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Outcomes of fundoplication in oesophageal atresia associated gastrooesophageal reflux disease

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ABSTRACT

Aim of the study: Conservative management of gastrooesophageal reflux (GORD) in oesophageal atresia (OA) is sometimes inefficient, and fundoplication is required. We assessed the outcomes of fundoplication among OA patients from 1980 to 2016.
Methods: After ethical consent, hospital records of 290 patients, including 22 referred patients, were reviewed. Included were 262 patients with end–to–end repair. Excluded were patients who underwent oesophageal reconstruction (n = 23) or no repair (n = 5). Primary outcome measures included survival, retaining the native oesophagus, resolution of GGORD symptoms, failure of fundoplication, and long-term endoscopic results.
Main results: Gross types of OA in 262 patients were A (n = 12), B (n = 2), C (n = 217), D (n = 10), E (n = 19), and F (n = 2). Eighty-six (33%) patients, type A (n = 12, 100%), B (n = 2, 100%), C (n = 69, 31%), D (n = 3, 30%), and F (n = 1, 50%), underwent fundoplication at the median age of 5.4 (IQR 3.1–16) months. Main indications included recalcitrant anastomotic stenosis (RAS) in 41 (48%), respiratory symptoms in 16 (19%), and acute life threatening events (ALTE) in 15 (17%) of patients. Associated tracheomalacia in 25 (29%) patients were treated with aortopexy. Median follow–up was 7.5 (IQR 1.8–15) years. RAS resolved in 30 (73%) patients, whereas 11 (27%) with unresolved RAS underwent oesophageal resection (n = 8) or replacement (n = 3). Six (7%) patients died of heart failure (n = 4), bolus impaction (n = 1), and ALTE (n = 1). Fundoplication failed in 27 (31%) patients, and 13 (15%) underwent redo fundoplication. Fundoplication failure was predicted by long-gap OA RR = 3.8 (95%CI = 1.1–13), P = 0.04. In total GORD associated symptoms persisted in 7 (8%) patients, including one with permanent feeding jejunostomy. Latest endoscopy showed moderate or severe oesophagitis in 7% of fundoplicated and in 3% nonfundoplicated patients and intestinal metaplasia in 3% and 1% (p = 0.20–0.29).
Conclusion: Fundoplication provided a safe and relatively effective control of OA associated symptomatic GORD and oesophagitis. The failure rate of fundoplication was high in those with long-gap OA.
Type of study: Treatment study.
Level of evidence: IV

After repair of oesophageal atresia (OA) gastrooesophageal reflux disease (GORD) is a common postoperative problem. The anatomy and the innervation of the repaired oesophagus differ considerably from a normal oesophagus. Functional impairment of the repaired oesophagus with no effective peristaltics and poor clearance of liquid and solid contents and without co-operation between the body of the oesophagus and the lower oesophageal sphincter (LES) muscle predispose to GORD. The symptoms of OA associated GORD include vomiting, dyspnoea, aspiration, wheezing, dysphagia and apneic spells. GORD may also predispose to recurrent anastomotic stenosis. Although the symptoms of OA associated GORD are not unlike GORD symptoms in otherwise healthy infants, an infant with OA associated GORD is frequently exposed to life-threatening events that require rapid response from the clinician. In such situations conservative management by positioning, antireflux medication or waiting of the disappearance of the symptoms by infants growth may be not be safe and effective, and antireflux surgery ie, fundoplication is the treatment of choice [1,2]. Although the incidence of fundoplication varies widely from 9% to 40% depending on the type of OA and treating centre [3–5] fundoplication is the most common major surgical procedure in patients with OA.

In this retrospective observational study we present the outcomes of fundoplication among 290 successive patients with OA from 1980 to 2016. Main outcome measures were survival, resolution of symptoms, preservation of native oesophagus, failure of fundoplication and long-term endoscopic results.

1. Materials and methods

Consent from the ethical board was obtained. Patients assessed in the present study have been assessed by the same authors in previous

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studies [6–12], but in the present study the focus is on fundoplications in patients with OA. Patients were identified with the help of manual operation theatre diary from 1980 to 1997 and from computerized archives with the help of ICD codes from 1990 to 2016. All patient data including surgical reports of the primary repair and fundoplication, endoscopic follow-up data and data of symptoms, radiologic imaging or other tests relevant for diagnosis of GORD were collected by review of the hospital records. The main indication for fundoplication was clinically acute GORD that was unmanageable with proton pump inhibitors (omeprazole or lanzoprazole 1–2 mg/kg once daily), positioning or feeding adjustments. In order to assess the oesophageal anastomosis and oesophagitis all patients with pending fundoplication underwent at least one oesophagogastroscopy combined with balloon dilatation (Pentax balloon dilatator w/wo wire guide) of anastomotic stenosis if necessary. Indication for endoscopic dilatation was dysphagia; contrast radiographs were not used routinely as the basis of performing a balloon dilatation. In case of recurring or recalcitrant anastomotic stenosis a minimum of six endoscopic balloon dilatations were performed before fundoplication was considered. Dilatations were performed by gradually increasing maximum balloon diameter from 6 mm in the first session (three weeks after the primary repair) to 10–11 mm in the later sessions with a minimum of one week interval between sessions. Oesophageal pH/impedance monitoring and upper gastrointestinal tract contrast series were used whenever clinically practicable. Endoscopies of the upper gastrointestinal tract were performed with small or baby-sized flexible videogastroscope (Pentax EG 2985, Japan) and endoscopies of airway with flexible videobronchoscope (Pentax, Japan) or with (2.5–4.5 mm) rigid bronchoscope (Karl Storz Endoskope, Germany). In patients who had cyanotic or apnea spells, assessment for laryngomalacia, supraglottic stenosis, vocal cord paralysis, tracheooseophageal cleft, initially missed proximal TEF and tracheomalacia was performed by tracheobronchoscopy in general anaesthesia with spontaneous breathing. Tracheomalacia was regarded significant if during expiration the tracheal lumen occluded 50% or more. If ALTE or respiratory problems could not be managed with maximum treatment of GORD and positive end respiratory pressure (PEEP) mask producing 5–8 H20cm PEEP, fundoplication combined with aortopexy was considered necessary. Recurrent TEF was excluded with endoscopic methylene blue test, air bubble test or with supine lateral oesophageal contrast radiograph [6]. Patients with congenital heart disease or with were re-referred to cardiologist assessment. Most fundoplications for early postrepair GORD were performed through open abdominal route as emergent or semiemergent operations preferably by the surgeon who performed or supervised the original repair. Because postrepair GORD symptoms are intermixed with features of stenotic oesophageal anastomosis, tracheomalacia and respiratory problems.

All patients with OA with or without fundoplication underwent a programmed endoscopic surveillance from one to 15 years of age. Non-scheduled endoscopies, contrast studies or pH/impedance-monitorings were performed when deemed necessary, for example, because of recurred GORD. In follow-up endoscopy patency of the fundoplication was assessed from oral direction and by viewing the gastrooesophageal junction and the fundoplication wrap from retrograde direction by inverting the gastroscope in air-filled stomach. Signs of failed fundoplication included loose or absent wrap, wrap retraction into thorax or hiatal and paraesophageal hernias [13]. Esophagitis was graded histologically as none, mild, moderate or severe. Of metaplastic changes only intestinal metaplasia (columnar epithelium and goblet cells) was recorded [14,15]. Mild esophagitis, a very common finding in GERD, was not considered significant. In pH monitoring acidic reflux over 10% of the total measurement time or 5% of total time minus two hours after meals or reflux periods exceeding five minutes [16] were considered pathologic. Impedance was recorded synchronously with the pH/impedance probe, but because impedance in a repaired oesophagus can be expected to be abnormal [17] and no reference values were available, impedance had no actual effect on the decision to perform fundoplication.

Main outcome measures were survival and degree of oral intake. Surgical complications were also recorded and assessed. Statistical calculations were made with StatView® 512computer programme (Brain Power, Calabasas CA, USA). Data are presented as frequencies or medians with interquartile range (IQR). Categorical variables were compared with Fisher's Exact Test, Risk Ratios with Logistic Regression Analysis. P values <0.05 were considered statistically significant. Data are quoted as median (interquartile range) unless otherwise indicated.

2. Results

During the study period 1980 to 2016 we treated 290 successive children with OA; twenty-two were referred from elsewhere. Five infants with Gross C-type OA and trisomy of chromosome 13 (n = 2), extreme prematurity (n = 1) died without undergoing definite repair and 23 (type A n = 11, B n = 4 and C n = 5) underwent oesophageal reconstruction without attempt of end-to-end repair. Included were 262 with native oesophagus at the time of fundoplication A (n = 12), B (n = 2), C (n = 217), D (n = 10), E (n = 19) and F (n = 2). A total of 86 of 262 (33%) underwent fundoplication at the median age of 5.4 (IQR 3.1–16) months. Fundoplications by atresia type and associated anomalies are outlined in Table 1.

2.1. Indications and techniques

Main indications for fundoplication included recalcitrant anastomotic stenosis (RAS) in 41 (48%) (type A n = 7, B n = 1, C n = 29, D n = 3, F n = 1) acute life threatening events (ALTE) in 15 (17%) (type C n = 14, D n = 1) respiratory symptoms in 16 (19%) (type A n = 2, C n = 14, D n = 1) persistent oesophagitis in 11 (13%) (type C n = 11) and persistent vomiting in 3 (3%) (A n = 1, B n = 1, C n = 1) patients.

Seventy-nine (92%) patients underwent an open operation (Nissen n = 49, Boix–Ochoa n = 23, Toupet n = 7) and seven (8%) had a laparoscopic Nissen fundoplication. Median age at open operation was 5.4 (IQR 3–17) months and at laparoscopic operation 8.5 (5.1–49) months (P = 0.28).

3. Results of fundoplication

3.1. Anastomotic stenosis

Median age of at fundoplication was 4.2 (IQR 2.7–6.3) months. Of 41 patients with recurrent anastomotic stenosis 30 (73%) eventually responded to postfundoplication endoscopic dilatations. Nine patients (types A n = 2, C n = 5, F n = 1) underwent rethoracotomy, resection of the stenosed anastomosis and end to end resection and eventually responded to continued dilatations. In addition, three patients with C-

Table 1
Fundoplications in 262 patients with native oesophagus and primary anastomosis. Rate of fundoplication by type of oesophageal atresia (OA) and by associated diseases.

Total (n = 262)	Fundoplication (n = 86) (32%)	No Fundoplication (n = 176) (68%)	
Type of OA (primary anastomosis)			
A (n = 12)	12 (100%)	0	
B (n = 2)	2 (100%)	0	
C (n = 217)	69 (32%)	147 (68%)	
D (n = 10)	3 (33%)	7 (67%)	
E (n = 17)	0 (0%)	17 (100%)	
F (n = 2)	1 (50%)	1 (50%)	
Associated disease (patients)			P
Congenital Heart Disease (n = 74)	24 (28%)	50 (28%)	0.99
Duodenal Atresia (n = 23)	9 (10%)	14 (9%)	0.49
Anorectal Malformation (n = 34)	13 (15%)	21 (12%)	0.56
Prematurity (n = 99)	40 (40%)	59 (32%)	0.06
Tracheomalacia/aortopexy (n = 32)	25 (29%)	7 (4%)	<0.001
Airway malformation (n = 40)	15 (17%)	20 (11%)	0.18

type OA had recalcitrant anastomotic stenosis and they underwent oesophageal reconstruction because of a long stenotic area (from 4 to 5 cm) and associated recurrent fistula in two patients. Reconstructions included jejunum interposition (n = 1), gastric pull-up (n = 1) and reversed gastric tube (n = 1).

3.2. Acute life threatening events (ALTE)

Median age of at fundoplication was 2.9 (IQR 2.2–4.6) months. Of fifteen patients with ALTE 9 (36%) underwent aortopexy for tracheomalacia. Fundoplication with or without aortopexy controlled ALTE in 10 (66%). In three children with congenital heart disease (Fallot's tetralogy) ALTE stopped only after heart surgery. In two patients who underwent fundoplication with aortopexy for tracheomalacia ALTE persisted for two and three months but eventually attenuated and ceased.

3.3. Respiratory symptoms

Median age at fundoplication was 17 (IQR 11–29) months. Of seventeen children who underwent fundoplication for respiratory GER symptoms three had undergone a previous aortopexy for tracheomalacia. Five (29%) children had an associated syndrome (CHARGE n = 2, Di George n = 1, Down's syndrome (n = 2). In all seventeen patients fundoplication attenuated respiratory symptoms, but none had total cessation of respiratory symptoms.

3.4. Persistent oesophagitis

Median age at fundoplication was 110 (IQR45–180) months. Eleven patients had GORD symptoms with endoscopically verified moderate or severe mucosal inflammation consistent with reflux oesophagitis. Before fundoplication all patients were administered proton pump inhibitors (1–2 mg/kg once daily) or ranitidine (5–10 mg/kg twice daily) for several months and the healing surveyed with repeated endoscopic biopsies. After a median of 115 (IQR 56–165) months of endoscopic follow-up eight (73%) children had no oesophagitis, two (18%) had mild oesophagitis, and one (9%) severe oesophagitis. In two with mild (n = 1) and severe (n = 1) oesophagitis biopsies showed also columnar (gastric) metaplasia.

3.5. Vomiting

Median age at fundoplication was 15 (IQR 9–26) months. Three children underwent fundoplication for persistent copious vomiting that was detrimental to enteral nutrition. One patient with A-type OA had a severe dumping syndrome. In all three vomiting was controlled by fundoplication and enteral nutrition was successfully continued.

3.6. Mortality, preservation of native oesophagus and long term endoscopic follow-up

Mortality in OA with fundoplication was 6/86 (7%) and in nonfundoplicated OA 17 /187 (9%) (P = 0.81). Of six children who died after fundoplication, four died of sequelae of heart surgery; one of the four had also severe associated tracheomalacia. One patient with isolated C-type OA with postrepair ALTE underwent fundoplication with aortopexy for moderate tracheomalacia and repair of minor laryngeal cleft by otolaryngologist. After four months and after a six-week remission of ALTE the child, however, succumbed to ALTE during his first probationary discharge. In addition, one child died of suffocation by a food bolus obstruction three months after fundoplication.

Three (3%) of 86 underwent oesophageal reconstruction (see anastomotic stenosis).

Endoscopic follow-up covered 244 (86%) of the 290 patients. Of the missing 46 patients 20 died before joining the follow-up program and 26 patients (OA type E n = 10, type C n = 16) were lost to follow-up. Patients included in the follow-up underwent a median of 3 (IQR 2–4) endoscopies during the follow-up. Results from the last endoscopy are outlined in Table 2. Children who underwent fundoplication had higher incidence of gastric metaplasia than nonfundoplicated patients. No cases with dysplasia or cancer were found. (See Table 3.)

Table 2
Indication for fundoplication in patients with oesophageal atresia (RAS = recalcitrant anastomotic stenosis, ALTE = acute life threatening events, Respiratory = respiratory symptoms).

	RAS (n = 41)	ALTE (n = 15)	Respiratory (n = 16)	Oesophagitis (n = 11)	Vomiting (n = 3)
A (n = 10)	7	0	2	0	1
B (n = 2)	1	0	0	0	1
C (n = 68)	29	14	14	11	1
D (n = 4)	3	1	0	0	0
F (n = 1)	1	0	0	0	0

3.7. Failed fundoplication

Endoscopic follow-up after the first fundoplication was found to be intact in 59 (69%) of children after a median of 7.8 (IQR 2.0–15) years. In 27 (31%) children, fundoplication failed after a median of 17 (IQR 8–183) months of follow-up. Failure rate in type A OA was 7/10 (70%), B 0/2 (0%), C 20/69 (29%), D 0/4(0%) and F 0/1 (0%). Logistic regression analysis of fundoplication failure showed that long gap OA (type A or B) was the only statistically significant predisposing factor, RR = 3.8 (95%CI = 1.1–13); P = 0.04.

Of 27 children with failed fundoplication two underwent oesophageal reconstruction because of recalcitrant anastomotic stenosis and recurrent tracheooesophageal fistula. Thirteen (54%) patients (OA type A n = 4, type C n = 9) underwent redo fundoplication because of recurrent significant symptoms of GORD a median of 17(IQR 5.6–37) months after the first fundoplication. Indications for redo fundoplication (RAS n = 2, respiratory symptoms n = 5, vomiting n = 5, dysphagia n = 1) differed from the indications from the original fundoplication (RAS n = 11, ALTE n = 1, respiratory symptoms n = 1). Among 13 children with redo fundoplications four (31%) had a new failure and nine remain with a patent fundoplication.

Among the remaining 12 children with failed fundoplication (type A OA n = 3, type C n = 9) (original indications RAS n = 6, ALTE n = 4, respiratory symptoms n = 1, oesophagitis n = 2, vomiting n = 1) GORD associated symptoms attenuated or were successfully managed nonoperatively in nine. Seven with failed first or redo fundoplication remained with significant GORD symptoms. Of these seven, three

Table 3
Endoscopic follow-up from birth to latest follow-up endoscopy, all OA patients from 1980- to 2016 (n = 290) included.

	No fundoplication (n = 204) Results available in 165 (81%)	Fundoplication (n = 86) Results available in 81 (92%)	P
Follow-up (median, yrs)	8.6 (IQR 3.0–16)	11 (IQR 5.5–17)	0.07
Oesophagitis			
• no	127 (77%)	54 (69%)	0.16
• mild	33 (20%)	19 (24%)	0.50
• moderate	5 (3%)	5 (6%)	0.30
• severe	0 (0%)	1 (1%)	0.32
• lost to follow-up	39	7	0.02
Metaplasia			
• No	156 (94%)	65 (82%)	0.04
• Gastric	8 (5%)	12 (15%)	0.01
• Intestinal	1 (1%)	2 (3%)	0.24

have died and four children were unfit for further antireflux surgery and are managed with feeding jejunostomy (n = 2) or gastrostomy (n = 2).

4. Discussion

About 1/3 of our present series of children born with OA are coming to fundoplication. We feel that our main findings are a relatively low mortality (7%) caused by OA associated diseases rather by the fundoplication itself. Fundoplication aided materially in the management of GORD related symptoms although complete control of symptoms was not achieved. This is mainly because of the etiology of ALTE and respiratory symptoms in patients with OA is multifactorial including GORD, tracheomalacia, heart disease and reactivity of the respiratory tract and the decision to fundoplication is often based on clinical findings. Management of GORD with fundoplication had positive effect on the resolution of recurring stenosis of the oesophageal anastomosis by endoscopic dilatation. However, in approximately one fourth of the patients with anastomotic stenosis fundoplication did not result in resolution of the stenosis by continued dilatations, and surgery was required. Failure rate of fundoplication was relatively high, 31%, but compared with contemporary literature not exceptionally high in patients with OA [18,19]. Lastly endoscopic follow-up showed that those who have undergone fundoplication, i.e. those with the severest form of OA associated GORD, have a similar rate of oesophagitis and intestinal metaplasia as other patients with OA.

The weakness of our study is its retrospective design. Excluding anastomotic stenosis that can be diagnosed with an endoscope with reasonable objectivity, detailed assessment or grading of GORD symptoms such as heartburn and respiratory symptoms and their attenuation after fundoplication by retrospective review of hospital records is difficult. We could not show in a statistical analysis how much fundoplication benefited the management of recalcitrant anastomotic stenosis, that is, whether lasting anastomotic patency was achieved with less endoscopic dilatations that would have been the case without fundoplication, because we had no control group of patients with recalcitrant anastomotic stenosis without fundoplication. Endoscopic follow-up, while being imposed on the majority of the patients, was not comparable of the modern diagnostic standards of Barrett's oesophagus.

GORD in those with OA is often persistent and it is known that the incidence of premalignant oesophageal mucosal changes such as Barrett's esophagus with intestinal metaplasia increases when the patients reach young adult age [9,10]. In the present series the incidences of oesophagitis and intestinal metaplasia were relatively low in patients both with and without fundoplication. Compared with the rest of the series the patients who underwent fundoplication had higher rate of gastric metaplasia. While gastric metaplasia may be a result of an oesophageal biopsy taken too distally in relation to the oesophagogastric junction, an error easily made in a fundoplicated patient, the presence of gastric metaplasia in the distal oesophageal mucosa may be a true finding and signal the coexistence of intestinal metaplasia [20]. Whether fundoplication offers any protection against Barrett's oesophagus cannot be confirmed by our results.

We found that failure of fundoplication was common in patients with OA, and those with long-gap OA are at the highest risk of failure. GORD could be managed conservatively after the failure of the fundoplication in less than half of our cohort. We observed that several patients who as infants underwent fundoplication and had successful treatment of RAS or ALTE suffered failure of the fundoplication but the remaining GORD symptoms could be managed conservatively. In the majority of patients, however, failure of fundoplication resulted in recurrence of symptoms of GORD, although often in other forms than RAS or ALTE. After failure of first fundoplication, a trial of conservative management may, however, be worth trying because we found a not insignificant failure rate also in redo fundoplications.

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