Published in final edited form as:
J Perinatol. 2010 June ; 30(6): 408–413. doi:10.1038/jp.2009.124.

Long-term morbidities associated with vocal cord paralysis after surgical closure of a patent ductus arteriosus in extremely low birth weight infants

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Abstract

Objectives: Determine associations between left vocal cord paralysis (LVCP) and poor respiratory, feeding, and/or developmental outcomes in extremely low birth weight (ELBW) infants following surgical closure of a patent ductus arteriosus (PDA).

Study design: ELBW infants who underwent PDA ligation between January 2004 and December 2006 were identified. We compared infants with and without LVCP following ligation to determine relationships between LVCP and respiratory morbidities, feeding and growth difficulties, and neurodevelopmental impairment at 18-22 month follow-up. Student's *t* test, Fisher exact test, and multivariable regression analyses were used to determine associations.

Results: 60 ELBW infants with a mean gestational age of 25 weeks and mean birth weight of 725 g had a PDA surgically closed. Twenty-two of 55 survivors (40%) were diagnosed with LVCP post-operatively. Infants with LVCP were significantly more likely to develop bronchopulmonary dysplasia (82% vs. 39%, $p = 0.002$), reactive airway disease (86% vs. 33%, $p<0.0001$), or need for gastrostomy tube (63% vs. 6%, $p<0.0001$).

Conclusions: LVCP as a complication of surgical ductal ligation in ELBW infants is associated with persistent respiratory and feeding problems. Direct laryngoscopy should be considered for all infants who experience persistent respiratory and/or feeding difficulties following PDA ligation.

Keywords

infant, premature; ductus arteriosus, patent; growth & development; infant nutrition disorders; bronchopulmonary dysplasia; asthma

Introduction

Patent ductus arteriosus (PDA) occurs in up to 80% of extremely low birth weight (ELBW, <1000 g birth weight) infants[1]. Persistent left-to-right shunting across the PDA alters

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pulmonary mechanics and may contribute to pulmonary edema, prolonged mechanical ventilation, and the development of bronchopulmonary dysplasia (BPD)[2, 3, 4]. In addition, ongoing ductal patency has been associated with intraventricular hemorrhage, necrotizing enterocolitis, and death[5, 6, 7, 8, 9].

Surgical closure of a PDA is commonly believed to be a procedure with a favorable risk-benefit ratio in ELBW infants, and is considered standard treatment for symptomatic neonates unresponsive to medical therapy[10, 11, 12, 13]. During the procedure, the perineurium of the left recurrent laryngeal nerve may be disrupted, or the nerve may be contused or injured by the clip or ligature. Iatrogenic left-sided vocal cord paralysis (LVCP) resulting from trauma to the nerve is a well described complication of PDA ligation[14, 15]. Duration of vocal cord dysfunction is variable and may be transient or persistent[16, 17]. Preterm infants, especially those with a gestational age of <28 weeks, are less likely to recover vocal cord function as compared to term infants[16].

Among all age groups, LVCP following surgical closure of a PDA has an overall incidence ranging between 1.7% and 11.5%[10, 14, 18, 19, 20]. However, recent single-center studies have found the incidence to be as high as 40% to 67% among ELBW infants[21, 22]. A previous report suggests that infants who weigh less and are younger at the time of operation are more likely to develop LVCP[14]. Sequelae associated with LVCP following surgical PDA ligation include aspiration secondary to impaired airway protection, need for prolonged tube feeding, and need for prolonged mechanical ventilation[19, 20].

To date, there has not been an investigation into the associations between surgical closure of a PDA complicated by LVCP and the development of long-term respiratory, feeding, or neurodevelopmental problems in extremely preterm infants. We hypothesize that LVCP as a complication of surgical ductal ligation in ELBW infants significantly increases the risk for development of chronic respiratory problems including BPD and reactive airway disease (RAD). We also hypothesize that LVCP in ELBW infants contributes to both long-term feeding complications and neurodevelopmental impairment (NDI).

Methods

In order to address these hypotheses, we identified all ELBW infants hospitalized in the neonatal intensive care unit at Duke University Medical Center (DUMC) between January 2004 and December 2006, who underwent surgical closure of their PDA because of contraindications to pharmacologic treatment with indomethacin or ibuprofen, or because of persistent symptomatic ductal patency following medical treatment. Approval from the DUMC institutional review board was obtained. Patient demographic data and clinical course during initial hospitalization and after discharge were recorded. Ligation was performed by one of two staff surgeons using principles of surgical therapy including: limited, muscle sparing posterior thoracotomy incision, minimal periductal dissection, and surgical clip ligation of the ductus. Post-operatively, infants suspected to have LVCP underwent flexible fiberoptic laryngoscopy performed by an attending pediatric otorhinolaryngologist to evaluate vocal cord and laryngeal structure and function. Infants underwent laryngoscopy if they were unable to be weaned from respiratory support, were noted to have stridor or a hoarse or absent cry, or demonstrated signs of cardiorespiratory distress with initiation of oral feedings. Infants with LVCP were included in this study only if a unilateral, left-sided, immobile vocal cord was observed during laryngoscopy.

We compared ELBW infants with and without symptomatic LVCP following PDA ligation to determine associations with respiratory morbidities, feeding and growth difficulties, and NDI. For respiratory morbidities, BPD was defined as dependency on supplemental oxygen at 36

weeks postmenstrual age. Development of RAD was determined by prescribed bronchodilator aerosol treatments at any time before the 18-22 month developmental follow-up examination.

Outcome variables for feeding and growth difficulties included aspiration, need for gastrostomy tube at discharge, and need for Nissen fundoplication. Aspiration was defined as penetration of barium across the vocal cords during videofluoroscopic swallow study, which was performed only in infants who demonstrated difficulties with oral feedings. In our practice, placement of a gastrostomy tube is indicated for infants with persistent aspiration during oral feeding, and/or continual inability to feed orally despite aggressive feeding therapy. Nissen fundoplication is recommended for infants with severe gastroesophageal reflux and a history of reflux-associated cardiorespiratory events unresponsive to maximal medical therapy.

For growth and neurodevelopmental outcomes, poor growth was defined as weight, length, and/or head circumference below the 10^{th} percentile for corrected age on the National Center for Health Statistics 2000 CDC growth chart (birth to 36 months)[23]. NDI was defined as mental development index (MDI) or psychomotor development index (PDI) <70 using the Bayley Scales of Infant Development, version II24 at 18-22 months corrected gestational age.

Student's *t* test or Fisher's exact test were used where appropriate. Logistic regression analysis was used to examine the effects of LVCP on the incidence of BPD, RAD, and NDI adjusting for gestational age and presence of severe (Grade 3 or 4) intraventricular hemorrhage (IVH). A two-tailed p value <0.05 was considered to be statistically significant. Statistical testing was performed using STATA 10 (College Station, TX).

Results

We identified 60 ELBW infants with a mean gestational age of 25 weeks [5^{th}, 95^{th}%tile; 23, 27] and mean birth weight of 725 g [510, 910] who had a PDA surgically closed. The mean age at ligation was 20 days [5, 41], and mean weight at time of surgery was 768 g [523, 1111]. Ninety-two percent (55/60) of infants survived to hospital discharge or were transferred back to their home hospital. Seventy-five percent (41/55) were evaluated in the Duke Special Infant Care Clinic at 18-22 months corrected age for the purpose of measuring growth and neurodevelopmental outcomes. Of the symptomatic infants who underwent flexible laryngoscopy post-operatively, 88% (22/25) were found to have LVCP. The remaining 30 infants in the cohort did not exhibit symptoms of LVCP, and were therefore not examined by laryngoscopy. Overall, 40% of survivors (22/55) were diagnosed with LVCP by laryngoscopy following surgical closure of their PDA.

There were no significant differences between infants with and without symptomatic LVCP in terms of baseline demographic characteristics or neonatal morbidities associated with extreme prematurity. Infants with LVCP trended towards undergoing ligation at an earlier chronologic age, being smaller at the time of ligation, and exhibiting more severe degrees of IVH, but these differences were not statistically significant. There were also no significant differences between the groups regarding indomethacin prophylaxis or treatment courses of ibuprofen or indomethacin (Table 1).

Respiratory Outcomes

Infants with LVCP following PDA ligation required significantly more days of mechanical ventilation compared to infants without LVCP (44 versus 29 days, p=0.008) and were more likely to develop BPD and RAD as defined in this study. Eighty-two percent (18/22) of infants with LVCP developed BPD compared with 39% (13/33) of those without LVCP (p=0.002). RAD was diagnosed in 86% (19/22) of infants with LVCP and 33% (11/33) of infants without

LVCP (p <0.0001) (Table 2). None of the three infants who had early clinical signs of LVCP but did not have LVCP on laryngoscopy developed BPD or RAD.

Feeding and Growth Outcomes

Infants with LVCP were more likely to undergo placement of a gastrostomy feeding tube prior to discharge (63% versus 6%, p <0.0001) because of abnormal swallow or aspiration with feedings. In addition, Nissen fundoplication was performed more often in infants with LVCP (41% versus 3%, p=0.001). At 18-22 months corrected age, there was a trend toward poorer weight gain in infants with LVCP but this difference was not statistically significant. The three infants who had clinical signs of LVCP but were found not to have LVCP on laryngoscopy did not undergo placement of a gastrostomy tube or Nissen fundoplication.

Neurodevelopmental outcomes

Among our cohort of infants, there were no statistically significant differences between the groups in terms of cognitive and/or motor impairment as defined in this study.

Multivariable analyses

Using logistic regression to control for gestational age and severe IVH, we observed that LVCP among surgically ligated ELBW infants continued to be strongly and independently associated with BPD and RAD, as well as with surgical intervention for feeding difficulties, including Nissen fundoplication and placement of a gastrostomy tube (Table 3).

Discussion

This single-center observational study demonstrating associations between iatrogenic LVCP and respiratory and feeding morbidities in a relatively large cohort of ELBW infants is a follow-up of a previously published case series describing three sets of siblings with post-ligation LVCP at our institution. The current study provides a larger, more thorough, systematic analysis of our entire cohort of ELBW infants who underwent ductal ligation, and compares long-term respiratory, feeding, and neurodevelopmental outcomes among infants who did and did not develop post-operative laryngoscopy-proven LVCP. Our study is the first to investigate these long-term outcomes of demographically similar ELBW infants with and without LVCP following PDA ligation. Our study population had a lower gestational age (mean 25 weeks) and birth weight (mean 725 g) than in previous single-center reports looking at associations between LVCP following surgical ductal ligation and the development of subsequent short-term respiratory or feeding compromise[20, 21].

The incidence of LVCP following PDA ligation was 40% in our cohort of 55 surviving ELBW infants. A previous single-site study in 1996 reported the incidence of LVCP following PDA ligation to be 22.7% among 22 ELBW infants who underwent laryngoscopy based on clinical suspicion for vocal cord paralysis, compared with 2.2% in 46 infants weighing more than 1000 g at birth[14]. The higher incidence in our patient population could be due to inclusion of a smaller and sicker patient population, reflective of the recent increase in survival rates for ELBW infants[25]. Pereira *et al* performed laryngoscopy on 61 of 100 patients who underwent surgical ductal ligation to investigate the clinical course of infants with LVCP after PDA ligation[20]. Seven of the 61 patients (11.5%) were found to have documented LVCP, but a significant number of patients were excluded because they remained intubated at the conclusion of the study or required a tracheostomy for failed extubation. Perhaps the more severe respiratory outcomes seen in the excluded patients were a result of LVCP.

Two studies, one a single-center retrospective cohort study, and the other a post-hoc analysis of the Trial of Indomethacin Prophylaxis in Preterms (TIPP) trial study cohort, have shown

that PDA ligation is associated with increased risk of BPD[26, 27]. However, these studies do not address whether those infants who developed BPD following PDA ligation were more likely to have LVCP. Our data suggest that surgical closure of a PDA resulting in LVCP may increase the risk for subsequent development of both BPD and RAD.

The exact relationship between LVCP and both acute and chronic respiratory problems remains unclear, but ongoing lung injury following extubation could be secondary to chronic microaspiration combined with pulmonary hypertension[21]. Because of impaired airway protection, LVCP increases the likelihood of aspiration during feedings. Farhath *et al* showed that chronic aspiration of gastric contents may contribute to worsening lung disease in preterm infants via a secondary inflammatory response resulting from chemical injury to the airways[28]. This ultimately alters pulmonary mechanics, interferes with surfactant production and function, and leads to lung injury[29]. Subsequent remodeling of the pulmonary architecture could then predispose to lung smooth muscle hyperreactivity and episodic bronchospastic episodes, manifested as RAD.

Similarly, reduction in functional residual capacity (FRC) has been shown to correlate with degree of BPD[30]. In order to create positive end expiratory pressure (PEEP), glottal closure is required. Extubated infants with VCP and secondary glottic incompetence may experience decreased pulmonary function, leading to prolonged mechanical support to maintain FRC. Prolonged duration of mechanical ventilation has been shown to be independently associated with an increased risk of CLD31. In addition, infants with LVCP may be at increased risk for aspiration of oral secretions around the endotracheal tube, which could induce lung injury as described above and contribute to prolonged duration of mechanical ventilation.

Vocal cord dysfunction following cardiothoracic surgery in older children is associated with significant feeding problems[32]. Sachdeva *et al* found a direct correlation between LVCP and abnormal swallowing by videofluoroscopic exam[32]. Similarly, Clement *et al* showed 7 out of 11 infants with LVCP to have frank aspiration during videofluoroscopic swallow study, all of whom were discharged home with need for tube feeding[21]. We found that in comparison to infants who did not have symptoms of LVCP following surgery, those with LVCP were more likely to have ongoing problems with feeding and growth. Infants with LVCP were significantly more likely to receive total or supplemental tube feedings at hospital discharge, and were more likely to have a Nissen fundoplication performed. Findings from our study show a trend toward poorer growth at 18-22 months corrected age, with 63% of infants with LVCP at or below the 10th percentile for weight, compared with 36% of infants without LVCP (p=0.12).

The TIPP study results suggest that ductal ligation is associated with an increased risk for NDI[26]. In our study, infants with LVCP exhibited more severe degrees of IVH (p=0.05) and trended toward an increased risk of MDI and/or PDI scores <70 (56% vs. 36%, p=0.34), but there was not a statistically significant difference between the groups in NDI at 18-22 months corrected age. It should be noted that MDI on the Bayley Scales of Infant Development, version II incorporates a child's combined verbal and non-verbal skills, which might prevent the detection of speech and language abnormalities in children with LVCP. Future studies are needed using the Bayley Scales of Infant Development, version III, which has a language subscale, in order to more closely investigate the relationship between LVCP and language impairment.

Our study is limited by its retrospective design. The incidence of LVCP in our cohort of infants may be underestimated because most asymptomatic patients did not undergo laryngoscopy. The “no LVCP” group, which included some infants whose vocal cords were not visualized by laryngoscopy, may have included infants with asymptomatic LVCP. Because of this, our

findings may represent a conservative approximation of the true incidence and long-term morbidities of LVCP following PDA ligation in ELBW infants. Also, some infants with LVCP, but not all, underwent videofluoroscopic swallow study in order to diagnose aspiration of thick and/or thin liquids. Consequently, it is likely that we missed some patients with clinically silent aspiration or microaspiration. We acknowledge that defining primary outcomes by use of therapies (oxygen at 36 weeks postmenstrual age for BPD, prescription of bronchodilators for RAD, gastrostomy tube placement for poor oral feeding or aspiration) is imperfect and subject to clinician bias[33].

Conclusion

As medical technology continues to evolve, and our ability to resuscitate and provide intensive care for extremely premature infants increases, ever smaller and sicker babies are surviving to hospital discharge[25, 34]. Because of this, there exists a growing population of premature infants with the potential need for surgical procedures, including PDA ligation. The implications of LVCP following PDA ligation in ELBW infants may be more serious than previously thought and may directly contribute to long-term respiratory and feeding morbidities. We believe that the potential impact of LVCP on outcomes of ELBW infants is underreported in the literature. Our results highlight the need for a larger cohort study using direct laryngoscopy by trained examiners for all infants following ductal ligation to define the true incidence and consequences of post-operative LVCP. In the meantime, our findings warrant consideration of direct laryngoscopy for infants who experience persistent respiratory or feeding difficulties following PDA ligation. In addition, healthcare providers must take into account the likely added risk of long-term feeding and respiratory complications, including BPD and RAD, when deciding whether to proceed with surgical ductal ligation in an ELBW infant. Further studies are needed to determine whether these patients would benefit from a longer trial of medical management before undergoing surgical intervention.

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Table 1

Demographic characteristics of infants with and without LVCP[1]

Variable		Survivors (*n* = 55)	LVCP[1] (*n* = 22)	No LVCP[1] (*n* = 33)	*P*
Birth weight (g)[2]		725 ± 127	722 ± 122	728 ±132	0.86
Gestational age (weeks) [2]		24.7 ± 1.2	24.5 ± 1.1	24.8 ± 1.3	0.42
Female sex – *n. (%)*		29 (53)	10 (45)	19 (57)	0.42
Race – *n. (%)* Black			9 (41)	19 (58)	0.43
White			11 (50)	11 (33)	
Other			2 (9)	3 (9)	
Inborn - *n. (%)*		41 (75)	17 (77)	24 (73)	0.76
Apgar score at 5 min		6	6	6	0.70
Day of life at ligation[2]		20 ± 12.7	17 ± 8.7	22 ± 14.5	0.13
Weight at ligation (g)[2]		768 ± 194	722 ± 140	798 ± 219	0.15
Received indomethacin prophylaxis – *n. (%)*			8 (36)	12 (36)	0.99
Treatment courses ibuprofen or indomethacin – *n. (%)*	None		2 (9)	5 (15)	0.32
	One		6 (27)	14 (42)	
	Two		14 (63)	14 (42)	
Received postnatal steroids – *n. (%)*			2 (9)	3 (9)	0.99
IVH[3] (Grade 3 or 4) – *n. (%)*		12 (22)	8 (36)	4 (12)	0.05
Cystic PVL[4]– *n. (%)*		5 (9)	4 (18)	1 (3)	0.15

[1] Left vocal cord paralysis

[2] Values are mean ± SD

[3] Intraventricular hemorrhage

[4] Periventricular leukomalacia

Table 2

Medical morbidities and developmental outcomes of infants with and without LVCP[1]

	LVCP[1] *n* (%)	No LVCP[1] *n* (%)	*P*
Respiratory Outcomes			
Reactive airway disease	19 (86)	11 (33)	<0.0001
Bronchopulmonary dysplasia	18 (82)	13 (39)	0.002
Total days of mechanical ventilation[2]	44 ± 24	29 ± 16	0.008
Aspiration	17 (77)	1 (33)	0.18
Feeding and Growth Outcomes			
Gastrostomy tube insertion	14 (64)	2 (6)	<0.0001
Nissen fundoplication	9 (41)	1 (3)	0.001
Need for GER[3] medications at discharge	12 (55)	13 (42)	0.41
Weight at 18-22 months CGA[4] <10th %ile	12 (63)	8 (36)	0.12
Length at 18-22 months CGA[4] <10th %ile	9 (47)	7 (32)	0.35
HC[5] at 18-22 months CGA[4] <10th %ile	12 (63)	15 (68)	0.75
Neurodevelopmental Outcomes			
MDI[6]<70	5 (33)	7 (36)	0.99
PDI[7]<70	8 (53)	6 (32)	0.26
Neurodevelopmental impairment[8]	10 (56)	8 (36)	0.34

[1] Left vocal cord paralysis

[2] Values are mean ± SD

[3] Gastroesophageal reflux

[4] Corrected gestational age

[5] Head circumference

[6] Mental Development Index

[7] Psychomotor Development Index

[8] Defined as MDI or PDI <70 on Bayley Scales of Infant Development

Table 3

LVCP[1] as predictor of morbidity, adjusted for gestational age and severe IVH[2]

	Odds Ratio [95% CI[3]]	*P*
Respiratory Outcomes		
Reactive airway disease	14.9 [3.2, 70.0]	0.001
Bronchopulmonary dysplasia	5.5 [1.4, 21.4]	0.01
Aspiration	6.4 [0.3, 127]	0.22
Feeding and Growth Outcomes		
Gastrostomy tube	47.8 [4.5, 502]	0.001
Nissen fundoplication	18.4 [1.7, 22.3]	0.02
Neurodevelopmental Outcomes		
Neurodevelopmental impairment	0.7 [0.1, 3.5]	0.62

[1] Left vocal cord paralysis

[2] Intraventricular hemorrhage (Grade 3 or 4)

[3] Confidence interval