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Interventions for dysphagia in long-term, progressive muscle disease (Review)

Jones K, Pitceathly RDS, Rose MR, McGowan S, Hill M, Badrising UA, Hughes T

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[Intervention Review]

Interventions for dysphagia in long-term, progressive muscle disease

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A B S T R A C T

Background

Normal swallowing function is divided into oral, pharyngeal, and oesophageal phases. The anatomy and physiology of the oral cavity facilitates an oral preparatory phase of swallowing, in which food and liquid are pushed towards the pharynx by the tongue. During pharyngeal and oesophageal phases of swallowing, food and liquid are moved from the pharynx to the stomach via the oesophagus. Our understanding of swallowing function in health and disease has informed our understanding of how muscle weakness can disrupt swallowing in people with muscle disease. As a common complication of long-term, progressive muscle disease, there is a clear need to evaluate the current interventions for managing swallowing difficulties (dysphagia). This is an update of a review first published in 2004.

Objectives

To assess the effects of interventions for dysphagia in people with long-term, progressive muscle disease.

Search methods

On 11 January 2016, we searched the Cochrane Neuromuscular Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, AMED, LILACS, and CINAHL. We checked references in the identified trials for additional randomised and quasi-randomised controlled trials. We also searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform on 12 January 2016 for ongoing or completed but unpublished clinical trials.

Selection criteria

We included randomised and quasi-randomised controlled trials that assessed the effect of interventions for managing dysphagia in adults and children with long-term, progressive muscle disease, compared to other interventions, placebo, no intervention, or standard care. Quasi-randomised controlled trials are trials that used a quasi-random method of allocation, such as date of birth, alternation, or case record number. Review authors previously excluded trials involving people with muscle conditions of a known inflammatory or toxic aetiology. In this review update, we decided to include trials of people with sporadic inclusion body myositis (IBM) on the basis that it presents as a long-term, progressive muscle disease with uncertain degenerative and inflammatory aetiology and is typically refractory to treatment.

Data collection and analysis

We applied standard Cochrane methodological procedures.

Main results

There were no randomised controlled trials (RCTs) that reported results in terms of the review's primary outcome of interest, weight gain or maintenance. However, we identified one RCT that assessed the effect of intravenous immunoglobulin on swallowing function in people with IBM. The trial authors did not specify the number of study participants who had dysphagia. There was also incomplete reporting of findings from videofluoroscopic investigations, which was one of the review's secondary outcome measures. The study did report reductions in the time taken to swallow, as measured using ultrasound. No serious adverse events occurred during the study, although data for the follow-up period were lacking. It was also unclear whether the non-serious adverse events reported occurred in the treatment group or the placebo group. We assessed this study as having a high risk of bias and uncertain confidence intervals for the review outcomes, which limited the overall quality of the evidence. Using GRADE criteria, we downgraded the quality of the evidence from this RCT to 'low' for efficacy in treating dysphagia, due to limitations in study design and implementation, and indirectness in terms of the population and outcome measures. Similarly, we assessed the quality of the evidence for adverse events as 'low'. From our search for RCTs, we identified two other non-randomised studies, which reported the effects of long-term intravenous immunoglobulin therapy in adults with IBM and lip-strengthening exercises in children with myotonic dystrophy type 1. Headaches affected two participants treated with long-term intravenous immunoglobulin therapy, who received a tailored dose reduction; there were no adverse events associated with lip-strengthening exercises. Both non-randomised studies identified improved outcomes for some participants following the intervention, but neither study specified the number of participants with dysphagia or demonstrated any group-level treatment effect for swallowing function using the outcomes prespecified in this review.

Authors' conclusions

There is insufficient and low-quality RCT evidence to determine the effect of interventions for dysphagia in long-term, progressive muscle disease. Clinically relevant effects of intravenous immunoglobulin for dysphagia in inclusion body myositis can neither be confirmed or excluded using the evidence presented in this review. Standardised, validated, and reliable outcome measures are needed to assess dysphagia and any possible treatment effect. Clinically meaningful outcomes for dysphagia may require a shift in focus from measures of impairment to disability associated with oral feeding difficulties.

P L A I N   L A N G U A G E   S U M M A R Y

Interventions for swallowing difficulty in long-term, progressive muscle disease

Review question

What is the effect of interventions for dysphagia in people with long-term, progressive muscle disease?

Background

People with progressive muscle disease often develop swallowing difficulties (dysphagia) as a result of weakness. These changes in swallowing function can lead to weight loss or inability to gain weight, as well as breathing problems due to food inhalation into the airways and recurrent respiratory infections. Fear or embarrassment about symptoms such as choking, coughing, or spluttering while eating and long meal times can also lead to psychological and social difficulties for those living with dysphagia. We wanted to find out how effective a range of different interventions are for treating dysphagia in people with long-term, progressive muscle disease.

Study characteristics

This review included one trial (22 participants), which compared the effect of three months' intravenous immunoglobulin (IVIg) therapy with placebo. Three participants were also treated with prednisone during the trial. Some limitations in the design, conduct, and reporting of the study might have affected the results. We were most interested in the degree to which treatment affected weight, in terms of either halting weight loss or producing weight gain.

Key results and quality of the evidence

We identified only one randomised controlled trial of intervention for managing dysphagia in one muscle disease, inclusion body myositis. There was not enough evidence for or against any specific intervention for dysphagia. Clinically relevant effects of IVIg for dysphagia in inclusion body myositis can neither be confirmed nor ruled out using the evidence in this review. This trial did not assess weight gain or maintenance or fully report effects of IVIg on swallowing, which the investigators measured using a self report questionnaire and videofluoroscopy (a moving X-ray of swallowing). Any harmful effects were not fully reported. Overall quality of the evidence was low due to limitations in study design and reporting.

The evidence is up to date to January 2016.

BACKGROUND

Description of the condition

Normal swallowing function is divided into oral, pharyngeal, and oesophageal phases. During the oral phase, food is prepared by the lips, tongue, and teeth to form a bolus which is propelled backwards by the tongue. In the pharyngeal phase, the tongue base retracts to push the formed bolus into the pharynx. Airway protection is achieved mainly by closure of the larynx; the associated upwards and forwards movement is also protective and serves to pull open the relaxed upper oesophageal sphincter, the main muscle of which is the cricopharyngeus. A drop in cricopharyngeal pressure created by the elevation of the hyoid and larynx pulling open the cricopharyngeus is understood to be the main source of pressure change propelling the bolus into the oesophagus. Top-to-bottom, sequential contraction of the pharyngeal constrictor muscles also squeezes the bolus downwards. Only the oral phase of swallowing is completely under voluntary control. During the oesophageal phase, the bolus moves towards the stomach by peristalsis, a movement which is regulated entirely by the autonomic nervous system.

Dysphagia can be defined on the basis of a symptom, a clinical sign, a radiological sign, or as a cause or an otherwise unexplained nutritional or respiratory problem. Feeding problems often develop insidiously, at first allowing the person to compensate for swallowing that may be assessed as abnormal when measured objectively. In conditions such as oculopharyngeal muscular dystrophy (OPMD), dysphagia forms part of a symptom complex and therefore occurs, to some degree, in all those affected by the condition. Dysphagia is also frequently under-reported in more generalised muscular dystrophies, where feeding difficulties are one aspect of a multi-system condition. An important complication of impaired swallowing is entry of the bolus into the airway, which is usually described by the extent of penetrance and can be divided into (i) laryngeal penetration, which is the passage of the bolus into the laryngeal vestibule but not further than the vocal cords, and (ii) aspiration, which is defined as passage of the bolus beyond the vocal cords.

Dysphagia in long-term, progressive muscle disease is primarily due to muscle weakness. Weakness of the tongue, face, and jaw or abnormal mouth architecture can impair the ability to prepare a bolus adequately and retrieve bolus particles. Palatal weakness may predispose to nasal regurgitation, and a weakness of the suprahyoid musculature can lead to impaired upper oesophageal sphincter opening; this in turn leads to impaired bolus transit, pooling in the pharynx, and an increased risk of aspiration. Muscle weakness can also compromise laryngeal function, affecting laryngeal closure and coughing. Furthermore, any ventilatory muscle weakness may be expected to compromise effective coughing and airway clearance, particularly in neuromuscular conditions such as myotonic dystrophy.

Many people with muscle disease are observed to develop dysphagia, although this is not necessarily a late-onset feature. According to Jaradeh 2006, OPMD and myotonic dystrophy (MD) are the forms of muscular dystrophy most commonly associated with dysphagia. OPMD is a late-onset autosomal dominant or autosomal recessive inherited disease related to expanded GCG repeats in the PABPN1 gene and with rimmed vacuoles in the muscle biopsy; voluntary swallowing muscles including the tongue

are affected in this condition (Palmer 2010), and in rare cases there is evidence of peripheral nervous system involvement (Abu-Baker 2007). Adult-onset oculopharyngodistal myopathy (OPDM) is considered a distinct hereditary muscle disease also characterised by oropharyngeal dysphagia of myopathic origin, although the genetic defect is unknown (Durmus 2011). Oropharyngeal dysphagia is a common feature of MD type I, the most prevalent inherited neuromuscular disease; MD type I is associated with expanded CTG repeats in the DMPK gene. Oropharyngeal dysphagia is less common in MD type II, which is associated with mutations in the CCTG repeat sequence in the ZNF9 gene (Tieleman 2009). The presentation of oropharyngeal dysphagia in MD has been attributed to myopathic weakness in the control and formation of the bolus, myotonia of muscles with a warm-up phenomenon, as well as possible central nervous system involvement in delayed swallow reflexes (Ertekin 2001). Other untreatable chronic muscle diseases that are often associated with dysphagia include inclusion body myositis (IBM), advanced Duchenne muscular dystrophy (DMD), and some types of metabolic myopathy. Congenital myopathies are less commonly associated with swallowing difficulties (Jaradeh 2006). The cause of dysphagia in DMD has been attributed to oral muscle weakness and facial and dental morphology changes (Straathof 2014). A combination of impaired cricopharyngeal muscle function and impaired sphincter opening has been implicated in cases of dysphagia in IBM (Cox 2009); impaired sphincter function in IBM, a late-onset non-hereditary rimmed vacuolar myopathy with inflammation and degeneration of muscles, could also be attributed to ageing processes (Cox 2009). It is further postulated that an individual's sense of effort in engaging appropriate submaximal swallowing pressures may not be adjusted for age-related muscle weakness and progressive muscle disease (Palmer 2010). Precise estimates of the prevalence of dysphagia remain difficult to determine across different muscle diseases, due, in part, to a lack of standardised assessment procedures (Archer 2013). Also, the swallowing effort perception may not be adequately evaluated in these assessments.

An early questionnaire-based study estimated a prevalence of dysphagia of 34.9% in people with inflammatory and progressive neuromuscular disorders (Willig 1994). However, the relative prevalence of dysphagia symptoms were not given for an apparently healthy population. Even respondents with facioscapulohumeral muscular dystrophy, which is not typically associated with swallowing difficulties, reported occasional choking episodes. Inconsistency in the definition and interpretation of dysphagia is perhaps also reflected in the highly variable estimated prevalence of dysphagia (approximately 40% to 80%) in people with IBM (Cox 2009). In a later study, Cox 2011 found that more than half of their sample population with IBM and dysphagia specified having a combination of obstruction-related symptoms (such as food becoming stuck in throat) and aspiration (choking). While questionnaires on swallowing function may be important for identifying dysphagia as a collection of symptoms or syndrome, the diagnostic accuracy of self reporting is yet to be established. In addition to a lack of standardised definition and assessment, the rate of change in swallowing indices is also not yet fully understood in muscle disease; this limits the identification of a clinically and statistically significant treatment effect size in clinical trials.

From a clinical and patient perspective, dysphagia can result in failure to maintain adequate nutritional intake and respiratory

complications, which can lead to a number of physical, social, and psychological consequences, including (i) weight loss or failure to gain weight, (ii) increased susceptibility to chest infections due to aspiration, (iii) breathing problems due to upper or lower airway blockage secondary to aspiration into the larynx, and (iv) poorer quality of life that may be associated with a loss of enjoyment of eating, fear of choking, embarrassment, and/or social isolation secondary to coughing, spluttering, and prolonged feeding times.

Description of the intervention

Despite the manifest importance of maintaining an adequate nutritional intake and preventing respiratory complications, there is no established best practice for managing dysphagia in chronic muscle disease.

Currently, the main interventions for managing oral feeding difficulties that can lead to dysphagia include dietary manipulation, adoption of safe swallowing techniques, surgical intervention, and enteral feeding. Generally, the first step is to alter the consistency of food and liquids and add appropriate dietary supplements (Ganger 1990; Martin 1991; O'Gara 1990). Manoeuvres to improve the safety of the swallow include changing posture during swallowing, effortful swallowing, and double swallows (Bülow 2001; Drake 1997; Ertekin 2001; Logemann 1994). Much of the supportive evidence for swallowing manoeuvres has been obtained from studies of stroke and other conditions affecting the brain and brain stem; it has not as yet been established whether these interventions are effective in muscle disease.

Indications for surgical intervention and enteral feeding typically include oral feeding difficulties and the prevention of recurrent aspiration. Percutaneous endoscopic gastrostomy (PEG) is often the preferred method for delivering nutritional support, but the current evidence for PEG insertion over nasogastric feeding in preventing aspiration is based mostly on stroke-related dysphagia, where consciousness level is sometimes reduced (Norton 1996). These findings may not apply to dysphagia in chronic muscle disease (Hill 2002b).

In a previous version of this review, the review authors reported findings from uncontrolled trials that suggested that both cricopharyngeal myotomy and upper oesophageal dilatation could offer symptom relief in cases of moderate to severe dysphagia secondary to OPMD (Hill 2004). However, there was limited information on people who were not offered the procedure, and no attempt was made to compare these interventions with each other, or with other interventions. It has therefore not been possible to determine whether cricopharyngeal myotomy and upper oesophageal dilation are safe and effective interventions in OPMD. Similarly, positive outcomes have been reported for cricopharyngeal myotomy in people with IBM, but there is a lack of available data on the long-term outcome (Darrow 1992; Wintzen 1988). Meanwhile, botulinum toxin injection of the cricopharyngeus muscle as treatment for dysphagia has gained popularity in the management of a variety of conditions. It is not yet clear what role, if any, botulinum toxin injection should have in managing dysphagia secondary to chronic muscle disease because no case-controlled or long-term follow-up studies are available. Some clinicians may have concerns about prescribing a substance that causes weakness if the dysphagia itself results from weakness.

Few studies have attempted to determine the benefit or otherwise of PEG feeding in people with primary muscle disease. Review authors previously identified one uncontrolled study of the introduction of gastrostomy feeding in six children with congenital myopathy (Philpot 1999). Following intervention, there was a reduction in respiratory infections and accelerated weight gain, but treated children appeared to be at increased risk of symptomatic gastro-oesophageal reflux. Seguy 2002 studied the nutritional effects and tolerance of PEG and surgical gastrostomy in 12 children and young adults with different types of neuromuscular disease (muscular dystrophy, spinal muscular atrophy, congenital myopathy, and polyradiculoneuritis). In this study, the indications for nutritional support by gastrostomy were undernutrition or swallowing disorders. The study authors found a significant improvement in z-scores for age- and height-adjusted weight, which was maintained in 10 participants followed up after one year. However, as in Philpot 1999, the trial authors highlighted possible occurrence or worsening of gastro-oesophageal reflux following intervention. Seguy 2002 emphasised that non-invasive techniques and orthopaedic supports need to be considered before gastrostomy.

Why it is important to do this review

This review aims to (i) assess the available RCT evidence for optimal management of swallowing function, and (ii) identify key considerations for future clinical trials of dysphagia in long-term, progressive muscle disease. This is an update of a review first published in 2004 (Hill 2004).

O B J E C T I V E S

To assess the effects of interventions for dysphagia in people with long-term, progressive muscle disease.

M E T H O D S

Criteria for considering studies for this review

Types of studies

We searched for randomised controlled trials (RCTs) and quasi-RCTs examining the effectiveness of different interventions to manage dysphagia in people with long-term, progressive muscle disease. From these searches we also identified non-randomised controlled trials that otherwise met our selection criteria for inclusion; we have provided details in the Discussion section.

Types of participants

All participants were adults or children with long-term, progressive primary muscle disease, including Duchenne muscular dystrophy (DMD), myotonic dystrophy (MD), oculopharyngeal muscular dystrophy (OPMD), oculopharyngodistal myopathy (OPDM), inclusion body myositis (IBM), metabolic myopathy, and congenital myopathy. Authors of a previous version of this review excluded trials involving people with muscle conditions of a known inflammatory or toxic aetiology. In this review update, we decided to include trials of people with sporadic IBM on the basis that it presents as a long-term, progressive muscle disease with uncertain degenerative and inflammatory aetiology and is typically refractory to treatment.

Types of interventions

We searched for studies investigating a range of interventions to manage swallowing function including swallowing manoeuvres, surgical and pharmacological interventions. We considered any comparison, for example other interventions, placebo, no intervention, or standard care.

Types of outcome measures

We applied prespecified outcome measures from a previous version of the review (Hill 2004).

Primary outcomes

The stabilisation of previously documented progressive weight loss not attributable to any other cause, weight gain of at least 5 kg in adults or increase in weight to at least the 10th centile in children, maintained for at least six months following the intervention.

Secondary outcomes

1. Reduction in laryngeal penetration of bolus and/or aspiration observed on videofluoroscopy (modified barium swallow), assessed between three and six months after the intervention.
2. Reduction in chest infections attributable to aspiration over a six-month period.
3. Reduction in the number of episodes of pharyngonasal or pharyngo-oral aspirations maintained for at least six months.
4. Improvement in quality of life using a validated rating scale maintained for at least six months.
5. Proportion of participants who refuse the intervention.
6. Proportion of carers who refuse the intervention.
7. Serious adverse events related to the intervention within the first 12 months after intervention, namely events that are life-threatening, result in hospitalisation or prolongation of stay in hospital, result in a temporary or permanent worsening of swallow, or result in increased disability.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Neuromuscular Specialised Register (11 January 2016), the Cochrane Central Register of Controlled Trials (CENTRAL in the Cochrane Register of Studies Online), MEDLINE (January 1966 to November 2015), EMBASE (January 1980 to January 2016), AMED (January 1985 to December 2015), CINAHL Plus (January 1937 to January 2016) and LILACS (January 1982 to December 2015).

The detailed search strategies are in the appendices: Appendix 1 (Cochrane Neuromuscular Specialised Register), Appendix 2 (CENTRAL), Appendix 3 (MEDLINE), Appendix 4 (EMBASE), Appendix 5 (AMED), Appendix 6 (CINAHL), and Appendix 7 (LILACS).

Searching other resources

We checked references in the identified trials for any additional randomised and quasi-randomised controlled trials. We also searched ClinicalTrials.gov (www.clinicaltrials.gov) on 12 January 2016 and the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/en/) on 12 January 2016 for ongoing or completed but unpublished clinical trials. The search strategies are in Appendix 8. We applied no language limitations.

Data collection and analysis

Selection of studies

Three review authors (TH, KJ, and RP) independently identified RCTs eligible for inclusion from the search results. In the absence of sufficient RCTs for meta-analysis, we also identified non-randomised studies through our searches. Review authors (including TH, KJ, and RP) discussed the selection of studies for inclusion in this review and resolved any differences in opinion by discussion.

Data extraction and management

Four review authors (UB, MH, KJ, and SM) independently extracted RCT and non-randomised trial data using a standardised data extraction form. Two review authors assessed each identified study and resolved any discrepancies in data extraction by discussion. The review authors would have attempted to obtain missing data from the trial authors if necessary, but were already aware that no additional data were available for the study included at this update. One review author (KJ) entered data, which another review author (from among UB, MH, and SM) checked. The review authors resolved any disagreements in data entry by discussion.

Assessment of risk of bias in included studies

We assessed risk of bias in the included studies, using the standard criteria of random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Two review authors (KJ and MR) assessed the risk of bias in included studies as 'high', 'low', or 'unclear' according to criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The review authors resolved any disagreements by discussion.

Measures of treatment effect

When considering the primary outcome measure, we planned to calculate the risk ratio and its 95% confidence interval (CI) of achieving sustained improvement in swallowing or nutrition with a given intervention. For continuous outcomes, we planned to report the mean difference with 95% CI for studies using the same measurement scale, or standardised mean difference with 95% CI for studies using different measurement scales for an outcome.

Unit of analysis issues

We planned to include randomised cross-over trials with a suitable wash-out period, as this design can be appropriate in slowly progressive conditions. We would have included suitable data from a paired analysis using the generic inverse variance facility in Review Manager (RevMan) 5.3 (RevMan 2014). If we suspected carry-over effects from the first period, we may have decided to report first-period data only, while acknowledging the drawbacks of this approach (Higgins 2011). We included only first-period data from the included cross-over study as it was not truly cross-over in design because participants chose the second-period intervention.

Assessment of heterogeneity

We would have assessed heterogeneity through visual assessment of forest plots. We would have used the I^2 statistic calculated by RevMan as a measure of statistical heterogeneity, as described

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in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Data synthesis

We anticipated that different studies would use different criteria to analyse the secondary outcome measure of a reduction in laryngeal penetration or aspiration as assessed by videofluoroscopy. Where possible, we planned to pool results from these studies to calculate a standardised mean difference with 95% CI. We planned to calculate change in weight and number of chest infections as mean differences with 95% CI. Where different studies used the same validated quality of life rating scale, we planned to calculate a mean difference with 95% CI, and where different scales were used, a standardised mean difference with 95% CI.

We planned to review all studies, randomised and non-randomised, to identify possible adverse events arising from an intervention and the cost-effectiveness of that intervention. If the studies were of sufficient quality, we would have calculated a risk ratio of an adverse event arising from a procedure. Where it was not possible to perform a statistical analysis, we planned to comment on adverse events and cost-effectiveness from the available non-randomised evidence.

We planned to pool results using RevMan software with a fixed-effect model, and to assess the results for heterogeneity. If we had found heterogeneity, we would have attempted to explain the heterogeneity by omitting the trials at high risk of bias. If there still appeared to be significant heterogeneity that we could not explain, we planned to repeat the meta-analysis using a random-effects model.

'Summary of findings' table

If future updates include more than one eligible study for any comparison, we will include a 'Summary of findings' table presenting the quality of evidence for key outcomes, namely:

1. The stabilisation of previously documented progressive weight loss not attributable to any other cause; weight gain of at least 5 kg in adults, or increase in weight to at least the 10th centile in children, maintained for at least six months following the intervention.
2. Serious adverse events related to the intervention within the first 12 months after intervention, namely events that are life-threatening, result in hospitalisation or prolongation of stay in hospital, result in a temporary or permanent worsening of swallow, or result in increased disability.

In the absence of a formal 'Summary of findings' table, we discussed the included study with reference to Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria in Quality of the evidence.

We will upgrade or downgrade the evidence based on the five GRADE considerations: study limitations, consistency of effect, imprecision, indirectness, and publication bias (Higgins 2011). We will provide footnotes to explain our decisions.

Subgroup analysis and investigation of heterogeneity

We planned to analyse adults and children (aged less than 18 years) with chronic muscle disease separately. For studies that examined an intervention in a specific condition such as OPMD, we planned to present the results for the specific condition, as well as for chronic muscle disease as a whole. Due to the rarity of many muscle conditions, we anticipated that most studies would look at an intervention in a range of progressive muscle conditions.

Sensitivity analysis

In the presence of heterogeneity, we would have examined the sensitivity of meta-analyses to studies at high risk of bias as described above.

R E S U L T S

Description of studies

Results of the search

The search strategies in the appendices produced the following results: Cochrane Neuromuscular Specialised Register 19 records, CENTRAL 206 records, MEDLINE 359 records, EMBASE 272 records, AMED 16 records, CINAHL Plus 256 records, and LILACS 29. We found 202 records of ongoing studies in ClinicalTrials.gov and 42 records of ongoing studies in the World Health Organization International Clinical Trials Registry Platform (Appendix 8). We have included a flow chart to illustrate the study selection process (see Figure 1) and a separate flow chart to illustrate the identification of potentially relevant ongoing studies (see Figure 2).
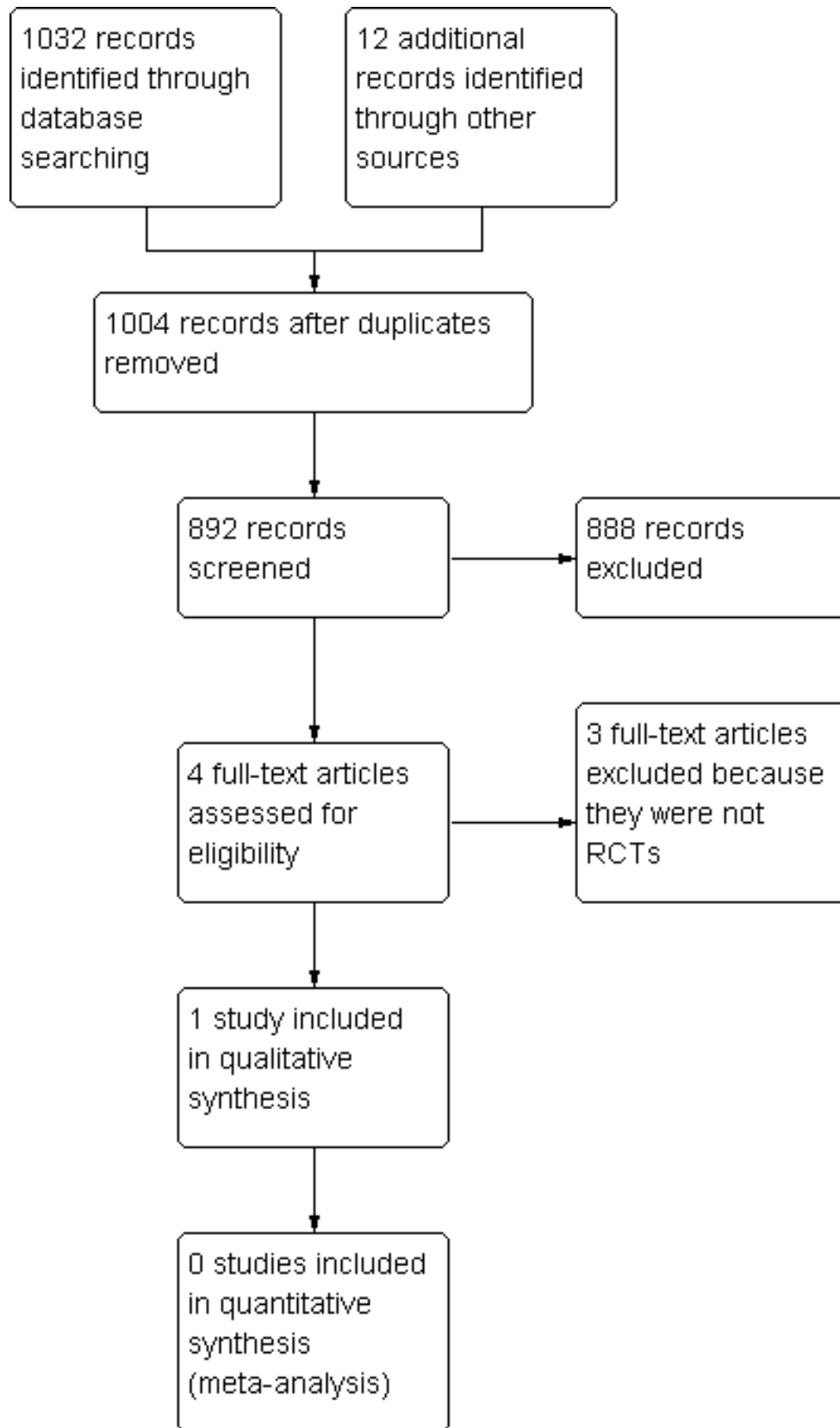
Figure 1. Study flow diagram.


```
┌─────────────────────┐     ┌─────────────────────┐
│ 1032 records        │     │ 12 additional       │
│ identified through  │     │ records identified  │
│ database            │     │ through other       │
│ searching           │     │ sources             │
└─────────────────────┘     └─────────────────────┘
            │                         │
            └───────────┬─────────────┘
                        ▼
        ┌─────────────────────────────┐
        │ 1004 records after duplicates│
        │ removed                     │
        └─────────────────────────────┘
                        │
                        ▼
        ┌─────────────────┐          ┌─────────────────────┐
        │ 892 records     │─────────▶│ 888 records         │
        │ screened        │          │ excluded            │
        └─────────────────┘          └─────────────────────┘
                        │
                        ▼
        ┌─────────────────┐          ┌─────────────────────┐
        │ 4 full-text     │─────────▶│ 3 full-text articles│
        │ articles        │          │ excluded because    │
        │ assessed for    │          │ they were not       │
        │ eligibility     │          │ RCTs                │
        └─────────────────┘          └─────────────────────┘
                        │
                        ▼
        ┌─────────────────┐
        │ 1 study included│
        │ in qualitative  │
        │ synthesis       │
        └─────────────────┘
                        │
                        ▼
        ┌─────────────────┐
        │ 0 studies       │
        │ included in     │
        │ quantitative    │
        │ synthesis       │
        │ (meta-analysis) │
        └─────────────────┘
```

Figure 2. Ongoing study flow diagram.


```
┌──────────────────────┐       ┌──────────────────────┐
│ 202 records          │       │ 42 records           │
│ identified through   │       │ identified through   │
│ searching            │       │ searching World      │
│ ClinicalTrials.gov   │       │ Health               │
│                      │       │ Organization         │
│                      │       │ International        │
│                      │       │ Clinical Trials      │
│                      │       │ Registry Platform    │
└──────────────────────┘       └──────────────────────┘

         ┌──────────────────────┐
         │ 244 records          │
         │ screened             │
         └──────────────────────┘

         ┌──────────────────────┐
         │ 2 records            │
         │ included in          │
         │ Ongoing Studies      │
         └──────────────────────┘
```
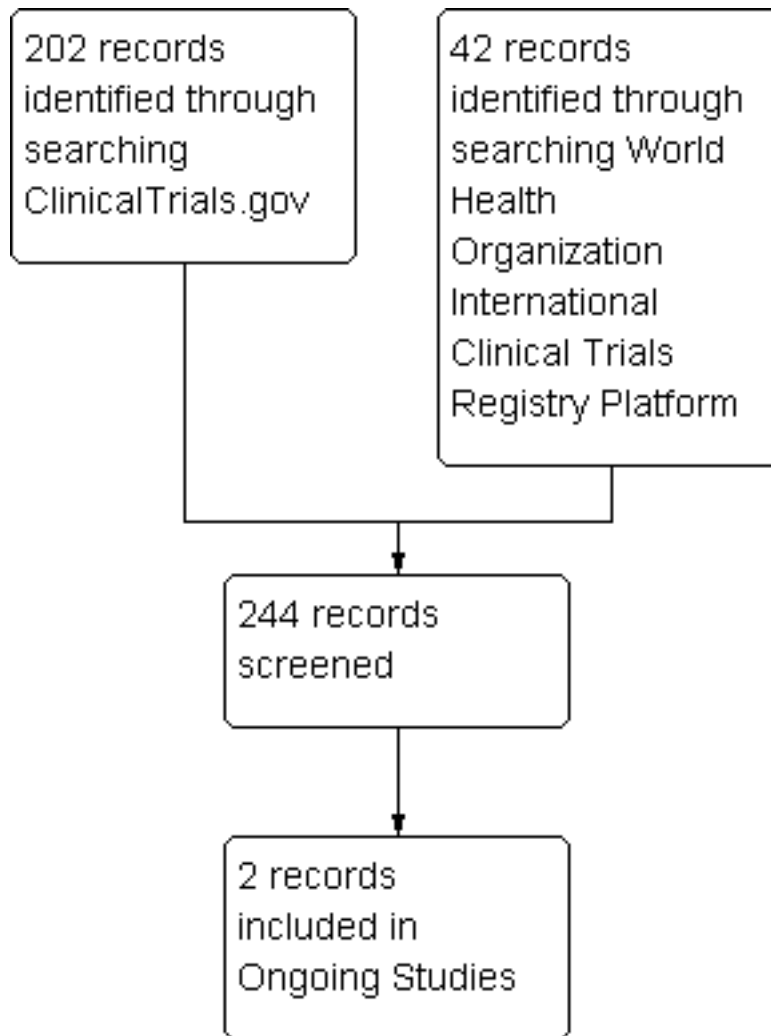
Included studies

We identified one study fulfilling the selection criteria (Dalakas 1997). This RCT investigated the effect of intravenous immunoglobulin (IVIg) on swallowing function in inclusion body myositis (IBM); see Characteristics of included studies.

In Dalakas 1997, 22 adults (19 analysed) with IBM, diagnosed according to Griggs 1995 diagnostic criteria, undertook a cross-over study of three months' IVIg and three months of placebo, separated by a wash-out period of at least one month. The placebo consisted of dextrose in half normal saline, and IVIg dosage was 2 g/kg body weight. However, three participants also received concomitant treatment with prednisone. Both trial interventions were administered once every three months by blinded assessors. The participants were also blinded to treatment intervention and were block randomised at the pharmacy to intervention groups, although they were subsequently given the option of crossing over to the alternative treatment. The primary outcome for this trial of IVIg therapy was muscle strength sum scores, as assessed in another Cochrane review (Rose 2015). However, trial authors also examined the change in bulbar muscle strength using ultrasound swallowing and videofluoroscopy, as well as changes in swallowing function using a self assessment questionnaire. Age and muscle strength were reported to be comparable between IVIg and placebo groups at baseline, although there were differences in mean swallowing duration in ultrasound studies. Funding sources were not disclosed.

Excluded studies

We excluded one ongoing trial, NCT00773227, and three completed trials that did not meet our inclusion criteria because they were not randomised (Dobloug 2012; Horowitz 1987; Sjögreen 2010). Dobloug 2012 investigated the effects of long-term IVIg therapy on swallowing dysfunction in people with IBM. Horowitz 1987 also only included a one-off administration of metoclopramide for delayed gastric emptying rather than an intervention for dysphagia per se. Sjögreen 2010 studied the effects of lip-strengthening exercises in people with myotonic dystrophy type 1, assessing change in strength and functional capacities.

Ongoing studies

We identified a potentially relevant ongoing RCT of IV trehalose (Cabaletta) drug treatment in oculopharyngeal muscular dystrophy, NCT02328482, and an RCT comparing

different treatment methods for cricopharyngeal dysfunction, ISRCTN84905610. See Characteristics of ongoing studies.

Risk of bias in included studies

One controlled trial fulfilled the inclusion criterion for attempting to randomise participants to two or more different interventions (Dalakas 1997). Despite adequate initial randomisation and allocation concealment, participants were allowed to choose whether to change their intervention during the second cross-over period, breaking randomisation. We also identified a high risk of reporting bias across the results of both cross-over periods, and possible attrition bias associated with dropouts following the first period of the trial (see Risk of bias in included studies and Figure 3). We therefore considered the trial to have a high overall risk of bias.

Figure 3. **Risk of bias summary: review authors' judgements about each risk of bias item for the included study.**
Green (+) = low risk of bias; yellow (?) = unclear risk of bias; red (-) = high risk of bias.
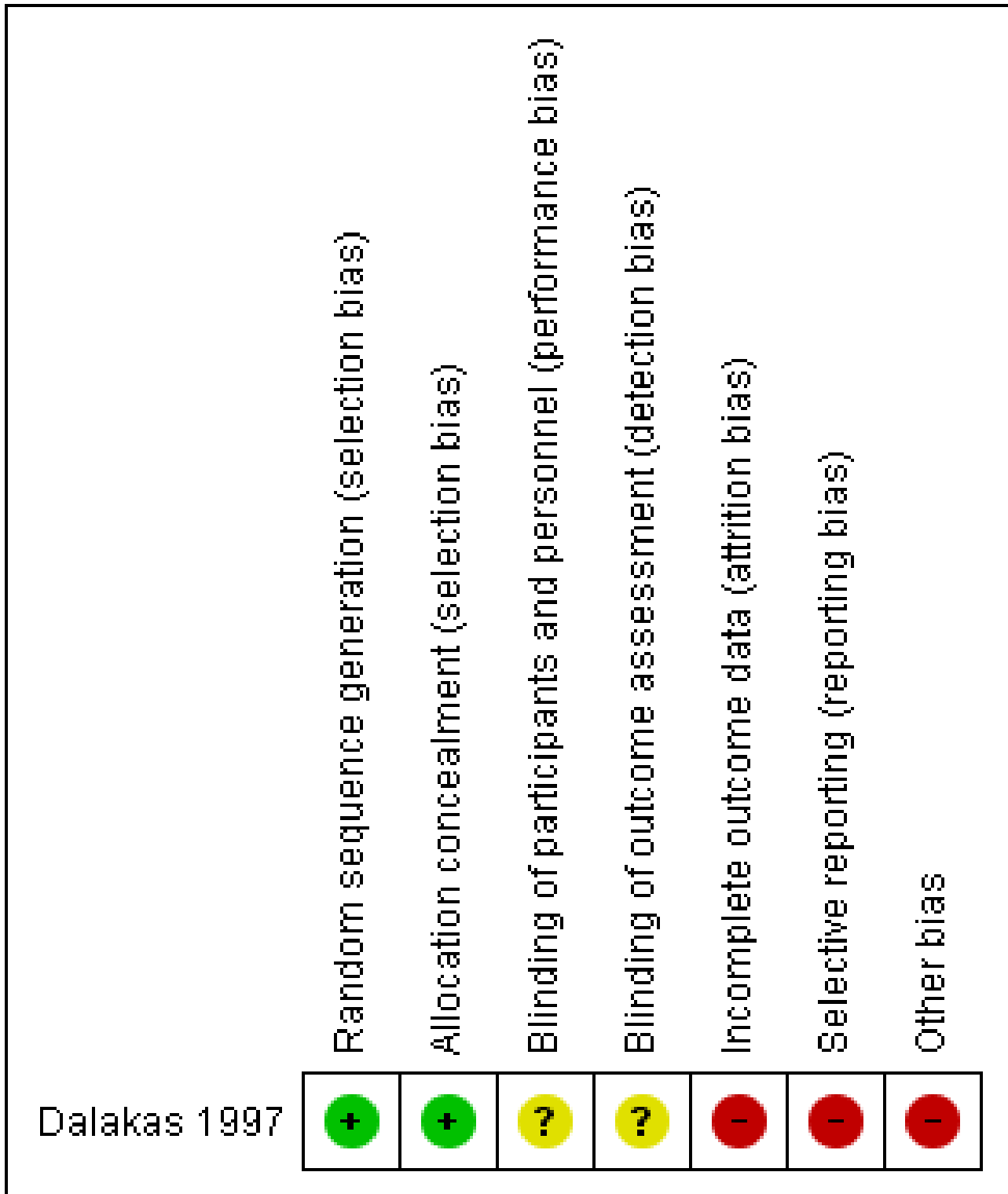
Effects of interventions

IVIg versus placebo in IBM

Efficacy

Eighteen participants chose to cross over intervention, and one participant refused to cross over from IVIg to placebo. Two other participants also dropped out during the first period of the trial, although it is unclear if they were allocated to IVIg or placebo. As the second period of this cross-over trial was not randomised, we reviewed only the first-period results. The trial presented no data for the primary outcome measure of this review, weight gain or maintenance.

No efficacy data were available for the review's secondary outcome measures, although the trial investigators undertook videofluoroscopy.

The trial authors found some supporting evidence for IVIg treatment effect in ultrasound swallowing studies. Specifically, a reduction in mean swallowing duration (seconds) was used as an indicator of improved swallowing function. Baseline mean swallowing duration was consistently lower for participants randomised to IVIg compared with placebo; this effect was reported as statistically significant ($P < 0.05$) for the second of three dry swallows and the final third wet swallow. However, the reporting of outcome data was incomplete because the study did not provide standard deviation values alongside the mean changes in swallowing duration. Furthermore, no corrections were made for multiple comparisons, which could produce statistically significant results by chance. The trial authors reported a significant improvement in the duration of swallows following three months' IVIg and worsening following placebo, but did not include a statistical between-group comparison for the first-period results. Instead, the trial authors analysed the within-group before-after data, which may be influenced by period effects. The trialists measured but did not report swallowing function using videofluoroscopy and a self assessment questionnaire, although they included a subjective evaluation of overall treatment effect, whereby 13 of the 19 participants who completed the trial experienced some improvement with IVIg. Sixteen participants were able to correctly identify their intervention allocation, suggesting possible unblinding and an increased risk of performance bias.

Data were insufficient to generate a 'Summary of findings' table. However, in accordance with the GRADE considerations, we double-downgraded the quality of the available efficacy evidence to 'low' due to limitations in the study design and implementation (incomplete outcome reporting), and indirectness, as the presence of dysphagia at the start of the study was not quantified.

Adverse events

Trial authors did not identify any serious adverse events as defined in this review. Although some participants retrospectively reported headaches, it was unclear whether these adverse events occurred in the treatment or placebo group. The trial did not report an overall incidence of adverse events. Three unexplained dropouts (14% attrition) occurred during the study, including one participant who refused to continue after completing the IVIg period. It is unclear whether the other two participants dropped out of the IVIg or placebo period.

Using GRADE considerations, we double-downgraded the quality of the available evidence for adverse events to 'low' due to limitations in the study design and implementation (incomplete outcome reporting) and indirectness.

D I S C U S S I O N

Summary of main results

One RCT of 22 adults with inclusion body myositis (IBM) fulfilled the inclusion criteria for our review (Dalakas 1997). The study assessed change in swallowing function without defining the swallowing impairment. Dalakas 1997 produced some findings that supported an improvement in swallowing function with IVIg treatment, but the study was associated with a high risk of bias, and the clinical relevance of these findings remains unclear. Applying GRADE criteria, we assessed the quality of the evidence from the trial as low. We downgraded the evidence twice, for study design and implementation limitations, and indirectness.

In the absence of sufficient RCTs for meta-analysis, we also considered the evidence from non-randomised studies assessing the effects of intervention for managing dysphagia in long-term, progressive muscle disease. As part of this discussion, we considered outcome measures for eating and drinking difficulties along with the assessment of swallowing indices, as it was possible that prespecified review outcome measures were inappropriate. For example, our primary outcome referred to a generic weight gain with intervention, which could be considered too prescriptive.

Evidence from non-RCTs

Long-term IVIg in IBM

Dobloug 2012 included 16 adults with IBM according to Griggs 1995 diagnostic criteria, treated with IVIg over a mean period of 23 months. The trial used a standard treatment protocol in which participants received a total IVIg dose of 2 g/kg body weight, infused over three to five days. Trialists administered this treatment monthly or once every third month and "tailored according to the perceived need of each individual patient", including dose adjustment in response to side effects. The IVIg-treated cohort received a total of 10 infusions on average. Seven participants in the cohort received concomitant drug therapy (corticosteroids or corticosteroids combined with methotrexate); one of these participants received infusions of methylprednisone before IVIg therapy. Retrospective assessment included comparison of the cohort with an internal control group composed of six adults with IBM who were treated with other drugs (prednisolone, methotrexate, and azathioprine). Dysphagia was assessed subjectively by participants and using barium X-rays of the oesophagus to detect and quantify the presence of dysmotility. The study made no comparison between the baseline characteristics of the control and intervention groups.

Efficacy

In addition to blood tests and manual muscle strength testing, Dobloug 2012 reviewed self reported dysphagia and dynamic studies of the oesophagus by barium X-ray. The study authors did not complete group-level analyses to assess the effect of long-term IVIg use across the cohort. Three participants treated with IVIg indicated subjective improvement in swallowing function during their follow-up compared to none in the control group. However, study authors did not specify the timing of subjective assessment,

which could have varied between 11 and 48 months across intervention and control groups. Radiological dynamic studies of the oesophagus found that only 2 of 14 people treated with IVIg who were assessed had normal oesophageal motility; however, the study authors did not assess change in dysmotility over time as part of this study.

Adverse events

There were no serious adverse events. Mild-to-moderate headaches during and after IVIg infusions were reported as side effects. Two participants received a dose reduction because of side effects, but the study paper did not report overall incidence of side effects associated with treatment.

Lip-strengthening exercises in myotonic dystrophy type 1

In Sjögreen 2010, eight school-aged children diagnosed with either congenital or childhood-onset myotonic dystrophy type 1 undertook a cross-over study of 16 weeks' training with an oral screen and 16 weeks without intervention to assess the effect of lip-strengthening exercises. The training involved 16 minutes of active and passive exercises with an oral screen performed five days per week at home or in school. The exercises could be completed independently by the child or with support from a teacher or parent. The trial authors did not directly assess dysphagia but used a range of outcome measures to assess eating and drinking difficulties, including: maximal lip force measured using a force meter; endurance of lip muscles measured at 50% maximal lip force; 3D-analysis of lip mobility; lip articulation assessment using the Swedish Articulation and Nasality Test (SVANTE); and parental assessment of eating and saliva control by questionnaire. The study authors made no comparison between the children's baseline characteristics immediately prior to the intervention and non-intervention periods. The study authors also did not describe any wash-out period between intervention and non-intervention periods.

Efficacy

There was no significant difference between the change in maximal lip force following intervention and non-intervention periods (z = -0.911; P = 0.362), although half of the participants showed significant improvement in maximal lip force and endurance (P value unspecified). Trial authors reported "wide intra-individual variation for speech and eating ability within and between assessments". They observed that changes in lip strength and endurance did not necessarily result in improved function. This study did not provide group-level results for speech and eating function.

Adverse events

Trial authors reported no adverse events, but highlighted that recurrent infections affected routine training in some children.

Overall completeness and applicability of evidence

Since publication of the original review (Hill 2004), there remains a lack of supporting evidence for interventions to manage dysphagia in long-term, progressive muscle disease. However, the existing trials highlight a fundamental issue: that we still have no standardised approach for assessing swallowing function and its change over time. The value of intervention trials in dysphagia is therefore unclear while outcome measures are inadequate to

assess the effect of treatment. There was also a lack of evidence from the studies discussed in this review on the cost-effectiveness of different interventions for dysphagia.

The sensitivity of weight change as a primary outcome measure in dysphagia is uncertain. The severity of dysphagia is expected to influence the absolute amount of weight change with intervention. Establishing a stable baseline or pre-morbid weight could also be difficult in some progressive muscle diseases. Manometry and videofluoroscopy are established clinical methods for investigating swallowing function. Videofluoroscopy is often considered to be the gold standard for assessing dysphagia, but its visual interpretation has poor inter-rater reliability, particularly when dysfunction is less obvious (Scott 1998). Philpot 1999 included abnormal findings on videofluoroscopy as a criterion for offering enteral feeding to participants, but the normal and abnormal findings corresponded inconsistently with weight gain. A later study of young people with juvenile dermatomyositis, a form of inflammatory myopathy, also found that the normality of videofluoroscopic swallow studies was not always consistent with symptom assessment (McCann 2007). Similarly, upper oesophageal manometry does not appear to reliably discriminate between those people with clinically relevant dysphagia and an apparently healthy population (Pandolfino 2005). Although intervention with either cricopharyngeal myotomy or upper oesophageal sphincter dilatation may affect upper oesophageal pressures, Pandolfino 2005 clarified that no meaningful relationship has been established between manometric abnormality and functional abnormality of either bolus transit or particular symptoms.

There are several barriers to the development of robust RCTs even with the application of a standard method of assessing dysphagia. Blinding procedures may be difficult to incorporate into interventional studies due to the nature of the interventions for dysphagia, such as surgery. An active comparator may be considered in place of a non-intervention comparator, as in the ongoing study of balloon dilation versus surgery for cricopharyngeal dysfunction (ISRCTN84905610); however, this does not remove the risk of bias associated with lack of blinding. Longitudinal data on how patients perceive the effort of swallowing, as well as the frequency, severity, and rate of progression of dysphagia across different progressive muscle conditions are insufficient. The heterogeneity in muscle disease is an additional complication, although studies of a single, well-defined patient group should be feasible. Indeed, a 12-year follow-up study of people with IBM identified mixed obstruction- and aspiration-related symptoms affecting the majority of a surveyed cohort, suggesting that a complex of symptoms or symptom descriptions may be required to monitor dysphagia. Although the rate of symptom progression was not determined, cachexia was identified as a leading cause of death in this study, illustrating the potential impact of dysphagia symptoms at the end stage of disease (Cox 2011). We also postulate that existing clinical trials of interventions for dysphagia may not adequately account for prevalent, concurrent breathing-related impairments. Factors such as reduced forced vital capacity and an ineffective cough may have critical implications for airway clearance in people with swallowing difficulties.

The two non-randomised studies discussed in this review presented very low-quality evidence (Dobloug 2012; Sjögreen 2010). As Dobloug 2012 was a retrospective rather than prospective

study, the long-term follow-up of an IVIg-treated cohort was subject to a high risk of selection and reporting bias. In Sjögreen 2010, the response to lip-strengthening exercises appeared to be highly individual and variable among a small number of children with myotonic dystrophy type 1. Together, the RCT and non-RCTs applied a range of outcome measures, which are expected to assess different and potentially unrelated indicators of treatment effect. In relation to dysphagia, the studies included subjective assessment and objective examination that failed to demonstrate baseline similarity, or depended on within-study estimates of apparently normal swallowing duration and oesophageal motility. Trialists also indirectly assessed dysphagia through subjective assessment of eating and drinking function and objective examination of lip strength and endurance. Where reported, within-participant variations in objective measurements made it difficult to interpret any change as evidence of treatment effect. As small, non-randomised studies, these were underpowered to determine group-level treatment effect from any change in the reported outcomes.

We propose that our search for answers on managing dysphagia may benefit from a more holistic approach by instead considering interventions for oral feeding difficulties. This approach could help to identify potential determinants of whether a person is able to feed by mouth, with or without detectable changes in swallowing indices. Findings from Sjögreen 2010 appear to support this need to refocus our attention on patient experiences of difficulties associated with eating and drinking; these difficulties may include, for example, external factors such as food consistency and the availability of carers. In terms of defining a normal range for swallowing function at the level of disability rather than impairment, Hughes 1996 previously combined quantitative indices for drinking a fixed volume of water with qualitative observation of this bedside test. The trial authors established that age, sex, and height were major determinants of swallowing function in apparently healthy adults, based on timed swallowing indices. Results from this study were validated by the association between reduced swallowing capacity and the number of symptoms and signs indicative of a swallowing problem in people with motor neuron disease (Hughes 1996). However, the predictive value of such swallowing indices remains to be determined across different muscle diseases.

Quality of the evidence

In this review, the included study and one of the non-randomised studies reviewed in the Discussion assessed the same intervention in the same patient population, IBM (Dalakas 1997 and Dobloug 2012). Only one of the identified trials was an RCT (Dalakas 1997), and we assessed this as at a high risk of bias (see Risk of bias in included studies). Similarly, there was a high risk of bias in the two non-randomised trials identified in this review. In addition to such limitations of study design and implementation, none of the trials included data for the prespecified primary outcome of weight maintenance or change. The trials reported the occurrence of adverse events but not according to predefined review criteria. The indirectness of outcome measures for dysphagia also lowered the quality of the evidence. We could only consider overall quality of the evidence low or very low for the identified trials.

Potential biases in the review process

No review author was an investigator or author in any of the identified trials. To help ensure that relevant expertise was represented in the review process, our review authors included specialist medical and allied health professionals to evaluate the effects of various pharmacological, surgical, and supportive interventions for managing dysphagia in muscle disease.

One potential bias in the review process was that RCTs could be inadequate to identify adverse events over a 12-month period after intervention, as specified in the review's secondary outcomes.

Another potential bias in the review process was that we identified non-randomised trials through the search for randomised trials; we did not perform a separate search for non-randomised trials, which might have identified relevant studies for discussion.

Agreements and disagreements with other studies or reviews

In this review, eating and drinking ability were assessed as part of a controlled trial of lip-strengthening exercises (Sjögreen 2010). The trialists identified a high degree of variability in lip force measurements and concluded that improvement in such indices does not automatically correspond with improvement in eating and drinking. Elsewhere, lingual training with an air-filled bulb has been associated with improved strength in a single case study in IBM (Malandraki 2012); controlled studies would be required to investigate the possible treatment effect further. The therapeutic potential of the Mendelsohn manoeuvre, defined as voluntary prolongation of hyolaryngeal elevation at the peak of the swallow (McCullough 2012), has also been studied in cases with IBM and dysphagia; Oh 2008 found that participants' weight was maintained over a review period of one to five years, and there were no reported incidences of aspiration. It is important to highlight, however, that adherence can be problematic in the application of exercise and swallowing techniques for dysphagia. For example, Sjögreen 2010 acknowledged that training was interrupted by recurrent infections for some participants. Another study reported that 21% of participants never complied with the advice given on safe swallowing (Low 2001). In a systematic review of children with swallowing disorders, there was no clear evidence to support treatment with oral motor exercises (Arvedson 2010).

Despite potential issues with intervention adherence, the previous review highlighted that trialists considered participants' subjective evaluation of swallowing to be a reliable method of detecting improvement following interventions (Hill 2004). All three studies appraised in this review included subjective evaluation, although none detailed the validity and reliability of selected outcome measures. There is a clear need for validated, reliable and standardised assessment of dysphagia that can be applied and reported in clinical trials.

In this review, we found that IVIg therapy was the only pharmacological treatment for which a change in swallowing function was assessed as part of a controlled trial (Dalakas 1997; Dobloug 2012). The results were subject to a high risk of bias and did not specifically target participants with swallowing impairment. We propose that findings of an improvement in swallowing function in both the short- and longer-term studies of IVIg are attributable to large inter- and intra-participant variation in individual responses,

but the RCT did not report standard deviation values to confirm or refute this interpretation. These IVIg studies targeted people with IBM, a condition that may have a primary inflammatory rather than degenerative aetiology, and is not always associated with dysphagia. Any evidence of an IVIg treatment effect in these trials might therefore not be applicable to either long-term, progressive primary muscle disease or dysphagia. Furthermore, a Cochrane review of treatment for IBM could not determine whether IVIg improved or stabilised overall muscle strength because the relevant RCT data were not available for meta-analysis (Rose 2015).

AUTHORS' CONCLUSIONS

Implications for practice

There is currently a lack of evidence from randomised controlled studies on interventions for dysphagia in muscle disease. Clinically relevant effects of intravenous immunoglobulin for dysphagia in inclusion body myositis can neither be confirmed nor excluded using the evidence presented in this review.

Implications for research

Universal, validated, and reliable outcome measures are needed for assessing dysphagia. Clinically meaningful outcomes for dysphagia may require a shift in focus from measures of impairment to disability associated with oral feeding difficulties. In the absence of a definitive measurement for dysphagia, there is still a need to map proxy outcomes over time as part of a prospective longitudinal study; large-scale data collection will be essential for evaluating treatment effects in future clinical trials.

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C H A R A C T E R I S T I C S   O F   S T U D I E S

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

Dalakas 1997

Methods	Double-blind, placebo-controlled, cross-over study; 3 months' IVIg and 3 months of placebo, separated by a wash-out period of at least 1 month
Participants	22 randomised (gender not specified)
	IVIg group mean age: 61.2 (42 to 74 years); mean disease duration 5.6 (3 to 10 years)
	Placebo group mean age: 66.1 (35 to 76 years); mean disease duration 7.4 (4 to 16 years)
	Inclusion criteria: diagnostic criteria of s-IBM; active disease characterised by progressive muscle weakness; impaired ability to perform fully the activities of daily living; absence of another systemic illness *Exclusion criteria:* coronary artery disease; IgA deficiency; kidney dysfunction; bedridden patients
Interventions	3 months IVIg versus placebo with a wash-out period of at least 1 month. The placebo consisted of dextrose in half normal saline, and IVIg dosage was 2 g/kg body weight. 3 participants also received concomitant treatment with prednisone
Outcomes	• Change in manual muscle testing sum scores (deltoid; biceps brachii; triceps brachii; brachioradialis; wrist extensors; wrist flexors; iliopsoas; gluteus maximus; quadriceps femoris; hamstrings; neck, finger, and foot extension and flexion) graded using a modified (0 to 10) Medical Research Council (MRC) Scale. "The net differences in the MRC scores from baseline to the end of 3 months of treatment were compared between the patients randomized to the two treatment groups for each period. The cross-over data were analyzed separately, comparing the baseline scores after the washout period to the end of the 3-month treatment"
	• Change in upper and lower limb MRC scores (limb-by-limb analysis) "from baseline to the end of the 3-month treatment"
	• Change in quantitative muscle testing sum scores from baseline at cross-over to the end of the second period of treatment
	• Participants' assessment of their response to therapy at "the end of the study and prior to breaking the code"
	• Swallowing function by ultrasound assessment of the duration of both wet and dry swallowing "measured at baseline, at the end of the first 3 months of treatment, and at the end of the second phase"
	• 20-item self assessment questionnaire on swallowing function, "measured at baseline, at the end of the first 3 months of treatment, and at the end of the second phase"
	• Videofluoroscopy
	• "62 individual items of oral motor examination using validated scales"
Funding	Not reported

Dalakas 1997 *(Continued)*

Conflicts of interest	Not reported
Notes	"Patients were referred...for therapeutic studies during the period 1992-1994"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera-tion (selection bias)	Low risk	Random component in the sequence generation process described: "The pa-tients were assigned to receive IVIg or placebo by a block-randomization pro-cedure"
Allocation concealment (selection bias)	Low risk	Central allocation described: "Randomization was performed at the pharma-cy"
Blinding of participants and personnel (perfor-mance bias) All outcomes	Unclear risk	Insufficient information to permit judgement: "The principal investigator, the physicians, nurses, physical therapists, and statisticians were unaware of which treatment was administered" but "Sixteen of the 19 patients correctly identified the period during which they received placebo or IVIg"
Blinding of outcome as-sessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit judgement: blinding following allocation concealment not described fully
Incomplete outcome data (attrition bias) All outcomes	High risk	There were 3 dropouts after the first period of the trial (14% attrition); it was unclear whether 2 of the 3 dropouts received treatment or placebo
Selective reporting (re-porting bias)	High risk	Outcomes for swallowing function incompletely reported (videofluoroscopy and self assessment questionnaire). No standard deviation values reported. No published protocol available
Other bias	High risk	Randomisation was broken by giving participants the option to cross over in-tervention. There was a minimum wash-out period of 1 month, which may not be long enough to exclude a carry-over effect. There was also a possible car-ry-over effect from drug treatment taken prior to the trial

IgA: immunoglobulin A
IVIg: intravenous immunoglobulin
s-IBM: sporadic inclusion body myositis

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

Study	Reason for exclusion
Dobloug 2012	Non-randomised controlled trial
Horowitz 1987	Non-randomised controlled trial
NCT00773227	Treatment of dysphagia in oculopharyngeal muscular dystrophy by autologous transplantation of myoblasts. Single group assignment. Non-randomised controlled trial
Sjögreen 2010	Non-randomised controlled trial

Characteristics of ongoing studies [ordered by study ID]

ISRCTN84905610

Trial name or title	Comparative study on treatment methods in cricopharyngeal dysfunction
Methods	RCT (pilot)
Participants	Oropharyngeal dysphagia caused by cricopharyngeal dysfunction
Interventions	Balloon dilation versus laser myotomy
Outcomes	Videomanometry Sydney Swallow Questionnaire
Starting date	January 2008
Contact information	ÖNH Kliniken Skanes Universitetssjukhuset Jan Waldenström gata 18 Malmö 205 02 Sweden
Notes	

NCT02328482

Trial name or title	Continuation protocol to protocol BBCO-001
Methods	RCT
Participants	Oculopharyngeal muscular dystrophy
Interventions	Drug: IV trehalose (Cabaletta) 30 g
Outcomes	Changes in disease markers Changes in swallowing quality of life Safety and tolerability evaluation including adverse events, vital signs, safety labs, and physical examination
Starting date	January 2015
Contact information	BioBlast Pharma Ltd.
Notes	

RCT: randomised controlled trial

A P P E N D I C E S

Appendix 1. Cochrane Neuromuscular Specialised Register (CRS) search strategy

#1 MeSH DESCRIPTOR Deglutition Disorders Explode All [REFERENCE] [STANDARD]
#2 Dysphagi* or swallow* or deglutition* [REFERENCE] [STANDARD]
#3 #1 or #2 [REFERENCE] [STANDARD]
#4 MeSH DESCRIPTOR Muscular Diseases Explode All [REFERENCE] [STANDARD]
#5 "inclusion body" NEAR2 myositis [REFERENCE] [STANDARD]
#6 muscl* or muscul* [REFERENCE] [STANDARD]
#7 disease* or disorder* or weaknes* [REFERENCE] [STANDARD]
#8 #6 and #7 [REFERENCE] [STANDARD]
#9 #4 or #5 or #8 [REFERENCE] [STANDARD]
#10 #3 and #9 [REFERENCE] [STANDARD]
#11 (#3 and #9) AND (INREGISTER) [REFERENCE] [STANDARD]

Appendix 2. CENTRAL (CRSO) search strategy

Search run on Mon Jan 11 2016

#1 MESH DESCRIPTOR Deglutition Disorders EXPLODE ALL TREES1759
#2 (Dysphagi* or swallow* or deglutition*):TI,AB,KY3203
#3 #1 OR #2 4363
#4 MESH DESCRIPTOR Neuromuscular Diseases EXPLODE ALL TREES 4567
#5 "inclusion body" NEAR2 myositis 39
#6 (muscl* or muscul*):TI,AB,KY 36204
#7 (disease* or disorder* or weaknes*):TI,AB,KY 231720
#8 #6 AND #71 1750
#9 #4 OR #5 OR #8 15556
#10 #3 AND #9 206

Appendix 3. MEDLINE (OvidSP) search strategy

Database: Ovid MEDLINE(R) <1946 to November Week 3 2015>
Search Strategy:
----
1 randomized controlled trial.pt. (417624)
2 controlled clinical trial.pt. (92270)
3 randomized.ab. (309508)
4 placebo.ab. (159698)
5 drug therapy.fs. (1862631)
6 randomly.ab. (219030)
7 trial.ab. (322047)
8 groups.ab. (1378466)
9 or/1-8 (3517639)
10 exp animals/ not humans.sh. (4156219)
11 9 not 10 (2999126)
12 exp Deglutition Disorders/ (44220)
13 (Dysphagi$ or (swallow$ or deglutition$)).mp. (43420)
14 12 or 13 (68551)
15 exp Muscular Diseases/ (143257)
16 ((muscle$ or muscul$) adj5 (disease$ or disorder$ or weaknes$)).mp. (68927)
17 inclusion body myositis.mp. (1204)
18 or/15-17 (176206)
19 11 and 14 and 18 (368)
20 remove duplicates from 19 (359)

Appendix 4. EMBASE (OvidSP) search strategy

Database: Embase <1980 to 2016 Week 02>
Search Strategy:
----
1 crossover-procedure/ (45414)
2 double-blind procedure/ (124985)

3 randomized controlled trial/ (388894)
4 single-blind procedure/ (21252)
5 (random$ or factorial$ or crossover$ or cross over$ or cross-over$ or placebo$ or (doubl$ adj blind$) or (singl$ adj blind$) or assign$ or allocat$ or volunteer$).tw. (1533722)
6 or/1-5 (1616325)
7 exp animals/ (20527856)
8 exp humans/ (16476972)
9 7 not (7 and 8) (4050884)
10 6 not 9 (1460070)
11 limit 10 to embase (1200272)
12 exp Dysphagia/ (47908)
13 (Dysphagi$ or swallow$ or deglutition$).mp. (76279)
14 12 or 13 (78165)
15 exp Neuromuscular Disease/ (146270)
16 ((muscle$ or muscul$) adj5 (disease$ or disorder$ or weaknes$)).mp. (109756)
17 inclusion body myositis.mp. (2185)
18 or/15-17 (232644)
19 11 and 14 and 18 (272)

Appendix 5. AMED (OvidSP) search strategy

Database: AMED (Allied and Complementary Medicine) <1985 to December 2015>
Search Strategy:
----
1 Randomized controlled trials/ (1752)
2 Random allocation/ (313)
3 Double blind method/ (571)
4 Single-Blind Method/ (67)
5 exp Clinical Trials/ (3501)
6 (clin$ adj25 trial$).tw. (6280)
7 ((singl$ or doubl$ or treb$ or trip$) adj25 (blind$ or mask$ or dummy)).tw. (2602)
8 placebos/ (569)
9 placebo$.tw. (2823)
10 random$.tw. (15486)
11 research design/ (1828)
12 Prospective Studies/ (858)
13 meta analysis/ (156)
14 (meta?analys$ or systematic review$).tw. (2704)
15 control$.tw. (32082)
16 (multicenter or multicentre).tw. (897)
17 ((study or studies or design$) adj25 (factorial or prospective or intervention or crossover or cross-over or quasi-experiment$)).tw. (11549)
18 or/1-17 (49684)
19 (Dysphagi$ or (swallow$ or deglutition$)).mp. (881)
20 exp Muscular disease/ (7728)
21 ((muscle$ or muscul$) adj5 (disease$ or disorder$ or weaknes$)).mp. (5170)
22 inclusion body myositis.mp. (16)
23 or/20-22 (11376)
24 18 and 19 and 23 (16)
25 remove duplicates from 24 (16)

Appendix 6. CINAHL (EBSCOhost) search strategy

Monday, January 11, 2016 8:32:02 AM

S26 S24 AND S25 36
S25 EM 20141110- 476,011
S24 S18 and S23 256
S23 S19 and S22 794
S22 S20 or S21 59,299
S21 (muscle* or muscul*) and (disease* or disorder* or weaknes*) 36,180
S20 (MH "Muscular Diseases+") 32,523
S19 Dysphagi* or (swallow* or deglutition*) 10,190

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S18 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 801,400

S17 ABAB design* 91

S16 TI random* or AB random* 163,434

S15 (TI (cross?over or placebo* or control* or factorial or sham? or dummy)) or (AB (cross?over or placebo* or control* or factorial or sham? or dummy)) 325,199

S14 (TI (clin* or intervention* or compar* or experiment* or preventive or therapeutic) or AB (clin* or intervention* or compar* or experiment* or preventive or therapeutic)) and (TI (trial*) or AB (trial*)) 115,928

S13 (TI (meta?analys* or systematic review*)) or (AB (meta?analys* or systematic review*)) 42,524

S12 (TI (single* or doubl* or tripl* or trebl*) or AB (single* or doubl* or tripl* or trebl*)) and (TI (blind* or mask*) or AB (blind* or mask*)) 25,172

S11 PT ("clinical trial" or "systematic review") 131,254

S10 (MH "Factorial Design") 964

S9 (MH "Concurrent Prospective Studies") or (MH "Prospective Studies") 277,109

S8 (MH "Meta Analysis") 23,911

S7 (MH "Solomon Four-Group Design") or (MH "Static Group Comparison") 49

S6 (MH "Quasi-Experimental Studies") 7,671

S5 (MH "Placebos") 9,596

S4 (MH "Double-Blind Studies") or (MH "Triple-Blind Studies") 32,950

S3 (MH "Clinical Trials+") 195,146

S2 (MH "Crossover Design") 13,507

S1 (MH "Random Assignment") or (MH "Random Sample") or (MH "Simple Random Sample") or (MH "Stratified Random Sample") or (MH "Systematic Random Sample") 71,518

Appendix 7. LILACS (IAHx) search strategy

("deglutition disorders" or MH:C06.405.117.119$ or "trastornos de deglucion" or "transtornos de degluticao" or dysphagia or swallow$ or deglutition) and ("muscular diseases" or MH:C05.651$ "enfermedades musculares" or "doencas musculares" or ((muscle$ or muscular) and (disease$ or disorder$ or weakness))) and ((PT:"Randomized Controlled Trial" or "Randomized Controlled trial" or "Ensayo Clínico Controlado Aleatorio" or "Ensaio Clínico Controlado Aleatório" or PT:"Controlled Clinical Trial" or "Ensayo Clínico Controlado" or "Ensaio Clínico Controlado" or "Random allocation" or "Distribución Aleatoria" or "Distribuição Aleatória" or randon$ or Randomized or randomly or "double blind" or "duplo-cego" or "duplo-cego" or "single blind" or "simples-cego" or "simples cego" or placebo$ or trial or groups) AND NOT (B01.050$ AND NOT (humans or humanos or humanos)))

Appendix 8. Clinical trials registries search strategies

deglutition AND muscle

dysphagia AND muscle

WHAT'S NEW

Date	Event	Description
22 September 2015	New citation required and conclusions have changed	We also considered trials in inclusion body myositis in this review update. Katherine Jones, Robert DS Pitceathly, Michael R Rose, Susan McGowan, and Umesh A Badrising joined the review at this update; Chris Milford withdrew.
22 September 2015	New search has been performed	This is an update of a Cochrane review in which authors consider the latest randomised controlled trials of interventions for dysphagia in long-term, progressive muscle disease and the continuing challenges in study design. New searches incorporated.

HISTORY

Protocol first published: Issue 3, 2003
Review first published: Issue 2, 2004

Date	Event	Description
30 July 2008	Amended	Converted to new review format.
6 May 2008	New citation required and conclusions have changed	Substantive amendment
30 September 2007	New search has been performed	Searches updated to August 2007. Description of two more non-randomised studies and two case reports added.

CONTRIBUTIONS OF AUTHORS

All review authors were involved in data collection or critical appraisal of the included studies, or both.

All review authors reviewed drafts and agreed on the final text.

DECLARATIONS OF INTEREST

KJ: Her research contribution to this review has been paid for by grants from Myositis UK and the Association Française contre les Myopathies. KJ was Assistant Managing Editor of Cochrane Neuromuscular at the time of publication. Her work on the review largely predated this appointment.

RP: None known.

MR: None known.

SM: None known.

MH: None known for current review update. She works primarily as a consultant neurologist and Associate Professor at Swansea University. She also has an established private medical practice, and as part of this work could review patients with dysphagia secondary to muscle disease.

UB: None known for current review update. His institution received a consulting fee for trial design and a fee for an ongoing clinical trial of bimagrumab in inclusion body myositis from Novartis.

TH: None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Association Française contre les Myopathies, France.

  Grant: Katherine Jones
- Myositis UK, UK.

  Grant: Katherine Jones

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the updated review we changed the title of the review from 'Treatment for swallowing difficulties (dysphagia) in chronic muscle disease' to 'Interventions for dysphagia in long-term, progressive muscle disease' to clarify that we would include any type of intervention.

We did not specify the diagnostic criteria for dysphagia or muscle disease in the updated review on the basis that dysphagia is described as a syndrome and there are no standard criteria for diagnosis of dysphagia or muscle disease.

We included participants with inclusion body myositis in the updated review as explained in the main text.

An original review author, Chris Milford, did not co-author this review update. Katherine Jones, Robert DS Pitceathly, Michael R Rose, Susan McGowan, and Umesh A Badrising joined the review at this update.

The protocol did not describe methods for assessment of heterogeneity; we added these at this update to comply with current standards. We used the current Cochrane 'Risk of bias' tool (Higgins 2011), rather than the Jadad scale, for methodological quality assessment.

INDEX TERMS

Medical Subject Headings (MeSH)

Chronic Disease; Deglutition; Deglutition Disorders [*drug therapy] [etiology]; Immunoglobulins, Intravenous [*therapeutic use]; Immunologic Factors [*therapeutic use]; Muscular Diseases [*complications] [*drug therapy]; Myositis, Inclusion Body [complications] [drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans