Interventions for preventing and treating trismus in patients with head and neck cancer (Protocol)

Carvalho APV, McNeely ML, Vital FMR

Carvalho APV, McNeely ML, Vital FMR.
Interventions for preventing and treating trismus in patients with head and neck cancer.
DOI: 10.1002/14651858.CD012316.

www.cochranelibrary.com
# Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Header</td>
<td>1</td>
</tr>
<tr>
<td>Abstract</td>
<td>1</td>
</tr>
<tr>
<td>Background</td>
<td>1</td>
</tr>
<tr>
<td>Objectives</td>
<td>3</td>
</tr>
<tr>
<td>Methods</td>
<td>3</td>
</tr>
<tr>
<td>Acknowledgements</td>
<td>6</td>
</tr>
<tr>
<td>References</td>
<td>7</td>
</tr>
<tr>
<td>Appendices</td>
<td>9</td>
</tr>
<tr>
<td>Contributions of Authors</td>
<td>10</td>
</tr>
<tr>
<td>Declarations of Interest</td>
<td>11</td>
</tr>
<tr>
<td>Sources of Support</td>
<td>11</td>
</tr>
</tbody>
</table>
Interventions for preventing and treating trismus in patients with head and neck cancer

Alan PV Carvalho, Margaret L McNeely, Flávia MR Vital

1Urgency Medicine, Universidade Federal de São Paulo, São Paulo, Brazil. 2Department of Physical Therapy/Department of Oncology, University of Alberta, Edmonton, Canada. 3Department of Physiotherapy, Muriaé Cancer Hospital, Muriaé, Brazil

Contact address: Alan PV Carvalho, Urgency Medicine, Universidade Federal de São Paulo, Rua Pedro de Toledo, 598, São Paulo, São Paulo, 04039-001, Brazil. alanpedrosa@hotmail.com.

Editorial group: Cochrane ENT Group.

Citation: Carvalho APV, McNeely ML, Vital FMR. Interventions for preventing and treating trismus in patients with head and neck cancer. Cochrane Database of Systematic Reviews 2016, Issue 8. Art. No.: CD012316. DOI: 10.1002/14651858.CD012316.

Copyright © 2016 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of a) interventions for preventing trismus in patients with head and neck cancer before its onset and b) interventions for treating trismus after its onset.

BACKGROUND

Description of the condition

Head and neck cancers, which include cancers of the oral cavity, nasopharynx, oropharynx and larynx, are the sixth most common cancer worldwide, with an incidence of 633,000 cases and 355,000 deaths annually (Ferlay 2008). Trismus can be a negative effect of head and neck cancer treatments. It is a disorder characterised by a lack of ability to open the mouth fully due to a decrease in the range of motion of the muscles of mastication. It can be graded into three categories: mild (decreased range of motion without impaired eating), moderate (decreased range of motion requiring small bites, soft foods or purees) and severe (decreased range of motion with an inability to adequately feed or drink) (National Cancer Institute 2010). Trismus may be due to local invasion of the primary or metastatic tumour into the structures of mastication including the masseter and pterygoid muscle, the temporal mandibular joint and/or other supportive tissues (Stubblefield 2010). Alternatively it may be related to damage and fibrosis of the muscles of mastication caused by radiation therapy or surgery, which has the potential to create scar tissue with an abnormal proliferation of fibroblasts that can compromise normal mouth opening (Bensadoun 2011). Trismus can be easily diagnosed by clinical examination of the maximal inter-incisal distance (MID), which represents the distance from the incisal edge of the maxillary and mandibular incisors. This measurement can be performed even in edentulous patients, where the distances between the maxillary and mandibular alveolar ridges are recorded (Shulman 2008). A variety of criteria to determine trismus have been reported in the literature, however the most accepted cut-off point to indicate trismus in head and neck oncology is a mouth opening of 35 mm or less (Dijkstra 2006). At the time of head and neck cancer diagnosis, before oncological treatments, the prevalence of trismus has been reported to range...
from 2% to 55% (Dijkstra 2006). After conventional radiotherapy or chemoradiotherapy the mean prevalence is 25.4% and 30.7%, respectively (Bensadoun 2011). For oral and oropharyngeal cancer trismus has been reported in 30% of patients before surgery, 65% at hospital discharge and 54% at six-month follow-up (Scott 2011). Lee and colleagues reported a 47% prevalence before treatment for head and neck cancer, an incidence of 71% after surgery and an increase to 79% after surgery associated with radiotherapy (Lee 2012).

After a dose of 40 Gy, every additional 10 Gy in the pterygoid muscle is responsible for increasing the probability of trismus by 24% (Teguh 2008). Radiation-induced trismus evolves at different rates: during the period of radiotherapy the rate of decrease in mouth opening was shown to be 1.3% per month, after radiotherapy up until nine months the rate increased to 2.4% per month, and after 12 to 24 months the rate was 0.2%, totalling an average of 32% after four years (Wang 2005). The restriction of mandible movements in patients with head and neck cancer results in difficulties with daily activities such as eating, chewing, swallowing, breathing and speaking (Lee 2012). Furthermore, trismus interferes with oral hygiene, nutritional intake (contributing to weight loss) and dental examination and treatment, all of which have a direct impact on the quality of life of patients (Kent 2008). Compromised mastication also increases the risk of aspiration of food and of aspiration pneumonia in patients after concurrent chemoradiotherapy (Bensadoun 2011; van der Molen 2011).

**Description of the intervention**

In this review, we will include both studies of interventions to prevent trismus in participants with a diagnosis of head and neck cancer and interventions to treat those with trismus that has been diagnosed.

**Physical therapy modalities**

Physical therapy is generally considered the mainstay of trismus treatment and is used alone or in combination with other interventions (Stubblefield 2010). Physical therapy modalities include passive range of motion exercises, active range of motion exercises, mobilisation and electrotherapy, and may be associated with or without medications or other interventions for trismus.

**Devices**

Devices for stretching the muscles of mastication are often prescribed for the treatment of trismus. The 'Therabite' is a mechanical device with a lever system and two flat mouthpieces that are inserted between the teeth of the upper and lower jaw. The patient assists mouth opening by squeezing the handle of the device and is able to control the extent of stretch to the tissues (Buchbinder 1993; Melchers 2009). The 'Dynasplint Trismus System' is a more costly device that uses a low-torque and prolonged duration stretch designed to lengthen connective tissue (Shulman 2008; Stubblefield 2010). Stacked tongue depressors and corkscrew devices, which are less expensive options, are often used clinically to mobilise the jaw (Bensadoun 2011; Stubblefield 2010).

**Drug therapy**

Pentoxifylline is a methylxanthine derivative used in the treatment of a variety of vasculo-occlusive disease, such as peripheral vascular disease, cerebrovascular disease and a number of other conditions involving defective regional microcirculation. This medication is taken orally at a dose of 400 mg three times daily for eight weeks (Chua 2001; Ward 1987). Botulinum toxin is also used and applied directly into both masseter muscles by transcutaneous injection. A total of 50 units per muscle is used to produce a chemical denervation of muscles, improving pain and spasm (Hartl 2008; Royal 2003).

**Surgical procedures**

Coronoidectomy is a procedure in which the temporalis muscle fibres are stripped from the coronoid process after which it is resected (Mulder 2012). Different surgical approaches have been described, such as intraoral, extraoral and minimally invasive procedures using endoscopic assistance (Robiony 2012). The intraoral approach has the advantage of providing sufficient access without producing any extraoral scar but the disadvantage of postoperative haematoma formation or subsequent fibrosis (Kim 2014). Extraoral approaches have advantages such as less fibrosis and haematoma formation, no intraoral scarring and better exposure for resection of the coronoid process and release of the temporalis muscle, but the disadvantages are the risk of facial nerve damage and a visible scar (Mulder 2012).

**How the intervention might work**

**Physical therapy modalities**

These modalities are prescribed to improve the range of motion of the temporomandibular joint, reduce pain, prevent hypomobility, avoid fibrosis formation, strengthen the musculature and improve flexibility, tissue elasticity and blood circulation (Tang 2011).

**Devices**

Devices are generally used to improve mouth opening, usually with an appliance that induces active-assisted or passive range of movement to stretch the muscles of mastication responsible for closing
the mouth (masseter, medial pterygoid, temporalis) (Bensadoun 2011; Buchbinder 1993).

Drug therapy
Pentoxifylline is prescribed to improve microcirculation and tissue oxygenation by increasing red blood cell deformability, decreasing blood viscosity and increasing oxygen release from red blood cells. It also has immunomodulatory functions with down-regulation of certain cytokines, thus preventing the pathogenesis of radiation-induced fibrosis (Chua 2001). Botulinum toxin acts by blocking acetylcholine receptors. It cleaves soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins, which work to inhibit the exocytosis of acetylcholine by inhibiting the fusion of vesicles containing neurotransmitters in the presynaptic membrane (Hartl 2008).

Surgical procedures
When the coronoid process is removed after removing the temporalis muscles from its insertion, the temporomandibular joint gains a better range of motion because the temporalis are mouth-closing muscles and degeneration and fibrosis causes inability of these muscles to stretch (Bhrawy 2007; Gupta 2014; Lehman 2015).

Why it is important to do this review
At present, trismus is a common adverse event after head and neck cancer treatments. The treatments offered for preventing and treating this complication are not yet established and it is not clear which type of treatment is more effective and safe for this group of patients. A variety of studies have been published on interventions to prevent and treat trismus in head and neck cancer patients. In the light of this research, this review aims to synthesise the findings with the goal of guiding health care providers, consumers and policy-makers on what type of intervention is more effective and safe (Buchbinder 1993; Chua 2001; Melchers 2009; Shulman 2008; van der Molen 2011).

OBJECTIVES
To assess the effects of a) interventions for preventing trismus in patients with head and neck cancer before its onset and b) interventions for treating trismus after its onset.

METHODS

Criteria for considering studies for this review

Types of studies
Randomised controlled trials (RCTs). We will exclude quasi-randomised studies. We will include cluster-randomised and crossover studies.

Types of participants
Adults of both genders, with a clinical and histological diagnosis of head and neck cancer, including all stages of cancer (I, II, III and IV), who are undergoing or have undergone any type or cancer treatment or have not yet received any cancer treatment (radiotherapy, surgery and chemotherapy, combined or not).

Types of interventions
We will include the following types of interventions, with focus on preventing and treating trismus in head and neck cancer patients:
- Physical therapy modalities (passive range of motion exercises, active range of motion exercises, manual therapy including joint and muscle mobilisation and electrotherapy, associated or not with medications or other interventions for trismus).
- Devices for stretching the muscles of mastication (stacked tongue depressors, Therabite jaw motion rehabilitation system, Dynasplint Trismus System, corkscrew devices).
- Drug therapy (pentoxifylline, botulinum toxin).
- Surgery (coronoidectomy).
If any other co-intervention is used, this must be used in both treatment arms. We will allow as co-interventions: pain medication, physical therapy interventions or home orientations.

The main comparison pairs are:
- physical therapy modalities versus no treatment;
- physical therapy modalities versus other active interventions (other type of physical therapy or drugs).

Other possible comparison pairs are:
- drug therapy versus placebo;
- drug therapy versus any other active interventions;
- coronoidectomy versus no treatment;
- coronoidectomy versus any other active interventions.

Types of outcome measures
We will analyse the following outcomes in the review, but we will not use them as a basis for including or excluding studies.

Primary outcomes
- Incidence of trismus (defined as mouth opening ≤ 35 mm) (to assess the effectiveness of preventive interventions).
- Oral mouth opening: measured by the maximal inter-incisal distance from the central incisors and alveolar ridges for
edentulous patients (to assess effectiveness for both prevention and treatment).

- Adverse events:
  - for physical therapy modalities and devices: pain in the temporomandibular joint; stiffness of mouth closing muscles;
  - for pentoxifylline: dizziness, nausea or other events related to the drug;
  - for botulinum toxin: pain, weakness of the mouth closing muscles and infection;
  - for surgery: facial nerve injury, haematoma, fibrosis, pain and infection.

**Secondary outcomes**

- Quality of life (assessed by validated scales or questionnaires, such as the University of Washington Quality of life questionnaire (UW-QOL) (Hassan 1993); the Functional Assessment of Cancer Therapy - General (FACT-G) (Cella 1993) or (FACT-HN) (List 1996); the European Organization for Research and treatment of Cancer (EORTC QLQ-H&N35 (Bjordal 1994)).
- Pain (measured by visual analogue scale or other validated instrument for evaluating pain in the temporomandibular joint).
- Range of motion of the temporomandibular joint (lateral movements and protrusion).
- Nutritional status (assessed by anthropometric measurements (weight change, arm muscle circumference or tricep skinfold thickness), or by any validated scale (patient-generated subjective global assessment - PG-SGA (Bauer 2002), the malnutrition screening tool - MST (Ferguson 1999)).
- Functional status of swallowing (assessed by videofluoroscopic modified barium swallow - VMBS, or other questionnaires with swallowing evaluation), mastication and speech assessed by validated instruments.
- Incidence of aspiration pneumonia.
- Adherence to treatment.

We will collect secondary outcomes from both groups of studies: prevention and treatment interventions for trismus. We will group outcomes into short-term (immediately after intervention to three months), medium-term (three to six months) and long-term (more than six months).

**Search methods for identification of studies**

The Cochrane ENT Information Specialist will conduct systematic searches for randomised controlled trials and controlled clinical trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

**Electronic searches**

Published, unpublished and ongoing studies will be identified by searching the following databases from their inception:

- the Cochrane Register of Studies ENT Trials Register (search to date);
- the Cochrane Register of Studies Online (search to date);
- Ovid MEDLINE (1946 to date);
  - Ovid MEDLINE (In-Process & Other Non-Indexed Citations);
  - PubMed (as a top up to searches in Ovid MEDLINE);
  - Ovid EMBASE (1974 to date);
  - Ovid CAB abstracts (1982 to date);
  - LILACS (search to date);
  - KoreaMed (search to date);
  - IndMed (search to date);
  - PakMediNet (search to date);
  - Web of Knowledge, Web of Science (1945 to date);
  - CNKI (searched via Google Scholar to date);
  - ClinicalTrials.gov, www.clinicaltrials.gov (search via the Cochrane Register of Studies to date);
  - World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (search to date);
  - ISRCTN, www.isrctn.com (search to date);
  - Google Scholar (search to date);
  - Google (search to date).

The subject strategies for databases will be modelled on the search strategies designed for CENTRAL and MEDLINE (Appendix 1). Where appropriate, these will be combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0, Box 6.4.b. (Handbook 2011)).

**Searching other resources**

We will scan the reference lists of identified publications for additional trials and contact trial authors if necessary. In addition, the Information Specialist will search Ovid MEDLINE, TRIP-database, The Cochrane Library and Google to retrieve existing systematic reviews relevant to this systematic review, so that we can scan their reference lists for additional trials. We will search for conference abstracts using the Cochrane ENT Trials Register and EMBASE.

**Data collection and analysis**

**Selection of studies**
We will download all titles and abstracts retrieved by electronic searching to a reference management database (EndNote) and remove duplicates of the same report. Two review authors (CAPV, VFMR) will independently examine the remaining references and exclude those studies that clearly do not meet the inclusion criteria. We will obtain copies of the full text of potentially relevant references. Two review authors (CAPV, VFMR) will independently assess the eligibility of the retrieved papers. Disagreements will be resolved by discussion between the two authors and if necessary by a third author (MM). We will document the reasons for exclusion of studies.

Data extraction and management

Two review authors (CAPV, VFMR) will independently extract all data. If any difference occurs between the authors, it will be resolved by a discussion or by appeal to the third author (MM). We will contact the authors of primary trials if there are doubts regarding missing data or methodological details of the trial. We will use a paper data collection form specially designed for the review to extract the following data: characteristics of the study (design, duration of study, risk of bias); participants (inclusion criteria, age, gender, stage of the disease, previous cancer treatments received, number enrolled in each group); intervention (type of intervention used, frequency and duration of therapy, co-interventions, drugs and other multidisciplinary interventions); outcomes (types of outcome measures and their definition, unit of measurement, timing of outcomes and for scales the upper and lower limits). The primary author (CAPV) will enter all data extracted into Review Manager 5.3 (RevMan 2014). He will also identify and resolve discrepancies in the data extraction forms.

For dichotomous outcomes (e.g. incidence of trismus, incidence of aspiration pneumonia, adverse events and adherence to treatment) we will extract the number of patients in each treatment arm who experienced the outcome of interest and the number of patients assessed at endpoint, in order to estimate a risk ratio. For continuous outcomes (e.g. range of motion of temporomandibular joint, quality of life and pain measures), we will extract the final value and standard deviation of the outcome of interest between intervention and control groups and respective 95% CI. Where possible we will extract data to allow an intention-to-treat analysis, in which participants will be analysed in the groups to which they were assigned. We will note the time points at which outcomes were collected and reported.

Assessment of risk of bias in included studies

CAPV and VFMR will undertake assessment of the risk of bias of the included trials independently, with the following taken into consideration, as guided by the Cochrane Handbook for Systematic Reviews of Interventions (Handbook 2011):
- sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We will use the Cochrane ‘Risk of bias’ tool in RevMan 5.3 (RevMan 2014), which involves describing each of these domains as reported in the trial and then assigning a judgement about the adequacy of each entry: ‘low’, ‘high’ or ‘unclear’ risk of bias. If any discordance occurs between the authors, we will resolve this by discussing it with a third author.

Measures of treatment effect

We will use the following measures of the effect of treatment:

For dichotomous outcomes, we will use the risk ratio (RR) and respective 95% confidence interval (CI). For statistically significant results, we will also present the number needed to treat to benefit (NNTB) and the number needed to treat to harm (NNTH). For continuous outcomes, we will use the difference in means between intervention and control groups and respective 95% CI if the trials measured the same outcome of interest and used the same scale. If not, we will use the standardised mean difference (SMD).

Unit of analysis issues

If we find any cluster-randomised studies, we will meta-analyse the effect estimates and their standard errors from correct analyses using the generic inverse-variance method. We will incorporate cross-over trials but we will only include data from the first period. We will perform sensitivity analyses to investigate the robustness of the results presented. If any trials have multiple treatment groups, we will divide the ‘shared’ comparison group into the number of treatment groups and comparisons between each treatment group and treat the split comparison group as independent comparisons.

Dealing with missing data

We will request missing data from trial authors with the objective of collecting data for missing outcomes, summary data and individuals. For continuous outcomes (e.g. pain, range of motion) we will calculate missing standard deviations from confidence intervals, P values or standard errors. If we judge data to be missing at random, we will analyse the available data, but if we judge data to be not missing at random we will perform a sensitive analysis excluding these studies to investigate the effects of missing data on the results presented.
Assessment of heterogeneity

We will assess heterogeneity between studies by visual inspection of forest plots, by estimation of the percentage of heterogeneity between trials that cannot be ascribed to sampling variation (I² statistic) (Higgins 2003), by the Chi² test considering statistically significant P values inferior to 0.10 (Deeks 2001) and, if possible, by subgroup analyses. If there is evidence of substantial or considerable heterogeneity, we will investigate and report the possible reasons for this.

Assessment of reporting biases

We will use a test to assess funnel plot asymmetry if we identify more than 10 studies that can be included in a meta-analysis for a primary outcome (Egger 1997). We will interpret the results of the test in the light of visual inspection of funnel plots as recommended by the Cochrane Handbook for Systematic Reviews of Interventions (Handbook 2011).

Data synthesis

If we identify sufficient studies with comparable participants that underwent similar interventions for the prevention or treatment of trismus, we will perform meta-analyses using RevMan 5.3 (RevMan 2014). We will undertake a narrative synthesis of the included studies if there is clear evidence of poor homogeneity.

- For any dichotomous outcomes, we will calculate the risk ratio for each study and pool these.
- For continuous outcomes, we will pool the difference in means between the treatment arms at the end of follow-up if all trials measured the outcome on the same scale; otherwise we will pool data using the standardised mean difference.

We will use a random-effects model with inverse variance weighting for all meta-analyses (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

We will use subgroup analysis to investigate heterogeneity between specific groups of participants. It will be based on the following:

- Gender (male versus female).
- Severity of trismus: mild (decreased range of motion without impaired eating), moderate (decreased range of motion requiring small bites, soft foods or purées) and severe (decrease range of motion with inability to adequately feed or drink).
- Clinical stage of cancer: comparing advanced stage participants (III and IV) with non-advanced stage participants (I and II).
- Tumour site: oral cavity, nasopharynx, oropharynx, hypopharynx and larynx.
- Oncological treatments: patients that received concomitant chemoradiation versus patients that received surgery with adjuvant chemotherapy and/or radiotherapy; also grouping studies that included patients that received surgery alone versus radiotherapy alone.

- Period of intervention: range in time from the end of oncological treatments to the beginning of intervention: grouping studies with less than one year and more than one year.
- Dental status: edentulous versus dentulous participants.
- Trismus onset: grouping participants that developed trismus before oncological treatment versus after oncological treatment.

Sensitivity analysis

To test the robustness of the evidence, we will perform sensitivity analysis excluding studies with high risk of bias and unclear risk of bias from studies with low risk of bias.

GRADE and 'Summary of findings' table

Two authors will independently use the GRADE approach to rate the overall quality of evidence. The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct and we will apply this in the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high quality of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low quality implies that any estimate of effect obtained is very uncertain. The GRADE approach rates evidence from RCTs that do not have serious limitations as high quality. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision; and
- publication bias.

We will include a 'Summary of findings' table, constructed according to the recommendations described in Chapter 10 of the Cochrane Handbook for Systematic Reviews of Interventions (Handbook 2011). We will include the following outcomes in the 'Summary of findings' table: the primary outcomes incidence of trismus, oral mouth opening and adverse events, and the secondary outcomes quality of life, pain, nutritional status and functional status.

ACKNOWLEDGEMENTS

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure, Cochrane Programme
Grant or Cochrane Incentive funding to Cochrane ENT. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

REFERENCES

Additional references

Aaronson 1993

Bauer 2002

Bensadoun 2011

Bhrany 2007

Bjordal 1994

Buchbinder 1993

Cella 1993

Chua 2001

Deeks 2001

DerSimonian 1986

Dijkstra 2006

Egger 1997

Ferguson 1999

Ferlay 2008

Gupta 2014

Handbook 2011

Hartl 2008

Hassan 1993
Higgins 2003

Kent 2008

Kim 2014

Lee 2012

Lehman 2015

List 1996

Melchers 2009

Mulder 2012

National Cancer Institute 2010

RevMan 2014 [Computer program]

Rubiony 2012

Royal 2003

Scott 2011

Shulman 2008

Stubblefield 2010

Tang 2011

Teguh 2008

van der Molen 2011

Wang 2005

Ward 1987

* Indicates the major publication for the study
### Appendix 1. CENTRAL and MEDLINE search strategies

**CENTRAL**

1. MeSH descriptor: [Head and Neck Neoplasms] this term only
2. MeSH descriptor: [Mouth Neoplasms] explode all trees
3. MeSH descriptor: [Otorhinolaryngologic Neoplasms] explode all trees
4. MeSH descriptor: [Jaw Neoplasms] explode all trees
5. MeSH descriptor: [Pharynx] explode all trees
6. MeSH descriptor: [Mouth] explode all trees
7. MeSH descriptor: [Jaw] explode all trees
8. #5 or #6 or #7
9. MeSH descriptor: [Neoplasms] explode all trees
10. #8 and #9
11. ((mouth or gingival or lip or lips or palat* or tongue or Laryn* or pharyn* or hypopharyn* or oropharyn* or tonsil* or otorhinolaryngologic or oral or nasopharyn* or nose or nasal or paranasal or jaw or mandib* or throat or maxil*) near (cancer* or carcinoma* or neoplas* or tumor* or tumour* or malignan* or SCC)).ti,ab,kw
12. (head near neck near (cancer* or carcinoma* or neoplas* or tumor* or tumour* or malignan* or SCC)).ti,ab,kw
13. (HNSCC or SCCHN or OP-SCC or OPSCC or LPSCC or NPC).ti,ab,kw
14. #1 or #2 or #3 or #4 or #10 or #11 or #12 or #13
15. MeSH descriptor: [Temporomandibular Joint Disorders] explode all trees
16. MeSH descriptor: [Masticatory Muscles] explode all trees
17. MeSH descriptor: [Pentoxifylline] explode all trees
18. MeSH descriptor: [Trismus] explode all trees
19. MeSH descriptor: [Botulinum Toxins] explode all trees
20. MeSH descriptor: [Range of Motion, Articular] explode all trees
21. MeSH descriptor: [Myositis] this term only
22. MeSH descriptor: [Pentoxifylline] this term only
23. MeSH descriptor: [Motion Therapy, Continuous Passive] explode all trees
24. MeSH descriptor: [Muscle Stretching Exercises] explode all trees
25. (trismus or ((interincis* or incisal*) near (distance or open*)))ti,ab,kw
26. (Temporomandibular or TMJ or Myositis or polymyositis):ti,ab,kw
27. ((mouth or jaw or mandibular or Oromandibular or masticat* or masseter) near (open* or motion or mobiliz* or movement or mobility or function or hypomobil* or ROM or dystonia or)

**MEDLINE**

1. exp "Head and Neck Neoplasms"/
2. exp mouth neoplasms/
3. exp otorhinolaryngologic neoplasms/
4. exp jaw neoplasms/
5. exp larynx/ or exp pharynx/ or exp Mouth/ or exp jaw/
6. exp Neoplasms/
7. 5 and 6
8. ((mouth or gingival or lip or lips or palat* or tongue or Laryn* or pharyn* or hypopharyn* or oropharyn* or tonsil* or otorhinolaryngologic or oral or nasopharyn* or nose or nasal or paranasal or jaw or mandib* or throat or maxil*) adj6 (cancer* or carcinoma* or neoplas* or tumor* or tumour* or malignan* or SCC)).ab,ti
9. (head adj3 neck adj6 (cancer* or carcinoma* or neoplas* or tumor* or tumour* or malignan* or SCC)).ab,ti
10. (HNSCC or SCCHN or OP-SCC or OPSCC or LPSCC or NPC).ab,ti
11. 1 or 2 or 3 or 4 or 7 or 8 or 9 or 10
12. exp Trismus/
13. exp Temporomandibular Joint Disorders/
14. exp Masticatory Muscles/
15. exp Myositis/
16. exp Motion Therapy, Continuous Passive/
17. (trismus or ((interincis* or incisal*) adj3 (distance or open*))) or IID).ab,ti
18. (Temporomandibular or TMJ or Myositis or polymyositis).ab,ti
19. ((mouth or jaw or mandibular or Oromandibular or masticat* or masseter) adj3 (open* or motion or mobiliz* or movement or mobility or function or hypomobil* or ROM or dystonia or dysfunction*)).ab,ti
20. ((mouth or jaw or mandibular or Oromandibular or masticat* or masseter) adj6 musc* adj3 (strength* or stretch* or flex* or inflammm* or exercise* or fibrosi* or fibrotic or therap* or elastic* or train* or spasmm*)).ab,ti
21. (therabite or dynasplint or corkscrew or (stack* adj3 tongue) or (tongue adj3 depressor*) or coronoidectom*).ab,ti
22. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. 11 and 22
CONTRIBUTIONS OF AUTHORS

Conceiving the review: Carvalho APV and Vital FMR
Designing the review: Carvalho APV and Vital FMR
Co-ordinating the review: Vital FMR
Designing search strategies: Carvalho APV
Undertaking searches: Carvalho APV
Screening search results: Carvalho APV and Vital FMR
Organising retrieval of papers: Carvalho APV and Vital FMR
Screening retrieved papers against eligibility criteria: Carvalho APV, Vital FMR, McNeely ML
Appraising quality of papers: Carvalho APV, Vital FMR, McNeely ML
Extracting data from papers: Carvalho APV, Vital FMR, McNeely ML
Writing to authors of papers for additional information: Carvalho APV and McNeely ML
Providing additional data about papers: Carvalho APV and McNeely ML
Obtaining and screening data on unpublished studies: Carvalho APV, Vital FMR, McNeely ML
Entering data into RevMan: Carvalho APV
Analysis of data: Carvalho APV, Vital FMR, McNeely ML
Interpretation of data: Carvalho APV, Vital FMR, McNeely ML
Providing a methodological perspective: Carvalho APV, Vital FMR, McNeely ML
Providing a clinical perspective: Vital FMR
Writing the review (or protocol): Carvalho APV
Providing general advice on the review: Vital FMR
DECLARATIONS OF INTEREST

Alan PV Carvalho: none known.
Margaret L McNeely: none known.

SOURCES OF SUPPORT

Internal sources
- No sources of support supplied

External sources
- National Institute for Health Research, UK.
  Infrastructure funding for Cochrane ENT