**TITLE**

A critical analysis of the efficacy of antireflux surgery in normal and neurologically impaired children: a systematic review.

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**SOURCES OF FUNDING**

No funding was sought or received for this work.

**MANUSCRIPT CATEGORY**

Systematic review.

**PREVIOUS COMMUNICATION**

This study was presented at the British Association of Paediatric Surgeons’ 65th Annual International Congress held on the 18th–20th July 2018 at Liverpool, United Kingdom.

**ABSTRACT**

*Background:* Antireflux surgery (ARS) is commonly performed in children yet evidence of its efficacy is limited. We sought to determine the effect of ARS with regards to objective measures of quality of life (QoL) and utility of upper GI investigations in neurologically normal (NN) and neurologically impaired (NI) children.

*Method:*A systematic review [according to PRISMA] was conducted of articles reporting children undergoing ARS in whom pre- and post-operative objective testing was performed. Primarily, EMBASE, CINAHL, Medline and Pubmed were searched from inception to 04/19. MINORS criteria assessed article quality.

*Results:*Of 789 articles, 14 met eligibility criteria - 12 prospective observational and 2 retrospective studies. Median MINORS score was 59.4 % (IQR 23.4 %). 7 studies reported assessment of validated QoL measures before and after ARS in 148 children. Follow-up ranged from 1-180 months. All studies confirmed significant improvements in QoL measures amongst NN and NI children at all follow-up points. 11 studies reported on investigations pre- and post-operatively in 507 children. Follow-up ranged from 0.5-180 months. 9 studies confirmed improvements in gastro-esophageal reflux using 24h oesophageal pH monitoring +/- manometry, but conflicting results were identified for 3 studies reporting gastric emptying studies. No studies reported fluoroscopy or endoscopy adequately.

*Conclusion:* Of the low to moderate quality of studies identified, in short and medium-term follow-up, ARS improves QoL and reduces oesophageal acid exposure in NN and NI children. Despite ARS being a common elective operation, lack of rigorous pre- and post-operative evaluation(s) in the majority of patient reported studies is striking.

**INTRODUCTION**

Gastro-esophageal reflux disease (GERD) is a significant healthcare burden worldwide. In Europe and the USA, a prevalence of 10-20% is reported [1]. In adult practice, fundoplication has become a popular means of managing GERD when medical therapy fails, its efficacy in control of GERD is established through numerous RCTs [2,3]. Evidence for its use in the pediatric population is less robust, yet fundoplication remains one of the most common index operations in pediatric surgery in the US [4,5]. Concerns have been raised that antireflux surgery (ARS) is being performed by surgeons without a full structured assessment of GERD. Additionally, clinical outcomes following antireflux operations in the pediatric population are variably reported in the literature both in terms of their short and long-term efficacy [6]. This may be of greatest importance in neurologically impaired (NI) children in whom outcomes are traditionally considered poorer than in neurologically normal (NN) children [7,8]. A preoperative workup by means of objective assessment is emphasized by adult surgical and gastroenterological guidelines on GERD, with considerable variation(s) in what is considered adequate evaluation. Upper GI foregut endoscopy is generally considered mandatory [9-11]. UK national guidelines on the management of GERD in children recommend preoperative endoscopy at the very least [12] with consideration of an oesophageal pH study and upper GI foregut contrast series too. Conversely, joint North American and European gastroenterological guidelines do not make explicit recommendations on the precise role of preoperative investigations [13], but imply that many will require ‘a workup‘. In the majority of pediatric series, including some of the largest reported studies, many patients undergo ARS without key investigations [14,15]. Fewer studies still report objective measurements of GERD before and after surgery [7,16]. The aim of the current study was therefore to critically evaluate ARS with regards to - (1) objective measures of quality of life (QoL) scored and (2) the utility of upper GI investigations in both NN and NI children.

**METHODS**

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [17]. A local review protocol was established. Two reviewers (PSC, SS) performed the study selection, data extraction and quality assessment processes independently and all data was recorded in tabular form electronically. Disagreements were resolved by discussion or consultation with the third reviewer / senior corresponding author (PDL).

*Definitions*

For the purposes of this review, we did not strictly limit the definitions of terms employed. GERD was defined as that reported by studies, but troublesome symptoms, medical management and/or complications were considered mandatory; GER alone was not considered sufficient. Similarly, the definition of neurological impairment was not strict, and variations of the term were permitted. No limitation was placed on which upper GI tract investigations were used within studies, but we expected pH, manometric, endoscopic and contrast study results so included these within our search terms. Quality of life was defined as any objective parameters used to define impact of GERD on physical, social or psychological well-being of patients or their care-givers.

*Study selection*

A systematic search of the English language literature was conducted using a keyword algorithm (Figure 1). MeSH terms were not employed. The search was conducted using the indexed databases: EMBASE, CINAHL, Medline, and Pubmed, from inception to 1st October 2017 (the search was updated on 5th April 2019). Additional articles were sought through the Cochrane Database, Google Scholar, Scopus, Zetoc and Thomsons Reuters Web of Science. The reference listings of those articles yielded through the initial electronic database search and the conference proceedings of major pediatric surgical society congresses over the past decade were also searched. Eligibility criteria were then applied to remaining studies (Table 1).

*Data extraction*

The primary outcomes evaluated were differences in objective measurements of GERD, either in the form of validated questionnaire responses or the results of upper GI tract investigations beforeand after ARS. Additional data sought included patient demographic data, follow-up, morbidity and mortality.

*Quality assessment*

Quality of manuscripts was evaluated by using Jadad [18] and the Methodological Index for Non-randomized Studies (MINORS) criteria [19], as applicable. Inter-observer reliability was assessed with the kappa statistic. Bias was assessed at study and summary levels.

**RESULTS**

Of 789 screened articles, 14 studies met the eligibility criteria (Table 2). 12 were prospective observational studies and 2 were retrospective case series. No randomized controlled trials were included. Studies were published between 1982 and 2018. A total of 616 children were included amongst these studies, of which a minimum full data set was available for 419 children (148 with QoL data; 416-440 with upper GI investigation data).

*Quality assessment*

Quality of manuscripts is summarized in Figure 2 (and the raw cumulative data may be found in the supplemental material). The median MINORS score (expressed as percentage of best possible score) was 59.4 % (IQR 23.4 %). Articles scored well for consecutive inclusion of patients and number of patients retained at follow-up, but particularly poorly with regards unbiased assessment of endpoints. The overall kappa statistic for MINORS criteria was 0.82, equating to almost perfect agreement*.*

*Quality of life*

7 studies (describing a total of 4 cohorts) reported the assessment of validated QoL measures before and after ARS (Table 3 and Supplemental Table 3). All were prospective, observational studies from the Netherlands, USA and Germany. These series included 166 patients, of which 96 were considered NI. 148 children completed initial follow-up. Median age was not uniformly reported, however the majority of included children were under 10 years of age. A variety of surgical operations were deployed, notably laparoscopic Thal fundoplication, laparoscopic and classical ‘open‘ Nissen procedures in combination with and without gastrostomy. 8 different QoL measurement tools were employed. Follow-up ranged from 1 month to 15 years. All studies confirmed significant improvements in QoL measures amongst NN and NI at all follow-up points. These included patient and carer-reported assessments of symptoms, emotions, psychosocial and physical functioning. New onset dysphagia was reported amongst both NN and NI children postoperatively. There was not enough detail reported amongst studies to allow for commentary on the impact of the type of anti-reflux surgery and pre-existing or concomitant gastrostomy on quality of life.

*Upper GI tract investigations*

11 studies (describing a total of 9 cohorts) reported on investigations for ARS pre- and post-operatively (Table 4 and Supplemental Table 4). These were a combination of prospective and retrospective observational studies from the Netherlands, USA, Spain, Sweden, Austria, France and South Africa. 532 patients were included, of which over 197 cases were considered NI (reporting of the number of children with NI was lacking in several studies). Between 416 and 440 children completed initial follow-up (reporting of the number of children undergoing successful follow-up was lacking in a single study). Median age was not uniformly reported, however the majority of included children were less than 10 years of age. A variety of surgical operations were used, including open, laparoscopic and robotic techniques, using numerous forms of ‘antireflux wrap’, in combination with or without gastrostomy, gastropexy and pyloroplasty. Investigations employed here included 24h pH studies, gastric emptying studies by breath test or radionuclide technique, upper GI tract endoscopy, manometry and upper GI tract contrast studies. Follow-up ranged from 1 week to 15 years. There was not enough detail reported amongst studies to allow for commentary on the impact of the type of anti-reflux surgery and pre-existing or concomitant gastrostomy on upper GI tract investigations.

8 studies (describing 6 cohorts) confirmed improvements in all measured reflux parameters using 24h oesophageal pH monitoring after ARS in both NN and NI children. In the only series with follow-up >5 years [21,22], whilst the number of patients with pathological reflux significantly decreased from 84% preoperatively to 18% at 3-4 months, 43% patients were then considered to have pathological reflux at 10-15 years follow-up. 3 studies (describing 2 cohorts [23,25,32]) reported improvements in all reflux parameters on oesophageal manometry. NN and NI children achieved similar benefits in the single cohort study distinguishing these groups at follow-up. Conflicting results were identified for 4 study series (describing 3 cohorts [23,25,27,31]) reporting gastric emptying studies. In a single study, upper GI contrast study(s) were used to evaluate patients pre- and post-operatively, however, reporting of results was inadequate [33]. Similarly, no studies reported results of upper GI endoscopy examinations adequately. Therefore, conclusions may not be drawn with regards to the impact of ARS on results of GI endoscopy, upper GI contrast imaging and gastric emptying studies.

*Morbidity and mortality*

Morbidity and mortality were poorly reported amongst most series (Table 5), such that only 3 of 11 cohorts reported complications in detail, and still, insufficient detail was documented for Clavien-Dindo grading [26,28,29]. For example, some studies did not report complications [20,27], and in others, complications amongst neurologically normal and impaired children were not distinguished [21-25,30-33]. Surgical mortality was universally reported as zero, but deaths related to underlying comorbidities amongst NI children were substantial in some reports. In one of the largest series, a third of NI children died within an overall median follow-up period of 5.5 years. Reported complications varied amongst published studies more than tenfold with the lowest morbidity rate(s) reported as 3% and the highest almost 40%.

**DISCUSSION**

Despite its widespread adoption amongst pediatric surgeons worldwide, the true efficacy of ARS in both NN and NI children has not been fully established by scientifically rigorous study(s). That is to say there are no published RCTs comparing optimal medical management of GERD versus ARS, or any high-quality cohort or case-control studies with similar objective(s). In the absence of this level of evidence, we therefore conducted a systematic review to address the question of whether or not ARS is effective in improving objective measures of GER as determined by pre- and post-operative upper GI tract investigations, and validated QoL measures as reported by patients and/or their carers. Our findings suggest that, in short and medium-term follow-up, ARS appears to improve QoL and reduces oesophageal acid exposure in both NN and NI children, with the caveat that the studies supporting these statements are of low to moderate quality.

A recent systematic review of the surgical management of pediatric GERD by the American Pediatric Surgical Association Outcomes and Evidence-Based Practice Committee has highlighted the poor evidence base behind ARS in children. They state that ARS is expensive and potentially morbid, with uncertain benefits, yet is routinely performed in pediatric surgical practice [34]. The antireflux mechanism of fundoplication is not fully understood but includes a rise in baseline lower oesophageal sphincter pressure, a reduction of transient lower oesophageal sphincter relaxations, creation of a hydropneumatic valve mechanism, the elongation of the intra-abdominal oesophagus, accentuation of the angle of His, and repair of hiatus hernia [35-37]. In adult practice, laparoscopic fundoplication is considered the gold standard for PPI-resistant GERD [10], affirmed by a high quality RCT [3]. Only a handful of RCTs focusing on ARS exist in the pediatric literature, comparing classical ‘open’ versus laparoscopic fundoplication [38-42], and wrap technique [43]. Even these level one studies (Oxford Centre for Evidence-Based Medicine) do not report investigations for and objective measures of GERD both pre- and post-operatively.

It is widely believed that ARS benefits children with NI less than NN patients [7] and, in fact, this has become pediatric surgical dogma. Wrap formation with fundoplication may cause mechanical obstruction in a child with oesophageal dysmotility. Dysphagia, food bolus obstruction or gas bloat syndrome may result with forceful retching which is thought to be a major contributor of ‘wrap failure’. Numerous studies have shown higher complication(s), morbidity and reoperation rates in children with NI [6] yet the definition of GERD by objective assessment(s) is usually absent from such reports. In this systematic review, NI children appear to gain some benefit from ARS, though somewhat less it must be inferred than NN children. Furthermore, these benefits were observed into the follow-up period(s) reported. It may be worth noting here that insufficient pre-operative workup in NI patients (i.e. inappropriate patient selection) may explain a historically poorer outcome amongst this cohort.

*Limitations*

Systematic reviews can only draw conclusions based on the studies available in the literature and are therefore limited by the availability and quality of such publications. As previously highlighted by Lobe, there are several confounding factors which make comparison amongst published series challenging [44]. Firstly, ARS is a broad term which incorporates many different interventions. Fundoplication and ARS are often used interchangeably, but other less common operations may be used to target GERD, e.g. endoluminal endoscopic oesophago-gastric plication, surgical feeding jejunostomy and oesophago-gastric dissociation. With regards to fundoplication, there are variations in the operation deployed by the surgeon - (classical ‘open’, laparoscopic and robotic), type of wrap (Nissen, Thal, Dor, etc.), experience of the surgeon, degree of dissection undertaken, fixation of the wrap, and whether to perform gastrostomy concurrently, to name a few. Secondly, there exists reporting and selection bias amongst series with regards to patient selection criteria. For example – (1) patients with more severe GERD would be expected to gain greater benefit from ARS, (2) number of patients with comorbidities varies amongst published studies, (3) definition of NI is not consistently reported (nor was it an eligibility criterion in our study) and (4) threshold for performing surgery varies amongst surgeons and units, and authors do not uniformly report such information. These confounding factors are evident amongst the final studies included in this systematic review. Quality assessment highlighted issues with methodology(s) and reporting of included articles. In particular here, studies performed poorly with regards to unbiased assessment of endpoints and prospective calculation of study size. Furthermore, we should note that five studies [21-25], comprising two cohorts (82 patients), were published by a similar group of authors. The data provided by two of these [21,22] provided the longest follow-up data in our review, and whilst they scored relatively well in MINORS scoring, it is important that we highlight the potential bias that arises from prolific authorhood (in the absence of meta-analysis, a funnel plot is not available to help identify such bias).

Our search for this systematic review was not limited by publication date because we anticipated a limited number of available studies; our expectation was subsequently confirmed. We therefore included two (of a total of 14) studies from the 1980s [31,32]. Since then, a laparoscopic approach has become favored (in both series, open fundoplication was preferred), medical management has improved (e.g. better availability of proton pump inhibitors), and there have been changes to patient selection, standards and availability of pre-operative work-up investigations (although from this review, it seems less has changed than might be expected). These ‘pre-laparoscopic era’ studies [31,32] provide valuable information on the results of manometric testing, accounting for one of the only two papers which did so amongst the literature, and gastric emptying study results, accounting for one of only three studies which did so.

*Conclusion*

Of the low to moderate quality of studies identified, in short and medium-term follow-up, ARS appears to improve QoL and reduce oesophageal acid exposure in both NN and NI children. Whilst ARS is a common pediatric surgical operation, a lack of detailed information with regard pre- and post-operative patient outcomes in many reported studies during the course of our systematic review is striking.

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**FIGURE LEGENDS**

Table 1: inclusion and exclusion criteria.

Figure 1: PRISMA flow diagram and electronic database search strategy. N.B. bravo refers to Medtronic’s Bravo™ reflux testing system, an alternative method of pH testing; TIF refers to ‘transoral incisionless fundoplication’, an endoscopic anti-reflux method; Nissen, Thal, Toupet, Belsey, Dor, Lind and Guarner refer to various types of anti-reflux surgery; LINX refers to laparoscopic insertion of a magnetic bead band, namely UCI Health’s LINX® Reflux Management System.

Table 2: summarizes the final studies included in the review.

Figure 2: summarizes quality of manuscripts included for review.

Table 3: summarizes studies of anti-reflux surgery in children which include pre- and post-operative assessment of QoL. N.B. each row corresponds to a single cohort of patients which, in some cases, are reported amongst a number of publications.

Table 4: summarizes studies of anti-reflux surgery in children which include pre- and post-operative GI investigations. N.B. each row corresponds to a single cohort of patients which, in some cases, are reported amongst a number of publications.

Table 5: summarizes reported morbidity and mortality in included series. N.B. NR = not reported adequately. Each row corresponds to a single cohort of patients which, in some cases, are reported amongst a number of publications.