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

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[Intervention Review]

Botulinum toxin for upper oesophageal sphincter dysfunction in neurological swallowing disorders

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ABSTRACT

Background

Adequate upper oesophageal sphincter (UOS) opening is critical to safe and efficient swallowing due to the close proximity between the UOS and the airway entrance. Many people with neurological conditions, progressive and non progrerssive present with UOS dysfunction. The consequences fort 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, malnutrition. Tube feeding is often indicated 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. Botulinum toxin as an intervention for UOS dysfunction is gaining popularity over the past two decades 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 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 from all potentially relevant studies to identify further relevant trials. We handsearched published abstracts of conference proceedings from both the Dysphagia Research Society and also the European Society

of Swallowing Disorders. Digestive Disease Week (published in *Gastroenterology*) were also handsearched. Additionally, we searched ProQuest Dissertations & Theses for dissertation abstracts.

Selection criteria

Only randomised controlled trials (RCTs) were included

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. 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

[Summary title]

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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, multiple sclerosis can have UOS imp[airment. This results in difficulty swallowing food and liquids, resulting in choking and food enetrring 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 imprive UOS function. These include surgery, medications, 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 included in this review. Trials were sought through electronic searches of databases, searches of clinical trials registers, peer reviewed journals, published conference proceedings and reference lists of relevant articles.

No trials that met the inclusion criteria for the review were found.

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 suggest that this interventions is ineffective.

Adequately powered well designed trials are required. In addition to using sensitive measures looking at change in swallow function, measures are needed that examine client and carer satisfaction, changes in quality of life, psychological well being and in unwanted symptoms associated with the intervention.

Summary text]

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 form 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 transsphincteric flow of fluid or gas during antegrade (e.g. swallowing) and retrograde (e.g. 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 milliseconds and lasts 300 to 600 milliseconds. In the second phase; UOS *opening* occurs via the biomechanics of hyolaryngeal excursion (Cook 1989). 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 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 sensitivity and specificity of this examination in predicting UOS dysfunction are extremely poor. 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 cause of impaired UOS opening varies 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 which is 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, 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 use of postural strategies (e.g. head turn, chin tuck) (McCulloch 2010) and voluntary manoeuvres (e.g. 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 lift-

ing manoeuvres designed to strengthen suprahyoid muscles (i.e. mylohyoid, geniohyoid, stylohyoid and anterior belly of digastric) and infrahyoid muscles (i.e. thyrohyoid), which pull open the UOS during swallowing. The Mendelsohn manoeuvre involves purposeful prolongation of the anterio-superior 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) or 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 7 different subtypes of botulinum toxin, Botulinum toxin A (BTA) is the most commonly used sub type 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 available include Botox® (Allergan Inc.) and Dysport® (Ipsen Ltd). Both products differ in terms of molecular structure, 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. This resulted 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 candidacy criteria for BTA injections vary considerably across studies. Additionally, BTA brand and dosage (2.5 to 50 units Botox®; 60-360 units Dysport®); injection site, technique (rigid endoscopy, flexible endoscopy, transcervical with EMG, transcervical 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 with 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 twenty four months (Kim 2006; Masiero 2006). BTA has been used effectively in the past for the management of a number of hyperkinetic disorders (e.g. blepharospasm, torticollis, spasmodic dysphonia) with good results and limited side effects (Jankovic 1991). In more recent times, its use has 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 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 the fact that botulinum toxin is being used clinically to treat UOS dysfunction with 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 specific direction for future clinical trials and intervention studies in the area.

OBJECTIVES

1. To establish the efficacy and safety of botulinum toxin aimed at improving UOS dysfunction in people 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. A RCT is defined as an experiment in which an intervention (e.g. 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 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 +) both male and female with oro-pharyngeal dysphagia secondary to acute (e.g. stroke, traumatic brain injury (TBI) non progressive and progressive neurological disease (e.g. Parkinsons disease, motor neuron disease, multiple sclerosis). We excluded trials that include participants with congenital neurological conditions (e.g. 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 (e.g head and neck cancer, tracheostomy, oesophageal disease, structural abnormality such as pharyngeal or oesophageal diverticulum).

Types of interventions

We l considered all trials that involved delivery of all sub types of botulinum toxin injections into the upper oesophageal sphincter either endoscopically or transcutaneously. We included trials that involve all dosages and types (i.e. all commercial brands) of botulinum toxin). We considered reports of trials that included all injection sites within the UOS. We included studies which combined botulinum toxin injections with other dysphagia interventions that were provided in the intervention group, as long as all methods except for botulinum toxin injections were provided to both treatment and control groups and the specific effects of the botulinum toxin could be reliably determined.

Comparisons

- Botulinum toxin 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 is 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/No).
2. Reduction or elimination of aspiration or laryngeal penetration on food and/or fluids as rated on objective assessment (videofluoroscopy, fibreoptic examination of swallowing safety (FEES) (Yes/No).
3. Adverse events including increase in swallowing problems, compromised medical health, negative psychological consequences, negative social consequences, hospitalisation, death (Yes/No).
4. Client and/or carer satisfaction with intervention (Yes/No).

Secondary outcomes

1. Reduction or elimination of residue in the valleculae and/or pyriform sinus/ post swallow (Yes/No).
2. Positive change in quality of life (Yes/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 are 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) (*The Cochrane Library* (last update) (Appendix 1);
- Ovid MEDLINE (1950 to 2013) (Appendix 2);
- Elsevier EMBASE (1980 to 2013) (Appendix 3);

- EBSCO AMED (Allied and Complementary Medicine) 1941 to 2013 (Appendix 4);
- EBSCO CINAHL (Cumulative Index to Nursing and Allied Health Literature) 1937 to 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 translated for use on 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 from all included studies to identify further relevant trials. We handsearched published abstracts of conference proceedings from both the Dysphagia Research Society and also the European Society of Swallowing Disorders (both published in *Dysphagia*). Digestive Disease Week (published in *Gastroenterology*) were 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 titles and abstracts whether a study should be included, then we obtained copies of trials for further identification. We resolved any disagreement on selection of studies by consensus discussion. We listed those studies 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 for 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).
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Measures of treatment effect

we planned to carry out a meta-analyses of primary and secondary end pointsusing risk ratio (RR) and 95% confidence intervals (CI) for the analysis of dichotomous outcomes, and mean difference (MD) or standardized mean differences (SMD) and 95% confidence intervals (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 on the designs of included studies (simple parallel group design, cluster-randomised trial, repeated measurements, recurring events, etc). As this is a review of a pharmaceutical procedure, we included both cluster-randomised and individually-randomised trials. If cluster-randomised trials were included and data analysed appropriately, analysis using the Generic Inverse Variance method would be used. Where the same patient was included more than once only the first episode of treatment would l be included and if patients have been allowed to cross over into the other arm, the data will beanalysed strictly by intention-to-treat (ITT) analysis. We contacted 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 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 Chi^2 test (significance at $P < 0.1$) or an I^2 statistic (> 75%). If there was evidence of heterogeneity, we would explore which factor caused it and perform 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, evaluating this bias using funnel plot asymmetry testing, if necessary.

Data synthesis

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

Subgroup analysis and investigation of heterogeneity

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

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

If substantial heterogeneity (Chi² test P< 0.1 or an I^2 >50%) existed between studies for the primary outcome (i.e. aspiration/penetration and oral intake), we would explore the reasons for heterogeneity; such as dysphagia severity, 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 review.

RESULTS

Description of studies

See Characteristics of excluded studies.

Results of the search

In October 2012 and again in March 2013, searches were carried out according to the protocol. No randomised controlled trials were identified. Seventeen non randomised studies were retrieved.

Included studies

No included studies

Excluded studies

Seventeen studies were excluded following retrieval of full text.

Risk of bias in included studies

No eligible studies retrieved

Allocation

No eligible studies retrieved

Blinding

No eligible studies retrieved

Incomplete outcome data

No eligible studies retrieved

Selective reporting

No eligible studies retrieved

Other potential sources of bias

No studies retrieved

Effects of interventions

There is no strong evidence to support the use of botulinum toxin to improve UOS dysfunction in people with neurogenic dysphagia. However, non randomised studies suggest.....

DISCUSSION

Summary of main results

No RCTs were retrieved in 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. There is a growing use internationally 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 control

trials were found which investigate the use of botulinum toxin to treat dysphagia in adult neurological populations. The authors therefore cannot conclude at this time regarding this intervention.

Overall completeness and applicability of evidence

The lack of RCTs does not suggest 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 products available, whether BTA is preferable to BTB in some populations, the site most suited for injection, the preparation of the solution, calculations of ideal dosages, maximum dosage allowed, the safest method of delivery (calibre of needle, number of injection sites etc.), the use of general anaesthesia versus conscious sedation etc.

Quality of the evidence

No RCTs were retrieved.

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

AUTHORS' CONCLUSIONS

Implications for practice

Despite the large numbers of people receiving botulinum toxin for UOS dysfunction, there is no strong evidence 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, stronger evidence is urgently required to support its clinical use.

Implications for research

Currently, no evidence is available to support the routine use of botulinum toxin to treat neurogenic dysphagia. Methodologically sound randomised control 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 control 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 which might confound data (e.g. presence of tracheostomy)

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

- · clear description of the administration of botulinum toxin protocol within studies and consistency of protocols within studies (i.e. administrator, botox 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 carerr 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 intervention.

- · Rigorous method 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 botox)

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

- Power calculations should be performed on all studies with sufficient numbers of participants recruited into trails 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
Alberty 2000	Not RCT
Alfonsi 2010	Not RCT
Aoyagi 2012	to be completed
Di Pede 2012	to be completed
Haapaniemi 2007	Not RCT: Case studies
Kim 2006	Not RCT
Krause 2008	Not RCT: Single case study
Lee 2009	Not RCT. Retrospective study
Liu 2004	Not RCT. Case Studies
Masiero 2006	Not RCT. Case studies
Murry 2005	Non RCT
Parameswaran 2002	Not RCT
Rees 2012	to be completed
Restivo 2006	Not RCT
Restivo 2011	Not RCT
Schneider 1994	Not RCT
Shaw 2001	Not RCT
Sjogren 2011	to be completed
Terre 2008	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	Adequate/Inadequate/Unclear	Adequate/Inadequate/Unclear	Adequate/Inadequate/Unclear
· Allocation concealment	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 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	**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	**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	**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	**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	**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	**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	**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

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 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 protocol.

DECLARATIONS OF INTEREST

Authors have no declaration of interest to report.

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