

# Interventions for the management of oral submucous fibrosis (Review)

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[Intervention Review]

## Interventions for the management of oral submucous fibrosis

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### ABSTRACT

#### Background

Oral submucous fibrosis (OSF) is a chronic disease of the oral cavity which is more commonly found in patients in the Asian subcontinent and the Far East. It is characterised by the progressive build up of constricting bands of collagen in the cheeks and adjacent structures of the mouth which can severely restrict mouth opening and tongue movement and cause problems with speech and swallowing.

#### Objectives

To assess the effectiveness of interventions for the management of pain and restricted jaw opening or movement occurring as a result of oral submucous fibrosis.

#### Search strategy

We searched the Cochrane Oral Health Group's Trials Register to July 2008; CENTRAL (*The Cochrane Library* 2008, Issue 2); MEDLINE (from 1950 to July 2008); EMBASE (from 1980 to July 2008) and IndMED on 18th November 2007. There were no language restrictions.

#### Selection criteria

Randomised controlled trials comparing surgical interventions, systemic or topical medicines or other interventions to manage the symptoms of oral submucous fibrosis.

#### Data collection and analysis

Two authors independently assessed trial quality and extracted trial data. Disagreements were resolved by consultation with a third author. Attempts were made to contact study authors where necessary for clarification and for additional information.

#### Main results

Two trials, involving 87 participants, evaluated lycopene in conjunction with intralesional injections of a steroid, and pentoxifylline in combination with mouth stretching exercises and heat. Only two of the primary but none of the secondary outcomes of this review were considered in these trials and provided a limited amount of unreliable data. The data in one trial were based on inadequately defined evaluations of outcomes, and in the other trial are likely to be skewed due to a substantial number of withdrawals and therefore

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were not entered into the RevMan analyses. There were no reports of toxicity to the interventions but some side effects, which were mostly gastric irritation to pentoxifylline, were noted.

### Authors' conclusions

The lack of reliable evidence for the effectiveness of any specific interventions for the management of oral submucous fibrosis is illustrated by the paucity, and poor methodological quality, of trials retrieved for this review.

## PLAIN LANGUAGE SUMMARY

### Interventions for the management of oral submucous fibrosis

Oral submucous fibrosis is a chronic disease which is commonly found in patients in the Asian subcontinent and the Far East and is characterised by the build up of constricting bands of collagen in the cheeks and adjacent structures of the mouth. The precise cause is unknown but chewing of betel quid as well as other areca nut containing products, excessive use of chillies and spices, poor nutrition and vitamin and iron deficiency have been suggested.

Mucosal ulcers may occur at an earlier stage, whereas fibrous bands in the cheeks and lips, depigmented gums and a rubbery and deformed soft palate and blanched, leathery floor of the mouth are later developments. These changes can severely restrict mouth opening and tongue movement and cause problems with speech and swallowing whilst other symptoms include a burning sensation whilst eating spicy food, dry mouth and hearing loss.

Treatment options include iron and multivitamin supplements including lycopene, an extract of tomato, and a range of medicines (e.g. intralesional injection of steroids, hyaluronidase, human placenta extracts, chemotrypsin, pentoxifylline and collagenase). Surgery, including cutting of the fibrous bands and jaw muscles and joint, has been used for more extreme cases.

The review authors found two studies which evaluated the effectiveness of lycopene in conjunction with intralesional injections of a steroid, and pentoxifylline in combination with mouth stretching exercises and heat. These studies provided a limited amount of unreliable data which did not permit any firm conclusions to be made. There were no reports of toxicity but some side effects, which were mostly gastric irritation to pentoxifylline, were noted.

Future research should aim to provide evidence for people to make informed decisions about whether these treatments are effective and should also explore treatment plans which include patient education aimed at cessation of the chewing habit.

## BACKGROUND

Oral submucous fibrosis (OSF) is a chronic disease of the oral cavity. Worldwide estimates indicate that as many as 2.5 million people may be affected (Cox 1996). It is more commonly found in patients in the Asian subcontinent and the Far East but, as a result of transmigration of populations, an increasing number of cases are being seen in other countries (Reichart 2006).

It is characterised by the progressive build up of constricting bands of collagen in the cheeks and adjacent structures of the mouth, which can cause problems with speech and swallowing and severely restrict mouth opening and tongue movement.

### Aetiology and prevalence

The aetiology of oral submucous fibrosis is considered to be multifactorial: betel quid chewing, excessive use of chillies and spices, poor nutrition and vitamin and iron deficiency have been suggested as causative agents (Ahmad 2006). Chewing of betel quid (areca catechu, lime and tobacco) as well as other areca nut containing products (e.g. pan masala and guthka) for mouth freshening and the mild euphoric effect is a fairly common practice in India, Pakistan and Sri Lanka. Other combinations as well as variety of packaged products are available in parts of the Far East in particularly China, Taiwan and Malaysia.

Epidemiological studies have provided substantial evidence of a close correlation between betel quid chewing and the incidence of OSF (Lee 2003), as well as highlighting the significant contribution of smoking and alcohol consumption to the malignant transformation of OSF (Ho 2007).

Whilst the precise mode of action of the various chemical constituents of areca nut on mucosal tissue is still unclear, it has been suggested that these constituents interfere with the processes of deposition or of breakdown of collagen or both (Lin 2007). There is currently much interest in the effect of cumulative betel quid exposure on collagen-related genes in the pathogenesis of OSF (Tilakaratne 2006). Research also appears to confirm that the absence of tobacco in the variety of areca/betel quid, as is used in Taiwan, does not significantly reduce the likelihood of developing OSF (Yang 2001).

Prevalence varies widely between countries and even between communities and geographical regions within those countries. An epidemiological study in India reported OSF in a patient as young as 11 years of age and noted that three times as many males as females were regular users of guthka (Ahmad 2006), although the reverse of this male-female ratio has been reported in Pakistan (Aziz 1997) and South Africa (VanWyk 1997). The prevalence of betel quid chewing in China is reportedly the highest in the Hunan (64.5% to 82.7%) and Hainan provinces with signs of OSF in 0.9% to 4.7% of the population and with the 30 to 49 years age group being the most commonly affected (Zhang 2007). Similar figures were reported in a survey in Taiwan, with up to 69.5% of the sample chewing betel/areca quid on a daily basis (Yang 2001).

### Symptoms and diagnosis

Symptoms of oral submucous fibrosis vary and can include a range of complications: progressive inability to swallow or to open the mouth; pain and a burning sensation whilst eating spicy food; dry mouth and hearing loss. Clinical findings are largely dependant on the severity and staging of the disease with a tendency for stomatitis, mucosal ulcers and fibrosis of ruptured vesicles and ulcers to occur at an earlier stage, whereas the appearance of fibrous bands in the cheeks and lips, depigmented gums and mucosa, a rubbery and deformed soft palate and blanched, leathery floor of the mouth, are generally later developments (Pindborg 1989).

Diagnosis of OSF should be based on the history and clinical examination and confirmed by histopathology of the lesion.

### Treatment options

These include iron and multivitamin supplements and a range of medicines (e.g. intralesional injection of steroids, hyaluronidase, human placenta extracts, chemotrypsin, pentoxifylline and collagenase), most of which have shown mixed results. Lycopene, an

extract of tomato, has recently been shown to have some beneficial effect in the management of symptoms of OSF.

Where there is restriction of mouth opening surgical interventions have been tried. Sectioning of the fibrotic bands has been used in mild cases, whereas bilateral temporalis myotomy or coronoidectomy with split-thickness skin-grafting techniques have been used in more extreme cases.

In any event, all treatment plans should include patient education and aim at cessation of the chewing habit.

### Rationale for a systematic review

Significant morbidity, in particular malnutrition, is associated with oral submucous fibrosis with restricted mouth opening causing eating difficulties. Mortality figures are reflected in the rate of transformation (< 7%) of oral submucous fibrosis cases into oral cancer (Reichart 2003). As a result of increasing prevalence of OSF outside of Asia and the Far East, and with an improved understanding of the immunological basis of this disease, a systematic review is now required to assess the effectiveness of current and newly evolving therapies and to make recommendations for future research.

## OBJECTIVES

To assess the effectiveness of interventions in the management of pain and restricted jaw opening or movement occurring as a result of oral submucous fibrosis.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

Only randomised controlled clinical trials (RCTs) were considered in this review.

#### Types of participants

Individuals in any age group with a confirmed diagnosis, by clinical examination and biopsy, of oral submucous fibrosis with trismus or restricted jaw movement.

### Types of interventions

- (1) Surgical procedures either against each other or no treatment.
- (2) Systemic or topical drugs or medicines, at any dosage and over any time period, against each other or placebo.
- (3) Other (e.g. local heat therapy, jaw stretching exercises).

### Types of outcome measures

#### Primary outcomes

- (1) Resumption of normal eating, chewing and speech.
- (2) Change or improvement in maximal jaw opening, measured as the interincisal distance.
- (3) Improvement in range of jaw movement utilising any validated assessment tool.
- (4) Change in severity of oral/mucosal burning pain using any recognised validated pain scale.

#### Secondary outcomes

- (1) Postoperative discomfort or pain as a result of the intervention: patient-assessed using any validated pain scale.
- (2) Hospital admission: length of stay.
- (3) Quality of life as assessed by any validated questionnaire, either generic or oral health specific.
- (4) Patient satisfaction assessed by validated questionnaire.

#### Costs

Direct costs of medication, hospital bed days and any associated in-patient costs for the surgical interventions.

#### Adverse effects

Any specific adverse effects related to any clinically diagnosed reactions to any of the active interventions were noted.

### Search methods for identification of studies

#### Electronic searches

For the identification of studies included or considered for this review, detailed search strategies were developed for each database to be searched. These were based on the search strategy developed for MEDLINE but revised appropriately for each database. For the MEDLINE (OVID) search, the subject search was run with the Cochrane Highly Sensitive Search Strategy (CHSSS) for identifying randomised trials in MEDLINE: sensitivity maximising

version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.c of the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.0 (updated February 2008) (Higgins 2008).

#### Databases searched

The following databases were searched on the dates indicated:  
The Cochrane Oral Health Group's Trials Register (to July 2008)  
The Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2008, Issue 2)  
MEDLINE (1950 to July 2008)  
EMBASE (from 1980 to July 2008).

Details of the search strategies for the databases searched are provided in [Appendix 1](#); [Appendix 2](#); [Appendix 3](#) and [Appendix 4](#). We searched IndMED, a bibliographic database of Indian biomedical journals, available at <http://indmed.nic.in/>, using free text terms appropriate for this review (18th November 2007). Additional searches for ongoing trials were conducted on <http://www.clinicaltrials.gov/> (18th November 2007).

The library records at the University of Colombo Medical School, Sri Lanka were searched for relevant theses, dissertations and published and unpublished studies (December 2007).

#### Handsearches

No additional handsearching was done over and above that carried out on our behalf at the University of Colombo Medical School Library. We were unsuccessful in arranging for the handsearching of any of the oral health journals in the Far East which we considered might be a potential source of studies appropriate for this review.

We searched the reference lists of relevant articles and attempted to contact the investigators of both of the included studies by electronic mail to ask for further trial details and for information about any additional trials.

Attempts to contact several experts in this field also proved unsuccessful and, other than IndMED, we were unable to identify any additional databases from regions of the world which are considered to have a high incidence of oral submucous fibrosis.

A search of the Internet was undertaken for existing and potentially relevant meta-analyses and non-Cochrane systematic reviews using Google Scholar available at <http://scholar.google.com/>, and for online published dissertations using: <http://www.thesis.org>, <http://www.dissonline.de/>, <http://zippo.vtls.com/cgi-bin/ndltd/chameleon>.

#### Language

Although there were no language restrictions on included studies we did not locate any relevant non-English papers.

## Data collection and analysis

### Assessment of search results

Two review authors (Mojtaba Dorri (MD) and Zbys Fedorowicz (ZF)) independently assessed the abstracts of studies resulting from the searches. Full copies of all relevant and potentially relevant studies, those appearing to meet the inclusion criteria, or for which there were insufficient data in the title and abstract to make a clear decision were obtained. The full text papers were assessed independently by the two authors and any disagreement on the eligibility of potentially included studies were resolved through discussion with a third author (Mona Nasser (MN)). After assessment by the authors any duplicate publications or remaining studies that did not match the inclusion criteria were excluded from further review and the reasons for their exclusion noted in the [Characteristics of excluded studies](#) table.

### Data extraction

Study details and outcomes data were collected by two review authors (MD and ZF) independently using a predetermined form designed for this purpose. Study details were entered into the [Characteristics of included studies](#) table. Data would only be included if there was an independently reached consensus. Any disagreement would be discussed and if required a third review author would be consulted.

The following details were extracted.

- (1) Study methods: method of allocation, masking of participants and investigators (if feasible), exclusion of participants after randomisation and proportion of follow-up losses.
- (2) Participants: country of origin, sample size, age, sex, inclusion and exclusion criteria.
- (3) Intervention: type of surgical procedure, if medical or pharmacological: mode of administration, dose, frequency, and duration of usage.
- (4) Control: type, dose and frequency of any comparison or placebo.
- (5) Outcomes: primary and secondary outcomes.
- (6) Any adverse events.

If stated, the sources of funding of any of the included studies were recorded.

This information was used to assess the clinical homogeneity and the external validity of the trials.

### Assessment of methodological quality

Each review author then graded the selected studies independently and assessed every trial reporting a randomised controlled trial (RCT) according to the criterion grading system described in the *Cochrane Handbook for Systematic Reviews of Interventions* 5.0.0 (updated February 2008) ([Higgins 2008](#)). These review authors

compared the gradings and discussed and resolved any inconsistencies in the interpretation of inclusion criteria and their significance to the selected studies. The following parameters of methodological quality were assessed and used to help in evaluating the risk of bias within the included studies.

(1) Sequence generation.

This criterion was graded as adequate (A), or unclear (B). Adequate (A) included any one of the following methods of randomisation: computer generated or table of random numbers, drawing of lots, coin-toss, shuffling cards or throw of a dice.

(2) Allocation concealment.

The review authors graded this criterion as adequate (A), unclear (B), inadequate (C). Adequate (A) methods of allocation concealment included either central randomisation or sequentially numbered sealed opaque envelopes. This criterion was considered inadequate (C) if there was an open allocation sequence and the participants and trialists could foresee the upcoming assignment.

(3) Blinding of investigators, participants and outcomes assessment.

Albeit blinding of the investigators to surgical interventions may not be possible, the following criteria were assessed if feasible (detection and performance bias):

- (a) blinding of participants (yes/no/unclear)
  - (b) blinding of investigators (yes/no/unclear)
  - (c) blinding of outcomes assessment (yes/no/unclear)
  - (d) not feasible.
- (4) Handling of withdrawals and losses.

The review authors graded this criterion as yes (A), unclear (B) and no (C) according to whether there was a clear description given of the difference between the two groups of losses to follow up (attrition bias).

After assessment the included studies were grouped accordingly.

- (A) Low risk of bias (plausible bias unlikely to seriously alter the results): if all criteria were met.
- (B) Moderate risk of bias (plausible bias that raises some doubt about the results): if all criteria were at least partly met.
- (C) High risk of bias (plausible bias that seriously weakens confidence in the results): if one or more criteria were not met.

### Data synthesis

For future updates, when studies are identified for inclusion in this review with sufficient and appropriate data, the following methods will be applied.

The Cochrane Collaboration statistical guidelines will be followed for data synthesis. The data will be analysed by MN, Luming Shi (LS) and ZF using RevMan 5 and reported according to Cochrane Collaboration criteria.

In general, for continuous data, we will calculate the mean difference and 95% confidence intervals. Risk ratios and their 95% confidence intervals will be calculated for all dichotomous data.

We plan to assess clinical heterogeneity by examining the characteristics of the studies: the similarity between the types of participants, the interventions and the outcomes as specified in the criteria for included studies. Statistical heterogeneity will be assessed using a Chi<sup>2</sup> test and the I<sup>2</sup> test where I<sup>2</sup> values over 50% indicate moderate to high heterogeneity (Higgins 2003). Whilst recognising its limitations, if a sufficient number of RCTs are identified, an attempt will be made to assess publication bias using a funnel plot (Egger 1997).

Results of clinically and statistically homogeneous trials will be pooled to provide estimates of the efficacy of the interventions only if the included studies have similar interventions received by similar participants. Either the fixed-effect or random-effects models will be used but if there is significant heterogeneity between the studies we will use the random-effects model.

In the event that there are insufficient clinically homogeneous trials for any specific intervention or insufficient study data that can be pooled, a narrative synthesis will be presented.

We will conduct the following subgroup analyses if sufficient data are available: categorising and subsequent analysis of participants by stage and degree of restriction in jaw opening and movement, at the commencement of administration of any of the interventions.

### Sensitivity analyses

If there are sufficient included studies we plan to conduct sensitivity analyses to assess the robustness of our review results by repeating the analysis with the following adjustments: exclusion of studies with unclear or inadequate allocation concealment, unclear or inadequate blinding of outcomes assessment and completeness of follow up.

## RESULTS

### Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

### Finding the trials

The search strategy retrieved 81 (10 Cochrane Oral Health Group's Trials Register, 10 CENTRAL, 41 MEDLINE, 20 EMBASE) references to studies, which after de-duplication resulted in 41 potentially eligible studies. After examination of the titles and abstracts of these references, all but six studies (Gupta 1988; Jain 2000; Kakar 1985; Kumar 2007; Rajendran 2006; Tai 2001) were eliminated and excluded from further review. Full text copies of these remaining studies, and Kerr 2007 which was a commentary

on Kumar 2007, were obtained and subjected to further evaluation. The bibliographical references of these studies were examined but did not provide any additional citations to potentially eligible studies.

Our search of the IndMED database retrieved six references to publications, the titles and abstracts of which were examined and full text papers were obtained where appropriate but no additional eligible trials were found. The search of the Internet for non-Cochrane systematic reviews and online published dissertations provided no further trials and no ongoing clinical trials were retrieved in our search of the ClinicalTrials.gov database.

After further evaluation we excluded three studies (Gupta 1988; Kakar 1985; Tai 2001) and noted the reasons for their exclusion (see [Characteristics of excluded studies](#)). We also excluded an abstract to conference proceedings which we were unable to obtain (Jain 2000).

After discussion between the review authors any remaining uncertainties on the eligibility of any of the studies were resolved by consensus and subsequently two trials, involving 87 participants, met most of our inclusion criteria and were included in this review (Kumar 2007; Rajendran 2006).

### Characteristics of the trial setting and investigators

Both of the trials were conducted in India, and whilst neither report provided detailed information about the setting it may be assumed that they were conducted in a university or academic institute. Equally, no information was made available by the investigators in both trials about their sources of funding or any potential conflicts of interest and, although not explicitly stated, the providers and assessors of the treatments appeared to be research staff from a university or academic institute.

### Characteristics of the participants

Only adults were recruited for both of these trials, one of which excluded participants with significant systemic medical problems i.e. cardiac disease, diabetes or gastric ulcers (Rajendran 2006). Participants were only enrolled in Kumar 2007 if they satisfied two out of three criteria: they had difficulty in chewing; had restricted mouth opening with the presence of fibrous bands and had a diagnosis of oral submucous fibrosis which had been confirmed by biopsy. This report was also unclear, and we were unable to ascertain from the investigators, whether all of the participants who were enrolled in this study were randomised to the interventions. The inclusion criteria were less clear in the other study in which the participants were of "comparable disease progression" and only recruited if they had clinically advanced oral submucous fibrosis which were stated to have been judged by "clinico-pathological parameters" but these were not clearly defined in the reports (Rajendran 2006).

All of the participants in Kumar 2007 had chewed areca nut as a quid, gutkha or pan masala (1 to 20 chews per day, median 6.5)



for a period of 1 to 25 years (median 7 years). In the [Rajendran 2006](#) study the investigators reported no further details other than that the participants were habitual chewers of areca quid.

The participants in one trial ([Kumar 2007](#)) were actively encouraged by the investigators to discontinue their areca nut chewing habit during the course of the study and also at enrolment received a cleaning to remove tooth staining which it was stated would enable closer monitoring of any resumption of the chewing habit. No such instructions on habit cessation or its monitoring were reported in the other trial ([Rajendran 2006](#)).

### Characteristics of the interventions

The interventions in one trial consisted of oral lycopene, a natural pigment (carotenoid) occurring in fruits and vegetables which it is claimed has antioxidant properties; or lycopene together with twice weekly intralesional steroid injections; or a placebo, which were administered over a 2-month period ([Kumar 2007](#)). The report did not specify precisely which and how many of the oral lesions had received the steroid injections at each of the visits, nor if the time when the injections were administered coincided with that of the outcomes assessment.

The second trial, which was conducted over a 7-month period, compared oral pentoxifylline (Trental) taken 3 times per day against a single daily multivitamin tablet. Participants in both groups also received local heat therapy and underwent forceful mouth stretching exercises ([Rajendran 2006](#)). It is suggested that the vasodilator properties of pentoxifylline in addition to its effect in reducing platelet aggregation may lead to an increased vascularity of the affected oral tissues.

Assessment of participants' compliance was reported as 100% in one trial ([Rajendran 2006](#)) but it was unclear whether this referred only to medication usage or included the self-administered mouth stretching exercises and/or the heat therapy. Although there were substantial losses to follow up in the other study the investigators provided no information on the extent of the participants' compliance with the study protocol.

### Characteristics of outcome measures

Two of our primary outcomes were reported in both of the included trials.

Clinical assessments of maximal jaw opening were carried out weekly in [Kumar 2007](#) and monthly in [Rajendran 2006](#) and outcomes were expressed by measured change in the interincisal distance. The method used to measure these changes was not clear in [Rajendran 2006](#) but was more comprehensively reported in [Kumar 2007](#).

Neither of the trials carried out any assessment of improvement in the range of jaw movement.

Changes in severity of burning sensation were reported, but in both studies these parameters were poorly defined not based on any recognised and validated pain scale and the reports did not provide any reliable information on how the assessments were made or how the scores were calculated.

One of the trials ([Rajendran 2006](#)) assessed "relief from difficulty of speech" and whilst it included data for both intervention groups the report contained no information on how these speech evaluations were carried out.

None of our secondary outcomes were considered by the investigators in either of the included trials.

### Costs

No data were available.

### Adverse events

Both studies took note of adverse events but only one reported any side effects ([Rajendran 2006](#)).

For further details see [Characteristics of included studies](#) table.

### Risk of bias in included studies

See Additional [Table 1](#).

**Table 1. Quality of included studies**

Study ID	Randomisation	Allocation concealment	Blinding	Intention-to-treat	Attrition
Kumar 2007	Unclear (B)	Unclear (B)	(a) blinding of participants (not feasible) (b) blinding of investigators (not feasible) (c) blinding of outcomes assessment (no)	No. Only 58 out of 83 participants were analysed and the data from an unspecified number of participants were excluded from the analysis of improvement of jaw	30% drop outs. Unclear (B)

**Table 1. Quality of included studies** (Continued)

				opening.	
Rajendran 2006	Unclear (B)	Unclear (B)	(a) blinding of participants (unclear) (b) blinding of investigators (unclear) (c) blinding of outcomes assessment (no)	No. All of the participants were not included in the analysis.	Nil losses. Yes (A)

### The Kumar 2007 study

[Kumar 2007](#).

#### Sequence generation and allocation concealment

The participants were “randomly categorized by two investigators into one of three groups”, and therefore this criterion was graded unclear (B). The trialists did not indicate what methods were used to conceal the allocation sequence from either participants or trialists and therefore this criterion was also graded as unclear (B).

#### Blinding of participants, investigators and outcomes assessment

In view of the nature of the interventions blinding of the investigators was not possible and for similar reasons even though the oral medications were identically packaged adequate blinding of the participants would also not be feasible in this study. Most of the outcomes were evaluated by the investigators, who were likely to be aware which of the patients had received which intervention, and therefore this criterion was graded as no.

#### Handling of withdrawals and losses

Although the losses to follow up during the study were reported, the investigators failed to provide sufficient detail on the precise losses within individual groups and therefore this criterion was graded as unclear (B).

### The Rajendran 2006 study

[Rajendran 2006](#).

#### Sequence generation and allocation concealment

Participants were stated to have been “randomly selected”, and as there was no description of the methods used to conceal the allocation sequence from the trialists both of these criteria were rated as unclear (B).

#### Blinding of participants, investigators and outcomes assessment

Although the report was unclear if the interventions were similar in taste and packaging of the dosage regimen was clearly different between the intervention group (3 times per day) and the single daily dose for the control group, therefore blinding of both participants and investigators was graded as unclear. As most of the outcomes assessments were carried out by the investigators in this trial this criterion was graded as no.

#### Handling of withdrawals and losses

All participants were stated to have completed the trial, but data were missing for a number of outcomes although some but not all of these were in outcomes sought in this review. It was also not clear from the report that, although all the participants had attended for all follow-up appointments, this lack of data was because these assessments were not made for all participants at each visit. The data were complete for one of our primary outcomes: the change in maximal jaw opening. One participant was excluded from the analysis in the evaluation of changes in severity of oral burning pain, but the investigators indicated that this individual was asymptomatic at enrolment. Thus the handling of withdrawals for our outcomes of interest was graded as yes (A).

#### Assessment of risk of bias

The validity of each study was assessed as at low, moderate or high risk of bias. Both of the included studies were rated as at high risk

of bias (C) (plausible bias that seriously weakens confidence in the results - one or more criteria were not met).

### Effects of interventions

A limited amount of data which addressed two of the primary but none of the secondary outcomes, was provided by the two included trials. These data are based in one trial on inadequately defined evaluations of outcomes, and in the other are likely to be skewed by the substantial number of withdrawals, therefore we have not entered these data into the RevMan analyses and only provide a descriptive summary.

### Primary outcomes

(1) Resumption of normal eating, chewing and speech.

None of the included trials provided data for these outcomes.

(2) Change or improvement in maximal jaw opening, measured as the interincisal distance.

Although the data reported in [Kumar 2007](#) appeared to show statistically significant improvements for this outcome in the two active intervention groups, unclear information on withdrawals and incomplete data meant that the measured values cannot be considered interpretable in a quantitative sense. In [Rajendran 2006](#) the data reported for this outcome, included only the relative difference between the first and second month and the first and seventh month, and also failed to include the relevant baseline data and thus it was not possible to corroborate the reported scores.

(3) Improvement in range of jaw movement utilising any validated assessment tool.

Neither of the included trials provided data for this outcome.

(4) Change in severity of oral/mucosal burning pain using any recognised validated pain scale.

Pain intensity evaluations in [Rajendran 2006](#) were based on criteria which were inadequately defined, and the wide range of possible responses obtained as "interview data" is likely to make interpretation of an average score difficult and thus the data reported in this trial were not particularly useful. Systematic bias (attrition), as a result of losses to follow up and incomplete data, in [Kumar 2007](#) is likely to have reduced the value of any of their reported data for this outcome. Attempts to contact both sets of investigators to clarify these data proved unsuccessful.

### Secondary outcomes

No data were provided for any of these outcomes.

(1) Postoperative discomfort or pain as a result of the intervention: patient-assessed using any validated pain scale.

(2) Hospital admission: length of stay.

(3) Quality of life as assessed by any validated questionnaire, either generic or oral health specific.

(4) Patient satisfaction assessed by validated questionnaire.

### Adverse effects

The investigators in one of the trials ([Rajendran 2006](#)) reported that these included mild gastritis, gastric irritation and peripheral flushing but they did not record how many participants were involved, from which treatment group nor the severity or duration of any of these side effects, and stated only that these side effects were managed by unspecified dietary changes. No treatment related side effects were reported in the other trial ([Kumar 2007](#)).

## DISCUSSION

The lack of reliable evidence for the effectiveness of any specific interventions for the management of oral submucous fibrosis is illustrated by the paucity of trials retrieved for this review. Surgical interventions were not considered in either of the two included trials which evaluated only the following options: lycopene in conjunction with intralesional injections of a steroid, and pentoxifylline in combination with mouth stretching exercises and heat.

Questions remain unanswered as to whether management options based on therapeutic interventions with anti-inflammatory or antifibrotic properties would be the most effective. The adjunctive use of intralesional steroid injections with lycopene, both of which are recognised to have an anti-inflammatory effect, is likely to have confounded the possibility of any reliable assessment of the effectiveness of lycopene used alone, and the evidence presented for the effectiveness of pentoxifylline as both an anti-inflammatory and fibrinolytic agent proved to be inconclusive.

## AUTHORS' CONCLUSIONS

### Implications for practice

Although the investigators in both trials concluded that the results indicated that these interventions were safe, appeared to be effective in reducing symptoms and might prove beneficial in the therapeutic management of oral submucous fibrosis, the uncertain reliability of the limited amount of available data would not appear to support these contentions.

The mode of action and therapeutic benefits of lycopene are unclear, but its antioxidant properties more specifically in the prevention of oral premalignant lesions have come under increasing scrutiny over the last few years. To what extent, based on one of the included trials, these chemo-preventive properties can be translated into therapeutic benefits in the management of oral submucous fibrosis is debatable. It is also unclear from this trial to what extent lycopene might be effective in enhancing the anti-inflammatory properties of intralesional injections of steroid and thereby prove beneficial in ameliorating some of the symptoms of this disease.

## Implications for research

Because therapeutic regimens based on interventions with anti-inflammatory properties are likely to be more effective at earlier rather than later stages of oral submucous fibrosis a grouping of participants by disease progression and severity utilising proxy criteria i.e. a range of interincisal jaw measurements classified into stages, would be more likely to ensure an equal distribution between the intervention groups, of participants with disease related factors that might have an influence on the outcomes. The use of either stratified randomisation or minimisation, in which allocation to the intervention aims to reduce differences in the distribution of known or suspected factors which may influence outcomes, are options that might be considered in the design of future trials.

The nature of the intervention and control and the difficulty of blinding participants and investigators coupled with the probability of biased outcomes assessment and the substantial losses to follow up were some of the challenges faced in the included trials. If blinding of either participants or trialists to an intervention or the assessment of outcomes is not feasible, then strenuous efforts should be made to ensure that at least the data analysts are blinded. Patient reported outcomes, especially if used to measure pain, should also be supported by a validated and recognised pain scale that has been linguistically validated and culturally adapted and is appropriate for this type of intervention. Investigators should also explore methods that can be used to reduce withdrawals and losses to follow up which are appropriate for the specific settings of any future trials.

Although measurement of the interincisal distance is generally considered the 'gold standard', accuracy and reliability will be re-

flected in the sensitivity of the test and its ability to discern change particularly where the order of magnitude of that change is in millimetres as was the case in the two included trials. Whilst recognising the resource limitations in developing countries the use of more sensitive measurement techniques should be considered and future trials might try to incorporate some of the many tools available for image analysis e.g. photography, or digital morphometry in conjunction with cephalometric digital radiography and extra-oral imaging systems.

The problems faced by investigators in conducting trials in under resourced countries and particularly where this disease is prevalent should not be underestimated. It is important, however, that any further trials should be robust, well designed, and conducted and reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement (<http://www.consort-statement.org/>).

## ACKNOWLEDGEMENTS

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- \* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Kumar 2007

Methods	Parallel group trial (2 months) in India, no further setting details supplied. Participants “randomly categorized by 2 investigators into 1 of 3 groups”.
Participants	83 enrolled, unclear if all were randomised. n = 58 (all male age 18-70 years median 28). Group A: 21, B: 19, C: 18. Inclusion criteria: history of chewing areca nut, restricted mouth opening, difficulty in chewing, burning pain with spicy food. Positive biopsy. Drop outs 30%. Exclusion criteria: nil specified.
Interventions	Group A (n = 21): Oral lycopene 16 mg daily. Group B (n = 19): Oral lycopene 16 mg daily and intralesional injection betamethasone 8 mg twice weekly. Group C (n = 18): placebo capsules.
Outcomes	Follow up and review at weekly intervals. Improvement in mouth opening (interincisal distance in mm), in tongue protrusion (in units of 5 mm). Palpable fibrous bands in the buccal mucosa. Burning sensation (present/persisting/absent). Stated that other findings were graded on a 3-point severity scale but these were unspecified.
Notes	

#### *Risk of bias*

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

#### Rajendran 2006

Methods	Parallel group trial (7 months) in India (Government Dental College Kerala). Participants “randomly selected” (method not specified).
Participants	29 enrolled, graded as advanced and by established “clinico-pathological parameters” (unspecified). Age: Intervention group 39.64±7.2, Control 41.13±5.5 years. Gender ratio: male/female 9:5. Inclusion criteria: habitual chewers of areca quid. Exclusion criteria: hypertension, diabetes, cardiac disease, duodenal and gastric ulcers, bleeding dyscrasias. No drop outs recorded.
Interventions	14 intervention: pentoxifylline (Trental) orally 400 mg twice daily for the first 30 days, 3 times daily for further 6 months of study period. 15 control: multivitamin capsule once daily.

**Rajendran 2006** (Continued)

	Both groups: local heating therapy (hot water exercise and forceful mouth opening). No details provided.	
Outcomes	Follow up and review at monthly intervals. Improvement in mouth opening and swallowing, tongue protrusion. Relief from fibrotic bands, tinnitus, intolerance to spicy food and burning sensation. Improvement in salivation, mucosal rigidity, depapillation of tongue.	
Notes		
<b><i>Risk of bias</i></b>		
<b>Item</b>	<b>Authors' judgement</b>	<b>Description</b>
Allocation concealment?	Unclear	B - Unclear

**Characteristics of excluded studies** [ordered by study ID]

Gupta 1988	Non-RCT, poor quality and incomplete data.
Jain 2000	Abstract to conference proceedings, unobtainable.
Kakar 1985	Non-RCT, poor quality and incomplete data.
Tai 2001	Non-RCT.

RCT = randomised controlled trial

## DATA AND ANALYSES

This review has no analyses.

## APPENDICES

### Appendix 1. Cochrane Oral Health Group's Trials Register search strategy

("oral submucous fibrosis" or (submucous AND fibrosis AND (oral OR mouth)))

### Appendix 2. CENTRAL search strategy

#1 ORAL SUBMUCOUS FIBROSIS/  
#2 ((submucous NEXT fibrosis) AND (oral or mouth))  
#3 #1 or #2

### Appendix 3. MEDLINE (OVID) search strategy

1 ORAL SUBMUCOUS FIBROSIS/  
2 ("submucous fibrosis" AND (oral or mouth))  
3 OR/1-2

Cochrane search filter for MEDLINE (OVID):

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. humans.sh.
11. 9 and 10

### Appendix 4. EMBASE (OVID) search strategy

1. ("submucous fibrosis" AND (oral or mouth))

Search filter for EMBASE (OVID):

1. random\$.ti,ab.
2. factorial\$.ti,ab.
3. (crossover\$ or cross over\$ or cross-over\$).ti,ab.
4. placebo\$.ti,ab.
5. (doubl\$ adj blind\$).ti,ab.
6. (singl\$ adj blind\$).ti,ab.
7. assign\$.ti,ab.
8. allocat\$.ti,ab.
9. volunteer\$.ti,ab.
10. CROSSOVER PROCEDURE.sh.



11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
16. HUMAN/
17. 16 and 15
18. 15 not 17
19. 14 not 18

## WHAT'S NEW

Last assessed as up-to-date: 28 July 2008.

29 July 2008	Amended	Converted to new review format.
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## HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 4, 2008

## **CONTRIBUTIONS OF AUTHORS**

Zbys Fedorowicz (ZF), Mojtaba Dorri (MD) and Mona Nasser (MN) were responsible for:

Designing the review

Co-ordinating the review.

ZF and Luming Shi (LS) were responsible for:

Organising retrieval of papers

Writing to authors of papers for additional information

Providing additional data about papers.

ZF, MN, MD and Edwin Chan (EC) were responsible for:

Data collection for the review

Screening search results

Screening retrieved papers against inclusion criteria

Appraising quality of papers

Extracting data from papers

Obtaining and screening data on unpublished studies

Entering data into RevMan

Analysis of data.

ZF, MN, LS, MD and Tim Newton (TN) were responsible for interpretation of the data and writing the review.

ZF will be the guarantor for the review.

## **DECLARATIONS OF INTEREST**

There are no financial conflicts of interest and the review authors declare that they do not have any associations with any parties who may have vested interests in the results of this review.

## **DIFFERENCES BETWEEN PROTOCOL AND REVIEW**

The primary outcomes have been resequenced from the order they appear in the published protocol.

- (1) Resumption of normal eating, chewing and speech.
- (2) Change or improvement in maximal jaw opening, measured as the interincisal distance.
- (3) Improvement in range of jaw movement utilising any validated assessment tool.
- (4) Change in severity of oral/mucosal burning pain using any recognised validated pain scale.

## **INDEX TERMS**

### **Medical Subject Headings (MeSH)**

Carotenoids [therapeutic use]; Hot Temperature [therapeutic use]; Oral Submucous Fibrosis [\*therapy]; Pentoxifylline [therapeutic use]; Steroids [administration & dosage]; Vasodilator Agents [therapeutic use]

### **MeSH check words**

Adult; Humans