

Surgical Management of Gastro-oesophageal Reflux Disease (GORD) in Adults: A Systematic Review and Network Meta-Analysis

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Background

Gastro-oesophageal reflux disease (GORD) causes some of the most common presenting symptoms in both the primary and secondary care settings¹, and affects up to 20% of the population in the Western world², thus contributing to significant healthcare costs. It is defined as a condition which develops as a result of reflux of stomach contents into the oesophagus, due to failure of the anti-reflux barrier³. Although most patients have mild symptoms and require little or no medication¹, a small proportion have disease which is refractory to best medical treatment with proton pump inhibitors (PPIs), or are intolerant of PPIs due to its side effects⁴. This group is at risk of developing complications such as ulceration, strictures, haemorrhage, Barrett's oesophagus and ultimately, adenocarcinoma⁵. It is these patients who have traditionally been considered suitable for surgical intervention, in the form of a fundoplication or stomach wrap, where the fundus of the stomach is wrapped around the lower oesophagus and sutured into place, thus recreating a high pressure zone and preventing the reflux of acid on gastric contraction⁶. Additionally however, patients with mild to moderate symptoms are increasingly offered surgical treatment due to the considerable cost and inconvenience of long-term treatment with PPIs, and increasing concern regarding the long-term side effects of acid suppression^{1,7}. A recent evaluation based on a large multi-centre randomised trial provides clear evidence of the long-term cost-effectiveness of surgical intervention compared with continued medical management in patients who require long-term medication and who are eligible for both options⁸.

The 360° total or Nissen fundoplication was considered the gold standard surgical option for many years, with a symptom resolution rate of up to 90%¹. However its common side effects, including dysphagia and gas-related symptoms, have led to the development of a number of variations with the aim of achieving the same efficacy but with a lower risk of side effects^{9,10}. These include the development of a range of anterior and posterior partial wraps, division of the short gastric arteries to create a 'floppy' Nissen wrap, and variable lengths of fundoplication³. These may be carried out either open or laparoscopically. Although some authors have stated that laparoscopic fundoplication is now the gold standard⁶, and others have argued that robot-assisted fundoplication has 'distinct advantages'¹¹, most would agree that the evidence suggests that the fundoplication technique and the quality of postoperative care, as opposed to the method of surgical access, are the most important determinants of long-term, clinically relevant outcomes¹².

A number of randomised trials have compared various types of fundoplication surgery, and these have subsequently been pooled in several meta-analyses. However, all of these meta-analyses have either combined different partial fundoplication techniques together to compare with a total fundoplication^{6,13}, or made head-to-head comparisons of one technique with another^{7,9}. The suggestion from these analyses is that some partial fundoplications are as effective as a total fundoplication in controlling reflux symptoms with fewer side effects, but it has been difficult to establish if any of the partial fundoplication techniques are superior³. Furthermore, grouping a variety of partial fundoplication techniques together in a meta-analysis may not be appropriate, given that other randomised trials have demonstrated that they do not confer the same intervention effect⁹.

Over the last decade a number of endoscopic procedures have also been developed as an alternative to surgery for the treatment of GORD. Although initial reports showed some promise, subsequent sham-controlled studies have generally failed to demonstrate the efficacy of these techniques¹⁴. The placebo response in some was up to 50%¹⁵, there was no correlation between reported improvement in symptoms and reduced oesophageal acid exposure or reduction in PPI use¹⁶, and three of the most commonly used techniques have been withdrawn from the market; two because of safety and durability concerns. Some authorities have called for a moratorium on the use of these procedures, arguing that their use on patients outside of clinical trials is premature¹⁵. In view of this endoscopic anti-reflux procedures will not be included in the current review.

Although there are calls for more trials involving the various fundoplication options⁹, we believe that the evidence available thus far from randomised trials may be sufficient to answer some of the questions regarding risks and benefits of existing surgical treatments for GORD, if all the data are compared in a network meta-analysis. We could not find any existing network meta-analysis addressing this topic on review of the literature.

A multiple-treatments or network meta-analysis is an established research synthesis technique which offers a set of methods to visualise and interpret the wider picture of the evidence available when multiple interventions have been used and compared for the same disease and outcomes in various head-to-head trials¹⁷. It therefore has a distinct advantage over standard meta-analysis, which, by necessity, is restricted to pair-wise, direct comparisons¹⁸, therefore producing a plethora of information which is difficult to summarise and draw valid conclusions from¹⁹. The key strength of a network meta-analysis is that it uses the large amount of indirect evidence in addition to the direct evidence²⁰, therefore allowing valid comparisons to be made between different interventions, even if they have not been directly compared in a head-to-head trial. This in turn allows for a ranking of the different interventions with respect to both benefits and harms.

Objectives

To compare the effectiveness of the various surgical fundoplication techniques on the outcomes of GORD-related symptoms, postoperative side effects and quality of life in adults undergoing surgery for the treatment of GORD.

Methods

Types of studies

We will include all randomised and quasi-randomised clinical trials (RCTs) that compare different fundoplication techniques for the treatment of GORD. Trials that compare a fundoplication technique with best medical treatment with PPIs will also be included. We will include studies that used an open or laparoscopic approach. Trials comparing fundoplication techniques specifically in the context of management for established Barrett's, or exclusively for extra-oesophageal manifestations will be excluded, as these will incur different key indications for surgery and outcomes of interest. There will be no language, publication status, or year of publication restrictions. We will not exclude studies if they do not report either of the primary outcomes, as these will be used in the secondary outcome analysis and/or the narrative review. Trials comparing the use of endoscopic or robot-assisted approaches will be excluded. Non-randomised studies will be excluded, as they carry an increased risk of bias. Authors of published trials will be contacted for clarification if randomisation status is not clear.

Types of participants

All adults with an established diagnosis of GORD, based on symptoms and an objective measure such as endoscopy or pH manometry, deemed appropriate for surgical management.

Types of interventions

The interventions will include any fundoplication technique, whether performed by open or laparoscopic surgery. The intervention groups for the main analysis will be as follows:

1. Total (360°) fundoplication (with or without the division of the short gastric arteries)
2. 90° fundoplication
3. Anterior partial fundoplication (120° or more)
4. Posterior partial fundoplication (180°, 270°)
5. Medical treatment with PPIs (as a comparator)

Each of these techniques will be analysed as an independent intervention in the network. Interventions which include other variations such as variable wrap lengths, omission of a hiatoplasty or fixation to the right hiatal pillar as part of the procedure, or the non-use of a bougie will be permitted, but such variations will be noted.

Interventions involving fundoplication in combination with another procedure (such as Heller's myotomy for achalasia) will be excluded.

Types of outcome measures

Primary outcomes

1. Health-related quality of life scores, measured on an appropriate validated tool.

2. GORD-specific quality of life, measured on an appropriate validated tool.
3. Dysphagia, measured either as a dichotomous variable or on a validated scale (such as a Dakkak score).

For primary outcomes, data will be analysed separately in three groups where available: at 1 year follow-up, 2-5 year follow-up, and 5+ years (to longest follow-up).

Secondary outcomes

1. Reflux symptoms. We anticipate that most studies will report this as a dichotomous or categorical scale patient-reported outcome.
2. Oesophageal acid exposure, measured as a DeMeester score.
3. Total oesophageal acid exposure time (as a percentage) on pH monitoring.
4. Dilatation for dysphagia rate, defined as the need for oesophageal dilatation for symptomatic dysphagia postoperatively.
5. Reoperation rate, defined as the number of patients who required revision surgery for ongoing symptoms and/or objective findings of persistent GORD during the follow-up period.
6. Postoperative complications, as defined by the trial authors.
7. Gas bloating or hyper-flatulence, measured on a dichotomous, categorical or visual scale.

Search methods for identification of studies

Electronic searches

The following databases will be searched to identify eligible studies for this review:

1. The Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, most recent issue).
2. MEDLINE (1966 to current).
3. EMBASE (1980 to current).
4. Web of Science (1945 to current).

Language restrictions will not be applied. The search strategy will be developed using a combination of subject headings and free text terms relating to the surgical treatment of GORD, in consultation with an expert health librarian. The Cochrane sensitivity maximising search strategy will be used to search for RCTs in MEDLINE²¹. The BMJ's EMBASE Randomised Controlled Trial Strategy will be used to search for RCTs in EMBASE²².

Searching other resources

The World Health Organisation's International Clinical Trials Registry Platform and clinicaltrials.gov will be searched to identify ongoing trials. The contact authors for any such

trials will then be approached by letter or email requesting any available information to date (MAA).

The reference lists of all eligible studies and of reviews of the topic will be hand-searched to identify any additional studies. Experts in the field will also be contacted to identify any unpublished research or ongoing trials.

The CENTRAL search will include the Cochrane Upper Gastrointestinal and Pancreatic Disease Group Specialised Register, which incorporates the Group's hand-searching results of relevant journals and conference proceedings in the field.

Data collection and analysis

Selection of studies

The results of searches from both the electronic databases and other resources will be combined in a spreadsheet. Duplicate citation records will be excluded. Duplicate publications will be retained in case all data is not reported in both. Two authors (MAA and JLM) will independently screen all titles and abstracts for eligibility. The full text of potentially eligible trials will then be obtained and reviewed against the pre-defined inclusion criteria. Any exclusions at this point will be independently recorded (together with the reason for exclusion), before a final list of included trials is drawn up. Disagreement will be resolved by discussion and consensus. Failing this, a third author (GPH) will arbitrate.

Study selection will be reported as a PRISMA flow chart.

Data extraction and management

A pre-piloted data extraction form, based on the Cochrane Collaboration's Data Collection Form Template²³ will be used by two authors (MAA and MDS) to independently extract and record data. Discrepancies will be resolved by discussion, or if a consensus is unable to be reached, discussion with a third author (GPH). Any requests for further data will be made if required (MAA), by contacting the first or contact author of the relevant trial.

Assessment of risk of bias in included studies

The methodological quality of each included study will be independently assessed by two authors (MAA and MDS), using a standardised, pre-piloted form as part of the data extraction process. The assessment will be based on the Cochrane Collaboration's Risk of Bias tool²¹, using the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and any other potential sources of bias. Each domain will be assessed as low risk, high risk, or unclear. Disagreements will be resolved by discussion; and arbitration by a third author (GPH) where consensus cannot be reached. Where studies have three or more categories assessed as unclear, the study protocol will be reviewed if available, and contact will be made with the trial authors for further methodological clarification (MAA). We will report the results of this assessment as a Risk of Bias summary figure.

Measures of treatment effect

For each comparison between different techniques, we will present continuous data as mean difference or standardised mean difference, as appropriate, with 95% confidence intervals. For categorical data, we will present the odds ratio with 95% confidence intervals. An intention-to-treat analysis will be used.

Unit of analysis issues

Where trials have used a combination of different surgical techniques (i.e. more than one type of fundoplication) in one arm, we will seek individual patient data where it is not reported, by corresponding with the contact or first author to request numbers per technique (MAA). If this is not available, we will include the trial in the analysis if more than 80% of patients in the affected arm of the study underwent the same single procedure; and perform sensitivity analysis to explore the effect of these studies on the overall analysis. Failing these provisions, the study will be excluded from the main analysis, but will be included in the narrative discussion as appropriate.

Dealing with missing data

Where data is missing or not available, we will contact the study authors to request this (MAA). Where data is missing to the extent that the study cannot be included in the meta-analysis and attempts to obtain the relevant data have been exhausted, the results will be presented and discussed in the review, in the context of the findings.

We will calculate missing statistics such as standard deviations from the reported data where possible²¹. Where standard deviations cannot be calculated, we will impute these using the mean of the reported standard deviations from the other trials. Sensitivity analysis will be performed to explore the effect of imputed versus reported data.

Assessment of heterogeneity

We will assess the heterogeneity of included studies according to their clinical, methodological and statistical diversity. Clinical heterogeneity will be assessed using subgroup analysis. Statistical heterogeneity will be assessed by calculating predictive intervals²⁴. We will also assess inconsistency or incoherence of each independent three-way loop in the evidence structure²⁵, by calculating the difference between the direct and indirect estimates (the inconsistency factor) in each closed loop formed by the network of trials. This will be presented as an inconsistency plot²⁴. Any significant inconsistencies will be investigated further to determine possible causes, including methodological and clinical heterogeneity.

Assessment of reporting biases

We will assess publication bias by visual inspection of a funnel plot if there are enough studies to make this reasonable.

Data synthesis

A network, or multiple treatments, meta-analysis will be performed to use the available indirect evidence, in addition to the pair-wise comparisons. This is a method of synthesising information from a network of trials addressing the same question using different interventions²⁶, where both the direct (pair-wise) and indirect evidence can be used to produce a single effect size²⁰. This increases precision while randomisation is respected¹⁸. This also enables a ranking of the different interventions according to their effectiveness, as measured by different outcomes¹⁹. This will be performed within a frequentist framework using Stata²⁷, by running the routines available for network meta-analysis^{24,28,29}. The construct of the network will be reported as a network geometry figure¹⁷.

Subgroup analysis

We will perform the following subgroup analyses if possible:

1. Open versus laparoscopic surgery (per intervention technique).
2. Division of the short gastric arteries in 360° wraps.

Sensitivity analysis

We will conduct sensitivity analysis by excluding trials of low methodological quality and consider the results of this analysis in comparison to overall findings in the discussion section. We will also conduct sensitivity analysis to explore the effects of imputed data; and the effects of studies where more than one technique was used in the same arm.

Declarations

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