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Anti-reflux surgery in neonates and infants: analysis of indications, outcomes, and link to mortality among primary and secondary gastroesophageal reflux patients

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Abstract

Background: The indications and benefits of anti-reflux surgery (ARS) in neonates and infants are uncertain. Prematurity, operation before 1 year of age, neurological impairment (NI), and chronic lung disease (CLD) are risk factors for surgical failure. We aim to document the indications, management, and outcomes of ARS in this age group and compare them among primary and secondary gastroesophageal reflux (GERD).

Results: Between January 2008 and December 2019, 24 males and 22 females had ARS; 13 (28.3%) for primary while 33 (71.7%) for secondary GERD. The mean gestational age was 34.6 weeks (range 24–41) and mean birth weight was 2000 gm (range 600–3300). The weight at time of referral ranged from 1.4 kg to 4 kg (mean 2.2 kg). There were no significant differences between the two groups regarding the previous data. The group of primary GERD presented mainly with recurrent aspiration ($n = 8$), recurrent apnea ($n = 5$), and recurrent desaturations with or shortly after feeds ($n = 4$). The group of secondary GERD were referred for poor sucking with failure to thrive (FTT) ($n = 25$), recurrent aspiration ($n = 20$), and gastrostomy request ($n = 14$). The risk factors for secondary GERD were neurologically impaired ($n = 22$), post-esophageal atresia (EA) repair ($n = 9$), hiatus hernia ($n = 4$), thoracic stomach ($n = 2$), N-type tracheoesophageal fistula (TEF, $n = 4$), and congenital esophageal stenosis (CES, $n = 4$). The operations included open Nissen's fundoplication (ONF) ($n = 4$) and modified open Thal's fundoplication (MOTF) ($n = 42$). There were 8 mortalities in the secondary group, unrelated to surgery. Morbidities after Nissen's fundoplication included wrap migration, gas bloat, and reoperation in one, laparotomy for intestinal obstruction (IO) in one. Following MOTF, there were two cases of transient recurrent GERD which improved with time and laparotomy in one for IO.

Conclusions: Diagnostic tests remain a challenge. Isolated TEF and CES may require fundoplication for staged management. Cases of the primary group did better with MTF. Prematurity, CLD and age < 2 months were not significant risk factors for fundoplication failure or mortality. Neurological impairment was a risk factor for mortality.

Keywords: Gastroesophageal reflux, Fundoplication, Anti-reflux surgery, Thal's fundoplication, Tracheoesophageal fistula, Congenital esophageal stenosis, Chronic lung disease

Background

Spontaneous resolution is the usual outcome of GERD in infants and neonates. However, delaying ARS may lead to debilitating nutritional effects and respiratory problems in the early months [1]. Reflux may precipitate

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complications like apnea, acute life-threatening events (ALTEs), FTT, chronic respiratory problems, and esophagitis that may affect the quality of life [2]. In neonates and infants, GERD may represent a real diagnostic challenge due to the unavailability of a gold standard diagnostic test. The 24-h reflux index is unable to detect non-acidic reflux [3]. The multi-channel intraluminal impedance (MII) can assess the direction and velocity of liquids and gas flow through the esophagus [3, 4]. However, the testing time is long, probe stabilization is difficult, and the reference values in neonates and infants are not well-validated. Contrast study is helpful to diagnose anatomical abnormalities but has a low sensitivity and specificity for GERD.

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) have concluded that there is insufficient evidence to justify the routine use of prokinetics. Proton pump inhibitors have been approved in America for treatment of GERD with esophagitis [2]. However, the decrease of acid exposure would relatively increase non-acidic reflux, which is a main contributor to recurrent respiratory symptoms [5].

Only ARS can prevent recurrent aspiration pneumonia, recurrent apneic episodes, and chronic respiratory problems [3, 6]. Excellent results have been reported with improvement of symptoms and weight gain [3]. Others reported poor results after fundoplication in young infants with high failure rate especially in the NI children, after EA repair and CLD [6, 7]. Laparoscopic Nissen's fundoplication (LNF) can be performed safely and effectively in small children weighing less than 5 kg with similar outcomes and rates of complications to those reported in older children [8]. It is also reported that in the long term, open and laparoscopic Thal's fundoplication have similarly good outcomes [9]. The role of Nissen's fundoplication in neonates and infants is unclear and only few reports have been published [2, 3, 10]. Thal's fundoplication in neonates and infants is even less reported in the literature and its role needs to be further investigated in this group of patients.

Patients and methods

This is a retrospective study including neonates and infants who underwent ARS for GERD-related problems in a tertiary referral neonatal center, between December 2008 and December 2019. Data were collected for patients' demographics including gestational age, birth weight, gender, age, and weight at time of referral to surgeons and at fundoplication together with post-operative follow-up. Albeit retrospective, the management followed a unified protocol agreed

by the neonatologists and surgeons. When a baby had been unable to tolerate a given volume of milk for more than 5 days together with GERD, the patient was recognized as a poor feeder. Failure to thrive was defined as a decrease in weight to less than the 10th percentile. When a case presented with a clinical picture of GERD (usually atypical), no-drug conservative management was started with close medical supervision. If that was not successful, the pediatric surgical and ENT teams were consulted, and an upper GI video fluoroscopy was carried out, following a protocol that ensured maximum diagnostic benefit (swallowing, motility, N-type TEF, anatomical problems, and malrotation). Consideration was also given to microlaryngobronchoscopy (MLB) by the ENT team for selected cases.

Primary GERD cases were those having no associated diseases or with diseases not related to GERD like congenital heart disease, prematurity, low birth weight, and CLD. The secondary GERD group was associated with other comorbidities, e.g., NI, hiatal hernia, post-esophageal atresia (EA) and/or tracheoesophageal fistula (TEF), congenital abnormalities of the esophagus, syndromes with complex multiple congenital anomalies. A trial of full anti-reflux measures was commenced for 2–4 weeks. Some cases like acute respiratory events, post-EA repair or NI patients requiring gastrostomy were fast-tracked for surgery rather than going for a full course of conservative management. Operative, post-operative mortality or complications were studied. Post-operative follow-up period was a minimum of 24 months. Outcome evaluation included recurrence of symptoms, weight gain, upper GI radiological contrast studies and the need of a redo surgery. Post-operative poor weight gain was defined as losing weight, stable weight, or gaining less than 0.5 lbs. per month. Excellent weight gain was defined as gaining 2 lbs. or more per month while fair weight gain was in between.

Modified open Thal's fundoplication (MOTF)

Via a midline supraumbilical incision, the gastroesophageal junction was exposed, and esophagus dissected anteriorly towards both sides, preserving the anterior vagus nerve. An esophageal sling was applied with the posterior vagus included. Posterior dissection was kept to the minimum. The hiatus was narrowed with 1–2 loose silk stitches, anchored to the posterior esophageal wall avoiding the posterior vagus. A 270° anterior wrap was fashioned using non-absorbable stitches making an ascending, transverse and descending limbs (an inverted U-shape suture line). The sutures included the crura in the ascending and descending limbs and the phrenoesophageal ligament horizontally.

Data management and analysis

The collected data was revised, coded, tabulated, and introduced to a PC using Statistical package for Social Science (SPSS 20). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

Descriptive statistics

1. Mean, standard deviation (\pm SD), and range for parametric numerical data, while median and interquartile range (IQR) for non-parametric numerical data.
2. Frequency and percentage of non-numerical data.

Analytical statistics

1. Student's *t* test was used to assess the statistical significance of the difference between two study group means.
2. Mann–Whitney test (*U* test) was used to assess the statistical significance of the difference of a non-parametric variable between two study groups.
3. Chi-square test was used to examine relationship between two qualitative variables
4. Fisher's exact test was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells

Results

There were 24 males and 22 females, 13 of them (28.3%) had primary GERD while 33 patients (71.7%) had secondary GERD (Table 1). Patients' ages and weights at time of referral and surgery are shown in Table 2. It demonstrates that patients of the secondary group were referred later but with lower weight, however, with no statistical significance. Table 3 shows the different types of patients in both groups and their associated risk factors and comorbidities. Table 4 highlights that the main presenting features for the primary group were prematurity and aspiration pneumonia (8/13 each, 61.5%) while that for the secondary group were intolerance to feeds and FTT

Table 1 Gender

Item	Primary group	Secondary group	Total
Male	8	16	24
Female	5	17	22
Total	13	33	46

Table 2 Patients' weight and age at time of referral and time of surgery

Item	Data	Primary cases	Secondary cases
Gestational age (weeks)	Range	26–41	24–40
	Mean	34.6	35.7
Birth weight (kg)	Range	0.85–3.59	0.60–3.3
	Mean	2.1	2.1
Age at referral (days)	Range	26–150	2–450
	Mean	61	79
Weight at referral (kg)	Range	1.5–4	1.4–3.3
	Mean	2.6	2.3
Age at operation (days)	Range	28–240	14–460
	Mean	91	97.5
Weight at operation (kg)	Range	1.6–6	1.4–4.8
	Mean	2.8	2.2

(25/33, 75.8%). Apnea was significantly more common in the primary group than in the secondary group (38.5% vs 6.1% respectively) (*p* value = 0.014 F). Esophageal narrowing was present in 5 patients (10.9%), 4 of them were due to CES (1 isolated and 3 associated with EA) and one had refractory anastomotic stricture. Out of all patients, 28 (60.9%) had aspiration pneumonia and 28 (60.9%) had

Table 3 Types of patients and associated comorbidities

Item	Primary cases (n = 13)	Secondary cases (n = 33)	Total (n = 46)
NI	0	22 (66.6%)	22
EA/TEF or N-type TEF	0	13 (39%)	13
Hiatal hernia	0	6	6
CES	0	4	4
Laryngomalacia	3	2	5
Other comorbidities			
Cardiac	PDA 2	PDA 9	28
	ASD 6	ASD 6	
	VSD 2	VSD 3	
Trisomy 21	2	6	8
Other syndromes	–	Hyper-flexibility 1	12
	–	Fanconi's anemia 1	
	–	Arnold Chiari 1	
	–	Pierre Robin 1	
	–	Norman's 1	
	–	Edward's disease 1	
	–	Maple syrup urine 1	
	–	Myopathy 1	
	–	Single kidney 2	
	–	Tufting enteropathy 1	
–	IDDM & UC 1		

Table 4 Summary of patients' presentations

Item	Primary (n = 13)	Secondary (n = 33)	Total (n = 46)
<i>Respiratory:</i>			
Prematurity	8 (61.5%) ^a	15 (45.5%)	23 (50%)
CLD	5 (38.5%)	9 (27.3%)	14 (30.4%)
Apnea	5(38.5%)	2 (6.1%)	7
Aspiration pneumonia	8 (61.5%) ^a	20 (60.6%)	28 (60.9%)
Recurrent desaturations	4	9	13
Laryngomalacia	3	2	5
Tracheostomy	0	2	2
<i>GI:</i>			
Feeding intolerance /FTT	3 (23%)	25 (75.8%) ^b	28 (60.9%)
Recurrent vomiting	1	5	6
<i>Esophageal stricture:</i>			
CES	0	4	4 (8.7%)
Anastomotic stricture	0	1	1

^a Main presentation for the primary group^b Main presentation of the secondary group**Table 5** Results of video-fluoroscopy contrast studies

Finding	Primary group (n = 13)	Secondary group (n = 33)
Massive GER	13 (100%)	8 (24.2%)
Mild to moderate GER	–	25 (75.8%)
Poor sucking	–	22 (66.7%)
Hiatal hernia	–	6 (18.2%)
Bronchogram	–	5 (15.2%)
Major dysmotility	–	4 (12.1%)
CES	–	4 (12.1%)
Anastomotic stricture	–	1 (3%)

intolerance to feeds and FTT. In addition, 14/46 (30.4%) had CLD and 23/46 patients (50%) were premature.

The results of the contrast video-fluoroscopy studies are shown in Table 5. Five cases had bronchogram due to isolated TEF in 4 and over-spillage in one. Laryngomalacia was diagnosed in 5 by laryngoscopy. Esophagoscopy was used only in one patient with missed isolated distal CES to rule out peptic stricture, having had fundoplication in the neonatal period for a thoracic stomach, but was symptomatic. Surgeries included open Nissen's fundoplication (ONF) with GT in 2 patients, and without GT in 2, MOTF with GT in 21, without GT in 19 and MOTF with GT and esophageal myectomy in 2. Following ONF, we had gas bloating, trans-hiatal wrap migration and colonic herniation in one NI case that required reoperation. Another case had IO requiring laparotomy. Following MOTF, 2 cases had transient recurrent GER which improved conservatively and a third one had laparotomy

for IO. There were frequent minor recurrent complications for the GT. However, one gastrostomy dislodgment required revision.

Statistical analysis using the Fisher exact test (F) or the chi-square test (C) showed that operation before 2 months of age, at 2–4 months or more than 4 months neither increased the risk for morbidity (p value = 0.064 F) nor mortality (p value = 0.267 F) (Table 6). Similarly, prematurity was not a significant risk for morbidity (p value = 118 C) or mortality (p value = 1 F), nor was CLD for mortality (p value = 1F) (Table 7). Only NI was a significant risk for mortality (p value = 0.0142 F). There were 8 mortalities, all in the secondary group (Table 8). Weight gain was marginally superior among the primary group but not achieving statistical significance (Table 9).

Discussion

Common symptoms of GERD in this age are atypical supra-esophageal symptoms like irritability, coughing, choking, wheezing, and other respiratory symptoms [11]. Moreover, many patients have non-acidic reflux. A pH-MII values as high as 12% have been recorded in asymptomatic healthy neonates indicating that the criteria for an abnormal reflux load are less clearly defined in this age [12]. Also, many other differential diagnoses like anatomical abnormalities, tracheoesophageal fistulas, tracheomalacia, aspiration due to incoordinate swallowing, and primary pulmonary disorders should be excluded before surgery. Failure of medical management, which is an indication for surgery, relies only on subjective symptoms and fewer than 4% of infants with GERD undergo diagnostic testing [13]. A Trial of

Table 6 Mortalities

Patient Number	Patient characteristics	Cause of death	Age at mortality (months)	Interval from fundoplication to mortality (months)	wt. before / wt. after surgery (kg)
1	Premature, 1.7 kg, NI, brain ischemia, EA/TEF, Down's syndrome, PDA, recurrent aspiration	Severe sepsis	4	1.5	1.7 / 2
2	Premature, 990 gm, CLD, NI, EA/TEF, distal CES, major aspiration/brain damage, recurrent TEF, major esophageal dysmotility, severe sepsis	Severe sepsis	21	18	1.9 / 10
3	IUGR, 1.6 kg, NI, Down's syndrome, CAH, recurrent desaturations, ventriculomegally, severe sepsis	Severe sepsis	42	27	1.7 / 5
4	IUGR, 1.8 kg, NI, Edward' syndrome, IDDM, CLD, diaphragmatic eventration, brain atrophy, ulcerative colitis	Septic shock + sagittal sinus thrombosis	60	24	2.1 / 8
5	Premature, 1.5 kg, NI, EA/TEF, distal CES, Skeletal anomalies, Fanconi's anemia, PDA	Refractory sepsis (Fanconi anemia)	30	29	1.8 / 3
6	NI, 2.5 kg, apnea, neurodegenerative disorder, esophageal dysmotility	Sepsis, neuro-degenerative disease	8	1.5	2.8 / 3.8
7	2.9 kg, Down's syndrome, CLD, PDA, PFO, Laryngomalacia	RSV bronchiolitis	24	15	2.9 / 6.5
8	Premature, 1.75 kg, IVH, NI, inability to feed, sepsis	Severe gram – ve and candida sepsis	13	11	1.8 / 6

PDA patent ductus arteriosus, IUGR intrauterine growth retardation, CAH congenital adrenal hyperplasia, IDDM insulin-dependent diabetes mellitus, CLD chronic lung disease, PFO patent foramen oval, IVH intraventricular hemorrhage, Wt weight

Table 7 Mortalities among premature babies and patients with CLD (impact of prematurity and CLD)

Group	Mortality/prematurity	Mortality/CLD
Primary group (n = 13)	0/8	0/5
Secondary group (n = 33)	3/15	2/9
Total	3/23	2/14

A total of 9 patients had combined prematurity and CLD one of them died

Table 8 Mortality among each group

Item	Primary group (n = 13)	Secondary group (n = 33)	Total (n = 46)
Survivors	13 (100%)	25 (75.8%)	38 (82.6%)
Mortality	0 (0%)	8 (24.2%)	8 (17.4%)

Table 9 Post-operative weight gain among survivors (n = 38), excluding 8 mortalities

Weight gain	Primary group (n = 13)	Secondary group (n = 25)	Total (n = 38)
Excellent	9 (69.2%)	10 (40%)	19 (50.0%)
Fair	4 (30.8%)	11 (44%)	15 (39.5%)
Poor	0 (0%)	4 (16%)	4 (10.5%)

continuous enteral feeding through a nasogastric or nasojejunal tube may clinch the diagnosis before surgery. Moreover, patients with gasstrojejunal feeding have demonstrated more reflux-related hospital visits in some reports [14].

The clinical picture, video fluoroscopy, MLB and occasionally upper GI endoscopy were our diagnostic tools. Scintiscan of the lung can be useful, but it was not consistently available, and it has many false negatives, and not always easily performed in patients with respiratory distress [15]. Bronchoscopy was our routine in cases of isolated TEF to confirm the diagnosis and aid identification during surgery. If the proper bronchoscope size was not available and GER was massively endangering life before repairing the N-TEF, a preliminary fundoplication with GT was a good option practiced in the current study in 4 patients. Neurologically impaired patients referred for GT who had active reflux symptoms and GER on pre-gastrostomy contrast studies underwent fundoplication [16]. Esophageal biopsy to diagnose esophagitis is rarely practiced in this age group [4]. The esophageal pH can be misleading and cannot detect non-acidic reflux. Limitations of pH-MII studies are the availability and high cost. Also, probe stabilization is difficult and there is lack of normative data in neonates that make it impractical for this group [17, 18]. Recently, a great step has been

undertaken towards pediatric reference values for pH-MII, promising to improve diagnosis of GERD [19].

Most patients were subjected to therapeutic conservative treatment including prokinetics and H2 blockers but with variable periods of time. Proton pump inhibitors (PPI) has the risk for community acquired pneumonia (CAP), gastroenteritis, candidemia, and necrotizing enterocolitis in the premature babies [11, 20]. Used alone or together with H2 blockers, PPI is associated with an increased bone fracture problem, which is increased by duration of use and earlier consumption [21]. Moreover, PPIs cause a significant decrease in acid reflux with relative increase in non-acidic reflux, therefore, not affecting the recurrent respiratory symptoms [5]. Some institutions recommend PPIs after repair of EA despite low evidence level to support [22].

In 2006, Esposito et al. in a large series comparing long-term outcome of laparoscopic Nissen's, Toupet's, and Thal's fundoplication in children, found no difference in success or complications between any of the techniques, concluding that the choice of operation should be determined by the surgeon's experience [23]. Another author, in 2007, had better results for LNF having introduced some modifications. The length of the fundoplication was suggested to be 2 cm. Post-operative wrap trans-hiatal migration was minimized by esophago-crural sutures, avoiding the division of the phreno-esophageal membrane and minimal esophageal mobilization [16]. Similarly, the modifications on the Thal's procedure in the current study, as shown in the methodology section, were useful to avoid such complications.

Results of fundoplication in early infancy in previous series [23–25] have generally reported a poor outcome with high failure rate. These studies have predominantly reported fundoplication in infants after esophageal atresia repair or with co-existent neurological problems. Better results have been documented in primary GER [5, 24].

Based on a meta-analysis in children, LNF was associated with long term recurrence rate more than ONF [26]. Following Thal's operation, patients are usually able to burp and vomit with less dysphagia or gas bloat. A partial fundoplication may be more appropriate in patients with esophageal dysmotility after esophageal atresia repair [27]. Temporary recurrent symptoms must be distinguished from recurrent GERD [28]. After open ARS, revisional operation was reported to be 11.8% in NI patients [27] and up to 23% in early infancy [7]. Kubiak et al. in 2011 reported a high failure rate of laparoscopic Thal's fundoplication (LTF) (15.9%) [28]. However, the same author, in 2014, reported that the long-term open and laparoscopic Thal's fundoplication had similarly good outcomes and that the mean duration of surgery was significantly less in the open group [9]. Wafa et al., in 2017,

showed that LTF offered an effective alternative to LNF with less complications and no recurrences. The authors found that the operative time was significantly longer in the LTF group than in the LNF group, and that the post-operative duration of dysphagia was shorter in the Thal's group but without statistical significance [25].

Our preferred procedure in this subset of patients was the MOTF because the general condition of many of our patients was too unwell to tolerate laparoscopy and because of the possible long-term recurrence rate being more in the laparoscopic than the open surgery [26]. In our experience, MOTF offered an effective alternative to Nissen's fundoplication without post-operative gas bloat or trans-hiatal herniation into the mediastinum. Only two patients had recurrent symptoms which improved conservatively, and one had adhesion IO. In our series, the primary group cases had neither mortalities nor morbidities despite the fact that 8 patients were premature, 5 had CLD (3 had combined prematurity and CLD). The post-operative evaluation relied mainly on the clinical condition, weight gain, contrast studies, and the need for a redo ARS which occurred in only one, post-ONF. The primary group weight gain was excellent in 69% of patients, fair in 31%. In the secondary group, the weight gain was excellent in 40%, fair in 44% and poor in 16%. Congenital esophageal stenosis is an under-estimated risk factor for morbidities. There should be a high index of suspicion especially in cases of EA as they frequently require anti-reflux surgery with a GT [29, 30].

Conclusions

The main presenting features were aspiration pneumonia, feeding intolerance and FTT. Diagnosis of GERD remains a challenge in this age group. NI was a significant risk factor for mortality while prematurity, CLD and age < 2 months were not. Isolated TEF may require a fundoplication and GT as a first step of management, if the patient is too small for bronchoscopy. The MOTF was better tolerated than Nissen's. Also, CES may require a fundoplication. Mortalities were due to comorbidities and not related to surgery. The superiority of ARS over medical treatment needs to be ascertained by a randomized trial to get high-quality evidence. The study is limited by the relatively small number of patients and by the retrospective nature of data, albeit following a unified protocol.

Abbreviations

ARS: Anti-reflux surgery; NI: Neurological impaired/neurologically impaired; CLD: Chronic lung disease; GERD: Gastro-esophageal reflux disease; FTT: Failure to thrive; EA: Esophageal atresia; ONF: Open Nissen's fundoplication; MOTF: Modified open Thal's fundoplication; CES: Congenital esophageal stenosis; IO: Intestinal obstruction; ALTE: Apparent life-threatening event; MII: Multi-luminal; NASPGHAN: North American Society for Pediatric Gastroenterology,

Hepatology and Nutrition; ESPGHAN: European Society for Pediatric Gastroenterology, Hepatology and Nutrition; LNF: Laparoscopic Nissen's fundoplication; ENT: Ear, nose and throat; MLB: Microlaryngobronchoscopy; SD: Standard deviation; IQR: Inter-quartile range; GT: Gastrotomy tube; CAP: Community acquired pneumonia; PPI: Proton pump inhibitors; LTF: Laparoscopic Thal's fundoplication.

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Authors' contributions

All authors actively participated in the management of these cases. IM: data analysis, literature review and writing the manuscript. HH, SK, AH, and MG: conceptualization, data collection and analysis, and manuscript review. AI: conceptualization, protocolization of management, literature review, writing the manuscript, and supervision of the whole process as the most senior clinician. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

A consent was obtained from the local ethical committee (Reg: H-06-KM-001, Code: AFHSRMREC/2018/PEDIATRIC SURGERY/303).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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