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Anti-Gastroesophageal Reflux Surgery in Infants with Severe Bronchopulmonary Dysplasia

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Summary

Gastroesophageal reflux may exacerbate lung disease in infants with bronchopulmonary dysplasia (BPD). Anti-reflux surgery may therefore reduce the severity of this disease in some infants. We report a retrospective series of 22 infants with severe BPD who underwent anti-reflux surgery. Our experience indicates that these procedures can be safely performed in this population and that early post-operative initiation of gastric feeds is well tolerated. Modest post-operative reductions in required oxygen and median respiratory rate were observed.

Keywords

Fundoplication; Chronic Lung Disease; Aspiration

Introduction

Bronchopulmonary dysplasia (BPD) remains a common chronic complication of prematurity.[1] Gastroesophageal reflux (GER) with pulmonary aspiration may exacerbate lung disease in infants with BPD.[2,3] Anti-reflux surgery may therefore benefit some patients unable to be weaned from respiratory support. Published reports of anti-reflux surgery largely include infants with complex medical and surgical disorders, and report minimal data on respiratory outcomes.[4-6] This report focuses on early post-operative changes in several clinical markers of respiratory disease severity following anti-reflux surgery in infants with severe BPD.

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Methods and Methods

Subjects

The Newborn and Infant Chronic Lung Disease (NeoCLD) Program at our institution constructed a prospective database of all infants with severe BPD (based on the NHLBI/NICHD definition)[7] admitted to the neonatal intensive care unit. The database was queried to identify all infants with severe BPD who underwent anti-reflux surgery between September 2010 and April 2012.

Outcomes and Data Collection

Demographic and respiratory characteristics were compared between infants with and without a history of anti-reflux surgery. For all infants who underwent surgery, the a-priori primary outcome was a statistically significant post-operative change in any of the following markers of respiratory disease severity: mode of respiratory support, inspired oxygen concentration (FiO_2), and median and maximum daily respiratory rate. For ventilated patients, a composite score of mean airway pressure × FiO_2 was also evaluated. Secondary outcomes were post-operative days needed to initiate and reach full feeds, pre- and post-operative average daily weight gain, and mode of respiratory support at discharge. Data for each of the primary respiratory outcomes was collected on five days over two weeks prior to surgery (pre-operative days 1, 3, 5, 7, and 14) and on day 14 following surgery. Mode of respiratory support and FiO_2 were recorded as documented at 8 a.m. on study days. All respiratory rates recorded during 12-hour daytime nursing shifts were collected. Average daily weight gain for each infant was determined from the linear change in weight over two weeks prior to and following surgery. To assess growth effects of enteral rather than parenteral nutrition, post-operative weights were collected for two weeks after full feeds were reached (120cc/kg/day).

Demographic and basic respiratory data were obtained from the NeoCLD database. All pre- and post-operative respiratory and surgical data were retrospectively abstracted from the medical record. Pulmonary arterial hypertension (PAH) was diagnosed by cardiac catheterization or echocardiography. PAH was defined on echocardiogram as either an estimated systolic pulmonary artery pressure > 40mmHg in the presence of a measurable tricuspid regurgitant jet velocity or when both right ventricular hypertrophy and intraventricular septal flattening were present.[8] Airway malacia, including laryngeal, tracheal, and/or bronchial malacia was diagnosed by bronchoscopy or low-dose, high-resolution computed tomography with angiography (CTA). Institutional Review Board approval was obtained.

Statistical Analysis

Demographic data were summarized with standard descriptive statistics. Normally distributed data are reported as mean ± SD and non-normally distributed as medians and inter-quartile ranges. Chi-square tests were used to compare categorical data. To evaluate for postoperative change in the markers of respiratory disease severity, values recorded on the day prior to anti-reflux surgery were first compared to values recorded two weeks following surgery using paired t-tests or Wilcoxon sign rank tests. In cases of earlier discharge, values

recorded the day prior to discharge were used. For each marker found to be significantly different ($p \leq 0.05$) in the initial analysis, generalized estimating equations were used to create longitudinal models to compare the post-operative value to all recorded pre-operative values.

Results

Fifty consecutively admitted infants with severe BPD were identified, 22 (44%) of whom underwent anti-reflux surgery. Demographic and respiratory characteristics of the infants with and without a history of anti-reflux surgery are compared in Table 1. Gestational age, birth weight, and admission respiratory support were similar between the groups, however pulmonary arterial hypertension and tracheostomy placement were more common in infants with a history of anti-reflux surgery.

Surgical and post-operative feeding results for the infants who underwent anti-reflux surgery are summarized in Table 2. Three infants had abbreviated post-operative follow-up (up to 7, 8, and 13 days), although full nutrition and weight data were obtained. Prior to surgery, 14 infants (64%) underwent gastroesophageal scintigraphy (milk scan) with gastrically administered contrast. Radiographic evidence of GER but not aspiration was found in each case. All infants were maintained on trans-pyloric feeds for a minimum of two weeks prior to surgery except one, who received only parenteral nutrition. Surgery was well tolerated in all cases without significant complications. Each infant had a gastrostomy tube placed at the time of surgery. Average daily weight gain was similar pre- and post-operatively (25g/day vs. 20g/day, $p=0.21$). Respiratory results are summarized in Table 3. Of the evaluated markers of disease severity, decreases in the median daily respiratory rate and FiO_2 were statistically significant. In the longitudinal model including all pre-operative values, significant differences in both the median respiratory rate and FiO_2 remained ($p=0.02$). All infants with a history of anti-reflux surgery survived to discharge. Twelve (55%) underwent tracheostomy. In 7 cases, tracheostomies were placed prior to surgery (median of 33 days pre-operatively; range: 7-143 days). Of the 5 remaining tracheostomies, 1 infant underwent tracheostomy concurrent with fundoplication and 4 underwent tracheostomy following anti-reflux surgery (median of 30 days post-operatively; range: 11-57 days). Exclusion of the three infants who underwent tracheostomy during the study period did not change the significance of the respiratory results.

Discussion

These results indicate that anti-reflux surgery can be safely performed in infants with severe BPD. Infants selected for anti-reflux surgery in this cohort suffered higher rates of pulmonary arterial hypertension and were more likely to require supplemental oxygen and tracheostomy at discharge from the NICU. Although not statistically significant, large airway disease (malacia) was also more common in infants who underwent anti-reflux surgery.

Although respiratory disease severity did not rapidly improve following anti-reflux surgery, a modest but statistically significant reduction in median respiratory rate and FiO_2 was

observed. While the overall clinical importance of these findings is unclear, in a minority of infants the post-operative improvement was unequivocal. In 4 cases, the required FiO_2 decreased post-operatively by 20-32%. The demographic data, procedure type, and pre- and post-operative respiratory support characteristics were similar for those infants with and without post-operative decreases in FiO_2 and respiratory rate (data not shown). The observed differences in postoperative improvement may reflect the degree GER associated chronic aspiration perpetuated lung disease. Since nearly all infants in this series received trans-pyloric feeds (rather than gastric feeds) prior to surgery, the overall effect may also be underestimated.

There are currently no reliable diagnostic or clinical criteria to guide anti-reflux surgery, including for infants with BPD. Since decisions to proceed to surgery remain subjective, we have adopted a systematic approach to aid in identifying infants with likely GER and aspiration. On admission to the NeoCLD Program, infants with severe BPD are transitioned to trans-pyloric feeds for up to several weeks to reduce any potential additive lung injury from GER. Between 45-50 weeks PMA (earlier in infants weaned to minimal or no respiratory support), infants undergo a closely monitored return to gastric feeds. If there is evidence of respiratory decompensation indicated by an increase in required respiratory support, clinical signs of respiratory distress, or evidence of aspiration on chest radiography during that trial, anti-reflux surgery is considered.

When evaluating anti-reflux surgery in infants with severe BPD, non-respiratory outcomes including the ability to safely administer gastric feeds and to transition to non-intensive care settings should be considered. This study indicates early post-operative initiation of gastric feeds is safe and well tolerated and results in similar post-operative weight gain. Data on long-term outcomes following anti-reflux surgery in infants with severe BPD remain scarce. Most reports include infants with a wide range of comorbidities and proportionately few with severe BPD.[9-12] Rates of long-term morbidity and mortality were high in those series, although patient heterogeneity makes any conclusions about this population difficult. All infants in this series who underwent anti-reflux survived to discharge, although the majority required tracheostomy, an additional risk factor for long-term morbidity.[13,14]

This study has several limitations including its retrospective, observational nature and relatively narrow window of post-operative follow-up. While a longer period may have yielded more robust results, in the absence of a control group, causative inferences about the effect of anti-reflux surgery on respiratory disease severity are difficult to make. To limit potential confounding by unmeasured factors, we chose a narrow time-interval between intervention and outcome. The use of longitudinal models inclusive of multiple pre-operative time points aids in evaluating whether the observed changes in clinical markers of disease severity are outside those predicted by a pre-operative trend. While prospective studies to determine the efficacy and long-term outcomes of these procedures are needed, this study suggests anti-reflux surgery may be associated with at least short-term respiratory benefit in some infants with severe BDP.

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Table 1

Characteristics of Infants with Severe BPD

	Anti-reflux Surgery N=22	No Anti-reflux Surgery N=28	p-value
Gestational Age, wks*	26.7 (23-30)	26 (23-33)	0.15
Birth Weight, g*	725 (510-1390)	701 (453-1357)	0.32
Post-Menstrual Age at Admission, wks*§	41 (36-48.1)	38.6 (36-48.6)	0.14
Respiratory Support on admission, n (%)§			0.60
Nasal Cannula	0 (0)	1 (4)	
Non-Invasive Positive Pressure	7 (32)	7 (25)	
Mechanical Ventilation	15 (68)	20 (71)	
Airway Malacia, n (%)¶	11 (50)	9 (32)	0.20
Pulmonary Arterial Hypertension, n (%)Ψ	18 (82)	13 (46)	0.01
Respiratory Support at NICU Discharge			<0.01
Room Air	0 (0)	4 (14)	
Nasal Cannula	10 (45)	10 (36)	
Tracheostomy	12 (55)	6 (21)	
Died/Care Withdrawn	0 (0)	8 (29)	

Abbreviations: BPD: bronchopulmonary dysplasia; NICU: neonatal intensive care unit; wks: weeks; g: grams.

*Values given as median (inter-quartile range).

§Post-menstrual age and respiratory support assessed at 36 weeks post-menstrual age or upon transfer, whichever came first.

¶Airway malacia included laryngeal, tracheal, and/or bronchial malacia was diagnosed by bronchoscopy or low-dose, high-resolution CT with angiography.

ΨPulmonary arterial hypertension was diagnosed by cardiac catheterization or echocardiography (defined as an estimated systolic pulmonary artery pressure > 40mmHg in the presence of a measurable tricuspid regurgitant jet velocity or both right ventricular hypertrophy and intraventricular septal flattening).

Table 2

Surgical and Post-Operative Feeding Results

Post-Conceptual Age at Surgery, wks*	52.5 (47.3-65.6)
Weight at Surgery, kg*	5.1 (3.6-8.5)
Fundoplication Type, n (%)	
Nissen	17 (77)
Toupet	4 (18)
Thal	1 (5)
Laparoscopic Approach, n (%)	18 (82)
Post-Operative Day Gastric Feeds Initiated*	2.5 (1-7)
Post-Operative Day Full Gastric Feeds Reached*	6.5 (2-23)

*Values given as mean (range)

Table 3

Pre- and Post-Operative Respiratory Status

	1 Day Pre-Op	14 Days Post-Op	*P*-value
Mode of Respiratory Support, n (%)			
Non-Invasive Positive Pressure	10 (45)	12 (55)	0.55
Mechanical Ventilation	12 (55)	10 (45)	
Inspired Oxygen Concentration (FiO_2)*	35% (28-40)	30% (26-40)	0.03
Mean Airway Pressures × FiO_2*§	4.5 (3.6-6)	4.5 (3.5-7)	0.96
Median Respiratory Rate¶	55 ± 10	51 ± 12	0.05
Maximum Respiratory Rate¶	81 ± 16	74 ± 16	0.08

Abbreviations: FiO_2: Fraction of Inspired Oxygen.

*Values given as median (IQR).

§Only determined for patients mechanically ventilated pre- and post-operatively (n=10).

¶Values given as mean ± SD.