Botulinum toxin for upper oesophageal sphincter dysfunction in neurological swallowing disorders (Review)

Regan J, Murphy A, Chiang M, McMahon BP, Coughlan T, Walshe M

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Julie Regan[1,2], Anne Murphy[3], Mindy Chiang[2], Barry P McMahon[4,5], Tara Coughlan[6], Margaret Walshe[2]

[1]Speech & Language Therapy Department, Tallaght Hospital, Dublin, Ireland. [2]Clinical Speech and Language Studies, Trinity College Dublin, Dublin, Ireland. [3]Tallaght Hospital Library, Tallaght Hospital, Dublin, Ireland. [4]Medical Physics & Clinical Engineering, Tallaght Hospital, Dublin, Ireland. [5]Department of Clinical Medicine, Trinity College Dublin, Dublin, Ireland. [6]Age Related Health Care, Tallaght Hospital, Dublin, Ireland

Contact address: Julie Regan, reganju@tcd.ie.

A B S T R A C T

Background

Adequate upper oesophageal sphincter (UOS) opening is critical to safe and efficient swallowing due to the close proximity of the UOS to the airway entrance. Many people with neurological conditions, progressive and non-progressive, present with UOS dysfunction. The consequences for the person include difficulty swallowing food with subsequent choking and aspiration (passage of material into the trachea beyond the level of the true vocal cords). Clinical complications include aspiration pneumonia, weight loss, dehydration and malnutrition. Tube feeding is often indicated but is associated with increased mortality. Quality of life is also frequently impacted. A range of interventions exist that aim to improve UOS function and swallowing. These include compensatory strategies, rehabilitation techniques, pharmacological interventions and surgery. Over the last two decades, botulinum toxin has been gaining popularity as an intervention for UOS dysfunction, with some evidence to suggest that it is successful in improving swallow function. Despite a number of studies investigating its efficacy, there is a lack of consensus regarding whether this intervention is effective in improving swallowing for individuals with UOS dysfunction associated with neurological disease.

Objectives

To establish the efficacy and safety of botulinum toxin use aimed at improving UOS dysfunction in people with swallowing difficulties (dysphagia) associated with non-progressive and progressive neurological disease.

Search methods

We searched the following electronic databases for published trials: the Cochrane Central Register of Controlled Trials (CENTRAL); Ovid MEDLINE (1950 to 2013); EMBASE (1980 to 2013); AMED (Allied and Complementary Medicine) (1941 to 2013); CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1937 to 2013). We also searched major clinical trials registers: CCT (http://www.controlled-trials.com); Clinical Trials (http://www.clinicaltrials.gov); Chinese Clinical Trial Register (www.chictr.org); ACTR (http://www.actr.org.au/. We examined the reference lists of all potentially relevant studies to identify further relevant trials. We handsearched published abstracts of conference proceedings from both the Dysphagia Research Society and the European Society of Swallowing Disorders. Digestive Disease Week (published in *Gastroenterology*) was also handsearched. Additionally, we searched ProQuest Dissertations & Theses for dissertation abstracts.

Selection criteria

Only randomised controlled trials were sought.

Data collection and analysis

Independent searches were completed by JR, AM, MC and MW. Two review authors (JR and MW) independently inspected titles, abstracts and key words identified from the literature search.

Main results

No randomised controlled studies were retrieved. Twenty-nine studies were excluded, mainly on the basis of trial design.

Authors' conclusions

It was not possible to reach a conclusion on the efficacy and safety of botulinum toxin as an intervention for people with UOS dysfunction and neurological disease. There is insufficient evidence to inform clinical practice. Directions for future research are provided.

PLAIN LANGUAGE SUMMARY

Botulinum toxin for swallowing disorders

Many people have problems swallowing because of an impairment of the upper oesophageal sphincter (UOS), a high pressure zone within the tube that carries food from the mouth to the stomach. Many people with neurological conditions such as stroke, traumatic brain injury, Parkinson's disease or multiple sclerosis can have UOS impairment. This results in difficulty swallowing food and liquids, resulting in choking and food entering into the lungs (aspiration). This has serious consequences for the patient and can cause dehydration, malnutrition and aspiration pneumonia. The person's quality of life can be affected as they are unable to have food or liquids safely by mouth. Tube feeding and hospitalisation is often required.

Many interventions are used to improve UOS function. These include surgery, medications including botulinum toxin, rehabilitation exercises, diet modification and other compensatory techniques.

There is no clear consensus on whether botulinum toxin is safe and effective in managing UOS dysfunction in people with neurological conditions. This makes it hard to decide which intervention will be safest and most effective to improve swallowing and quality of life.

Only randomised controlled trials were sought for inclusion in this review. Trials were looked for through electronic searches of databases, searches of clinical trials registers, from peer reviewed journals, published conference proceedings and reference lists of relevant articles. No trials met the inclusion criteria for the review.

There is insufficient evidence to support the use of botulinum toxin to improve swallowing in people with UOS dysfunction and neurological disease. The lack of trials does not mean that this intervention is ineffective. Adequately powered well designed trials are required. In addition to using sensitive measures looking at changes in swallow function, measures are needed that examine client and caregiver satisfaction, changes in quality of life, psychological well-being and unwanted symptoms associated with the intervention.

Botulinum toxin compared with other dysphagia interventions for upper oesophageal sphincter dysfunction in neurological swallowing disorders
Patient or population: adults with oro-pharyngeal dysphagia secondary to acute neurological disease **Settings:** **Intervention:** botulinum toxin **Comparison:** other dysphagia interventions
Comments
Currently, no evidence is available to support the routine use of botulinum toxin to treat neurogenic dysphagia. Methodologically sound randomised controlled trials are urgently required in order to verify its safety and clinical value across various adult neurogenic groups and to determine optimal candidacy and protocols

BACKGROUND

Description of the condition

The upper oesophageal sphincter (UOS), or pharyngo-oesophageal segment (POS), is defined physiologically as a high pressure zone forming a barrier between the pharynx and the oesophagus. This obstruction prevents diversion of air into the oesophagus during inspiration. It also protects the airway from any retrograde passage of material refluxed from the oesophagus or stomach (Singh 2005). Three muscles contribute to the formation of the UOS, the cricopharyngeus (CP) muscle; the most inferior muscle fibres of the inferior pharyngeal constrictor muscle; and the most superior portion of the longitudinal oesophageal muscular fibres (Sivarao 2000). First described by Valsalva in 1717, the cricopharyngeus is the main component of the UOS. Arising from the lateral borders of the cricoid lamina, it is a C-shaped muscle which forms a sling around the wall of the superior aspect of the cervical oesophagus (Sivarao 2000). At rest the sphincter has a slit-like configuration, with the CP making up the lateral and posterior walls and the cricoid lamina positioned anteriorly. The CP is bordered superiorly by the inferior constrictor muscle and merges inferiorly with the muscular layers of the cervical oesophagus. While the UOS is normally in a tonic state of contraction, it relaxes intermittently to allow trans-sphincteric flow of fluid or gas during antegrade (for example swallowing) and retrograde (for example emesis or belching) events (Cook 2000).

In order for the swallow to be safe and efficient, the UOS needs to open adequately to allow material to pass from the pharynx into the oesophagus. Adequate UOS opening is critical to safe and efficient swallowing due to the close proximity between the UOS and the airway entrance. Manofluoroscopic studies have demonstrated that UOS opening occurs by a combination of CP relaxation, anterior and superior hyolaryngeal excursion and bolus pressure (Cook 1989). In the initial relaxation phase, there is vagal inhibition of the tonic contraction of the CP muscle, as observed by needle electromyography (EMG) (Ertekin 2002). This precedes UOS opening by 200 msec and lasts 300 to 600 msec. In the second phase, UOS opening occurs via the biomechanics of hyolaryngeal excursion (Cook 1989). The suprahyoid muscles (geniohyoid, mylohyoid, stylohyoid, hyoglossus and the anterior belly of the digastric) contract causing the hyoid bone to be pulled both anteriorly and superiorly. This movement, paired with contraction of the thyrohyoid, an infrahyoid muscle which is the main connection between the hyoid bone and the larynx, pulls the laryngeal complex in a superior and anterior direction. As the UOS is connected to the laryngeal complex via CP muscle attachment to the cricoid cartilage, the anterior portion of the UOS is pulled open. The UOS assumes an oval cross section and is raised 2 to 2.5 cm in an orad direction. In the third distension phase, pressure applied by the weight and volume of the onrushing bolus distends the lumen of the UOS. This distension collapses in the fourth phase as the bolus passes through the sphincter. Finally, in the fifth phase the UOS closes as the cricopharyngeus actively contracts (Cook 1989).

UOS dysfunction during swallowing has been reported in numerous acute and progressive neurological conditions including, but not limited to, brainstem stroke (Bian 2009), motor neuron disease (Higo 2002), Parkinson's disease (Restivo 2002), myasthenia gravis (Colton-Hudson 2002) and inclusion body myositis (Oh

2008). The prevalence of UOS dysfunction in people with neurological dysphagia (difficulty swallowing) varies in the literature as rates depend on the definitions of UOS used, the heterogeneity in neurological populations studied and the evaluation methods employed. For example, the reported prevalence for UOS dysfunction in people with Parkinson's disease varies from 21% (Ali 1996) to 43% (Higo 2001), and in stroke from 15% (Steinhagen 2009) to 44% (Bian 2009). Diagnosis of UOS dysfunction cannot be made from a clinical swallow examination as the sensitivity and specificity of this examination are extremely poor in predicting UOS dysfunction. Videofluoroscopy, fibreoptic endoscopic evaluation of swallowing (FEES), manometry (Butler 2009) and EMG (Ertekin 2002) are the most commonly employed instrumental evaluations to evaluate UOS function for swallowing. The causes of impaired UOS opening vary across neurological conditions and can result from disordered neurally-mediated CP muscle relaxation, suboptimal anterior and superior hyolaryngeal excursion, weak bolus propulsion, cricopharyngeal fibrosis or a combination of these factors (Cook 2000). Dysphagia frequently results, characterised by the prevention of material passing safely and efficiently from the pharynx into the oesophagus during swallowing. Solid food can pose particular problems and can lead to choking and multiple swallowing. This typically leads to aspiration (passage of material into the trachea beyond the level of the true vocal cords), post-swallow and pharyngeal retention of material. Clinical complications include aspiration pneumonia, weight loss, dehydration, malnutrition, the need for tube feeding and increased mortality (Martino 2005; Smithard 1996). Quality of life is also frequently affected (Leow 2010).

Management of impaired UOS opening during swallowing varies across individuals and intervention can be pharmacological, compensatory, rehabilitative or surgical in nature. Frequently it involves a combination of these methods. Compensation includes the use of postural strategies (for example head turn, chin tuck) (McCulloch 2010) and voluntary manoeuvres (for example effortful swallow) (Hiss 2005), which are employed clinically to improve and prolong UOS opening hence minimising aspiration and facilitating bolus clearance during swallowing. Rehabilitation programs designed to target impaired UOS opening during swallowing include jaw exercises (Wada 2012), the Shaker 'head lifting' exercises (Shaker 1997; Shaker 2002) and the Mendelsohn manoeuvre (Kahrilas 1991). The Shaker exercises are isokinetic and isometric head lifting manoeuvres designed to strengthen the suprahyoid muscles (that is the mylohyoid, geniohyoid, stylohyoid and anterior belly of digastric) and infrahyoid muscles (that is the thyrohyoid), which pull open the UOS during swallowing. The Mendelsohn manoeuvre involves purposeful prolongation of the anteriosuperior displacement of the larynx at mid-swallow. In cases where patients have demonstrated little or no benefit from a trial period of rehabilitation, among other factors, they may be considered for surgical or pharmaceutical interventions to optimise UOS opening. Surgical approaches employed to treat UOS dysfunction comprise cricopharyngeal myotomy (Kelly 2000; Kos 2010) and upper oesophageal dilatation (Hatlebakk 1998; Hu 2010). Pharmacological treatment consists of botulinum toxin injections into the CP muscle to improve UOS opening during swallowing (Alberty 2000; Alfonso 2010; Krause 2008; Moerman 2006).

Description of the intervention

While there are seven different subtypes of botulinum toxin, botulinum toxin A (BTA) is the most commonly used subtype in the treatment of UOS dysfunction. While botulinum toxin B (BTB) is used to treat conditions such as cervical dystonia and drooling, particularly when patients have developed a resistance to BTA (Costa 2005), it is used less widely in clinical practice to treat UOS dysfunction. BTA formulations that are available include Botox® (Allergan Inc) and Dysport® (Ipsen Ltd). These products differ in terms of molecular structure and manufacturing processes, and use different methods for determining biological activity (Heinen 2006). One unit of Botox® is estimated to be comparable to three to four units of Dysport® (Fuster Torres 2007). Schneider 1994 initially described the use of BTA for the treatment of CP dysphagia, resulting in a temporary relaxation of the CP musculature and improved opening of the UOS during swallowing. Seventy per cent of participants had more efficient bolus transport into the oesophagus during swallowing and reduced aspiration events. The intervention usually brings improvement in deglutition but most patients require reinjection in three to five months (Krause 2008). Also, reported side effects include inadvertent injection outside the cricopharyngeus, which may result in temporary paralysis of the laryngeal musculature causing dysphonia and, rarely, aspiration. In cases where there is uncertainty regarding the diagnosis of impaired UOS dysphagia, a positive response to a trial of botulinum toxin treatment can suggest candidacy for cricopharyngeal myotomy (Krause 2008).

Since this initial 1994 study, cricopharyngeal BTA injection has been reported in over 200 patients with dysphagia of varying aetiologies with success rates between 43% and 100% (Alberty 2000; Alfonso 2010; Chiu 2004; Krause 2008). However, studies have recruited heterogeneous diagnostic groups and the candidacy criteria for BTA injections vary considerably across studies. Additionally, BTA brand and dosage (2.5 to 50 units Botox®; 60 to 360 units Dysport®), injection site, technique (rigid endoscopy, flexible endoscopy, transcervical with EMG, transcervical computed tomography (CT)-guided) and outcome measure evaluations (videofluoroscopy, manometry, EMG), among other factors, have differed across studies. This has led to confusion regarding the usefulness of this technique.

How the intervention might work

Botulinum toxin is a neurotoxin that inhibits presynaptic acetylcholine release and hence chemically denervates the motor endplate. Once injected, botulinum toxin binds rapidly to presynaptic cholinergic nerve terminals, impairing the release of acetylcholine (chemical denervation) at the neuromuscular junction. This results in a temporary dose-related weakness or reversible palsy of the innervated muscle. Therapeutic effects are usually seen within three days of the injection. Peripheral neuronal sprouting prevents the effects from being permanent. Reports to date suggest that effects last from two to up to 24 months (Kim 2006; Masiero 2006). BTA has been used effectively in the past for the management of a number of hyperkinetic disorders (for example blepharospasm, torticollis, spasmodic dysphonia) with good results and limited side effects (Jankovic 1991). In more recent times, its use has been expanded to treat UOS dysfunction in neurogenic dysphagia (Alberty 2000; Alfonso 2010; Bian 2009; Kim 2006; Parameswaran 2002; Restivo 2002; Zaninnotto 2004). However, several methodological aspects of these studies vary and its usefulness remains unclear.

Why it is important to do this review

Clinicians working with people with dysphagia secondary to UOS dysfunction as a result of acute or progressive neurological disease have difficulty determining the efficacy of botulinum toxin injections to treat dysphagia in individuals with neurogenic dysphagia. The most effective formulation, sites for injection, the optimum dosage, the method of delivery (endoscopic or transcutaneous) and the length of time before the effects wear off are as yet undetermined. There are currently no systematic reviews examining the efficacy of botulinum toxin to treat UOS dysfunction in acute or progressive neurological populations despite it being a topical issue. Given that botulinum toxin is being used clinically to treat UOS dysfunction, supported by a limited evidence base, as well as the adverse events associated with the intervention, a systematic review of the evidence is required in this area. Evidence is required not only from a clinical perspective but also to identify the specific direction for future clinical trials and intervention studies in the area.

OBJECTIVES

1. To establish the efficacy and safety of botulinum toxin use aimed at improving UOS dysfunction in people with swallowing difficulties (dysphagia) associated with non-progressive and progressive neurological disease.

2. To provide the best evidence to inform clinical practice.

3. To assist with future research planning.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomised controlled trials (RCTs) were included in the review. An RCT is defined as an experiment in which an intervention (for example botulinum toxin) and one control treatment or no treatment are compared by being randomly allocated to participants. In most trials one intervention is assigned to each individual but sometimes assignment is to defined groups of individuals or both interventions are assigned within individuals (for example in different orders or to different parts of the body). Crossover trials would only be included if the washout period of the botulinum toxin was known.

We did not apply any language limits on published studies or date restrictions on trials.

Types of participants

We planned to include all trials involving adults (18 years or older), both male and female, with oro-pharyngeal dysphagia secondary to acute (for example stroke, traumatic brain injury (TBI)) non-progressive and progressive neurological disease (for example Parkinson's disease, motor neuron disease, multiple sclerosis). We excluded trials that included participants with congenital neurological conditions (for example cerebral palsy) as dysphagia in these diagnostic groups is multifactorial.

We excluded trials that included participants with independent or co-morbid non-neurological causes of dysphagia (for example head and neck cancer, tracheostomy, oesophageal disease, a structural abnormality such as pharyngeal or oesophageal diverticulum).

Types of interventions

Comparisons

- Botulinum toxin (all subtypes, methods of delivery, injection sites within the UOS, dosages and commerical brands) versus no intervention
- Botulinum toxin versus placebo
- Botulinum toxin versus other intervention (i.e. traditional dysphagia rehabilitation)
- Botulinum toxin and traditional rehabilitation approach versus traditional rehabilitation approach (where traditional rehabilitation was identical in both groups)

Types of outcome measures

Binary outcomes were reported for all primary and secondary outcomes.

Primary outcomes

1. Positive change to oral intake status (Yes or No)
2. Reduction or elimination of aspiration or laryngeal penetration of food or fluids, or both, as rated on objective assessment (videofluoroscopy, fibreoptic examination of swallowing safety (FEES) (Yes or No)
3. Adverse events including increase in swallowing problems, compromised medical health, negative psychological consequences, negative social consequences, hospitalisation, death (Yes or No)
4. Client or carer satisfaction, or both, with intervention (Yes or No)

Secondary outcomes

1. Reduction or elimination of residue in the valleculae or pyriform sinus, or both, or post-swallow (Yes or No)
2. Positive change in quality of life (Yes or No)

Regarding follow up of intervention effects, three time frames were considered: immediate (< one month), medium term (one to six months) and long term (> six months). Three time points were included to ensure that the long-lasting effects of botulinum toxin were captured.

Search methods for identification of studies

Electronic searches

We searched the following bibliographic databases for published trials:

- the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (August 2013) (Appendix 1);
- Ovid MEDLINE (1950 to August 2013) (Appendix 2);
- Elsevier EMBASE (1980 to August 2013) (Appendix 3);
- EBSCO AMED (Allied and Complementary Medicine) (1941 to August 2013) (Appendix 4);
- EBSCO CINAHL (Cumulative Index to Nursing and Allied Health Literature) (1937 to August 2013) (Appendix 5).

We searched major clinical trials registers:

- CCT (http://www.controlled-trials.com);
- Clinical Trials (http://www.clinicaltrials.gov);
- Chinese Clinical Trial Register (www.chictr.org);
- ACTR (http://www.actr.org.au/).

The search strategy was developed for Ovid MEDLINE and adapted for use in the CENTRAL, EMBASE, AMED and CINAHL databases. We searched for articles with combinations of subject headings and key words relating to botulinum toxin; and upper oesophageal sphincter; and dysphagia or deglutition or swallowing. We did not apply language limits and used the Cochrane highly sensitive search strategy for identifying randomised controlled trials in Ovid MEDLINE.

Searching other resources

We scanned the reference lists of all included studies to identify further relevant trials. We handsearched published abstracts of conference proceedings from both the Dysphagia Research Society and the European Society of Swallowing Disorders (both published in *Dysphagia*). Digestive Disease Week (published in *Gastroenterology*) was also handsearched. Additionally, we searched ProQuest Dissertations & Theses for dissertation abstracts.

Data collection and analysis

Selection of studies

Two review authors (JR and MW) independently inspected titles, abstracts and key words identified from the literature search. Duplicate items were removed. The results of the literature search were categorised as 'potentially relevant', 'relevant', and 'not relevant'. If it was unclear from the titles and abstracts whether a study should be included, then we obtained copies of the trials for further assessment. We resolved any disagreement on the selection of studies by consensus discussion. We listed the studies that were excluded in the Characteristics of excluded studies table.

Data extraction and management

A data extraction form was prepared for data extraction. Two review authors (JR and MW) planned to independently extract details of all included studies and, where practicable, to contact study authors to obtain incomplete details or missing data. It was planned that a third review author would extract data from a random sample of 20% of included studies.

Assessment of risk of bias in included studies

It was planned that two review authors would independently assess risk of bias in each included study, addressing the following issues which may be associated with biased estimates of treatment effect: sequence generation; allocation sequence concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other potential threats to validity (Higgins 2011).

Measures of treatment effect

We planned to carry out a meta-analysis of the primary and secondary endpoints using risk ratio (RR) and 95% confidence interval (CI) for dichotomous outcomes, and mean difference (MD) or standardised mean differences (SMD) and 95% confidence interval (CI) for continuous outcomes.

Unit of analysis issues

To make sure the analysis matched the level of randomisation, we planned to identify the numerous variations in the design of included studies (simple parallel group design, cluster-randomised trial, repeated measurements, recurring events, etc). As this is a review of a pharmaceutical procedures, we included both cluster-randomised and individually-randomised trials. If cluster-randomised trials were included and the data were analysed appropriately, analysis would be by the generic inverse variance method. Where the same patient was included more than once, only the first episode of treatment would be included and if patients had been allowed to cross over into the other arm, the data would be analysed strictly by an intention-to-treat (ITT) analysis. We would have contacted the original authors whenever necessary and sought input from the Cochrane Upper Gastrointestinal and Pancreatic Diseases Group editorial base for analysis issues involving any included trials with multiple treatment groups and cluster-randomised designs.

Dealing with missing data

In the event of missing data, we agreed to contact the original trial authors to obtain this data or to seek clarification. Alternatively, we would perform a sensitivity analysis and address the potential impact of the missing data on the findings of the review in the 'Discussion' section, as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions (*Higgins 2011).

Assessment of heterogeneity

Heterogeneity tests were planned using a standard Chi² test (significance at P < 0.1) or an I² statistic (heterogeneity at > 50 %). If there was evidence of heterogeneity, we would explore which factor caused it and perform a subgroup analysis according to the possible reasons.

Assessment of reporting biases

It was planned to report biases (publication bias, time lag bias, duplicate publication bias, location bias, citation bias, language bias or outcome-reporting bias) and minimise reporting bias through a comprehensive search for studies, inclusion of unpublished studies and use of trial registries. We would evaluate this latter bias using funnel plot asymmetry testing, if necessary.

Data synthesis

A meta-analysis was planned for all RCTs included in the review, considering all the outcomes listed for data synthesis. We would use a random-effects model for the primary analysis, then use the fixed-effect model as a sensitivity analysis to check that the results were robust regardless of which method was chosen.

Subgroup analysis and investigation of heterogeneity

We planned to conduct a subgroup analysis focusing on the following:

- endoscopic versus transcutaneous botulinum toxin injections;
- site of injections;
- needle used;
- botulinum type and formulation;
- dosage of botulinum toxin.

If substantial heterogeneity (Chi² test P < 0.1 or an I² value > 50%) existed between studies for the primary outcome (that is aspiration or penetration and oral intake) we would explore the reasons for the heterogeneity, such as severity of dysphagia, age and neurological diagnosis.

Sensitivity analysis

We planned to undertake sensitivity analysis to explore the potential influences on effect size. If heterogeneity resulted from low quality trials, we would exclude the lowest quality trials from this analysis.

RESULTS

## Description of studies

Results of the search

Searches were carried out according to the protocol published in August 2013. The electronic search identified 480 citations, shown in Figure 1. Two authors independently reviewed the references and the full texts of 29 studies that were retrieved for further consideration. None met the eligibility criteria for an RCT.

Figure 1. Study flow diagram.
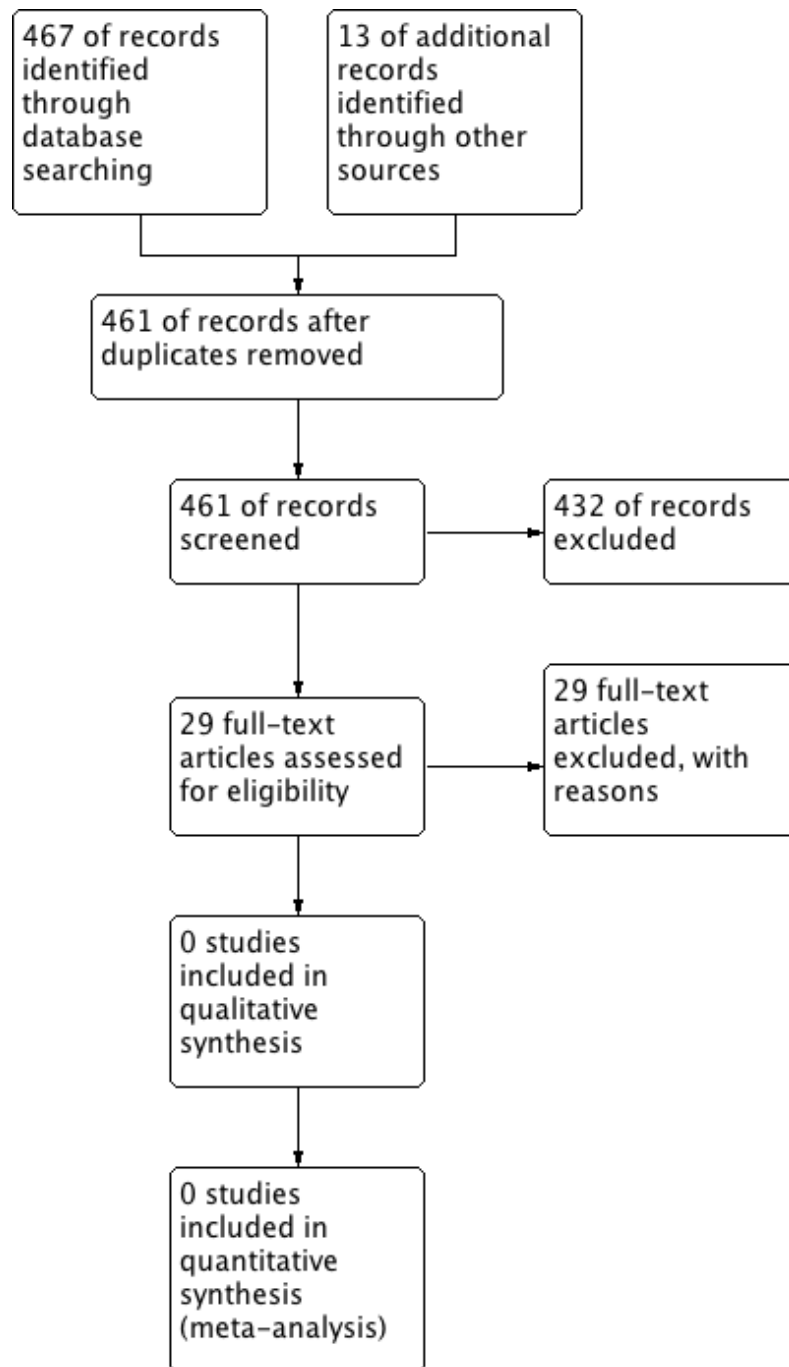
Included studies

No studies were eligible for inclusion.

Excluded studies

Twenty-nine studies were excluded following retrieval of the full text reports, details of which appear in the table Characteristics of excluded studies.

Risk of bias in included studies

There were no included studies, so bias could not be evaluated.

Effects of interventions

See: **Summary of findings for the main comparison**
There is insufficient evidence to judge the effectiveness of botulinum toxin use to improve UOS dysfunction in people with neurogenic dysphagia.

D I S C U S S I O N

Summary of main results

No RCTs were retrieved for this review, therefore no conclusions can be reached on the efficacy and safety of botulinum toxin in the treatment of UOS dysfunction and dysphagia in adults with neurological disease. Internationally, there is a growing use of botulinum toxin to treat neurogenic dysphagia. Despite this, there is a lack of methodologically sound evidence to demonstrate the efficacy of this intervention. Specifically, no randomised controlled trials (RCTs) were found which investigated the use of botulinum toxin to treat dysphagia in adult neurological populations. The authors therefore cannot reach any conclusions at this time regarding this intervention.

Overall completeness and applicability of evidence

The lack of RCTs does not indicate that this intervention is ineffective but rather that RCTs are required on this intervention with this population. Despite the increasing popularity of botulinum toxin as an intervention for UOS dysfunction, there is no evidence-based consensus on the population of adults with UOS dysfunction most suited to this intervention, the differences between

the products that are available, whether BTA is preferable to BTB in some populations, the site most suited for injection, the preparation of the solution, ideal dosages, maximum dosage allowed, the safest method of delivery (calibre of needle, number of injection sites etc.) and the use of general anaesthesia versus conscious sedation.

Potential biases in the review process

The authors are not aware of any potential biases in the review process.

Agreements and disagreements with other studies or reviews

To the authors' knowledge no other systematic reviews have been completed in this area.

A U T H O R S '   C O N C L U S I O N S

Implications for practice

Despite the large numbers of people receiving botulinum toxin for UOS dysfunction, there are no randomised controlled trials to support this approach. This lack of evidence is both from a clinical and a quality of life viewpoint. Given the potential safety issues associated with this intervention, better evidence is urgently required to support its clinical use.

Implications for research

Currently, there is no evidence derived from high quality randomised controlled trials to support the routine use of botulinum toxin to treat neurogenic dysphagia. Methodologically sound randomised controlled trials are urgently required in order to verify its safety and clinical value across various adult neurogenic groups and to determine optimal candidacy and protocols.

Randomised controlled trials should address numerous methodological design issues, lacking in clinical studies to date. These include:

  • examination of homogeneous clinical groups within studies using clear inclusion and exclusion criteria that might confound data (e.g. presence of tracheostomy);

  • precise information regarding the clinical presentation of participants including staging or severity of disease (e.g. time post-acute stroke, stage of Parkinson's disease);

- clear description of the protocol for administration of botulinum toxin within studies and consistency of the protocols within studies (i.e. administrator, botulinum type and commercial brand, methods of dilution if used, dosage, syringe type and size used, injection site, delivery method (endoscopic or transcutaneous), preparation of patient for procedure with information on whether general anaesthesia or conscious sedation was used);

- use of objective and reliable evaluation tools that can reliably capture UOS opening during swallowing (i.e. videofluoroscopy or FEES);

- psychometrically sound outcome measures must be used; the use of parameters that examine not only changes in the swallow function but the satisfaction of patient and carer with the intervention must also be measured. The impact of the intervention on quality of life and psychological well-being should be included in studies to examine the wider impact of the intervention;

- rigorous methods of randomisation;

- sufficient trial numbers with adequate matching of control and clinical groups;

- blinding of researchers and participants to the intervention received (i.e. placebo or botulinum);

- evaluation post-intervention at multiple time frames (i.e. immediate, medium term and long term intervals);

- if crossover trials are used then the washout period for botulinum toxin must first be established;

- the presence and severity of all adverse effects of botulinum toxin should be reported to enable investigators to calculate the number needed to harm; and so that patients, families and carers can make informed decisions on the risks and side effects associated with the intervention;

- the clients should be followed up for at least 18 months to examine the long term effects of the interventions; follow up should include examination of adverse effects;

- studies examining the number of botulinum toxin injections, and the number of repeat injections needed to maintain UOS function effectively, should be undertaken. These studies should consider the washout period for these interventions and systematically measure the adverse effects of repeated botulinum toxin injections and repeated doses of medications. Measurement of the client and carer satisfaction with these interventions should be included in these studies;

- power calculations should be performed for all studies, with sufficient numbers of participants recruited into trials thus avoiding false negative conclusions;

- data should be analysed on an intention-to-treat basis;

- confidence intervals must be calculated and reported for the results of outcomes;

- all trials should be reported according to the guidelines set out in the CONSORT Statement (Consort 2010).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Ahsan 2000	Not RCT
Alberty 2000	Not RCT
Alfonsi 2010	Not RCT
Aoyagi 2012	Not RCT
Atkinson 1997	Not RCT
Blitzer 1997	Not RCT
Chiu 2004	Not RCT
Di Pede 2012	Not RCT
Dunne 1993	Not RCT
Haapaniemi 2001	Not RCT
Kelly 2013	Not RCT
Kim 2006	Not RCT
Krause 2008	Not RCT
Lee 2009	Not RCT
Liu 2004	Not RCT
Masiero 2006	Not RCT
Murry 2005	Non RCT
Parameswaran 2002	Not RCT
Rees 2010	Not RCT
Restivo 2006	Not RCT
Restivo 2011	Not RCT
Restivo 2013	Not RCT

(Continued)

Schneider 1994	Not RCT
Shaw 2001	Not RCT
Sjogren 2011	Not RCT
Terre 2008	Not RCT
Terré 2013	Not RCT
Woisard-Bassols 2013	Not RCT
Zanninoto 2004	Not RCT

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix 1. CENTRAL search strategy

1. (deglutition adj5 (disturbance$ or disorder$ or difficult$ or dysfunction$ or impair$ or condition$ or abnormal$ or damage$ or injur$)).mp.
2. dysphagia.mp.
3. (swallowing adj5 (disturbance$ or disorder$ or difficult$ or dysfunction$ or impair$ or condition$ or abnormal$ or damage$ or injur$)).mp.
4. deglutition/
5. deglutition disorders/
6. esophageal motility disorders/ or esophageal achalasia/ or esophageal spasm, diffuse/
7. swallow$.ti,ab.
8. or/1-7
9. pharyngeal muscles/ or esophageal sphincter, upper/
10. cricopharyn$.tw.
11. (uos or ues).tw.
12. esophagus/pp
13. cp muscle.mp.
14. or/9-13
15. exp Botulinum Toxins/
16. (botulin$ adj2 tox$).mp.
17. dyspor$.mp.
18. boto$.mp.
19. btx.ab,ti.
20. (bont adj1 a).ab.
21. oculinu$.tw.
22. Neuromuscular Agents/
23. or/15-22
24. (8 or 14) and 23

Appendix 2. MEDLINE search strategy

1. randomized controlled trial.pt.
2. randomi*ed.ab.
3. randomi*ed.ti.
4. drug therapy.fs.
5. randomly.ab.
6. trial.ab.
7. groups.ab.
8. or/1-7
9. exp animals/ not humans.sh.
10. 8 not 9
11. (deglutition adj5 (disturbance$ or disorder$ or difficult$ or dysfunction$ or impair$ or condition$ or abnormal$ or damage$ or injur$)).mp.

12. dysphagia.mp.
13. (swallowing adj5 (disturbance$ or disorder$ or difficult$ or dysfunction$ or impair$ or condition$ or abnormal$ or damage$ or injur$)).mp.
14. deglutition/
15. deglutition disorders/
16. esophageal motility disorders/ or esophageal achalasia/ or esophageal spasm, diffuse/
17. swallow$.ti,ab.
18. or/11-17
19. pharyngeal muscles/ or esophageal sphincter, upper/
20. cricopharyn$.tw.
21. (uos or ues).tw.
22. esophagus/pp
23. cp muscle.mp.
24. or/19-23
25. exp Botulinum Toxins/
26. (botulin$ adj2 tox$).mp.
27. dyspor$.mp.
28. boto$.mp.
29. btx.ab,ti.
30. (bont adj1 a).ab.
31. oculinu$.tw.
32. Neuromuscular Agents/
33. or/25-32
34. 10 and (18 or 24) and 33

Appendix 3. EMBASE search strategy

1. 'Randomized controlled trial'/exp
2. 'Randomization'/exp
3. Random*:ab,ti
4. 'double-blind procedure'/exp
5. 'single-blind procedure'/exp
6. (doubl* NEAR/1 blind):ab,ti
7. (singl* NEAR/1 blind):ab,ti
8. assign*:ab,ti
9. allocat*:ab,ti
10. trial:ab
11. groups:ab
12. or/1-11
13. 'animal'/exp NOT humans.sh.
14. 12 not 13
15. (deglutition NEAR/5 (disturbance* or disorder* or difficult* or dysfunction* or impair* or condition* or abnormal* or damage* or injur*)):ab,ti
16. dysphagia/de
17. swallowing/de
18. (swallowing NEAR/5 (disturbance* or disorder* or difficult* or dysfunction* or impair* or condition* or abnormal* or damage* or injur*)):ab,ti
19. deglut*:ti,ab
20. 'esophagus motility'/de or esophagus function disorder'/de / or 'esophagus achalasia'/de or 'esophagus spasm'/de
21. swallow*:ti,ab
22. or/15-21
23. 'pharyngeal muscle'/de or 'upper esophagus sphincter'/de

24. 'cricopharyngeus muscle'/de
25. cricopharyn*:ti,ab
26. uos:ti,ab or ues:ti,ab
27. esophagus/exp AND [physiology and endocrinology]/lim
28. 'cp muscle':ab,ti
29. or/23-28
30. 'botulinum toxin'/de
31. 'botulinum toxin A'/de
32. (botulin* NEAR/2 tox*):ab,ti
33. dyspor*:ab,ti
34. boto*:ti,ab
35. btx:ab,ti.
36. (bont NEAR/1 a):ab,ti
37. oculinu*:ab,ti
38. 'Muscle relaxant agent'/de
39. or/30-38
40. 14 and (22 or 29) and 39

Appendix 4. AMED search strategy

31.   8 and (15 or 21) and 30
30.   or/22-29
29.   (DE "Neuromuscular Agents")
28.   TX oculinu
27.   AB (bont N1 a)
26.   TX btx
25.   TX boto*
24.   TX dyspor*
23.   TX (botulin* N2 tox*)
22.   (DE "Botulinum Toxins")
21.   or/16-20
20.   TX 'cp muscle'
19.   (DE "esophagus")
18.   TX uos or TX ues
17.   TX cricopharyn*
16.   (DE "pharynx")
15.   or/9-14
14.   TX swallow*
13.   (DE "deglutition disorders")
12.   (DE "deglutition")
11.   TX (swallowing N5 (disturbance* or disorder* or difficult* or dysfunction* or impair* or condition* or abnormal* or damage* or injur*))
10.   TX dysphagia
9.   TX (deglutition N5 (disturbance* or disorder* or difficult* or dysfunction* or impair* or condition* or abnormal* or damage* or injur*))
8.   or/1-7
7.   AB trial
6.   TX randomly
5.   TX 'random?ed'
4. (DE "Single blind method)
3.   (DE "Double blind method)
2.   (DE "Random allocation)

1.   (DE "Randomized controlled trials)

Appendix 5. CINAHL search strategy

39.   15 and (23 or 29) and 38
38.   or/30-37
37.   (MH "Neuromuscular Agents")
36.   TX oculinu*
35.   AB (bont N1 a)
34.   TX btx
33.   TX boto*
32.   TX dyspor*
31.   TX botulin* N2 tox*
30.   (MH "Botulinum Toxins")
29.   or/24-28
28.   TX 'cp muscle'
27.   (MH "esophagus/pp")
26.   TX uos or TX ues
25.   TX cricopharyn*
24   (MH "pharyngeal muscles")
23.   or/16-22
22.   TX swallow*
21.   (MH "esophageal motility disorders") or (MH "esophageal achalasia")
20.   (MH *deglutition disorders")
19.   (MH "deglutition")
18.   TX (swallowing N5 (disturbance* or disorder* or difficult* or dysfunction* or impair* or condition* or abnormal* or damage* or injur*))
17.   TX dysphagia
16.   TX (deglutition N5 (disturbance* or disorder* or difficult* or dysfunction* or impair* or condition* or abnormal* or damage* or injur*))
15.   13 not 14
14.   (MH "animals+") not (MH "humans")
13.   or/1-12
12.   AB groups
11.   AB trial
10.   AB randomly
9.   AB placebo
8.   TI "randomi*ed"
7.   AB "randomi*ed"
6.   (MH "Triple-Blind Studies")
5.   (MH "Therapeutic Trials")
4.   (MH "Single-Blind Studies")
3.   (MH "Intervention Trials")
2.   (MH "Double-Blind Studies")
1.   (MH "Randomized Controlled Trials")

Appendix 6. Data Extraction Form

Botulinum Toxin for Upper Oesophageal Sphincter Dysfunction in Neurological Swallowing Disorders- Study Selection, Quality Assessment & Data Extraction Form

Study ID:·················   Lead author:·····················   Reviewer Initials:··············   Date or review: ·············

General Study Information

First author	Year	Journal/Conference Proceedings etc	Country	Language	Single/Multicentre Trial	Study Duration

STUDY ELIGIBILITY

RCT	Relevant participants	Relevant interventions	Relevant outcomes
Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear	Yes / No* / Unclear

* issue relates to selective reporting - when authors may have taken measurements for particular outcomes, but not reported these within the paper(s). Reviewers should contact trialists for information on possible non-reported outcomes & reasons for exclusion from publication. Study should be listed in 'Studies awaiting assessment' until clarified. If no clarification is received after three attempts, study should then be excluded.

Do not proceed if any of the above answers are 'No'.
If study to be included in 'Excluded studies' section of the review, record below the information to be inserted into 'Table of excluded studies'.

Participants and trial characteristics

Participant characteristics			
Participants :	**Treatment group**	**Comparison group 1**	**Comparison group 2 (N/A)**
	N=	N=	N=

(Continued)

Age (mean, median, range, SD):	Mean: Median: Range: SD:	Mean: Median: Range: SD:	Mean: Median: Range: SD:
Gender of participants: (numbers / %, etc)	Male N= Female N = Both N = Not clear	Male N= Female N = Both N = Not clear	Male N= Female N = Both N = Not clear
Relevant neurological conditions within groups :	1._____ N=____ 2._____ N=____ 3._____N=____ 4._____N=____	1._____ N=____ 2._____ N=____ 3._____N=____ 4._____N=____	1._____ N=____ 2._____ N=____ 3._____N=____ 4._____N=____
Can relevant neurological disease groups be extracted?	Yes No Unclear/to contact authors	Yes No Unclear/to contact authors	Yes No Unclear/to contact authors
Co-morbidities within exclusion criteria present/ reported? (e. g. H&N Ca, tracheostomy, congenital neuro condition, oesophageal disease, structural abnormality)			

Trial characteristics

	Treatment group	Comparison group 1	Comparison group 2 (N/A)
Interventions: a) botulinum toxin injections b) placebo intervention c) dysphagia rehabilitation (describe nature & intensity) d) other	a)b)c)d)	a) b) c) d)	a) b) c) d)

(*Continued*)

How was participant eligibility defined?			
Type/brand of drug treatment(s) used?			
Dosage of drug treatment?			
Method used to identify injection site ?			
Injection methods (i.e. transcutaneous or endoscopic?)			
Site of injection?			
Size and calibre of needle			
Injection administered by:			
Time points of measurement collected?			
Time-frames considered: Immediate change (e.g. within one week) Medium change (1-6 months) Long term change (>6 months)	Yes/ no/ unclear Yes/ no/ unclear Yes/ no/ unclear	Yes/ no/ unclear Yes/ no/ unclear Yes/ no/ unclear	Yes/ no/ unclear Yes/ no/ unclear Yes/ no/ unclear
Trial design (e.g. parallel / cross-over*)			

Methodological quality

STUDY DESIGN	Treatment Group	Comparison Group 1	Comparison group 2…N/A
Selection bias: · Sequence generation · Allocation concealment	Adequate/Inadequate/Unclear Adequate/Inadequate/Unclear	Adequate/Inadequate/Unclear Adequate/Inadequate/Unclear	Adequate/Inadequate/Unclear Adequate/Inadequate/Unclear

(Continued)

Performance Bias · Blinding of participants · Blinding of other personnel	Yes/No/Unclear Yes/No/Unclear		Yes/No/Unclear Yes/No/Unclear		Yes/No/Unclear Yes/No/Unclear	
Detection Bias · Use of outcome measure(s) apparent · Blinding of outcome assessors	Yes/No/Unclear Yes/No/Unclear		Yes/No/Unclear Yes/No/Unclear		Yes/No/Unclear Yes/No/Unclear	
Reporting Bias · Time lag to publication · Language *(Please state)* · Duplicate publication · Citation reporting · Outcome reporting	Yes/No/Unclear ▬▬▬▬▬▬ Yes/No/Unclear Yes/No/Unclear Yes/No/Unclear		Yes/No/Unclear ▬▬▬▬▬▬ Yes/No/Unclear Yes/No/Unclear Yes/No/Unclear		Yes/No/Unclear ▬▬▬▬▬▬ Yes/No/Unclear Yes/No/Unclear Yes/No/Unclear	
Attrition Bias · Incomplete outcome data · Reasons specified	Yes/No/Unclear Yes/No/Unclear		Yes/No/Unclear Yes/No/Unclear		Yes/No/Unclear Yes/No/Unclear	
Intention to Treat	All participants entering trial	15% or fewer excluded	More than 15% excluded	Not analysed as 'intention-to-treat'	Unclear	Were withdrawals described? Yes Š No Š No Š not clear Š

Data extraction

Outcomes relevant to your review			
	Treatment group	Comparison group 1	Comparison group 2 (N/A)
Positive change to oral intake status	Yes/No	Yes/No	Yes/No
Reduction or elimination of aspiration or laryngeal penetration on food and/or fluids as rated on objective assessment (videofluoroscopy, FEES)	Yes/No	Yes/No	Yes/No
Adverse events including increase in swallowing problems, compromised medical health, negative psychological consequences, negative social consequences, hospitalisation, death	Yes/No	Yes/No	Yes/No
Client and/or carer satisfaction with intervention	Yes / No	Yes / Nor	Yes / No
Reduction or elimination of residue in the valleculae and/or pyriform sinus/ post swallow	Yes/No	Yes/No	Yes/No
Change in quality of life	Yes/No	Yes/No	Yes/No

Other information which you feel is relevant to the results	Other information which you feel is relevant to the results	Other information which you feel is relevant to the results	Other information which you feel is relevant to the results	Other information which you feel is relevant to the results	Other information which you feel is relevant to the results	Other information which you feel is relevant to the results	Other information which you feel is relevant to the results
Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review	Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review	Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review	Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review	Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review	Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review	Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review	Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review

References to trial

Check other references identified in searches. If there are further references to this trial link the papers now & list below. All references to a trial should be linked under one *Study ID* in RevMan.

Code each paper	Author(s)	Journal/Conference Proceedings etc	Year
A	*The paper listed above*		
B	*Further papers*		

References to other trials

Did this report include any references to published reports or unpublished data of potentially eligible trials not already identified for this review? If yes, give list contact name and details		
First author	Journal / Conference	Year of publication

Overall Quality Score (GRADE rating)	
· **High** · **Moderate** · **Low** · **Very low**	**High** (Randomised trial /double upgraded Ix studies Further research is very unlikely to change our confidence in the estimate of effect
	Moderate: Downgraded randomised trials /Upgraded observational studies Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
	Low: Double downgraded randomised trials/Observational studies Low quality- Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
	Very Low : Triple down graded randomised trials/downgraded observational studies/case series/case reports. Any estimate of effect is very uncertain

Review Author Comments:
Signed: …………………………
Date: …………………………

CONTRIBUTIONS OF AUTHORS

J Regan and M Walshe wrote the protocol. A Murphy developed the search strategy and performed the searches along with M Walshe, M Chiang and J Regan. B McMahon and T Coughlan reviewed the protocol.

DECLARATIONS OF INTEREST

The authors have no declaration of interest to report.

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