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[Intervention Review]

Fundoplication versus postoperative medication for gastro-oesophageal reflux in children with neurological impairment undergoing gastrostomy

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ABSTRACT

Background

Children with neurological impairments frequently experience feeding difficulties, which can lead to malnutrition and growth failure. Gastrostomy feeding is now the preferred method of providing nutritional support to children with neurological impairments who are unable to feed adequately by mouth. Complications may arise as a result of gastrostomy placement, and the development or worsening of gastro-oesophageal reflux (GOR) has been widely reported. This has led to the frequent use of surgical antireflux treatment in the form of a fundoplication, or other antireflux procedures. Fundoplication is associated with a high recurrence rate, surgical failure, and significant morbidity and mortality.

Since proton pump inhibitors (PPIs) were introduced in the 1990s, they have come to play a larger part in the medical management of GOR in children with neurological impairments. Uncontrolled studies suggest that PPIs may be a safe, appropriate treatment for GOR. Other agents currently used include milk thickeners, acid suppression drugs, acid buffering agents, gut motility stimulants and sodium alginate preparations.

There are risks and benefits associated with both surgical and medical interventions and further comparison is necessary to determine the optimal treatment choice.

Objectives

To compare the effectiveness of antireflux surgery and antireflux medications for children with neurological impairments and GOR who are undergoing placement of a gastrostomy feeding tube.

Search methods

We searched the following databases on 23 March 2012: the Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE, EMBASE, CINAHL, LILACS and ISI Web of Science. Previously, we searched the Child Health Library in June 2009. We also performed online searches of trial registries, medical journals, conference proceedings, dissertations and theses. We contacted specialists in the medical and industry setting for knowledge of completed or ongoing trials.

Selection criteria

We sought to include randomised controlled trials that recruited children up to the age of 18 years with neurological impairments and GOR who were undergoing gastrostomy tube insertion.

Data collection and analysis

The review authors worked independently to select trials; none were identified.

Main results

We identified no trials that satisfied the criteria for this review.

Authors' conclusions

There remains considerable uncertainty regarding the optimal treatment when faced with the decision of fundoplication surgery versus antireflux medications for children with GOR and neurological impairment who are undergoing gastrostomy insertion. There is a need for robust scientific evidence in order to provide data on the comparable risks or benefits of the two interventions.

PLAIN LANGUAGE SUMMARY**Surgery versus medication for treating acid reflux in brain-damaged children having a feeding tube inserted**

Children with cerebral palsy often have oral motor impairment and need help with eating and drinking. Frequently this entails surgery to place a feeding tube (gastrostomy) directly into their stomach. They may also be found to have gastro-oesophageal reflux (where stomach acid flows back up into the feeding tube (oesophagus)), which can be made worse by gastrostomy surgery. Reflux can be treated either with additional surgery at the same time as the gastrostomy (a fundoplication) or with antireflux medications. We carried out this review to determine which was the safest and most effective form of treatment. We found no randomised controlled trials that provided scientific evidence on which to base a conclusion, highlighting the need for a trial comparing the two interventions.

BACKGROUND

Description of the condition

Children with neurological impairments frequently experience profound feeding difficulties, which can lead to malnutrition and growth failure. These are often seen as inevitable consequences of many neurological disorders due to their associated physical abnormalities, communication difficulties and motor impairments (Samson-Fang 2003).

The causes of malnutrition in children with neurological impairments are multifactorial. Physiological abnormalities may manifest as oro-motor dysfunction and the associated inco-ordination of oropharyngeal reflexes (Puntis 2000; Wadie 2002). Children may also be severely compromised in their inability to feed independently and subsequently experience frustration and behavioural problems (Puntis 2000). Many of the factors that lead to malnutrition and failure to thrive dictate a need to find alternative measures of providing adequate nutrition, such as an enteral feeding tube (Wadie 2002).

Enteral feeding is considered to be justified to prevent or reverse growth failure when other efforts to increase nutritional intake, such as dietary supplementation, have failed (Puntis 2000). The placement of a gastrostomy feeding tube is now the preferred method of providing long-term nutritional support to children with neurological impairments. A gastrostomy is considered when enteral feeding is required beyond the short-term period (that is, greater than six weeks), when there are prolonged feeding times, inadequate weight gain and an unsafe swallow (Sullivan 1997; Samson-Fang 2003). The use of gastrostomy tube feeding has previously been shown to increase weight, improve overall health and decrease feeding times for children with neurological impairment (Sullivan 2005). It has also demonstrated a significant, measurable improvement in the quality of life of carers (Sullivan 2004). The literature on prevalence of gastrostomy insertion in this population is limited but a study carried out in the UK by Sullivan 2000 showed that 8% of children with neurological impairments were gastrostomy fed (Sullivan 2000).

Gastrostomy tube insertion can be performed by laparotomy, laparoscopy or endoscopy, and the most favoured procedure for tube placement has become percutaneous endoscopic gastrostomy (PEG), which was introduced by Gauderer in 1981 (Gauderer 1981). PEG is associated with decreased morbidity in comparison with other techniques for gastrostomy insertion and has been assessed to be both efficient and cost-effective (Byrne 1990; Samuel 2002). Complications may arise as a result of gastrostomy placement including infection, perforation, bleeding, tube migration/dislocation, intestinal fistulas and obstruction (Razeghi 2002). In addition, the development or worsening of gastro-oesophageal reflux (GOR) has been widely reported and is considered to be one of the long-term sequelae of gastrostomy placement (Mollitt 1985; Razeghi 2002).

GOR in children with neurological impairments is a well-described phenomenon. It is attributed to a motility disturbance affecting the oesophagus and the lower oesophageal sphincter (LOS) mechanism, and leads to retrograde, involuntary, effortless regurgitation of gastric contents into the oesophagus (Rosen 2000; Vandenplas 2000; Richards 2001). The prevalence of GOR among children with neurological impairments has been reported to range

from 14% to 75% depending on the diagnostic criteria of GOR used, highlighting the fact that the role of reflux in this group is not well understood and may have a wide range of manifestations and symptoms (Sullivan 1992; Reyes 1993; Gangil 2001). The pathophysiological mechanisms of GOR are multifarious. The underlying neurological damage may cause delayed gastric emptying and oesophageal dysmotility, while scoliosis, seizures, spasticity of abdominal musculature or constipation can all cause increased abdominal pressure. Due to their often profound physical disabilities, many children spend long periods in the supine position, thus minimising the effect of gravity to aid oesophageal clearance (Halpern 1991; Spitz 1993; Vandenplas 2000).

Description of the intervention

For children with neurological impairments who have pre-existing GOR and are referred for the insertion of a gastrostomy, the placement itself can lead to a worsening of symptoms with severe vomiting and aspiration (Mollitt 1985; Wheatley 1991). Historically, medical management of GOR in children with neurological impairments has had a high failure rate (Cheung 2001; Gold 2002). This has led to the frequent use of surgical treatment in the form of an antireflux procedure (ARP) such as a Nissens, Thal, Toupet or Belsey fundoplication (Ostlie 2002; Hassall 2005). Fundoplication involves strengthening the barrier to acid reflux by wrapping the fundus of the stomach around the oesophagus at the gastro-oesophageal junction. Fundoplication procedures vary according to the degree of fundal wrap that is performed at the distal oesophagus and can range from a full 360° wrap to a partial 180° wrap depending on the operation performed (Hassall 2005). The fundoplication is designed to prevent GOR by correcting hiatal herniation, lengthening the intra-abdominal portion of the oesophagus, tightening the crura and increasing the pressure of the LOS (Di-Lorenzo 2002).

Despite its value in preventing GOR, fundoplication has other consequences. It permanently alters the gastro-oesophageal anatomy and function, and, as has been shown in animal work, may lead to vagal nerve damage that sensitises the emetic reflex (Richards 2000). Complications may ensue from these changes (Di-Lorenzo 2002). These may be related to the underlying condition of the child; for example, seizure disorders or pulmonary disease may lead to increased abdominal pressure, or may arise from the effect of the surgery itself (Kimber 1998). Complications directly related to the surgery may include gas bloat syndrome, impaired gastric accommodation, gastric hypersensitivity, rapid gastric emptying (or 'dumping syndrome'), retching or dysphagia (Di-Lorenzo 2002; Connor 2005). The challenging anatomy and physiology of this group of children mean they suffer from many conditions seemingly unrelated to GOR, such as scoliosis and epilepsy, which subsequently make it difficult for any antireflux intervention to be a guaranteed success. The ARP (fundoplication) is associated with a high recurrence rate and significant morbidity and mortality in this group of children, with a 40% surgical failure rate (Isch 1997; Kimber 1998). About 12% to 30% of children with neurological impairments experience recurrent reflux post fundoplication, while 59% of children experience postoperative complications with a 1% to 3% mortality rate (Byrne 1990; Sullivan 1999).

Traditional medical therapies for GOR in this group of children include milk thickeners, acid suppression drugs (histamine 2 receptor antagonists (H2RAs)), acid buffering agents (antacids)

and gut motility stimulants (prokinetics). These therapies have poor response rates with studies showing that only 13% of neurologically impaired children respond completely to medical management, the remainder experiencing persistence of symptoms (Wilkinson 1981; Cheung 2001; Gold 2002). The prokinetic drug, cisapride, was withdrawn from the market in many countries following concerns over safety and a lack of robust evidence of efficacy (Gold 2002), and there is now no effective prokinetic drug available.

Since the 1990s, proton pump inhibitors (PPIs), for example omeprazole, have played a larger part with the medical management of GOR in children with neurological impairment. Uncontrolled studies of omeprazole have reported high levels of tolerability and efficacy suggesting high rates of healing, symptom relief and reduction of vomiting in up to 90% of participants (Cheung 2001; Hassall 2005). PPIs are reported to work by decreasing the acidity of the refluxate and decreasing gastric acid secretion volume, thereby improving gastric emptying (Hassall 2005). The long-term effects of PPI use are not known at this point, but after a decade of use in the adult population, this group of medications have been found to have a good safety profile (Gold 2002).

Why it is important to do this review

This review aims to assess the efficacy of fundoplication for neurologically impaired children who are at a high risk of ARP failure compared with medical antireflux treatment. This is clinically important as there is some evidence of poor outcomes from surgery and the uncontrolled studies suggest that PPIs may be a safe, appropriate, cost-effective alternative (Heudebert 1997; Hassall 2000; Cheung 2001).

OBJECTIVES

To compare the effectiveness of antireflux surgery and antireflux medications for children with neurological impairment and GOR who are undergoing placement of a gastrostomy feeding tube.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Children up to 18 years of age with neurological impairments (as defined by trialists) and GOR who are undergoing insertion of a gastrostomy feeding tube.

We excluded studies if there were neurologically normal children included in the trial (unless studied as a separate subgroup) or if the majority of children participating had neurological impairments that were caused by degenerative or metabolic conditions.

Types of interventions

Any type of surgical fundoplication ARP compared with the use of antireflux medications.

Types of outcome measures

Primary outcomes

- Resolution of clinically measured, identifiable symptoms of GOR following gastrostomy surgery.

Secondary outcomes

- Adverse events: morbidity - including wrap failure, retching, dumping, dysphagia, drug side effects and interactions.
- Adverse events: mortality.
- Pain: measured by parental reporting, behavioural observations.
- Health-related quality of life for child or carer, or both: measured using validated scales.

Search methods for identification of studies

The searches for previous versions of this review were run in June 2006 and June 2009. We performed the searches for this update on 23 March 2012.

Electronic searches

We searched the following databases on 23 March 2012.

1. The Cochrane Central Register of Controlled Trials (CENTRAL) 2012 (Issue 1)
2. Ovid MEDLINE, 1966 to March 2012
3. EMBASE (Ovid), 1980 to week 12, 2012
4. CINAHL (EBSCO), 1982 to March 2012
5. ISI Web of Science, 1970 to March 2012
6. LILACS, 1982 to March 2012
7. ClinicalTrials.gov
8. Current Controlled Trials
9. CenterWatch
10. UK Clinical Research Network

The following online resources were searched for previous versions, but were not available to us in 2012.

- Child Health Library, last searched June 2009
- National Research Register Archive (contains records up to 2007), last searched in June 2009
- ClinicalStudyResults.org, last searched June 2009
- TrialsCentral, last searched June 2006
- Pharmaceutical Industry Clinical Trials Database, last searched June 2009
- International Federation of Pharmaceutical Manufacturers and Associations, last searched June 2009

Please see [Appendix 1](#) for the most recent search strategies and [Appendix 2](#) for the original and 2009 update search strategies. We used subject headings as well as free-text terms where available.

We used RCT filters, where appropriate, with the search strategies. We searched bibliographies of identified articles for additional studies when the original article was directly on the topic, even if not reporting an RCT itself. We did not apply any language or date restrictions.

Searching other resources

Journals

We searched the following online journals using their web-based search engines.

- *American Journal of Surgery* (1926 to 2012)
- *Archives of Disease in Childhood* (1973 to 2012)
- *British Medical Journal* (1994 to 2012)
- *Child Care Health and Development* (1975 to 2012)
- *Developmental Medicine and Child Neurology* (1960 to 2012)
- *Gastroenterology* (1965 to 2012)
- *Gastrointestinal Endoscopy* (1995 to 2012)
- *Journal of Paediatric Gastroenterology and Nutrition* (1982 to 2012)
- *Journal of Pediatric Surgery* (1966 to 2012)
- *Journal of Pediatrics* (1932 to 2012)
- *Pediatrics* (1948 to 2012)
- *Surgery* (1995 to 2012)
- *Surgical Endoscopy* (1986 to 2012)

Pharmaceutical companies and equipment manufacturers

Manufacturers of relevant equipment (gastrostomy tubes) and pharmaceutical companies that produce the antireflux medication were contacted previously. These included: Wyeth UK; Altana Pharma ([Kapoor 2006 \[pers comm\]](#)); Merck Pharmaceuticals ([Armstrong 2006 \[pers comm\]](#)); Vygon ([Edwards 2006 \[pers comm\]](#)); AstraZeneca ([MacDonald 2006 \[pers comm\]](#)), and Fresenius Kabi.

We searched the following pharmaceutical websites in June 2012.

- International Federation of Pharmaceutical Manufacturers and Associations (www.ifpma.org/).
- GlaxoSmithKline (ctr.gsk.co.uk/welcome.asp).
- AstraZeneca (www.astrazenecaclinicaltrials.com/).
- Roche Pharmaceuticals (www.roche-trials.com/).

Grey Literature

The following databases/websites were searched in an attempt to identify grey literature in the form of theses, abstracts or conference proceedings: Index to Theses (searched March 2012), ProQuest Digital Dissertations (searched June 2012), ISI Proceedings (1990 to 2012), Cambridge Scientific Abstracts (CSA), Illumina (searched March 2012) and the System for Information on Grey Literature in Europe (SIGLE) (searched March 2012).

For the original review, the team wrote to leading experts in the field, either known to them or identified as authors of studies specific to the review topic, to ask whether they were aware of any studies not identified by the searches described above ([Gottrand 2006 \[pers comm\]](#); [Spitz 2006 \[pers comm\]](#); [Lloyd 2006 \[pers comm\]](#); [Di-Lorenzo 2006 \[pers comm\]](#); [Esposito 2006 \[pers comm\]](#); [Gold 2006 \[pers comm\]](#); [Kawahara 2006 \[pers comm\]](#); [Vandenplas 2006 \[pers comm\]](#); [Gremse 2006 \[pers comm\]](#); [Hassall 2006 \[pers comm\]](#); [Orenstein 2006 \[pers comm\]](#), [Tolia 2006 \[pers comm\]](#); [Langer 2006 \[pers comm\]](#); [Heine 2006 \[pers comm\]](#)). None of these colleagues were able to report relevant RCTs undertaken in the past or in progress.

Data collection and analysis

Please see [Table 1](#) for the methods that we would have used if there had been any included studies in our review.

RESULTS

Description of studies

Results of the search

We identified 1033 reports from the original electronic searches. Papers identified varied from reviews and editorials, to different study designs, both retrospective and prospective. The search update from June 2006 to June 2009 produced a further 476 reports but identified no trials meeting the inclusion. We revised the search strategies in 2012 and ran searches on 23 March 2012, which produced 385 reports, none of which met the inclusion criteria.

[Figure 1](#) shows a study flow diagram including the number of identified reports, duplicates and discarded studies.

Figure 1. Study flow diagram for 2012 searches

Included studies

We identified no trials meeting the inclusion criteria.

Rejected articles

Through our search of the grey literature, we identified one thesis that was an RCT of surgical versus medical management for clinically significant GOR, but this was in adults ([Whelan 1979](#)).

We identified one ongoing study in our search of the online trials registries that matched the inclusion criteria (Lloyd 2000); however, we contacted the lead investigator who subsequently explained that the trial had been registered but not started due to methodological problems with the randomisation of children following previous failed medical management.

The other papers we discarded involved, for example, alternative options for reflux treatment, effectiveness studies of different surgical antireflux techniques, and risk and benefit studies of gastrostomy surgery with fundoplication. The studies identified did not meet inclusion criteria either because they involved children who were neurologically normal or they were not RCTs or they did not compare medical versus surgical treatments.

Risk of bias in included studies

We identified no trials meeting the inclusion criteria.

Effects of interventions

We identified no trials meeting the inclusion criteria.

DISCUSSION

The objective of this review was to compare the effectiveness of antireflux fundoplication surgery with the use of antireflux medications in children with neurological impairments undergoing gastrostomy feeding tube insertion. We identified no relevant RCTs. This review has demonstrated that there is no evidence available from reliable sources on which to draw any conclusions. We cannot provide data on the comparable risks or benefits of either treatment and are subsequently unable to provide recommendations for the best approach in this group of children.

AUTHORS' CONCLUSIONS

Implications for practice

There continues to be considerable uncertainty regarding optimal treatment option when faced with the decision of performing surgery or prescribing medications for gastro-oesophageal reflux (GOR) in children with neurological impairment who are undergoing a gastrostomy. As surgeons and physicians should ensure that parents are fully informed about the risks and benefits of both treatments, the fact there is a lack of high-quality evidence regarding the relative merits and drawbacks of each option should be shared with families.

It is important to highlight the fact that, although this review deals specifically with the comparison of fundoplication versus medication, other surgical and endoscopic treatment options are becoming available for managing GOR in this group of children. The durability and long-term outcomes are not yet known within the paediatric population and further research is required before they are included as part of clinical practice.

Implications for research

A randomised controlled trial of fundoplication versus postoperative medication for children with neurological impairment and severe GOR undergoing gastrostomy should be

undertaken to resolve the current uncertainties about the optimal management strategy, for preference, a large multicentre trial. Due to the nature of the two treatment options, it would not be possible to blind trialists or participants to allocation, but assessor blinding may be possible when measuring pre- and postoperative GOR. The trial would have to be analysed on an intention-to-treat basis as those randomised to the medication arm of the trial could subsequently suffer worsening reflux and require fundoplication, but those having surgery could not revert to the medication arm post procedure. There would need to be strict inclusion and exclusion criteria to identify those children with very severe GOR, such as those experiencing life-threatening events, in whom a fundoplication is strongly indicated.

Through personal communication with Professor David Lloyd (Lloyd 2006 [pers comm]) and Professor Jacob Langer (Langer 2006 [pers comm]), an ethical consideration was brought to the review authors' attention with regards to the process of randomisation. Children with neurological impairments who are referred for gastrostomy insertion and have pre-existing reflux may have previously been treated with medications that have not resolved their symptoms. It would not be ethical in this instance to allocate them randomly to a treatment group knowing that one of the two options had previously failed to alleviate symptoms. This would not provide a fair chance of symptom relief from either therapy. In order to avoid this issue when performing a trial, children would need to be randomised to a treatment arm as soon as the diagnosis of GOR was made, and the gastrostomy surgery, with or without fundoplication, should proceed as soon as possible.

While it is important to acknowledge that any research performed with this group of children will be difficult due to their anatomical and physiological problems, this is a population with ever increasing health needs and this is an area that is critically in need of research.

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ADDITIONAL TABLES

Table 1. Methods to be used in future updates

Selection of studies	Titles and abstracts of studies will be identified from the search and read independently by two review authors (AVR and PBS). Those that do not meet the inclusion criteria will be discarded and any disagreements over suitability for inclusion will be resolved by discussion or adjudication, or both by editors of the Cochrane Developmental, Psychosocial and Learning Problems Group. If further information is sought from trial authors, the study will be categorised as awaiting assessment.
Data extraction and management	Data extraction forms will be designed to include study design, participant characteristics, study setting, intervention type and outcomes. Data will be extracted independently by two review authors (AVR and PBS) and disagreements will be resolved through discussion or by contacting the study author for further information. Data will be organised using Review Manager 5.2.
Assessment of risk of bias in included studies	<p>Selected studies will be independently evaluated by two review authors (AVR and PBS) using The Cochrane Collaboration's tool for assessing the risk of bias (Higgins 2011). Disagreements over suitability for inclusion will be resolved by discussion or adjudication, or both, by editors of the Cochrane Developmental, Psychosocial and Learning Problems Group. The tool will assess the following items: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of bias. Studies will be assigned a quality category (high, low and unclear risk of bias) and supporting evidence will be presented in a 'Risk of bias' table. We will make our judgements based on the following criteria.</p> <p><i>Adequate sequence generation</i></p> <ul style="list-style-type: none"> 'low' indicates that adequate methods of concealment were used for random allocation. This would include computer-generated random numbers, a random numbers table, coin-tossing or dice throwing if the procedure was performed by someone not otherwise involved in participant recruitment. 'unclear' indicates uncertainty as to whether allocation was adequately concealed from trialist or participant. This would include methodology where the method of concealment is not known. If the method of concealment and allocation is unclear the study authors will be contacted to obtain precise information.

Table 1. Methods to be used in future updates (Continued)

- 'high' indicates that although the methods of randomisation were described, the method was inadequate to guarantee allocation concealment. This would include alternation, dates of birth or any procedure that is transparent before allocation such as an open list of random numbers.

Allocation concealment

- 'low' indicates the use of centralised or pharmacy-controlled randomisation, telephone randomisation or sequentially numbered, sealed, opaque envelopes.
- 'unclear' indicates that allocation concealment was not clearly stated or the methods were not described.
- 'high' indicates that the allocation sequence was not concealed from investigators or participants.

Blinding of participants and personnel

Blinding to the study intervention following allocation would not be possible either for trialists or participants in these studies. The intervention compares a surgical procedure to a medication regimen following insertion of a gastrostomy feeding tube. This means it would be very difficult to eliminate detection and performance bias.

Incomplete outcome data

In the event that data are missing or unclear in any aspect of the trial (from methodological aspects to trial results) primary investigators will be contacted. Data will, if possible, be analysed on an intention-to-treat basis.

Follow-up

- 'low' indicates that losses to follow-up were equally distributed between treatment and comparison groups, and the reasons for dropout or withdrawal were adequately reported.
- 'unclear' indicates that information about losses to follow-up was unavailable.
- 'high' indicates that losses to follow-up were in excess of 30% or unevenly (more than 10% difference) distributed between treatment and comparison groups.

Intention to treat

- 'low' indicates that intention-to-treat analyses was performed or could be performed using available data.
- 'unclear' indicates that information about whether intention-to-treat analyses were performed was not available and could not be acquired by contacting the researchers of the study.
- 'high' indicates that intention-to-treat analyses were not performed and could not be done using available data.

Selective reporting

- 'low' indicates that the prespecified primary outcomes have been reported and all collected data has been reported.
- 'unclear' indicates that it is insufficient information to allow a judgement to be made.
- 'high' indicates that the primary outcome data have not been reported or have been reported incompletely.

Other sources of bias

We will attempt to avoid publication bias by seeking data from all sources including conference proceedings and unpublished data from pharmaceutical companies (see search strategy). Should sufficient data be identified, funnel plots will be drawn to investigate any relationship between effect size and study precision (closely related to sample size). Such a relationship could be due to publication or related biases, systematic differences between small and large studies, or poor methodology. If a relationship is found, clinical diversity of the studies will be further examined as a possible explanation.

Measures of treatment effect *Binary data*

Table 1. Methods to be used in future updates (Continued)

For dichotomous data, the risk ratio and its 95% confidence interval will be calculated.

Continuous data

For studies using standardised assessment tools that have generated a scored outcome measure, we will calculate a mean difference. For studies using different scales, we will calculate the standardised difference in means with a 95% confidence interval.

Assessment of heterogeneity	Result consistency will be examined graphically to determine overlap of confidence intervals, poor overlap signifying heterogeneity. We will also consider the I^2 descriptive statistic available in Review Manager 5.1 to calculate the proportion of variation that is due to heterogeneity rather than chance. Both fixed-effect and random-effects analyses will be performed.
Data synthesis	Where meta-analysis is feasible (that is, if two or more included studies are identified that are considered sufficiently homogeneous), we will perform a meta-analysis.
Subgroup analysis and investigation of heterogeneity	If sufficient data are identified, we anticipate undertaking subgroup analyses as follows: <ol style="list-style-type: none"> 1. degree of clinically measured symptomatic gastro-oesophageal reflux prior to gastrostomy surgery; 2. level of disability; 3. presence of underlying seizure disorders or pulmonary disease.
Sensitivity analysis	We will conduct a sensitivity analysis to assess the impact of study quality on the outcome of the meta-analysis. This will determine whether, for example, studies with unclear allocation concealment or high rates of loss to follow-up are more likely to show positive outcomes.

APPENDICES

Appendix 1. Search strategies for the 2012 update

CENTRAL

Cochrane Central Register of Controlled Trials (CENTRAL), 2012, Issue 1, part of *The Cochrane Library*
Searched 23 March 2012

- #1 MeSH descriptor Gastrostomy explode all trees
- #2 (gastrostom*)
- #3 (#1 OR #2)
- #4 MeSH descriptor Fundoplication explode all trees
- #5 (fundoplicat*)
- #6 (nissen) and (operation*)
- #7 (thal)
- #8 (toupet)
- #9 (belsey)
- #10 (anti-reflux)
- #11 (anti) and (reflux)
- #12 (antireflux)
- #13 (#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)
- #14 MeSH descriptor Child explode all trees
- #15 MeSH descriptor Infant explode all trees
- #16 MeSH descriptor Adolescent explode all trees
- #17 (baby) or (babies)
- #18 (infant*)
- #19 toddler*
- #20 child*
- #21 girl*

#22 boy*
 #23 pre-school*
 #24 preschool
 #25 teen*
 #26 adolescen*
 #27 (#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26)
 #28 MeSH descriptor Cerebral Palsy explode all trees
 #29 (cerebral) and (palsy)
 #30 little* and disease*
 #31 spastic near/6 diplegia
 #32 spastic near/6 quadraplegia
 #33 neuro* near/6 disab*
 #34 neuro* near/6 impair*
 #35 (#28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34)
 #36 (#3 AND #13 AND #27 AND #35)

MEDLINE

Ovid MEDLINE, 1966 to March 2012
 Last searched 23 March 2012

1. gastrostomy/
2. gastrostom\$.tw.
3. or/1-2
4. fundoplication/
5. fundoplicat\$.tw.
6. nissen operation\$.tw.
7. thal.tw.
8. toupet.tw.
9. belsey.tw.
10. anti-reflux.tw.
11. anti reflux.tw.
12. antireflux.tw.
13. or/4-12
14. exp child/
15. infant/
16. adolescent/
17. (baby or babies).tw.
18. infant\$.tw.
19. toddler\$.tw.
20. child\$.tw.
21. girl\$.tw.
22. boy\$.tw.
23. pre-school\$.tw.
24. preschool\$.tw.
25. teen\$.tw.
26. adolescen\$.tw.
27. or/14-26
28. cerebral palsy/
29. cerebral palsy.tw.
30. little\$disease.tw.
31. (spastic adj3 diplegia).tw.
32. (spastic adj3 quadriplegia).tw.
33. (neuro\$ adj3 disab\$).tw.
34. (neuro\$ adj3 impair\$).tw.
35. or/28-34
36. 3 and 13 and 27 and 35
37. randomized controlled trial.pt.
38. controlled clinical trial.pt.
39. randomized controlled trials.sh.
40. random allocation.sh.
41. double blind method.sh.
42. single-blind method.sh.

43. or/37-42
44. (animals not human).sh.
45. 43 not 44
46. clinical trial.pt.
47. exp clinical trials as topic/
48. (clin\$ adj25 trial\$).ti,ab.
49. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
50. placebos.sh.
51. placebo\$.ti,ab.
52. random\$.ti,ab.
53. research design.sh.
54. or/46-53
55. 54 not 44
56. 55 not 45
57. comparative study.sh.
58. exp evaluation studies/
59. follow up studies.sh.
60. prospective studies.sh.
61. (control\$ or prospectiv\$ or volunteer\$).ti,ab.
62. or/57-61
63. 62 not 44
64. 63 not (45 or 56)
65. 45 or 56 or 64
66. 36 and 65

EMBASE

EMBASE (Ovid), 1980 to week 12 2012

Last searched 23 March 2012

1. gastrostomy/
2. gastrostom\$.tw.
3. or/1-2
4. fundoplication/
5. fundoplicat\$.tw.
6. nissen operation\$.tw.
7. thal.tw.
8. toupet.tw.
9. belsey.tw.
10. anti-reflux.tw.
11. anti reflux.tw.
12. antireflux.tw.
13. or/4-12
14. exp child/
15. infant/
16. adolescent/
17. (baby or babies).tw.
18. infant\$.tw.
19. toddler\$.tw.
20. child\$.tw.
21. girl\$.tw.
22. boy\$.tw.
23. pre-school\$.tw.
24. preschool\$.tw.
25. teen\$.tw.
26. adolescen\$.tw.
27. or/14-26
28. cerebral palsy/
29. cerebral palsy.tw.
30. little\$ disease.tw.
31. (spastic adj3 diplegia).tw.
32. (spastic adj3 quadraplegia).tw.
33. (neuro\$ adj3 disab\$).tw.

34. (neuro\$ adj3 impair\$).tw.
35. or/28-34
36. 3 and 13 and 27 and 35
37. clin\$.tw.
38. trial\$.tw.
39. (clin\$ adj3 trial\$).tw.
40. singl\$.tw.
41. doubl\$.tw.
42. trebl\$.tw.
43. tripl\$.tw.
44. blind\$.tw.
45. mask\$.tw.
46. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
47. randomi\$.tw.
48. random\$.tw.
49. allocat\$.tw.
50. assign\$.tw.
51. (random\$ adj3 (allocat\$ or assign\$)).tw.
52. crossover.tw.
53. 52 or 51 or 47 or 46 or 39
54. exp randomized controlled trial/
55. exp double blind procedure/
56. exp crossover procedure/
57. exp single blind procedure/
58. exp randomization/
59. 54 or 55 or 56 or 57 or 58 or 53
60. 36 and 59
61. 36 and 59

CINAHL

CINAHL (EBSCO), 1982 to March 2012
Last searched 23 March 2012

- S34 S24 and S25 and S32 and S33
- S33 S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10
- S32 S26 or S27 or S28 or S29 or S30 or S31
- S31 neuro* AND impair*
- S30 neuro* AND disab*
- S29 spastic AND quadriplegia
- S28 spastic AND diplegia
- S27 little* disease
- S26 cerebral palsy
- S25 S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23
- S24 S1 or S2
- S23 toddler*
- S22 adolescen*
- S21 teen*
- S20 preschool*
- S19 pre-school*
- S18 boy*
- S17 girl*
- S16 child*
- S15 infant*
- S14 baby or babies
- S13 adolescent
- S12 infant
- S11 child Expanders - Apply related words
- S10 antireflux
- S9 anti reflux
- S8 anti-reflux
- S7 belsey
- S6 toupet

S5 thal
S4 nissen operation
S3 fundoplicat*
S2 gastrostom*
S1 gastrostomy/

ISI Web of Science

ISI Web of Science was searched via Web of Knowledge (1970 to March 2012)

reflux
reflux AND child*
reflux AND child* AND gastrostom*
reflux AND child* AND gastrostom* AND fundoplicat*
reflux AND child* AND gastrostom* AND fundoplicat* AND neuro*

LILACS

LILACS searched 1982 to March 2012

Tw gastrostomy AND child* AND reflux

Appendix 2. Search strategies for the original review and the 2009 update

CENTRAL

Issue 2, 2009 of Cochrane Central Register of Controlled Trials (CENTRAL) was searched via *The Cochrane Library*

#1 MeSH descriptor gastrostomy explode all trees
#2 gastrostom* in All Text
#3 (#1 or #2)
#4 MeSH descriptor fundoplication explode all trees
#5 fundoplicat* in All Text
#6 (nissen in All Text and operation* in All Text)
#7 thal in All Text
#8 toupet in All Text
#9 belsey in All Text
#10 anti-reflux in All Text
#11 (anti in All Text and reflux in All Text)
#12 antireflux in All Text
#13 (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12)
#14 MeSH descriptor child explode all trees
#15 MeSH descriptor infant explode all trees
#16 MeSH descriptor adolescent explode all trees
#17 (baby in All Text or babies in All Text)
#18 infant* in All Text
#19 toddler* in All Text
#20 child* in All Text
#21 girl* in All Text
#22 boy* in All Text
#23 pre-school* in All Text
#24 preschool* in All Text
#25 teen* in All Text
#26 adolescen* in All Text
#27 (#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26)
#28 MeSH descriptor cerebral palsy explode all trees
#29 (cerebral in All Text and palsy in All Text)
#30 (little* in All Text and disease in All Text)
#31 (spastic in All Text near/6 diplegia in All Text)
#32 (spastic in All Text near/6 quadriplegia in All Text)
#33 (neuro* in All Text near/6 disab* in All Text)
#34 (neuro* in All Text near/6 impair* in All Text)
#35 (#28 or #29 or #30 or #31 or #32 or #33 or #34)
#36 (#3 and #13 and #27 and #35)

MEDLINE

MEDLINE was searched through Ovid (1966 to June 2009)

1 Gastrostomy/
2 gastrostom\$.tw.
3 or/1-2
4 Fundoplication/
5 fundoplicat\$.tw.
6 nissen operation\$.tw.
7 thal.tw.
8 toupet.tw.
9 belsey.tw.
10 anti-reflux.tw.
11 anti reflux.tw.
12 antireflux.tw.
13 or/4-12
14 exp Child/
15 Infant/
16 Adolescent/
17 (baby or babies).tw.
18 infant\$.tw.
19 toddler\$.tw.
20 child\$.tw.
21 girl\$.tw.
22 boy\$.tw.
23 pre-school\$.tw.
24 preschool\$.tw.
25 teen\$.tw.
26 adolescen\$.tw.
27 or/14-26
28 Cerebral Palsy/
29 cerebral palsy.tw.
30 little\$ disease.tw.
31 (spastic adj3 diplegia).tw.
32 (spastic adj3 quadriplegia).tw.
33 (neuro\$ adj3 disab\$).tw.
34 (neuro\$ adj3 impair\$).tw.
35 or/28-34
36 3 and 13 and 27 and 35
37 randomized controlled trial.pt.
38 controlled clinical trial.pt.
39 randomized controlled trials.sh.
40 random allocation.sh.
41 double blind method.sh.
42 single-blind method.sh.
43 or/37-42
44 (animals not human).sh.
45 43 not 44
46 clinical trial.pt.
47 exp Clinical Trials/
48 (clin\$ adj25 trial\$).ti,ab.
49 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)).ti,ab.
50 placebos.sh.
51 placebo\$.ti,ab.
52 random\$.ti,ab.
53 research design.sh.
54 or/46-53
55 54 not 44
56 55 not 45
57 comparative study.sh.
58 exp Evaluation Studies/

59 follow up studies.sh.
60 prospective studies.sh.
61 (control\$ or prospectiv\$ or volunteer\$).ti,ab.
62 or/57-61
63 62 not 44
64 63 not (45 or 56)
65 45 or 56 or 64
66 36 and 65

EMBASE

EMBASE was searched via Ovid (1980 to week 23 2009)

1 Gastrostomy/
2 gastrostom\$.tw.
3 or/1-2
4 Fundoplication/
5 fundoplicat\$.tw.
6 nissen operation\$.tw.
7 thal.tw.
8 toupet.tw.
9 belsey.tw.
10 anti-reflux.tw.
11 anti reflux.tw.
12 antireflux.tw.
13 or/4-12
14 exp Child/
15 Infant/
16 Adolescent/
17 (baby or babies).tw.
18 infant\$.tw.
19 toddler\$.tw.
20 child\$.tw.
21 girl\$.tw.
22 boy\$.tw.
23 pre-school\$.tw.
24 preschool\$.tw.
25 teen\$.tw.
26 adolescen\$.tw.
27 or/14-26
28 Cerebral Palsy/
29 cerebral palsy.tw.
30 little\$ disease.tw.
31 (spastic adj3 diplegia).tw.
32 (spastic adj3 quadriplegia).tw.
33 (neuro\$ adj3 disab\$).tw.
34 (neuro\$ adj3 impair\$).tw.
35 or/28-34
36 3 and 13 and 27 and 35
37 clin\$.tw.
38 trial\$.tw.
39 (clin\$ adj3 trial\$).tw.
40 singl\$.tw.
41 doubl\$.tw.
42 trebl\$.tw.
43 tripl\$.tw.
44 blind\$.tw.
45 mask\$.tw.
46 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
47 randomi\$.tw.
48 random\$.tw.
49 allocat\$.tw.
50 assign\$.tw.

51 (random\$ adj3 (allocat\$ or assign\$)).tw.
52 crossover.tw.
53 52 or 51 or 47 or 46 or 39
54 exp Randomized Controlled Trial/
55 exp Double Blind Procedure/
56 exp Crossover Procedure/
57 exp Single Blind Procedure/
58 exp RANDOMIZATION/
59 54 or 55 or 56 or 57 or 58 or 53
60 36 and 59

CINAHL

CINAHL was searched via Ovid (1982 to December 2008)

1 Gastrostomy/
2 gastrostom\$.tw.
3 or/1-2
4 fundoplicat\$.tw.
5 nissen operation\$.tw.
6 thal.tw.
7 toupet.tw.
8 belsey.tw.
9 anti-reflux.tw.
10 anti reflux.tw.
11 antireflux.tw.
12 exp Child/
13 Infant/
14 Adolescent/
15 (baby or babies).tw.
16 infant\$.tw.
17 toddler\$.tw.
18 child\$.tw.
19 girl\$.tw.
20 boy\$.tw.
21 pre-school\$.tw.
22 preschool\$.tw.
23 teen\$.tw.
24 adolescen\$.tw.
25 or/12-24
26 Cerebral Palsy/
27 cerebral palsy.tw.
28 little\$ disease.tw.
29 (spastic adj3 diplegia).tw.
30 (spastic adj3 quadriplegia).tw.
31 (neuro\$ adj3 disab\$).tw.
32 (neuro\$ adj3 impair\$).tw.
33 or/26-32
34 or/4-11
35 3 and 25 and 33 and 34
36 randomi\$.mp. [mp=title, subject heading word, abstract, instrumentation]
37 clin\$.mp. [mp=title, subject heading word, abstract, instrumentation]
38 trial\$.mp. [mp=title, subject heading word, abstract, instrumentation]
39 (clin\$ adj3 trial\$).mp. [mp=title, subject heading word, abstract, instrumentation]
40 singl\$.mp. [mp=title, subject heading word, abstract, instrumentation]
41 doubl\$.mp. [mp=title, subject heading word, abstract, instrumentation]
42 tripl\$.mp. [mp=title, subject heading word, abstract, instrumentation]
43 trebl\$.mp. [mp=title, subject heading word, abstract, instrumentation]
44 mask\$.mp. [mp=title, subject heading word, abstract, instrumentation]
45 blind\$.mp. [mp=title, subject heading word, abstract, instrumentation]
46 (40 or 41 or 42 or 43) and (44 or 45)
47 crossover.mp. [mp=title, subject heading word, abstract, instrumentation]
48 random\$.mp. [mp=title, subject heading word, abstract, instrumentation]

Fundoplication versus postoperative medication for gastro-oesophageal reflux in children with neurological impairment undergoing gastrostomy (Review)

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49 allocate\$.mp. [mp=title, subject heading word, abstract, instrumentation]
50 assign\$.mp. [mp=title, subject heading word, abstract, instrumentation]
51 (random\$ adj3 (allocate\$ or assign\$)).mp.
52 Random Assignment/
53 exp Clinical Trials/
54 exp Meta Analysis/
55 51 or 47 or 46 or 39 or 36 or 52 or 53 or 54
56 55 and 35

ISI Web of Science

ISI Web of Science was searched via Web of Knowledge (1970 to June 2009)

reflux
reflux AND child*
reflux AND child* AND gastrostom*
reflux AND child* AND gastrostom* AND fundoplicat*
reflux AND child* AND gastrostom* AND fundoplicat* AND neuro*

The Child Health Library

The Child Health Library (searched in June 2009)

reflux
gastrostomy* AND reflux

National Research Register

National Research Register (to the end of 2007) (archived)

#1 GASTROSTOMY single term (MeSH)
#2 gastrostom*
#3 (#1 or #2)
#4 FUNDOPLICATION single term (MeSH)
#5 fundoplicat*
#6 (nissen next operation*)
#7 thal
#8 toupet
#9 belsey
#10 anti-reflux
#11 (anti next reflux)
#12 antireflux
#13 (#4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12)
(#3 and #13) (1)

LILACS

LILACS (1982 to June 2009)

Tw gastrostomy and (Tw fundoplicat\$ or Tw nissen operation\$ or Tw thal or Tw toupet or Tw belsey or Tw anti-reflux or Tw anti reflux or Tw antireflux)

WHAT'S NEW

Date	Event	Description
11 September 2012	New citation required but conclusions have not changed	No new studies suitable for inclusion found.
23 March 2012	New search has been performed	Updated searches run.

HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 1, 2007

Date	Event	Description
11 August 2009	New search has been performed	Searches repeated and review updated
15 September 2008	Amended	Converted to new review format.
14 November 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Both review authors (AVR and PB) independently selected abstracts and screened potential trials. Both review authors (AVR and PB) contributed to writing the text of this review. Joanne Abbott (previous TSC of the Cochrane Developmental, Psychosocial and Learning Problems Group) developed the search strategy.

DECLARATIONS OF INTEREST

Angharad Vernon-Roberts - research nurse salary funded by Cerebra (Charity for Brain Injured Children and Young People).
Peter B Sullivan - has received grant funding, speakers fees and consultancy fees from Nutricia Ltd. Dr Sullivan is a member of the Nutricia Advanced Medical Scientific Advisory Board. Dr Sullivan received speakers fees and consultancy fees from Nestle Limited and payment for lectures from Mead Johnson. Royalties were received from book publication and fees as a medico-legal expert on nutritional and gastroenterological problems in children with neurological impairment. Grant support was received for an RCT on optimising nutrition in children at risk of brain damage from SPARKS, The Castang Foundation and Nutricia.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Cerebra (Charity for Brain Injured Children and Young People), UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The protocol for this review was published in *The Cochrane Library* in Issue 3, 2006. The Methods section of the original protocol has been reorganised and some parts of it re-labelled to meet the standards of the latest version of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). The search strategy was updated for this version.

NOTES

This is an update of:

Vernon-Roberts A, Sullivan PB. Fundoplication versus post-operative medication for gastro-oesophageal reflux in children with neurological impairment undergoing gastrostomy. Cochrane Database of Systematic Reviews 2007, Issue 1. Art. No.: CD006151. DOI: 10.1002/14651858.CD006151.pub2

INDEX TERMS

Medical Subject Headings (MeSH)

*Fundoplication; *Gastrostomy; Cerebral Palsy [complications]; Gastroesophageal Reflux [*drug therapy] [*surgery]; Gastrointestinal Agents [*therapeutic use]; Postoperative Care; Proton Pump Inhibitors [*therapeutic use]

MeSH check words

Child; Humans