Unilateral Vocal Cord Paralysis Following Patent Ductus Arteriosus Ligation in Extremely Low-Birth-Weight Infants

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**Objective:** To determine if unilateral vocal cord paralysis (UVCP) following patent ductus arteriosus (PDA) ligation is associated with respiratory and swallowing morbidities in extremely low-birth-weight (ELBW) infants.

**Design:** Case-control study.

**Setting:** Tertiary care neonatal intensive care units and pediatric hospital.

**Participants:** Twenty-three infants undergoing PDA ligation (subdivided into the main study group of 12 infants with UVCP and 11 without paralysis) and 12 weight- and gestational age–matched ELBW controls.

**Main Outcome Measures:** Incidence of UVCP, time requiring supplemental oxygen and ventilatory support, length of hospital stay, incidence and duration of tube feeding following discharge, and incidence of chronic lung disease.

**Results:** The overall incidence of UVCP was 52% (12/23), increasing to 67% (12/18) in ELBW infants. Infants without UVCP following PDA ligation were heavier ($P = .006$), with a more advanced gestational age ($P = .03$). Patients with UVCP required longer tube feeding (relative risk, 8.25; 95% confidence interval, 1.93-46.98; $P = .003$), supplemental oxygen ($P = .004$), and ventilatory support ($P = .001$) and had a longer hospital stay ($P < .001$). In comparison to matched controls, infants with UVCP required longer tube feeding (relative risk, 9.00; 95% confidence interval, 2.08-51.30; $P = .003$), supplemental oxygen ($P = .03$), and ventilatory support ($P = .002$) and had a longer hospital stay ($P < .001$).

**Conclusions:** There was a high incidence of occurrence of UVCP (67%) associated with PDA ligation in ELBW infants. Unilateral vocal cord paralysis following PDA ligation does seem to be associated with increased requirements for tube feeding, respiratory support, and hospital stay in these ELBW infants.


**PATENT DUCTUS ARTERIOSUS (PDA) ligation has been reported to be a safe and well-tolerated procedure in premature and low-birth-weight infants.**

**Laryngeal Paralysis:**

Laryngeal paralysis (VP) can have a significant effect on voice and swallow, with between 39% and 56% of these patients complaining of dysphagia. These findings are supported by videofluoroscopic swallow study (VFSS) and functional endoscopic evaluation of swallow study evidence, in which up to 76% of patients have demonstrable abnormalities. Paradoxically, it is often inferred that this complication has minimal consequences in children and infants, ascribing it to an eventual return of function to the paralyzed cord or compensation from the opposite half of the larynx to close the glottic gap.

There has, however, been limited research into the swallowing and respiratory sequelae of this complication in small and preterm infants. In infants with UVCP following PDA ligation, Fan et al. in 7
Ethical approval was obtained from the University of Alberta, Edmonton, Health Ethics Board. All infants admitted to the neonatal intensive care units (NICUs) at Stollery Children’s Hospital and Royal Alexandra Hospital between October 21, 2003, and June 27, 2003, were included. Three subgroups from this period were to be compared: (1) those infants who underwent PDA ligation and whose procedure was complicated by postoperative vocal cord paralysis (PDA ligation with UVCP group [PDA study group]), (2) those infants who underwent PDA ligation and who did not have postoperative vocal cord paralysis (PDA ligation with no UVCP group [PDA control group]), and (3) a group of infants who were matched for gestational age and weight to the vocal cord paralysis group (no PDA ligation and no UVCP group [matched control group]). During the first phase of the study, between October 21, 2003, and May 21, 2004, standard treatment involved prophylactic treatment with 3 doses of indomethacin sodium for all premature infants younger than 27 weeks’ gestational age and/or those weighing less than 1000 g. Echocardiography was routinely performed within 24 hours of the final dose to assess the patency of the ductus arteriosus. If the ductus was patent, the infant proceeded to surgical ligation. If the infant later developed a clinically significant PDA, which was confirmed by echocardiography, the neonatologist caring for that infant would consider either a second course of indomethacin or surgical ligation. Concern with the apparent incidence of UVCP led to a review of the literature and an examination of the outcomes of the infants who were treated for PDA, and the clinical guideline was changed. During the second phase of the study, from May 22, 2004, until June 27, 2005, indomethacin continued to be given prophylactically to infants younger than 27 weeks’ gestational age and/or those weighing less than 1000 g; however, echocardiography was not performed routinely. Echocardiography was only performed in infants with suspected clinically significant PDAs or for other suspected cardiac lesions. If a clinically and echocardiographically significant PDA was confirmed and the infant could not be managed medically, surgical ligation was then undertaken. All matched controls were taken from the second period of the study. They were matched for weight and gestational age with infants who underwent a PDA ligation and acquired UVCP. Other inclusion criteria for this control group included survival beyond NICU discharge and no known laryngeal paralysis. Throughout the entire study period, a standardized NICU feeding protocol with respect to introducing infants to oral feeding was used. All infants who underwent PDA ligation were routinely assessed by a staff otolaryngologist (H.E.-H.) postoperatively after extubation and when ready to start oral feeding. Endoscopic laryngeal assessment was not routinely performed in the matched control group.

The aims of the study were to determine and assess the following: (1) the incidence of UVCP following isolated PDA ligation in VLBW and ELBW infants, (2) the incidence of recovery of UVCP in these infants, (3) if patient variables influenced the incidence of UVCP, and (4) if UVCP had significant effect on clinical outcomes.

Outcomes were divided into respiratory, swallowing, and others. Specific respiratory variables included the time requiring positive pressure ventilation and the presence of chronic lung disease. Chronic lung disease was defined as the requirement of supplemental oxygen at 36 weeks’ gestational age. Swallowing variables were the incidence of tube feeding at discharge, its duration after discharge, and the incidence of subsequent swallowing problems requiring intervention. Other outcomes measured included the length of hospital stay and the incidence of readmission within 1 year of discharge and mortality.

Statistics for categorical data (available at http://statpages.org/ctab2x2.html) were calculated using the Fisher exact test. Paired data were analyzed using the Wilcoxon matched pairs test, and unpaired data were analyzed using the Mann-Whitney test (available at http://www.loni.ohsu.edu/Service/Statistics.html).

Twenty-three infants underwent PDA ligation during the study period. There were no perioperative deaths, and all infants who underwent this procedure are alive. Of the 23 infants, 20 underwent an endoscopic examination of their larynx by a staff otolaryngologist (H.E.-H.). The overall incidence of vocal cord paralysis was 52% (12/23). Subgroup analysis of the ELBW group of 18 infants showed that all 12 with UVCP were from this group, demonstrating a higher incidence of 67% (12/18) in this group.

The change in the NICU clinical guideline significantly altered the incidence of PDA ligation throughout the study. During the first phase of the study, between October 21, 2003, and May 21, 2004, 39 ELBW infants were born and 17 of these infants proceeded to undergo PDA ligation. During the second phase of the study, between May 22, 2004, and June 27, 2005, 73 ELBW infants were born and only 1 infant underwent PDA ligation. Throughout the total study period, 5 VLBW infants also underwent PDA ligation. The Figure shows the flow of patients through the study.

When comparing those infants who had acquired UVCP after PDA ligation (PDA study group) with those who did not (PDA control group), there were no statistically significant differences between the 2 groups for sex, age at ligation, and incidence of other airway abnormalities. Infants without UVCP were, however, heavier, with a more advanced gestational age (Table 1).

Of the 12 infants with UVCP, 11 underwent a VFSS while an inpatient. Seven of these infants showed signs of frank aspiration. These 7 infants were discharged still requiring tube feeding. The mean time of tube feeding placement from discharge was 69.6 days (range, 3-202 days) for the 5 patients who did not undergo gastrostomy tube insertion. Another 2 infants later required insertion of nasogastric feeding tubes for recurrent aspiration symptoms, both within 3 months of discharge. The mean time
of tube feeding placement for these 2 patients was 214.5 days (range, 183-246 days). Three infants underwent gastrostomy tube insertion: 1 for severe gastroesophageal reflux disease and 1 for chronic aspiration; 1 sustained a major head injury after discharge, which necessitated long-term tube feeding. The mean age at gastrostomy tube insertion was 16 months for the 2 who had continuous swallowing difficulties. The overall relative risk of requiring tube feeding after discharge in the PDA study group was 16 months for the 2 who had continuous swallowing difficulties.

In the PDA control group, 1 patient was fed nasogastrically for up to 170 days but has since been lost to follow-up. Comparisons of results for inpatient stay, hospital readmission, and requirement of tube feeding and for respiratory outcomes are summarized in Table 2 and Table 3, respectively. The 2 groups were comparable for incidence of complications and comorbidities. Seven infants in the PDA study group had complications and comorbidities, including 3 with intraventricular hemorrhages, 1 with meningitis, 1 with stroke syndrome, 1 with cerebral palsy, 1 with chronic lung disease and 1 for chronic aspiration; 1 sustained a major head injury after discharge, which necessitated long-term tube feeding. The mean age at gastrostomy tube insertion was 16 months for the 2 who had continuous swallowing difficulties. The overall relative risk of requiring tube feeding after discharge in the PDA study group was 16 months for the 2 who had continuous swallowing difficulties.

Abbreviation: PDA, patent ductus arteriosus.

\( a \) Data are given as mean (range) unless otherwise indicated. The PDA study group included infants who had a PDA ligation complicated by vocal cord paralysis, and the PDA control group included infants without vocal cord paralysis.

\( b \) This difference was significant.

\( c \) Data are given as number/total (percentage).

Abbreviation: PDA, patent ductus arteriosus.

\( a \) Data are given as number (percentage) of patients in each group unless otherwise indicated. The PDA study group included infants who had a PDA ligation complicated by vocal cord paralysis, and the PDA control group included infants without vocal cord paralysis.

\( b \) This difference was significant.

\( c \) Data are given as mean (range).
in the PDA control group had complications and comorbidities, including 5 with intraventricular hemorrhages, 3 of whom required ventriculoperitoneal shunts because of posthemorrhagic hydrocephalus, and 3 with severe necrotizing enterocolitis requiring bowel resection (some infants had >1 complication or comorbidity).

None of the matched control group was known to have vocal cord paralysis. All are alive. Echocardiography was performed on 9 of these infants. This identified 2 infants with PDAs; 7 had no signs of a PDA. When the PDA study group was compared with the matched control group, there were no statistical differences between the 2 groups for sex, birth weight, gestational age, and associated airway abnormalities (Table 4). In the PDA study group, 1 infant had laryngomalacia and 1 had mild subglottic stenosis. In the control group, 2 infants underwent assessment of their airway. One infant had laryngomalacia and 1 had tracheomalacia; neither had vocal cord paralysis. None of the infants with these airway anomalies required any surgical interventions. Four infants in the control group had VFSS assessment for swallowing difficulties. One infant had laryngeal inlet penetration, 2 had dysfunctional swallows, and 1 had a normal swallow. The first 3 infants were managed conservatively and progressed well; the last infant required gastrostomy tube placement because of severe gastroesophageal reflux disease. The relative risk of requiring tube feeding at discharge in the PDA study group was 7.00 (95% confidence interval, 2.08-51.30). Comparing the risk of requiring tube feeding following discharge was 1.48 (95% confidence interval, 1.48-41.85). The overall relative risk of requiring tube feeding following discharge was 9.00 (95% confidence interval, 2.08-51.30).

Comparisons of results for inpatient stay, hospital readmission, and requirement of tube feeding and for respiratory outcomes are summarized in Table 5 and Table 6, respectively. The 2 groups were comparable for incidence of complications and comorbidities. Five infants had intraventricular hemorrhages, with 1 developing periventricular leukomalacia. Two infants had severe gastroesophageal reflux disease.

Comparison of the matched control group with the PDA ligation group with no vocal cord paralysis (PDA control group) revealed only statistically significant differences for birth weight (P = .006), as expected, and duration of continuous positive airway pressure use (P = .04).

### Table 4. Comparison of Demographic Data for the PDA Study Group vs a Matched Control Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>PDA Study Group</th>
<th>Matched Control Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male to female ratio</td>
<td>6.6</td>
<td>7.5</td>
<td>&gt; .99</td>
</tr>
<tr>
<td>Birth weight, g</td>
<td>725 (580-887)</td>
<td>728 (583-890)</td>
<td>.74</td>
</tr>
<tr>
<td>Gestational age, wk</td>
<td>24.8 (24-26)</td>
<td>25.3 (24-26)</td>
<td>.08</td>
</tr>
<tr>
<td>Other airway abnormalities</td>
<td>2/12 (17)</td>
<td>2/12 (17)</td>
<td>&gt; .99</td>
</tr>
</tbody>
</table>

Abbreviation: See Table 2.

- **a** Data are given as mean (range) unless otherwise indicated. The PDA study group included infants who had a PDA ligation complicated by vocal cord paralysis, and the control group was matched for weight and gestational age and did not have vocal cord paralysis.
- **b** Data are given as number/total (percentage).

### Table 5. Comparison of Feeding and Other Outcome Data for the PDA Study Group vs a Matched Control Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>PDA Study Group</th>
<th>Matched Control Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tube feeding at discharge</td>
<td>7 (58)</td>
<td>1 (8)</td>
<td>.03&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tube feeding at any time after discharge</td>
<td>9 (75)</td>
<td>1 (8)</td>
<td>.003&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>G-tube insertion</td>
<td>3 (25)</td>
<td>1 (8)</td>
<td>.34</td>
</tr>
<tr>
<td>Hospital stay, d&lt;sup&gt;c&lt;/sup&gt;</td>
<td>148.2 (124-218)</td>
<td>109.0 (89-143)</td>
<td>&lt; .01&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Readmission within 12 mo</td>
<td>6 (50)</td>
<td>2 (17)</td>
<td>.19</td>
</tr>
</tbody>
</table>

Abbreviations: G-tube, gastrostomy tube; PDA, patent ductus arteriosus.

- **a** Data are given as mean (range) days unless otherwise indicated. The PDA study group included infants who had a PDA ligation complicated by vocal cord paralysis, and the control group was matched for weight and gestational age and did not have vocal cord paralysis.
- **b** This difference was significant.
- **c** Data are given as number (percentage).

### Table 6. Comparison of Respiratory Outcomes for the PDA Study Group vs a Matched Control Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>PDA Study Group</th>
<th>Matched Control Group</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilatory support</td>
<td>91.8 (77-118)</td>
<td>71.5 (60-93)</td>
<td>.002&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>IPPV</td>
<td>50.3 (29-63)</td>
<td>31.6 (4-53)</td>
<td>.001&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>CPAP</td>
<td>41.5 (20-66)</td>
<td>39.6 (20-59)</td>
<td>.85</td>
</tr>
<tr>
<td>Supplemental oxygen</td>
<td>113.7 (83-140)</td>
<td>92.5 (66-143)</td>
<td>.03&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>CLD&lt;sup&gt;c&lt;/sup&gt;</td>
<td>12/12 (100)</td>
<td>10/12 (83)</td>
<td>.48</td>
</tr>
</tbody>
</table>

Abbreviations: See Table 3.

- **a** Data are given as mean (range) days unless otherwise indicated. The PDA study group included infants who had a PDA ligation complicated by vocal cord paralysis, and the control group was matched for weight and gestational age and did not have vocal cord paralysis.
- **b** This difference was significant.
- **c** Data are given as number/total (percentage).

There were no statistically significant differences for all other demographic characteristics and outcomes.

In the PDA study group, none of the 12 infants had any recovery of vocal cord paralysis (mean follow-up, 8.4 months; range, 3-12 months). Eight of these infants were observed for more than 6 months. Eleven infants had definite laryngeal compensation, with 1 continuing to aspirate. This child had had a stroke syndrome, and it is uncertain if the chronic aspiration was because of this or his UVCP.

**COMMENT**

The incidence of UVCP (67%) in ELBW infants in this study is much higher than previously reported for VLBW and smaller preterm infants. Only one previous study has examined the incidence of this problem in ELBW infants. These researchers reported an incidence of UVCP of 22.9% in 22 ELBW infants. They commented that by examining only infants with airway symptoms, the true incidence had most likely been underestimated. Only one study<sup>14</sup> of the incidence of UVCP in preterm infants has...
been performed prospectively. These researchers identified an incidence of UVCP of 11.5%. However, it is uncertain from their data how many of these were ELBW infants or what the incidence was in this subgroup. Our higher figure of paralysis may be related to our unit guideline of routinely examining infant larynges following PDA ligation during this time; to our NICU guideline of early PDA ligation during the initial phase of the study and, thereby, operating on smaller infants; or to the high rate of survival in our study group. The progressive salvage rates of smaller infants may well be another factor producing the increasing incidence of UVCP following this procedure.

The paralyzed larynges never recovered function during the follow-up, in agreement with the literature on infants undergoing PDA ligation who are younger than 1 year. Only 4 studies\textsuperscript{12-15} have examined the incidence of recovery of UVCP following PDA surgery in infants (aged \textless 1 year). Only the findings of Hines et al\textsuperscript{11} differed significantly, with a recurrence of function rate of 80% by the age of 18 months. The results of all other studies\textsuperscript{12,14,15} concur with our results of a 0% return to function with a comparable follow-up to our own. Because compensation does seem to occur in all infants over time, and reports of recovery of UVCP have been found up to 11 years after the initial injury,\textsuperscript{25} it may be argued that this is an unimportant outcome. The long-term consequences of this complication in this age group as yet, however, remain unknown.

The requirement of prolonged ventilation has also been noted in association with UVCP.\textsuperscript{12} Although the exact relation is unknown, it can be hypothesized that microaspiration, pulmonary hypertension, or a combination of these 2 factors may play a role. The same researchers\textsuperscript{12} also found that 29% of their preterm infants with UVCP were discharged requiring tube feeding. Fan et al\textsuperscript{12} found a similar incidence (29%) of aspiration in 7 VLBW infants with UVCP following PDA ligation. The incidence of aspiration and swallowing difficulties in our study was again much higher than previously reported. We suspect that this was because of our infants being of a younger gestational age than reported in previous series and that because these infants have a more immature swallow, they were more severely affected by a recurrent laryngeal nerve injury. It may also be because of failure of previous studies to report this as a complication, because it has recently been reported that swallowing difficulties are the most common manifestation of an airway complication following cardiac thoracic surgery.\textsuperscript{26} Two other studies,\textsuperscript{23,24} both examining swallowing difficulties following major cardioracic surgical procedures, 1 in infants and 1 in children, have found that UVCP was associated with an increased incidence of swallowing difficulties and that an increased incidence of swallowing difficulties was associated with an increased length of hospital stay.

We acknowledge that there are several weaknesses in this study. First, it is retrospective. Second, the study groups are small. Small studies such as this are always at risk of type I errors. Unilateral vocal cord paralysis, however, is a relatively uncommon complication, and there remains a relatively high mortality rate in these ELBW infants.\textsuperscript{1} With the general trend steering away from early surgical ligation toward policies of more watchful waiting, it is unlikely that this study will be repeatable prospectively, except over an exceedingly long period. Another potential criticism may arise regarding the comparison between the PDA study group and the PDA control group with respect to swallowing and respiratory outcomes, because of the original difference in gestational age and weight. This was not an unexpected finding because previous studies\textsuperscript{10-16} indicated an increasing incidence of UVCP occurring with decreasing infant birth weight. Older infants are less likely to have chronic lung disease and, therefore, have a more effective swallow.\textsuperscript{27} Ideally, the PDA ligation with the UVCP group would have been compared with a weight- and gestational age–matched group that had also undergone PDA ligation. We factored this into our study design and included a control group of gestational age–and weight-matched infants.

We understand that another potential bias exists because not all infants in the matched control group had PDAs and PDAs have themselves been associated with other adverse outcomes.\textsuperscript{28} During the second part of the study, routine echocardiography was abandoned, and because of this and the few infants, in total, we were unable to collect a group of matched controls all with PDAs. Patent ductus arteriosus have been associated with an increased incidence of chronic lung disease, prolonged ventilator dependence, intraventricular hemorrhage, and necrotizing enterocolitis.\textsuperscript{28} The differences between these 2 groups were not statistically significant for chronic lung disease or intraventricular hemorrhage in this study. The latter, in fact, was greater in our control group, although this did not reach statistical significance. During our study, no infant in the UVCP group or the control group developed necrotizing enterocolitis.

A VFSS was performed only on symptomatic infants and was not performed routinely on all infants, and the reliability of this investigation may also be questioned. Even in a prospective study, it would have been considered unethical to expose nonsymptomatic infants to radiation. There have been no studies, to our knowledge, in ELBW infants assessing the reliability when examining for aspiration and/or laryngeal penetration or the sensitivity or specificity of this test. All our infants were observed clinically and reassessed at regular intervals, making the possibility of false-positive test results less likely.

In conclusion, there was a high incidence of occurrence of UVCP (67%) associated with PDA ligation in ELBW infants. This complication does seem to be associated with increased requirements for tube feeding, respiratory support, and hospital stay in these ELBW infants.
and design: Clement, El-Hakim, Phillipos, and Cote. Acquisition of data: Clement, El-Hakim, Phillipos, and Cote. Analysis and interpretation of data: Clement, El-Hakim, and Cote. Drafting of the manuscript: Clement and El-Hakim. Critical revision of the manuscript for important intellectual content: El-Hakim, Phillipos, and Cote. Statistical analysis: Clement and El-Hakim. Administrative, technical, and material support: Clement, El-Hakim, Phillipos, and Cote. Study supervision: El-Hakim and Phillipos.

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REFERENCES