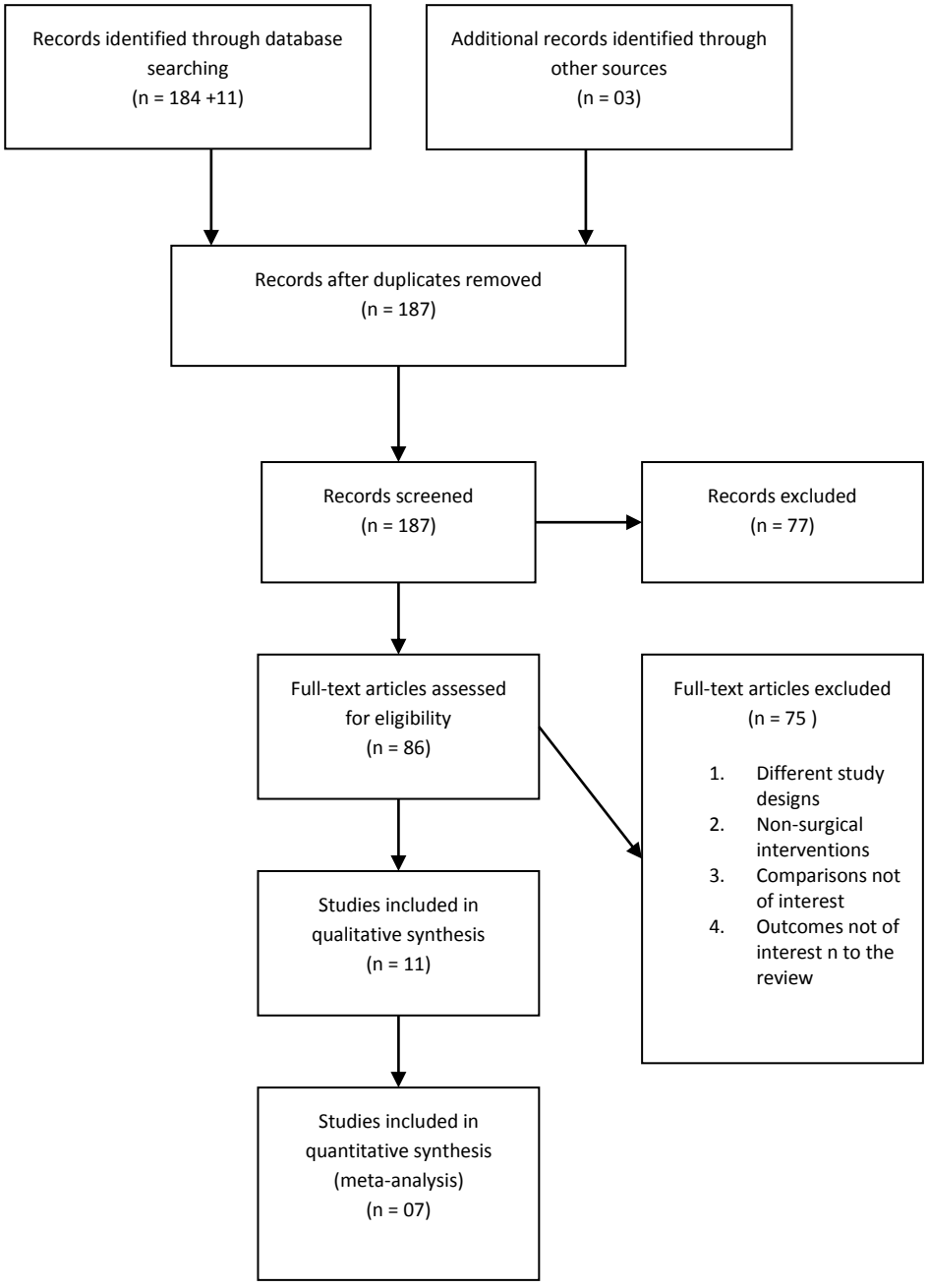


**Figure 1** PRISMA Flow Diagram for identification of studies



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### Dealing with missing data

We contacted investigators in order to obtain missing data where possible.

### Assessment of heterogeneity

We analyzed statistical heterogeneity through $Chi^2$ test (P value < 0.10) and used $I^2$ statistic to quantify heterogeneity amongst the studies in each analysis. We regarded heterogeneity as considerable if $I^2$ was more than 75%, substantial if it was between 50% to 90%, moderate if it was between 30% to 60% and mild if less than 40% (Higgins and Green, 2011).

### Data synthesis

We undertook a meta-analysis only if participants, interventions, comparisons and outcomes were found to be similar. We used RevMan 2014 for undertaking meta-analysis (RevMan, 2014). If studies seemed considerably heterogeneous; we reviewed the data narratively and did not pool the results. If heterogeneity was found to be moderate or substantial, then we applied the random-effects model in meta-analysis. In the presence of mild or no heterogeneity, we applied a fixed-effect model. For continuous variables, we calculated differences in means and 95% CI. When the outcome measurements across the studies were done with same scale; we used mean difference (MD) as a summary statistics in meta-analysis. However; when the studies evaluated the same outcome but measured it in different ways; we had planned to standardize the results by using the standardized mean difference (SMD)(Higgins and Green, 2011). For dichotomous variables, we calculated treatment effects as risk ratios (RR) with 95% confidence interval (CI). In presence of considerable or substantial heterogeneity; we undertook subgroup analysis for duration of treatment.

### Assessment of reporting biases

In presence of more than ten studies assessing an outcome; we had planned to create and examine a funnel plot to explore possible small study biases.

## 3. RESULTS

### Results of the search

We identified 195 reports from electronic sources and three additional records from which we screened 187 abstracts for eligibility after removing duplicates and irrelevant reports. We obtained and screened 86 potentially relevant full text articles for eligibility. We excluded 75 articles that did not meet the eligibility criteria and finally included seven studies in the quantitative synthesis (Fig 1) (Alam et al., 2013; Bande et al., 2013; Lai et al., 1995; Mehrotra et al., 2009; Pradhan et al., 2012; Rai et al., 2014; Thakur et al., 2015).

### Description of studies

We have described seven included studies in detail in Characteristics of included studies table (Table 1).

**Table1** Characteristics of included studies

| Study | Methods | Participants | | | | | Intervention | Outcomes Reported |
|---|---|---|---|---|---|---|---|---|
| | Study design<br>Duration<br>Total participants | Mean age+ SD/ Age range | Gender (Male/ Female) | Severity | Inclusion criteria | Exclusion criteria | | |
| Thakur et al., (Thakur et al., 2015)<br><br>(MP, India) | Design: RCT<br><br>Duration: 1 month<br><br>Total participants: 10 | G1: 28.8±1.92Y<br><br>G2: 30.6±3.21Y | | IID <20mm | 1.ASA Class I patients<br><br>2.IID <20 mm<br><br>3.Age >18 years<br><br>4.No prior surgical or medical T/t for OSMF | NR | G1: B/L Fibrotomy + Choronoidectomy + BFP grafting followed by TPE (n=5)<br><br>G2: B/L Fibrotomy + choronoidectomy + | 1. Mouth opening |



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| | | | | | | | BFP grafting without TPE (n=5) | |
| Rai et al., (Rai et al., 2014)<br><br>(MS, India) | Design: Prospective comparative study<br><br>Duration: 12 months<br><br>Total participants: 20 | 18 to 49Y | 17/03 | IID <20mm | 1.IID <20 mm<br><br>2.Patients with burning sensation to spices<br><br>3.Habit of betel nut or tobacco chewing<br><br>4.Histologically proven OSMF | IID >20 mm | G1: B/L Fibrotomy + Choronoidectomy + extraction of 3rd molar + grafting with extended NLF followed by PhT (n=10)<br><br>G2: B/L fibrotomy + choronoidectomy+ extraction of 3rd molar + grafting with BFP followed by PhT (n=10) | 1. Mouth opening<br>2. Complications (Extra-oral scars, hair growth, partial flap necrosis scars, soft palate perforation) |
| Bande et al., (Bande et al., 2013)<br><br>(MS, India) | Design: RCT<br><br>Duration: 36 months<br><br>Total participants: 20 | 18Y to 41Y | 18/02 | IID <25mm | IID <25 mm | IID >25 mm | G1: B/L fibrotomy + choronoidectomy + extraction of 3rd molar + grafting with extended NLF followed by PhT (n=10)<br><br>G2: B/L fibrotomy + choronoidectomy + extraction of 3rd molar + grafting with platysma myocutaneuos muscle flap followed by PhT (n=10) | 1. Mouth opening<br>2. Complications (Extra-oral scars, subluxation, distortion of commissure, partial necrosis of flap, fish mouth, soft palate perforation) |
| Pradhan et al., (Pradhan et al., 2012)<br><br>(UP, India) | Design: RCT<br><br>Duration: 42 days<br><br>Total participants: 30 | G1: 33.27±14.57Y<br><br>G2: 39.40±14.86Y | G1: 13/2<br>G2: 12/3 | | Clinically diagnosed OSMF | Chronic and debilitating diseases | G1: B/L fibrotomy defect grafted with dry collagen sheet (n=15)<br><br>G2: B/L fibrotomy defect grafted with BFP (n=15) | 1. Mouth opening<br>2. Restoration of normal color of mucosa<br>3. Post-op pain<br>4. Post-op swelling |
| Mehrotra et al., (Mehrotra et al., 2009)<br><br>(UP, India) | Design: RCT<br><br>Duration: 24 months<br><br>Total participants: 100 | G1: 33.96±9.78Y<br><br>G2: 36.12±10.59Y<br><br>G3: 37.80±11.00Y<br><br>G4: 35.72±9.96Y | G1: 21/4<br>G2: 16/9<br>G3: 16/9<br>G4: 16/9 | | 1.IID <20 mm<br><br>2.Gr III and Gr IV OSMF | Gr I and Gr II OSMF | G1: B/L fibrotomy defect grafted with BFP (n=25)<br><br>G2: B/L fibrotomy defect grafted with anteriorly based tongue flap (n=25)<br><br>G3: B/L fibrotomy defect grafted with inferiorly based NLF (n=25) | 1. Mouth opening<br>2. Esthetics<br>3. Function<br>4. Relapse<br>5. Complications (Hair grow, Difficulty in speech, Post-op pain) |



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| | | | | | | | G4: B/L fibrotomy defect grafted with SSG (n=25) | |
| Lai et al., (Lai et al., 1995)<br><br>(Taiwan) | Design:<br><br>Duration: 24 months<br><br>Total participants: 150 | Mean age: 12.5Y | All males | | Biopsy-proven OSMF with IID <20mm | 1.Patients with TMJ problems<br><br>2.Pericoronitis with lower 3rd molar | G1: B/L fibrotomy defect grafted with SSG (n=50)<br><br>G2: B/L fibrotomy defect grafted with fresh anmion (n=50)<br><br>G3: B/L fibrotomy defect grafted with BFP (n=50) | 1. Mouth opening<br>2. Complications |
| Alam et al., (Alam et al., 2013)<br><br>(UP, India) | Design: RCT<br><br>Duration: 6 months<br><br>Total participants: 30 | G1: 21Y to 40Y | | | 1. Gr III and IV OSMF<br>2. Biopsy proven cases | 1. Gr I and II OSMF | G1: B/L Fibrotomy + choronoidectomy + extraction of 3rd molar + BFP grafting/NLF/ collagen membrane followed by topical application of aloe vera gel (n=15)<br><br>2: B/L Fibrotomy + choronoidectomy + extraction of 3rd molar + BFP grafting/NLF/collagen membrane without topical application of aloe vera gel (n=15) | 1. Mouth opening<br>2. Complication (Burning sensation) |

MP: Madhya Pradesh; MS: Maharashtra State; UP: Uttar Pradesh; OSMF: Oral Submucous fibrosis; IID: Inter--incisal distance; TPE: Topical Placental Extract; NLP: Nasolabial Flap; PhT: Physiotherapy; BFP: Buccal Fat Pad; SSG: Split Skin Graft

Five trials were parallel RCTs and two were observational studies. None of the included studies reported the funding status. Except for one study which was conducted in Taiwan; all other studies were conducted in India. Age of the participants in the studies ranged between 18 to 49 years. Total number of participants included in this analysis was 360 of which 315 were males and 45 were females. All the patients included in these studies had inter-incisal opening less than 25 mm.

All the included trials provided fibrotomy in the treatment arms. Four trials conducted fibrotomy with choronoidectomy (Alam et al., 2013; Bande et al., 2013; Rai et al., 2014; Thakur et al., 2015). One study (Thakur et al., 2015) assessed the effect of topical placental extract (TPE) on BFP graft after bilateral fibrotomy with choronoidectomy. One study (Rai et al., 2014) assessed the difference between grafting with extended NLF verses grafting with BFP; while another study (Bande et al., 2013) assessed the difference between with extended NLF verses grafting with platysma myocutaneuos muscle flap after bilateral fibrotomy with choronoidectomy and extraction of 3rd molar followed by physiotherapy. One study (Alam et al., 2013) compared the efficacy of topical application of aloe vera gel on BFP grafting/NLF/ collagen membrane after bilateral fibrotomy with choronoidectomy and extraction of 3rd molar. Three studies compared BFP graft verses dry collagen sheet (Pradhan et al., 2012), bilateral anteriorly based tongue flap or inferiorly based NLF or SSG (Mehrotra et al., 2009), or SSG or fresh amnion (Lai et al., 1995). The duration of the included studies ranged between 42 days to three years.

Primary outcome of mouth opening was compared in all the included studies. Each of two studies assessed relapse (Lai et al., 1995; Mehrotra et al., 2009), extra-oral scars (Bande et al., 2013; Rai et al., 2014), and hair growth (Mehrotra et al., 2009; Rai et al.,



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2014). None of the included studies reported data on malignant transformations, Quality of Life (QoL), and other adverse events or complications like post-operative pain, post-operative swelling, or commissural distortion. Also we did not find any studies that reported the costs of the surgical interventions.

**Risk of bias in included studies**

Most studies were at unclear risk of bias in the five domains we assessed (Figs 2 and 3). Lai et al., (Lai et al., 1995) and Rai et al., (Rai et al., 2014) were at unclear risk of selection bias as they provided no information on randomization or baseline characteristics of the participants in different groups. Bande et al., (Bande et al., 2013), Alam et al., (Alam et al., 2013), Mehrotra et al., (Mehrotra et al., 2009), Thakur et al., (Thakur et al., 2015) and Pradhan et al., (Pradhan et al., 2012) reported that the participants were randomly assigned and hence were at low risk of selection bias. None of the included studies provided any data on blinding of the outcome assessor and none of the studies reported loss to follow-up. Hence all the studies were at unclear risk for detection bias and low risk for attrition bias. Except for Lai et al., (Lai et al., 1995), which presented the data in range and not the exact mean with standard deviation, all the studies were at unclear risk of reporting bias.

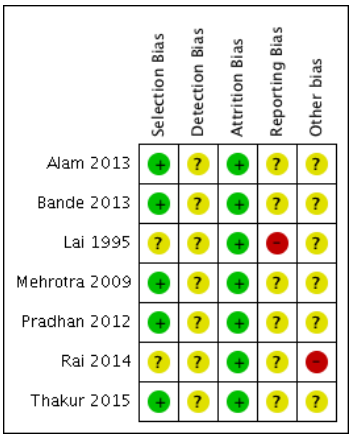


**Figure 2** Risk of bias summary: review authors' judgements about each risk of bias item for each included study

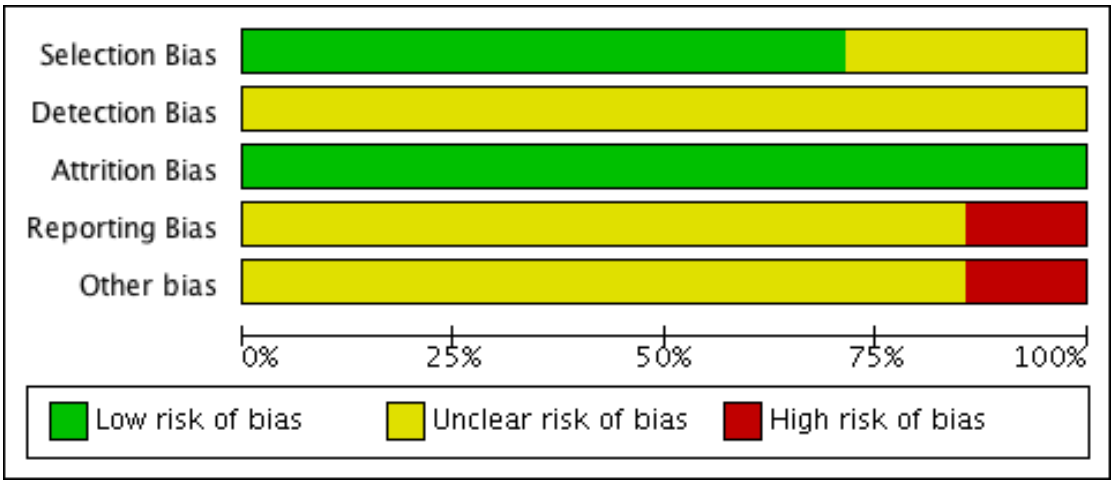


**Figure 3** Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies

**Effects of interventions**

There was a limited scope for meta-analysis because of the range of different interventions and outcomes measured across the small number of existing studies. We did not find any data on relapse, malignant transformations, QoL and costs estimates of different surgical interventions for treating OSMF.



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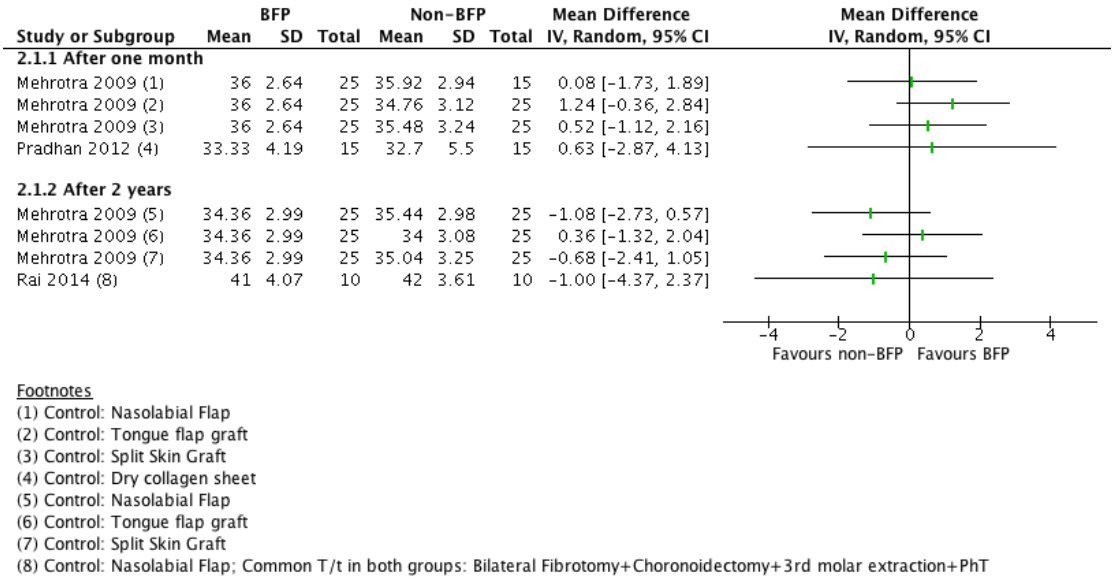
**Comparison 1: One surgical intervention versus the other surgical intervention**

***a. BFP versus Non-BFP***

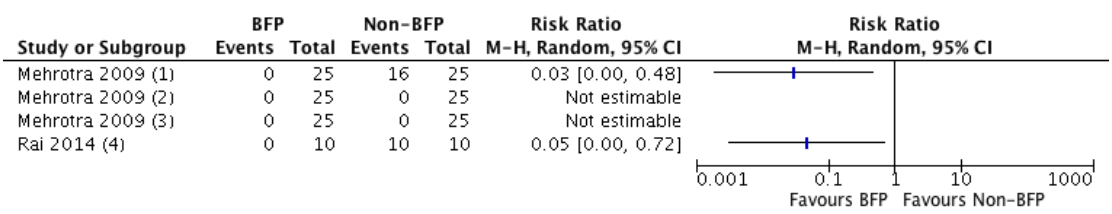
*a1: Mouth opening*: Three studies compared between BFP and non-BFP (Mehrotra et al., 2009; Pradhan et al., 2012; Rai et al., 2014). Mehrotra et al., (Mehrotra et al., 2009) compared the effects after one month, six months, one year, and after two years, Pradhan et al., (Pradhan et al., 2012) assessed the effects after one month and Rai et al., (Rai et al., 2014) after two years. Hence we carried out the subgroup analysis on the basis of time of outcome assessment as after one month and after one year (Fig 4). Mehrotra et al., (Mehrotra et al., 2009) had four comparison groups viz. fibrotomy defect grafted with BFP, NLF, tongue flap, or SSG. Pradhan et al., (Pradhan et al., 2012) compared fibrotomy defect grafted with BFP verses fibrotomy defect grafted with dry collagen sheet; while Rai et al., (Rai et al., 2014) compared fibrotomy defect grafted with BFP verses fibrotomy defect grafted with NLF. As we were comparing all the three non-BFP groups of Mehrotra et al., in one analysis; we did not do the subtotals and totals. Instead; we depicted the results in the forest plots with only Mean Difference and Confidence Interval of each study. After one month; mouth opening was better with Buccal Fat Pad as compared to tongue flap (MD 1.24, 95% CI -0.36 to 2.84mm; Fig 4), Split Skin Graft (MD 0.52, 95% CI -1.12 to 2.16 mm; Fig 4), and dry collagen sheet (MD 0.63, 95% CI -2.87to 4.13 mm; Fig 4). However; mouth opening after two years was better though insignificant with NLF (MD -1.08, 95% CI -2.73 to 0.57 mm; Fig 4), Split Skin Graft (MD-0.68, 95%CI -2.41 to 1.05 mm; Fig 4) as compared to Buccal Fat Pad.




Footnotes
(1) Control: Nasolabial Flap
(2) Control: Tongue flap graft
(3) Control: Split Skin Graft
(4) Control: Dry collagen sheet
(5) Control: Nasolabial Flap
(6) Control: Tongue flap graft
(7) Control: Split Skin Graft
(8) Control: Nasolabial Flap; Common T/t in both groups: Bilateral Fibrotomy+Choronoidectomy+3rd molar extraction+PhT

**Figure 4** Forest plot of comparison: One surgical intervention versus the other surgical intervention (BFP versus Non-BFP) for Mouth opening

*a2. Adverse effects (Hair Growth):* Two studies that assessed the effect of BFP verses Non-BFP on hair growth (Mehrotra et al., 2009; Rai et al., 2014). The studies depict that NLF has lesser risk of hair growth as compared to BFP (Fig 5).




Footnotes
(1) Control: Nasolabial Flap
(2) Control: Tongue Flap
(3) Control: Split Skin Graft
(4) Control: Nasolabial Flap; Common T/t in both groups: Bilateral Fibrotomy+Choronoidectomy+3rd molar extraction+PhT

**Figure 5** Forest plot of comparison: One surgical intervention versus the other surgical intervention (BFP versus Non-BFP) for adverse effects (Hair growth)



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*a3: Other adverse events:* One study reported that the outcome score at one month after surgery for pain, esthetics, and function was highest with BFP and lowest with tongue flap, and that there was difficulty in tongue movement, causing discomfort to the patients in the tongue flap group (Mehrotra et al., 2009).

***b. NLF versus Non-NLF***

*b1: Adverse effects (Extra-oral scars):* Two studies (Bande et al., 2013; Rai et al., 2014) assessed the risk of extra-oral scars after fibrotomy defect closed with NLF graft verses fibrotomy defect closed with non-NLF graft. Non-NLF grafts like Buccal Fat Pad and Platysma Muscle Flap were found to have significantly lesser risk of extra-oral scars as compared to NLF graft (RR 21.00, 95% CI 3.09 to 142.82; 40 participants; two studies; $I^2$=0%; Fig 6). Almost all the patients treated with NLF had extra-oral scars while none of the patients treated with BFP or platysma flap had extra-oral scars. In both the studies choronoidectomy with extraction of 3rd molars and physiotherapy was administered to intervention as well as control arm.

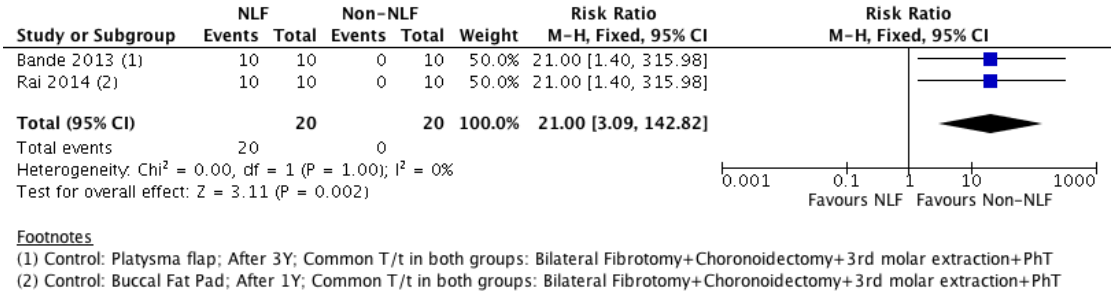


**Figure 6** Forest plot of comparison: One surgical intervention versus the other surgical intervention (NLF versus Non-NLF) for adverse effects (Extra-oral scars)

*b2: Other complications:* More number of complications were noted in participants with NLF like intraoral hair growth, partial flap necrosis, broadening of the oral commissure, subluxation of temporo-mandibular joint, "fish mouth" deformity, and palatal perforation than non-NLF (Bande et al., 2013; Rai et al., 2014). Complications were also noted in few participants with the platysma muscle flap like transient paraesthesia over lateral side of neck, and subluxation of mandible (Bande et al., 2013). There were no delayed complications in participants with the platysma muscle flap (Bande et al., 2013).

***c. BFP versus NLF***

*c1: Mouth opening:* Two studies (Mehrotra et al., 2009; Rai et al., 2014) compared mouth opening after fibrotomy defect closed with NLF graft and fibrotomy defect closed with non-NLF graft. The pooled meta-analysis shows that the mouth opening was better after NLF as compared to BFP (MD -1.06, 95% CI -2.55 to 0.42 mm; 70 participants; two studies; $I^2$=0%; Fig 7)

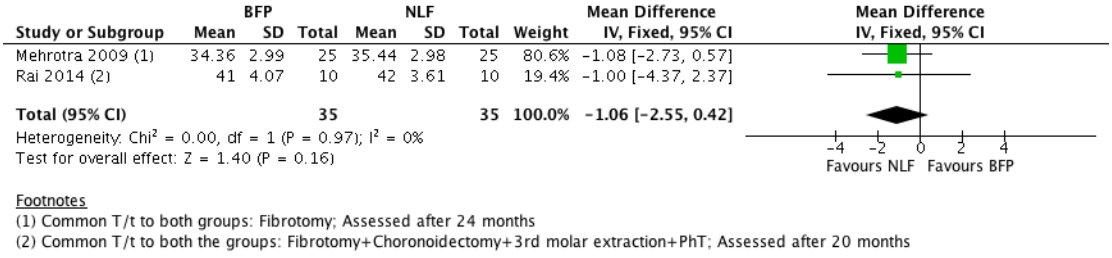


**Figure 7** Forest plot of comparison: One surgical intervention versus the other surgical intervention (BFP versus NLF) for mouth opening

*c2: Hair Growth:* Two studies (Mehrotra et al., 2009; Rai et al., 2014) assessed the risk of extra-oral scars after fibrotomy defect closed with Buccal Fat Pad graft and fibrotomy defect closed with Nasolabial Flap. The risk of hair growth was significantly lesser (96%) with Buccal Fat Pad as compared to Nasolabial Flap (RR 0.04, 95% CI 0.01 to 0.26; 70 participants; two studies; $I^2$ = 0%; Fig 8)



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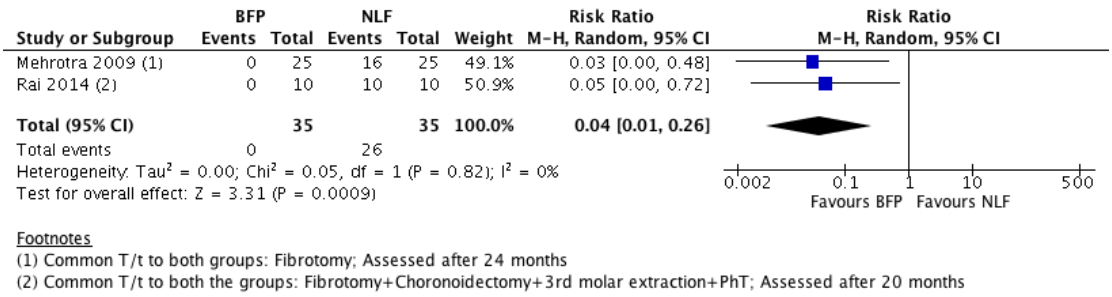


**Figure 8** Forest plot of comparison: One surgical intervention versus the other surgical intervention (BFP versus NLF) for adverse effect (Hair Growth)

*c3: Other complications:* Most common immediate complications in participants with Nasolabial Flap and Buccal Fat Pad was subluxation of temporo-mandibular joint, palatal perforation and partial necrosis of flap; whereas delayed complication was Fish mouth (Rai et al., 2014).

**Comparison 2: One surgical intervention with additional intervention versus the same surgical intervention without the additional intervention**

***a. Grafting with adjunct T/t v/s grafting without adjunct T/t***

*a1. Mouth opening:* After one months; aloe vera gel as an adjunct treatment to BFP/NLF/collagen membrane (Alam et al., 2013) did not seem to provide any additional improvement in mouth opening (SMD 0.05 95% CI-0.66 to 0.77 mm; Fig 9). However; placental extract as a topical gel on postoperative fibrotomy wound closed with BFP (Thakur et al., 2015) showed significant beneficial effects (SMD 3.02, 95% CI 0.91 to 5.12 mm; Fig 9) as compared to those without placental extract.

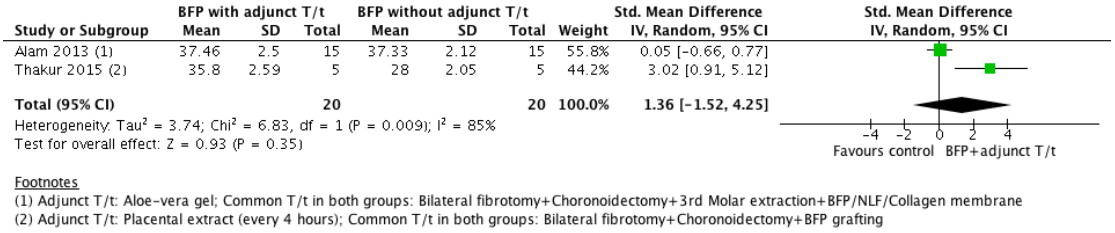


**Figure 9** Forest plot of comparison: One surgical intervention with additional intervention versus the same surgical intervention without the additional intervention (Grafting with adjunct T/t v/s grafting without adjunct T/t) for mouth opening after I month

*a2: Other complications:* No major differences were observed in postoperative discomfort between BFP with placental extract or without placental extract (Thakur et al., 2015). However; wound healing and formation of granulation tissue was more rapid with application of placental extract (Thakur et al., 2015).

## 4. DISCUSSION

A total of seven studies included in quantitative synthesis in this review provide information on mouth opening and adverse events like hair growth and extra-oral scars after closing fibrotomy wound with interpositional flaps and grafts in patients of OSMF. Overall the existing evidence indicates that mouth opening is better with BFP after one month and better with non-BFP (like NLF or Split Skin Graft) after two years (Figs 4 and 7). Application of placental extract provides additional benefit to BFP in improving mouth opening (Fig 9). The risk of hair growth and extra-oral scars seems to be higher with NLF as compared to other grafts (Fig 5, Fig 6, and Fig 8). We did not find any data on relapse, malignant transformations, QoL and costs estimates of the surgical interventions for treating OSMF. However; providing any judgment needs assessment in larger numbers of people with OSMF. The included studies recruited patients with stages of submucosal fibrosis, which should increase the applicability of the results.

We assessed the overall quality of the evidence using the GRADE approach through Summary of Findings table (Table 2) (developed by Evidence Prime, Inc., 2015; Schünemann et al., 2013). The overall methodology of studies in this review was reasonable as assessed by The Cochrane Collaboration's 'Risk of bias' tool. Many studies were assessed as having a low risk or



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unclear risk of bias across a number of domains. This review included pre-post studies as well as randomized trials, meaning that selection bias is a possible concern. Most of the included trials clearly reported the participant flow and none of the included studies had loss to follow-up. Some trials provided inadequate information to make judgements about the RoB; highlighting the need for more careful reporting of research methods. Besides; we were not able to assess the effects of publication bias in funnel plots due to the inadequate number of trials included in the review. As most of the included studies were very small; imprecision is also a risk in this review. The quality of evidence was very low for all the comparisons thereby indicating that we have very little confidence in the effect estimate and that the true effect is likely to be substantially different from the estimate of effect (Table 2). Hence, the results of this review need to be translated with this in mind.

**Table 2** Summary of findings table

| Summary of findings: Nasolabial flaps (NLF) compared to non-nasolabial flaps (Non-NLF) for oral submucosal fibrosis | | | | | | |
|---|---|---|---|---|---|---|
| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) | Comments |
| | Risk with Non-NLF | Risk with NLF | | | | |
| Extra-oral scars (Follow-up period: 1-3 years) | 0 per 1,000 | 0 per 1,000 (0 to 0) | RR 21.00 (3.09 to 142.82) | 40 (2 studies) | ⊕◯◯◯ VERY LOW [a] | a. Serious RoB: Most of the domains are in high RoB<br>b. Serious imprecision: Wide CI (3.09 to 142.82) |
| Summary of findings: Buccal fat pad (BFP) compared to nasolabial flaps (NLF) for oral submucosal fibrosis | | | | | | |
| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) | Comments |
| | Risk with NLF | Risk with BFP | | | | |
| Mouth opening (Follow-up: After 2 years) | The mean mouth opening was 0 | The mean mouth opening in the intervention group was 1.06 lower (2.55 lower to 0.42 higher) | Not applicable | 70 (2 studies) | ⊕◯◯◯ VERY LOW [a,b] | a. Serious RoB: Most of the studies are in unclear or high risk of bias<br>b. Serious Imprecision: The confidence interval of the estimates of the studies as well as the pooled estimates cross the line of no effect and sample size is smaller than the optimal information size. |
| Hair growth (Follow-up: After 1 year) | 743 per 1,000 | 30 per 1,000 (7 to 193) | RR 0.04 (0.01 to 0.26) | 70 (2 studies) | ⊕◯◯◯ VERY LOW [a] | |
| Summary of findings: BFP with adjunct treatment compared to BFP without adjunct treatment for oral submucosal fibrosis | | | | | | |
| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | № of participants (studies) | Quality of the evidence (GRADE) | Comments |
| | Risk with BFP without adjunct treatment | Risk with BFP with adjunct treatment | | | | |



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Summary of findings: Nasolabial flaps (NLF) compared to non-nasolabial flaps (Non-NLF) for oral submucosal fibrosis

| Outcomes | Anticipated absolute effects* (95% CI) | | Relative effect (95% CI) | Nº of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Risk with Non-NLF | Risk with NLF | | | | |
| Mouth opening (Follow-up: After 1 year) | The mean mouth opening was 0 | The mean mouth opening in the intervention group was 3.87 higher (3.64 lower to 11.38 higher) | Not applicable | 40 (2 RCTs) | ⨁◯◯◯ VERY LOW [a,b] | a. Serious heterogeneity: $I^2$=95%<br>b. Serious Imprecision: The pooled estimate crosses the line of no effect and sample size is smaller than the optimal information size. |

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; MD: Mean difference; RR: Risk ratio; RoB: Risk of Bias
GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Detailed search strategies revealed two systematic reviews (SR) (Awan et al., 2014; Kerr et al., 2011) on medical interventions, one SR (Kamath, 2015) on surgical interventions and two SRs (Aziz, 2009; Fedorowicz et al., 2008) on medical as well as surgical interventions for management of OSMF. Kamath et al., (Kamath, 2015) collated literature of the different modalities of surgical management of OSMF, but did not undertook meta-analysis. Though Fedorowicz et al., (Fedorowicz et al., 2008) aimed to include surgical as well as medical interventions for treatment of OSMF, the review found only two studies that evaluated medical interventions and no studies on surgical interventions. Also; none of these SRs undertook meta-analysis. A systematic review on efficacy and safety of different interpositional flaps and grafts for closing fibrotomy wound in patients of OSMF has not been conducted till date to the best of our knowledge. Hence this systematic review and meta-analysis was undertaken.

Seven trials met the inclusion criteria for this review. Available data from small and short-term studies provide some information about the efficacy of different interpositional flaps and grafts for closing fibrotomy wound in patients of OSMF. Evidences in hand suggest that mouth opening is better with BFP as compared to NLF after one month. However, after two years, mouth opening is found to be better with NLF. Extra-oral scars and hair growth is common complication with NLF but not with other surgical interventions. We have very little confidence in the effect estimate, and the true effect may be substantially different from the estimate of the effect. We also do not have enough data to comment on efficacy of different interpositional flaps and grafts for closing fibrotomy wound in patients of OSMF. Hence; recommendations for any surgical treatment has to be considered as preliminary until its safety is proven beyond doubt. Economic evaluations must be highlighted in future research to provide well-informed decisions to warrant its implementation. Hence; the efficacy and safety of different interpositional flaps and grafts for closing fibrotomy wound in patients of OSMF remains unclear. These results should be considered as exploratory and interpreted with caution. Important concerns vented here are concerning limited number of high quality RCTs, small sample size, short term studies, lack of validated instruments for estimation of subjective outcomes and inconsistent reporting which highlights the necessity for consistency in conducting and reporting of clinical trials.

We feel that the possible bias in this review is low. The search was as broad as possible. Selection of the studies, data extraction, and assessment of risk of bias done in pairs to avoid subjectivity in the review process. None of the authors of this review were involved in any of the included or excluded studies, and none of the authors have any commercial or any other conflicts of interest regarding interpositional grafts or flaps.



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## 5. CONCLUSION

We found very low quality of evidence regarding efficacy and safety of different interpositional grafts and flaps for closing fibrotomy wounds in surgically treated patients of OSMF, which calls for further research. There is a necessity of high-quality, long-term and large multi-centric randomized control trials to get a conclusive answer. Presently; there is a dearth of evidence on relapse, malignant transformation, Quality of Life (QoL) and costs. Evaluations of cost should also be undertaken. Participants from diverse regions with different ethnic groups could be studied as part of further extensive research. In future; we advocate larger studies powered to identify small changes, with longer follow-up periods on evaluations of relapse, malignant transformation, QoL and costs, to aid translation of research findings into applicable community health approaches for improving the life of patients with OSMF.

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**Competing Interest**

The authors declare that they have no competing interests

**Ethical approval**

Not required

**Patient consent**

Not required

**Consent for publication**

Not Applicable

**Availability of data and material**

Not Applicable

**Contributions of Authors**

RB envisioned the idea of the review. MNK developing and ran the search strategies. RB, PN, PH and MNK developed the protocol PN and PH screened title and abstract. PN and PH screened full texts. RB resolved disagreement amongst primary reviewers (for screening) through discussion. PN and PH extracted data. MNK, PN assessed the methodological quality of included systematic reviews and RB resolved disagreements amongst the primary reviewers. AG & MNK undertook Meta-analysis. SZQ and AG provided technical advice. SZQ and MNK undertook GRADE assessments. MNK, PN and PH drafted the review with clinical and methodological input from RB, AG and SZQ. All authors interpreted the data, read the manuscript, and approved the final version. The corresponding author attests that all listed authors meet the authorship criteria. All authors will be responsible for updating the review

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**Appendix A: Supplementary Material: Search strategy (PubMed)**

Search ((((((((((("submucous fibrosis"[Title/Abstract]) OR "submucus fibrosis"[Title/Abstract]) OR "oral fibrosis"[Title/Abstract]) OR "oral fibroses"[Title/Abstract]) OR "atrophica idiopathica mucosae oris"[Title/Abstract]) OR "palatal fibrosis"[Title/Abstract]) OR "palatal fibroses"[Title/Abstract]) OR "tongue fibosis"[Title/Abstract]) OR "atrophica idiopathica mucosae oris"[Title/Abstract]) OR "idiopathic scleroderma of mouth"[Title/Abstract]) OR vidari[Title/Abstract]) OR "Oral Submucous Fibrosis"[Mesh])) AND ((((((((((("buccal fat pad"[Title/Abstract]) OR BFP[Title/Abstract]) OR "nasolabial flap*"[Title/Abstract]) OR NLP[Title/Abstract]) OR "split skin graft"[Title/Abstract]) OR SSG[Title/Abstract]) OR "tongue flap*"[Title/Abstract]) OR "temporalis fascia flap*"[Title/Abstract]) OR "platysma flap*"[Title/Abstract]) OR "collagen membrane*"[Title/Abstract]) OR "interpositional flap*"[Title/Abstract]) OR "interpositional graft*"[Title/Abstract]) OR fibrotom*[Title/Abstract]).



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