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Botulinum toxin for masseter hypertrophy

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ABSTRACT

Background
Benign masseter muscle hypertrophy is an uncommon clinical phenomenon of uncertain aetiology which is characterised by a soft swelling near the angle of the mandible. The swelling may on occasion be associated with facial pain and can be prominent enough to be considered cosmetically disfiguring. Varying degrees of success have been reported for some of the treatment options for masseter hypertrophy, which range from simple pharmacotherapy to more invasive surgical reduction. Injection of botulinum toxin type A into the masseter muscle is generally considered a less invasive modality and has been advocated for cosmetic sculpting of the lower face. Botulinum toxin type A is a powerful neurotoxin which is produced by the anaerobic organism Clostridium botulinum and when injected into a muscle causes interference with the neurotransmitter mechanism producing selective paralysis and subsequent atrophy of the muscle.

Objectives
To assess the effects of botulinum toxin type A in the management of benign bilateral masseter hypertrophy.

Search strategy
We searched the following databases in August 2008: the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2008, issue 3); MEDLINE (via PubMed) (1950 to August 2008); EMBASE (via embase.com) (1980 to August 2008); and LILACS via BIREME. We searched two bibliographic databases of regional journals which may be expected to contain relevant trials (IndMED and Iranmedex) using free text terms appropriate for this review.

Selection criteria
Randomised controlled clinical trials (RCTs) and controlled clinical trials (CCTs) comparing intra-masseteric injections of botulinum toxin versus placebo administered for cosmetic facial sculpting in individuals of any age with bilateral benign masseter hypertrophy, which had been self-evaluated and confirmed by clinical and radiological examination. We excluded participants with unilateral or compensatory contralateral masseter hypertrophy resulting from head and neck radiotherapy.

Data collection and analysis

Botulinum toxin for masseter hypertrophy (Review)
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Two review authors conducted screening of studies in duplicate and independently, and although no eligible trials were identified, the two authors had planned to extract data independently and assess trial quality using standard Cochrane Collaboration methodologies.

Main results

We retrieved 167 references to studies, none of which matched the inclusion criteria for this review and all of which were excluded.

Authors’ conclusions

We were unable to identify any randomised controlled trials on the efficacy of intra-masseteric injections of botulinum toxin for people with bilateral benign masseter hypertrophy. The absence of high level evidence for the effectiveness of this intervention emphasises the need for well-designed, adequately powered, randomised controlled clinical trials (RCTs) and controlled clinical trials (CCTs).

PLAIN LANGUAGE SUMMARY

Botulinum toxin type A for benign bilateral masseter hypertrophy

Masseter muscle hypertrophy occurs as a soft enlargement of the jaw muscles near the angle of the lower jaw and seldom presents a major health problem. However, in some individuals the swelling can be associated with pain or may be so large that it causes facial disfigurement. Although the cause of the condition is unclear it does appear to be more common in certain ethnic groups.

Symptoms such as pain can be treated with muscle relaxants and may also include bite adjustments or involve the use of splints on the teeth. Surgical reduction of the jaw muscle or injections of botulinum toxin type A directly into the muscle are other treatment options.

Although the use of botulinum toxin injections might appear to have certain advantages over surgery the authors in this review did not find any high quality studies evaluating the effectiveness and potential harms of botulinum toxin type A in the management of benign masseter hypertrophy. The authors concluded that future research should aim to provide evidence for people to make informed decisions about whether botulinum toxin type A is effective and that further randomized controlled trials should be well designed and reported according to the ‘Consolidated Standards of Reporting Trials (CONSORT)’ statement (http://www.consort-statement.org).
BACKGROUND

Aetiology and prevalence

Benign masseter muscle hypertrophy is an uncommon clinical phenomenon of uncertain aetiology. It is characterised by a soft swelling, near the angle of the mandible, which can be associated with facial pain. The hypertrophy can be prominent enough to be considered cosmetically disfiguring. More than 250 cases of benign bilateral masseter muscle hypertrophy have been reported since its first published description (Legg 1880). Prevalence data are scarce but in a recent study (Sannomya 2006) 90 (4%) of the patients with masseter hypertrophy were less than 10 years and 3% were over 40 years of age (mean 30 years), with a male to female ratio of 1:1. The aetiology of masseter muscle hypertrophy has been attributed to a number of factors: emotional stress, chronic bruxism, masseteric hyper-function and para-function, and microtrauma (Harriman 1996; Serrat 1998; Wilson 1990). It reportedly occurs most frequently among Pacific Asians and is associated with ethnic characteristics (prominence of the mandibular angle) and dietary habits (Jin Park 2007). The findings of several investigators suggest that the increase in muscle size is not caused by work hypertrophy but as a result of compensatory enlargement due to lack of a certain type of muscle fibre. Tests have shown that the composition of muscle fibres in the enlarged masseter is very different from that in muscles with ‘work hypertrophy’ as well as that in normal masseter muscles (Satoh 2001), suggesting that the term ‘hypertrophy’ can be potentially misleading.

Other possible causes and associations have been suggested: clenbuterol induced hypertrophy, overuse of anabolic steroids (Skoura 2001), localised scleroderma and facial hemi-atrophy (Kim 2000), and a multifactorial origin in combination with a genetic basis (Giudice 1992). Benign masseter hypertrophy is also compatible with a rare genetic condition known as hypertrophic branchial myopathy (Kitagawa 2000).

Description of the condition

Signs and symptoms

Bilateral enlargement of the masseter muscles is often accompanied by pain, which may be intermitent and can be confused with pain arising from the parotid gland (Newton 1999; Nishida 1995). Clinical examination usually reveals a soft tissue mass near the angle of the mandible, which becomes more prominent on clenching of the teeth (Sannomya 2006). Limitation of mouth opening has been reported in some cases and particularly where the muscles are focally dystonic with tension in the region of the hypertrophied muscle (Papapetropoulos 2006). Midline deviation has also been observed in some cases, as well as masseteric (hemi-masticatory) spasm (Kim 2000). It has also been suggested that the hypertrophied muscles of the jaw can lead to increased pressure in the temporo-mandibular joints (TMJ), which can generate severe pain and mimic temporo-mandibular dysfunction syndrome (TMD) (Chikani 2003).

Diagnosis

Diagnosis cannot solely be based on clinical findings and there are conflicting recommendations in the literature for investigating patients presenting with benign bilateral masseter hypertrophy.

- Standard radiographs (not essential but can sometimes assist in diagnosis).
- Computed tomographic (CT) scan, magnetic resonance imaging (MRI) scan, or both (considered the gold standard in confirming a clinical suspicion).
- Muscle biopsy.
- Morphometric analysis.
- Ultrasonographic measurement.
- Electromyographic measurement.

Description of the intervention

Treatment options

A range of treatment modalities have been reported with variable degrees of success and failure.

1. Pharmacotherapy: anxiolytics, muscle relaxants and antidepressants.
2. Dental restorations and occlusal adjustments to correct premature contacts and malocclusions, and prevention of para-functional habits with orthotic appliances.
3. Botulinum toxin type A (BtA) injections into the muscle.
4. Radiofrequency volumetric reduction.
5. Intra-oral and extra-oral surgical reduction of masseter size, removal of mandibular angle, neurectomy of the masseteric nerve, and resection of the buccal fat pad.

How the intervention might work

Botulinum toxin type A (BtA) is a powerful neurotoxin produced by the anaerobic organism Clostridium botulinum. When botulinum toxin type A is injected into a muscle it causes interference with the neurotransmitter mechanism producing selective paralysis and subsequent atrophy of the muscle.

Why it is important to do this review

Surgery has historically been the standard treatment for cosmetic reduction of masseter hypertrophy, but injection of botulinum toxin type A into the muscle, which is generally considered a less invasive modality, has more recently been advocated. Although there have been several studies and case reports, to the best of our knowledge there has not been a systematic review of the effectiveness of botulinum toxin type A for the treatment of masseter hypertrophy.
OBJECTIVES
To assess the effects of botulinum toxin type A in the management of benign bilateral masseter hypertrophy.

METHODS
Criteria for considering studies for this review
Types of studies
Randomised controlled clinical trials (RCTs) and controlled clinical trials (CCTs).
Types of participants
Individuals in any age group with bilateral benign masseter hypertrophy which had been self-evaluated and confirmed by clinical and radiological examination. In view of the possible clinical diversity in presentation, we excluded studies involving participants with unilateral or compensatory contra lateral masseter hypertrophy resulting from head and neck radiotherapy from this review.

Types of interventions
Transcutaneous intra-masseteric injections of botulinum toxin versus placebo. We sought to include studies in which the intervention had been administered for cosmetic facial sculpting and where the masseter hypertrophy may have been co-associated with temporo-mandibular dysfunction syndrome (TMD). We considered studies involving a single injection cycle in addition to studies in which all participants entered into a trial had received repeat injections at similar time periods.

Types of outcome measures
Assessment was to include a follow-up period of up to two years after the intervention.

Primary outcomes
1. Self-assessed improvement in facial appearance and patient satisfaction using any validated scale or questionnaire.
2. Change in pain/discomfort (associated with the temporo-mandibular joints or jaw muscles): patient-assessed using any recognised validated pain scale.

Secondary outcomes
1. Objective evaluation of the change in facial contour, involving physical measurement.
   (a) Clinical photography.
   (b) Radiological measurement: three-dimensional computed tomographic (CT) scans, magnetic resonance (MR) imaging, ultrasonographic measurements of the thickness of the masseter muscle.

Adverse outcomes
We intended to report on any specific adverse effects, systemic or local toxicity, any clinically diagnosed hypersensitivity or other unacceptable or adverse events associated with this treatment.

Search methods for identification of studies
Electronic searches
For the MEDLINE search, we ran the subject search with the Cochrane Highly Sensitive Search Strategy (CHSS) for identifying randomised trials in MEDLINE: sensitivity maximising version (2008 revision) as referenced in Chapter 6.4.11.1 and detailed in box 6.4.10 of the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 (updated February 2008) (Higgins 2008).

Databases searched
We searched the following databases on the dates indicated:
- the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2008, Issue 3);
- MEDLINE (via Pubmed) (1950 to August 2008);
- EMBASE (via embase.com) (from 1980 to August 2008); and
- LILACS (via BIREME) (22 August 2008).

Although we did not search the Cochrane Movement Disorders Group Trials Register we clarified that it did not contain any relevant studies.

We also searched IndMED, a bibliographic database of Indian journals, available at (http://indmed.nic.in/) and a similar Iranian database, Iranmedex, available at (www.irannmedex.com), using free text terms appropriate for this review (20 August 2008).

For the detailed search strategies applied to each of the databases see Appendix 1; Appendix 2; Appendix 3 and Appendix 4.

Searching other resources
We did not conduct any handsearching of journals but searched the reference lists of relevant articles in addition to the review authors’ personal database of trial reports. We also contacted a number of investigators by electronic mail to ask for details of additional published and unpublished trials.

Language
There were no language restrictions on included studies and we arranged to translate any relevant non-English papers.

Data collection and analysis
Selection of studies
Two review authors (Zbys Fedorowicz (ZF) and Mohammed Al Muharraqi (MAM)) independently assessed the abstracts of studies resulting from the searches. We obtained full copies of all relevant and potentially relevant studies, those appearing to meet the inclusion criteria, and those for which there were insufficient data in the title and abstract to make a clear decision. The two review authors independently assessed the full text papers and resolved any disagreement on the eligibility of included studies through discussion and consensus, or through a third party (Mona Nasser (MN)). We excluded all irrelevant records and noted details of the studies and the reasons for their exclusion in the ‘Characteristics of excluded studies’ table in RevMan 5 (RevMan 2008).
Data extraction and management

Although no studies were identified for inclusion in this review the following methods of data extraction, assessment of risk of bias and data management will apply for subsequent updates, and when future studies are identified.

We will enter study details into the 'Characteristics of included studies' table in RevMan 5. The review authors will collect outcomes data using a pre-determined form designed for this purpose. Both authors (ZF and MAM) will enter extracted data into RevMan 5. The review authors will only include data if there is an independently reached consensus. We will resolve any disagreements by consulting with a third review author (RAB).

We will extract the following details.

1. Trial methods: (a) method of allocation: (b) masking of participants, trialists and outcomes assessors: (c) exclusion of participants after randomisation and proportion and reasons for losses at follow up.
2. Participants: (a) country of origin and location: private clinic or academic institute: (b) sample size: (c) age: (d) sex: (e) inclusion and exclusion criteria.
3. Intervention: (a) type, dosage, route of administration: (b) length of time in follow up.
4. Control: (a) type, dosage, route of administration: (b) length of time in follow up.
5. Outcomes: (a) primary and secondary outcomes mentioned in the 'Types of outcome measures' section of this review.

If stated, we will record the sources of funding of any of the included studies.

The review authors will use this information to help them assess heterogeneity and the external validity of the trials.

Assessment of risk of bias in included studies

Each review author will grade the selected trials and assess every trial using a simple contingency form following the domain-based evaluation described in the Cochrane Handbook for Systematic Reviews of Interventions 5.0.0 (Higgins 2008). We will compare the evaluations and discuss and resolve any inconsistencies and disagreements.

We will assess the following domains as 'Yes' (i.e. low risk of bias), 'Unclear' (uncertain risk of bias) or 'No' (i.e. high risk of bias):
1. sequence generation;
2. allocation concealment;
3. blinding (of participants, personnel and outcome assessors);
4. incomplete outcome data;
5. selective outcome reporting.

We will report these assessments for each individual study in the 'Risk of bias in included studies' table.

Measures of treatment effect

We will conduct analysis at the same level as the allocation. We will calculate risk ratios and their 95% confidence intervals (CIs) for all dichotomous data and as weighted mean difference (with 95% confidence intervals) for continuous outcomes, using the Peto fixed-effect method.

As it is likely that the timing of outcome assessment will vary between studies we will consider grouping the data according to the following time-points: six months and one and two years.

Unit of analysis issues

We expect to include trials of participants with bilateral hypertrophy in which the masseter muscles of an individual participant were the units of randomisation and subsequent analysis.

Dealing with missing data

We will make attempts to retrieve missing data from the investigators for any of the included trials, and if unsuccessful or the discrepancies are significant, we will provide a narrative synthesis of the data as reported.

Assessment of heterogeneity

We will 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. In view of the expectation of a degree of clinical heterogeneity between the studies we intend using the random-effects model with studies grouped by action. Statistical heterogeneity will be assessed using a Chi² test and the I² statistic, where I² values over 50% indicate moderate to high heterogeneity (Higgins 2003).

Assessment of reporting biases

To assess publication bias we will follow the recommendations on testing for funnel plot asymmetry as described in section 10.4.3.1 of the Cochrane Handbook for Systematic Reviews of Interventions 5.0.0 (Higgins 2008), and we will explore these in the Discussion if appropriate.

Data synthesis

We will seek statistical support from the Cochrane Movement Disorders Group. Two review authors (ZF and MAM) will analyse the data and report them as specified in Chapter 9 of the Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.0 (Higgins 2008).

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

Subgroup analysis and investigation of heterogeneity

If data are available we will analyse the data by splitting them into sub-categories by dose, i.e. a total low dose of botulinum toxin type A≤150 U per muscle and a medium to high dose of botulinum toxin type A>150 U per muscle.

Sensitivity analysis

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, blinding of outcomes assessment and completeness of follow up.

**RESULTS**

**Description of studies**

See: Characteristics of excluded studies.
No studies were included in this review.

**Results of the search**

The search strategy retrieved 167 references to studies (72 CENTRAL, 75 MEDLINE, 19 EMBASE, one LILACS). After examination of the titles and abstracts of these references, we eliminated all but 19 and excluded them from further review. We obtained full text copies of those remaining studies, translated them into the English language as required and subjected them to further evaluation. We examined the bibliographical references of these studies and, as with our searches of the IndMED and Iranmedex databases, they did not provide any further citations to potentially eligible studies. Two authors, Mohammed Al Muharraqi (MAM) and Zbys Fedorowicz (ZF), independently assessed all of the full text papers, and resolved any disagreement on their eligibility for this review through discussion and consensus.

**Included studies**

We retrieved a number of studies in our comprehensive search of the literature but none were eligible and therefore no trials were included in this review.

**Excluded studies**

We excluded all records which did not match our inclusion criteria and noted the reasons for their exclusion in the ‘Characteristics of excluded studies’ table.

**Risk of bias in included studies**

No trials were included.

**Effects of interventions**

None of the studies retrieved in our searches met our inclusion criteria and therefore no data were available for analysis.

**DISCUSSION**

The comprehensive search used in this review provided few references to trials and thus the lack of relevant randomised controlled trials as well as any robust evidence to support or refute the effectiveness of botulinum toxin for masseter hypertrophy, proved to be somewhat disappointing. Over the last 10 years a number of case reports and several recent cohort studies have sought to illustrate the effectiveness of botulinum toxin type A injections for benign masseter muscle hypertrophy, but questions remain unanswered as to whether management options based on this intervention can be considered both effective and safe.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

A lack of consensus on the aetiology of benign masseter hypertrophy together with an increasing concern about the long-term effects of botulinum toxin type A (BtA) would appear to underline the fact that its therapeutic benefits remain unclear. Therefore, before selecting this treatment option clinicians need to carefully consider, and indeed discuss, not only its benefits but also the possibility and implications of any potential harms with their patients.

**Implications for research**

A review of botulinum toxin for masseter hypertrophy provides an example of the implications for research when no eligible studies had been found. This review highlights the need for randomised or controlled clinical trials to evaluate the effectiveness of botulinum toxin in reducing the size and volume of the masseter muscles in people diagnosed with bilateral benign masseter hypertrophy. Although further research is required, conducting randomised controlled trials for this intervention will present challenges in terms of the possible unwillingness of participants to be enrolled into a trial where they may be allocated to an intervention which will result in unilateral facial deformity for the duration of the trial. Outcomes assessments should also aim to include both subjective and objective pre-post treatment evaluations, such as maximum bite force, clinical photography, physical measurements of changes in facial contour, cephalometry and electromyographic studies of masseter function.

Any future trials will also need to be rigorous in design and delivery, with subsequent reporting to include high quality descriptions of all aspects of methodology to enable appraisal and interpretation of results, and conform with the Consolidated Standards of Reporting Trials (CONSORT) statement (http://www.consortstatement.org/).

**ACKNOWLEDGEMENTS**

The review authors would like to acknowledge the assistance they have received from members of the Cochrane Movement Disorders Group and for the helpful comments on this review from the referees. We would like to thank Emma Low of GKT Dental Institute, King’s College Hospital University of London, who provided...
References to studies excluded from this review

Ahn 2007 [published data only]

Bhogal 2006 [published data only]

Castro 2005 [published data only]

Chikani 2003 [published data only]

Choe 2005 [published data only]

Hui 2002 [published data only]

IÅŸeri 2004 [published data only]

Kim 2003 [published data only]

Lee 2007 [published data only]

Misckowski 2005 [published data only]

Moore 1994 [published data only]

Niamtu 1999 [published data only]

Park 2003 [published data only]

Rogers 1995 [published data only]

Smyth 1994 [published data only]

To 2001 [published data only]

von Lindern 2001 [published data only]

von Lindern 2003 [published data only]

Yu 2007 [published data only]

Additional references

Giudice 1992
**Harriman 1996**

**Higgins 2003**

**Higgins 2008**

**Jin Park 2007**

**Kim 2000**

**Kitagawa 2000**

**Legg 1880**

**Newton 1999**

**Nishida 1995**

**Papapetropoulos 2006**

**RevMan 2008**

**Sannomya 2006**

**Satoh 2001**

**Serrat 1998**

**Skoura 2001**

**Wilson 1990**

* Indicates the major publication for the study

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**CHARACTERISTICS OF STUDIES**

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for Exclusion</th>
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<tbody>
<tr>
<td>Ahn 2007</td>
<td>Non RCT</td>
</tr>
<tr>
<td>Bhogal 2006</td>
<td>Review with no additional RCTs</td>
</tr>
<tr>
<td>Castro 2005</td>
<td>Non RCT</td>
</tr>
</tbody>
</table>

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Botulinum toxin for masseter hypertrophy (Review)

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<table>
<thead>
<tr>
<th>Author</th>
<th>Study Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chikani 2003</td>
<td>Characteristics of participants do not match our inclusion criteria, non RCT</td>
</tr>
<tr>
<td>Choe 2005</td>
<td>Non RCT</td>
</tr>
<tr>
<td>Hui 2002</td>
<td>Letter, no additional RCTs</td>
</tr>
<tr>
<td>IÄYeri 2004</td>
<td>Case study with no additional references to RCTs</td>
</tr>
<tr>
<td>Kim 2003</td>
<td>Non RCT, single intervention no control</td>
</tr>
<tr>
<td>Lee 2007</td>
<td>Non RCT</td>
</tr>
<tr>
<td>Mischkowski 2005</td>
<td>Case series in German (translated by Mona Nasser)</td>
</tr>
<tr>
<td>Moore 1994</td>
<td>n of 1 study and results not generalisable</td>
</tr>
<tr>
<td>Niamtu 1999</td>
<td>Review, no additional RCTs</td>
</tr>
<tr>
<td>Park 2003</td>
<td>No control, non RCT</td>
</tr>
<tr>
<td>Smyth 1994</td>
<td>Non RCT</td>
</tr>
<tr>
<td>To 2001</td>
<td>Non RCT</td>
</tr>
<tr>
<td>von Lindern 2001</td>
<td>Non RCT</td>
</tr>
<tr>
<td>von Lindern 2003</td>
<td>RCT but no participants with masseter hypertrophy</td>
</tr>
<tr>
<td>Yu 2007</td>
<td>Non RCT</td>
</tr>
</tbody>
</table>

RCT = randomised controlled trial.
DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. Medline (via Pubmed) search strategy

((((Masseter muscle [mh]) OR Mandible [mh] OR (Facial Muscles [mh]) OR masset*) OR (((Face OR Facial) AND Muscle*) OR (Masseter* AND Muscle*) OR Mandibl* OR (Myofac*)) AND (Hypertrophy [mh] OR hypertrop* OR enlarge* OR thick*) OR (Myofascial Pain Syndromes [Mesh])) AND ((Botulinum Toxins [mh]) OR (Botul* AND toxi*) OR (Botul* AND inject*)))

This was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity-maximising version (PubMed format).

#1 randomized controlled trial [pt]
#2 controlled clinical trial [pt]
#3 randomized [tiab]
#4 placebo [tiab]
#5 clinical trials as topic [mesh: noexp]
#6 randomly [tiab]
#7 trial [ti]
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 humans [mh]
#10 #8 and #9

Appendix 2. EMBASE (via embase.com) search strategy

#1 'botulinum toxin'/exp AND [embase]/lim
#2 botul* AND toxi* AND [embase]/lim
#3 botul* AND inject* AND [embase]/lim
#4 #1 OR #2 OR #3
#5 ('botulinum toxin'/exp AND [embase]/lim) OR (botul* AND toxi* AND [embase]/lim) OR (botul* AND inject* AND [embase]/lim)
#6 'hypertrophy'/exp OR hypertrop* OR enlarge* OR thick* AND [2004-2008]/py
#7 random$ OR factorial$ OR crossover$ OR cross AND over$ OR placebo$ OR double$ AND adj AND blind$ OR single$ AND adj AND blind$ OR assign$ OR allocat$ OR volunteer$ OR 'crossover procedure'/exp OR 'double blind' AND procedure OR randomized AND controlled AND trial OR 'single blind' AND procedure AND [embase]/lim
#8 (#5 OR #6) AND #7
#9 spacer (("face'/exp OR facial) AND muscle*) OR (masseter* AND muscle*) OR mandibl* OR (myofac*) AND [embase]/lim
#10 (#8 OR #9) AND #4

Appendix 3. LILACS (via Bireme) search strategy

((((Masseter muscle [Descritor de assunto]) OR (Mandible [Descritor de assunto]) OR (Facial Muscles [Descritor de assunto]) OR masset$) OR (((Face OR Facial) AND Muscle$) OR (Masseter$ AND Muscle$)) OR Mandibl$ OR (Myofac$)) AND (Hypertrophy [Descritor de assunto] OR hypertrop$ OR enlarge$ OR thick$)) OR (Myofascial Pain Syndromes [Descritor de assunto]) AND ((Botulinum Toxins [Descritor de assunto]) OR (Botul$ AND toxi$) OR (Botul$ AND inject$))
Appendix 4. CENTRAL

#1 Botulin* AND Toxin*
#2 Masseter Muscle OR Masset*
#3 Mandib* OR (Fac* AND Muscle*)
#4 (#2 OR #3)
#5 #1 AND #4

HISTORY

Review first published: Issue 1, 2009

15 September 2008 Amended Change in author string.

CONTRIBUTIONS OF AUTHORS

Zbys Fedorowicz (ZF), Mohammed Al Muharraqi (MAM), Reem Al Bareeq (RAB) and Mona Nasser (MN) were responsible for:

- organising the retrieval of papers;
- writing to authors of papers for additional information;
- screening search results;
- screening retrieved papers against inclusion criteria;
- appraising the quality of papers;
- data collection for the review;
- extracting data from papers; and
- obtaining and screening data on unpublished studies.

ZF and Jaffer Al Bareeq (JAB) were responsible for entering any extracted data into RevMan.
ZF and MAM were responsible for the analysis and interpretation of data.
ZF, MAM and RAB were responsible for:

- designing the review;
- co-ordinating the review; and
- data management for the review.

All review authors contributed to writing the review.
ZF and MAM conceived the idea for the review and are the guarantors for the review.
DECLARATIONS OF INTEREST

There are no financial conflicts of interest and the 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

We added Adverse outcomes under 'Types of outcome measures'.