

Effectiveness of transoral incisionless fundoplication compared to Toupet fundoplication for chronic or refractory gastroesophageal reflux disease: a systematic review protocol

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Review objective/question: The objective of this review is to determine which 270-degree fundoplication procedure has a better outcome in patients with chronic or refractory gastroesophageal reflux disease (GERD). This review will identify the fundoplication approach for chronic or refractory GERD that provides better reflux control with minimal post-procedure complications.

The question of this review is: what is the effectiveness of transoral incisionless fundoplication compared to Toupet fundoplication in adult patients with chronic or refractory GERD?

Keywords Gastroesophageal reflux disease; laparoscopic fundoplication; Toupet fundoplication; transoral incisionless fundoplication

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Introduction

Gastroesophageal reflux disease (GERD) is a complex disorder defined as symptoms or complications resulting from the reflux of gastric contents into the esophagus or beyond into the oral cavity or lungs.¹ The prevalence of GERD is 10–20% in western countries and reported to be lowest in Asia. In America, it is estimated that 20–25% of people have reflux symptoms weekly.² Clinically significant heartburn was seen among 6% of the population, and 16% reported to have regurgitation.¹ Patients with chronic or refractory GERD have an incomplete or lack of response to proton pump inhibitor (PPI) therapy. Recommended diagnostic tests for these patients include the following: an upper endoscopy to evaluate for reflux esophagitis and its complications, ambulatory 48-hour pH study to evaluate the relationship of the symptoms to acid exposure, esophageal manometry to evaluate the motor function of the esophagus, and impedance

testing to evaluate for esophageal peristalsis and lower esophageal sphincter pressures. Patients with chronic GERD or GERD refractory to standard therapy, and who have objective evidence of ongoing reflux without any motility disorders, are considered for additional surgical treatment for GERD.^{1,3}

Surgical therapy for GERD

Most reflux symptoms are primarily due to a defective barrier, otherwise known as relaxation of the lower esophageal sphincter at the gastroesophageal junction (GEJ). Indications for surgical therapy for chronic or refractory GERD are symptoms refractory to pharmacological therapy. Fundoplication is the surgical therapy for the treatment of GERD, and it can be performed as a traditional open surgery (Nissen fundoplication) or minimally invasive laparoscopic surgery using a variety of complete or partial wrap techniques (e.g. Nissen, Dor, Toupet). Fundoplication surgery creates a barrier at the GEJ resulting in significantly less acidic exposure to the esophagus. The procedure also increases lower esophageal sphincter pressure more than medical management alone.^{2,4} Currently, laparoscopic technique is preferred over open or complete fundoplication because

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it results in less dysphagia, bloating, and inability to belch.⁵ The most widely performed laparoscopic technique is the posterior fundoplication, which creates a wrap at the GEJ of 270 degree. This laparoscopic technique is called Toupet fundoplication and has been utilized since 1990.⁶

In the past five years, minimally invasive laparoscopic techniques have been the gold standard surgical therapy for patients with chronic or refractory GERD. However, these techniques are still associated with complications and long-term side effects. Toydemir and associates conducted a large study with 1000 subjects who underwent Nissen fundoplication and Toupet fundoplication.⁶ The post-operative outcomes were reported up to 43 months. Esophageal perforation, jejunal perforation and pulmonary emboli were the major adverse effects. Minor complications such as trocar site infection, hematoma, spleen capsule tear, liver laceration, diarrhea, hiccups and anxiety were evenly distributed between the two groups. The rate of post-operative dysphagia was 15.4% for Nissen fundoplication and 8.9% for Toupet fundoplication. Twenty patients (2%) had prolonged dysphagia after six months. Eight patients had esophageal dilatation for prolonged dysphagia. Patients were readmitted for gas bloat syndrome, psychological problems, wound-related complications and abdominal pain. This study demonstrated the efficacy of fundoplication by a recurrence rate of 2.2% for Toupet as compared to 1.8% for Nissen.⁶

A systematic review including eight studies demonstrated some controversial results on the dysphagia outcome. Toupet fundoplication reduced post-operative dysphagia and dilatation requirement in comparison to Nissen. This systematic review strongly suggests Toupet as a first-choice posterior fundoplication technique because of the lower rate of reoperation, fewer gas-related symptoms and better reflux control.⁷ In a recent meta-analysis of randomized controlled trials, laparoscopic fundoplication continued to show post-operative dysphagia, gas bloat syndrome, inability to belch and reoperation in comparison to Toupet. The fundoplication wrap length was not statistically significant between the two groups. Toupet is suggested as the better surgical approach for GERD and has fewer post-operative complications.⁸

Endoscopic therapy for GERD

Endoscopic therapies are becoming more valuable for patients because of the incisionless technique and

shorter hospitalization. The endoscopic approach to treat chronic or refractory GERD is widely developed and performed in numerous ways using different technologies. Lack of durability and poor long-term outcomes in the first generation of endoluminal therapies can largely explain their falling out of favor and ultimately being discontinued.⁹ The current widely used endoscopic procedure is transoral incisionless fundoplication (TIF), which was developed in 2007. It is performed transorally under general anaesthesia without external incisions. It reconstructs the GEJ by creating a 3-cm valve with a 270 degree wrap at the GEJ held in place with at least 20 polypropylene “H”-shaped fasteners for the mucosal fusion.¹⁰

Endoscopic therapy is an alternative anti-reflux treatment option to medication dependence and traditional surgery. TIF is based on the principles of conventional anti-reflux surgery. In a study on the long-term benefit of TIF, 45 patients who underwent TIF, after an average follow-up of 59 months, showed significant improvement in quality-of-life score ($P < 0.001$), and 32 patients eliminated the need for a PPI such as omeprazole, esomeprazole or dexlansoprazole.¹¹ Many US and European studies have been evaluated to confirm the long-term efficacy and safety concerns of TIF. A six-year follow-up study of 50 patients who underwent TIF showed that 75-80% of patients eliminated a daily PPI. This study also measured 24-hour pH impedance, esophageal manometry, endoscopy, and GERD questionnaire results for up to six years.¹² A five-year follow-up study focused on TIF versus medical PPI open-label trial, where troublesome regurgitation was eliminated in 97% and 93% of TIF patients at six months and at 12 months, respectively.¹³ These data offer strong reassurance and, most importantly, show resolution of typical and atypical symptoms that remained stable at the one-, three-, and five-year follow-up, indicating durability of TIF.

In gastroenterology clinical practice, with the available evidence to date, it is difficult to determine which posterior fundoplication treatment to offer for the chronic or refractory GERD patients. The 2013 national guidelines of North America on management of GERD recommend medications or surgery as the treatment choice for patients with refractory GERD. The guideline did not support the use of TIF or other endoscopic therapy for refractory GERD.¹ It is time to re-evaluate and synthesize long-term efficacy of posterior fundoplication techniques. Across all studies,

low complication rates for TIF have been reported.¹⁴ A 2013 systematic review found that out of 550 procedures, the major complication rate of TIF was 3.2%, which is comparable with laparoscopic fundoplication.¹⁵ In addition to a strong safety profile, the very low rates of dysphagia, gas-bloat syndrome and flatulence are significant advantages to the TIF procedure. Post-fundoplication syndromes are virtually non-existent. Thus, it appears that TIF can be positioned to fill the “therapy gap” between medical therapy and more invasive surgical procedures such as laparoscopic or open anti-reflux procedures.

The authors’ intention is to evaluate and compare endoscopic fundoplication with laparoscopic fundoplication to show the best results to control symptoms and complications of chronic GERD. This systematic review can be a valuable addition to determine the recommendation for 270-degree fundoplication techniques within the algorithm for the next guideline update in GERD treatment. A review of the leading medical databases including CINAHL, Cochrane Database of Systematic Reviews, *JBIR Database of Systematic Reviews and Implementation Reports*, PubMed, Embase, and SCOPUS showed that no systematic review on this topic has been conducted over the last decade or is in progress.

Inclusion criteria

Participants

The review will consider studies that include adult patients over 18 years of age with an established chronic GERD diagnosis and undergoing reflux procedures (TIF or laparoscopic Toupet procedure). Funduplications can be performed in patients with chronic or refractory GERD and with or without hiatal hernia less than 2 cm. The review will exclude patients who have a hiatal hernia larger than 2 cm or body mass index greater than 35 kg per m². Funduplications are commonly contraindicated in patients with bleeding disorders, esophageal strictures, esophageal diverticulae, obstructions, paraesophageal hernia, limited neck mobility, esophageal varices, esophageal infections, esophageal stenosis or any abnormal esophageal anatomy.¹⁶

Intervention

This review will consider studies designed to evaluate the effectiveness of TIF procedures. TIF is performed by gastroenterologists or gastroenterology

surgeons for patients with chronic or refractory GERD who have hiatal hernia less than 2 cm.

Comparator

This review will include the studies that compare FIT to the laparoscopic Toupet fundoplication procedure. Laparoscopic fundoplication performed in patients with chronic or refractory GERD with hiatal hernia less than 2 cm will be reviewed.

Outcomes

Effectiveness will be compared by evaluating symptomatic improvement and objective improvement. Symptomatic improvement should be reported in terms of post-operative use of PPIs, elimination of typical or atypical GERD symptoms, quality-of-life scores and patient reporting of flatulence, dysphagia and gas-bloat syndrome. Objective improvement will be analyzed by significant improvement of the pH measured by BRAVO pH study, and by healing of reflux esophagitis by one grade improvement objectively documented by esophagogastroduodenoscopy.

Types of studies

This review will consider both experimental and quasi-experimental study designs including randomized controlled trials, non-randomized controlled trials, before and after studies and interrupted time-series studies. In addition, analytical observational studies including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies will be considered for inclusion. This review will also consider descriptive observational study designs including case series, individual case reports and descriptive cross-sectional studies for inclusion.

Methods

The proposed systematic review will be conducted in accordance with the Joanna Briggs Institute methodology for systematic reviews of effectiveness evidence.¹⁷

Search strategy

The search strategy aims to find published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and CINAHL will be undertaken

followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe these articles. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all included studies will be hand searched for additional studies. Studies published in all languages will be included. Translation services will be approached for eligible foreign language studies after the search. Studies published from the inception of funduplications or anti-reflux procedures will be included in this review.

Information sources

All literature, published and unpublished, between the years of 1990 and 2018 will be considered.¹⁸ The databases to be searched for published literature will include PubMed, Embase, CINAHL and Scopus. The databases to be searched for unpublished literature will encompass Cochrane Central Register of Controlled Trials, ProQuest Dissertations and Theses and RePORT. In addition, literature from the gastrointestinal societies of America, Canada and Europe will be searched. A full search strategy is detailed in Appendix I.

Study selection

Following the search, all identified citations will be collated and uploaded into EndNote (Clarivate Analytics, PA, USA) and duplicates removed. Titles and abstracts will then be screened by two independent reviewers for assessment against the inclusion criteria for the review. Studies that may meet the inclusion criteria will be retrieved in full and their details imported into the Joanna Briggs Institute's System for the Unified Management, Assessment and Review of Information (JBI SUMARI; Joanna Briggs Institute, Adelaide, Australia).¹⁷ The full text of selected studies will be retrieved and assessed in detail against the inclusion criteria by two independent reviewers. Full-text studies that do not meet the inclusion criteria will be excluded, and reasons for exclusion will be provided in an appendix in the final systematic review report. Included studies will undergo a process of critical appraisal. The results of the search will be reported in full in the final report and presented in a PRISMA flow diagram. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer.

Assessment of methodological quality

Selected studies will be critically appraised by two independent reviewers at the study level for the assessment of methodological quality in the review using the standardized critical appraisal instruments from the Joanna Briggs Institute.¹⁷ The following study types will be reviewed: randomized controlled studies, case-control studies, cohort studies, quasi-experimental studies, analytical cross-sectional studies, case reports and case series. Any disagreements that arise will be resolved through discussion or with a third reviewer. All studies, regardless of their methodological quality, will undergo data extraction and synthesis (where possible).

Data extraction

Data will be extracted from papers included in the review by two independent reviewers using the standardized data extraction tool available in JBI SUMARI.¹⁷ The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. Any disagreements that arise between the reviewers will be resolved through discussion or with a third reviewer. Authors of papers will be contacted to request missing or additional data, where required. The results of critical appraisal will be reported in narrative form and in a table. All studies, regardless of the results of their methodological quality, will undergo data extraction and synthesis (where possible). Following critical appraisal, studies that do not meet a certain quality threshold will be excluded.

Data synthesis

Papers will, where possible, be pooled in statistical meta-analysis using JBI SUMARI. Effect sizes will be expressed as either odds ratios (for dichotomous data) and weighted (or standardized) mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard chi-squared and I^2 tests. The choice of model (random or fixed effects) and method for meta-analysis will be based on the guidance by Tufanaru, *et al.*^{17,19} Subgroup analyses will be conducted where there is sufficient data to investigate. Where statistical pooling is not possible, the findings will be presented in narrative form, including tables

and figures to aid in data presentation where appropriate.

Assessing certainty in the findings

A summary of findings table will be created using GRADEpro software (McMaster University, ON, Canada).²⁰ The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the quality of evidence will be followed. The Summary of Findings will present the following information where appropriate: absolute risks for treatment and control, estimates of relative risk and a ranking of the quality of the evidence based on study limitations (risk of bias), indirectness, inconsistency, imprecision and publication bias.

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Appendix I: Search strategy

PubMed

| # | Searches |
|-----------|---|
| 1 | “Gastroesophageal Reflux”[Mesh] OR “Gastroesophageal Reflux Disease” [KW] OR “Gastric Acid Reflux Disease” OR GERD |
| 2 | TOUPET fundoplication [KW] |
| 3 | fundoplication [KW] AND laparoscop* |
| 4 | 2 OR 3 |
| 5 | “Transoral incisionless fundoplication”[KW] |
| 6 | “TIF procedure” |
| 7 | (gastroesophageal OR transoral) AND fundoplication |
| 8 | 5 OR 6 OR 7 |
| 9 | 1 AND 4 AND 8 |
| 10 | (dose (“proton pump inhibitor*” OR PPI)) OR (duration (“proton pump inhibitor*” OR PPI)) |
| 11 | dysphagia |
| 12 | (“post-operative dilatation”) OR “excessive belching”) OR “unable to belch”) OR “inability to belch”) OR “excessive flatulence”) OR (“abdominal discomfort” AND bloat*) |
| 13 | 10 OR 11 OR 12 |
| 14 | 9 AND 13 |
| Filter(s) | Publication date from 1990/01/01 to 2018/12/31 |