Early or Late Surgical Ligation of Medical Refractory Patent Ductus Arteriosus in Premature Infants

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Optimal time to surgical ligation of patent ductus arteriosus (PDA) in very-low-birth-weight (<1500 g) premature infants remains an area of controversy. We compared the outcomes of early or late ligation of medical refractory PDA in very-low-birth-weight premature infants. Fifty-six infants underwent surgical closure of PDA after failure of or having contraindications to medical treatment. Thirty-three infants were in the early ligation (≤14 days) and 21 in the late ligation (>14 days) groups. Basic clinical features, major morbidity of prematurity and mortality were compared. Clinical features and major outcomes were similar. The early ligation group had earlier onset of symptomatic PDA (5.7 ± 1.6 days vs. 8.1 ± 3.6 days, p = 0.024), and fewer days of total parenteral nutrition (TPN) (39.6 ± 13.9 days vs. 60.4 ± 31.4 days, p = 0.025) and ventilator use (11.1 ± 6.7 days vs. 18.6 ± 10.5 days, p = 0.019). Early ligation of medical refractory PDA in very-low-birth-weight premature infants improves enteral feeding tolerance and reduces TPN and ventilator use, but long-term benefits need further investigation. [J Formos Med Assoc 2009; 108(1):72–77]

Key Words: indomethacin, patent ductus arteriosus, prematurity, surgery

Patent ductus arteriosus (PDA) in low-birth-weight premature infants that causes large left-to-right shunts is associated with congestive heart failure, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), intracranial hemorrhage, and death.1–4 For most preterm infants with PDA, the hemodynamic effects are not immediately life-threatening and can be controlled medically without interventional ductus closure. Small preterm infants weighing <1500 g at birth frequently have a prolonged course of ductus shunting, and characteristically require days or weeks of mechanical ventilation. Surgical ligation of the PDA in these infants improves lung compliance, decreases duration of assisted ventilation, and increases nutritional utilization.5,6

Although PDA ligation is a definitive treatment, the optimal time to ligation in very-low-birth-weight (<1500 g) premature infants remains controversial. Early surgical ligation has been advocated as the optimal therapy for PDA because it ensures definitive ductal closure with minimal morbidity and mortality.2,7 However, some studies have shown that PDA closure does not significantly influence outcome.8–10

We performed a retrospective study to compare the efficacy and side effects between early and late ligation of symptomatic PDA.
Early surgical intervention of PDA in premature infants

**Methods**

**Patients**

We retrospectively reviewed the charts of all premature infants with birth weight < 1500 g admitted between 1 January 2001 and 31 December 2003 to the neonatal intensive care unit (NICU) at the Children’s Hospital of New York-Presbyterian (CHONY). The Institutional Review Board for human subject research approved the chart review. We excluded patients transferred from other hospitals, and those with major congenital anomalies and complex congenital heart disease (CHD).

**Inclusion criteria**

Symptomatic PDA was diagnosed definitively by bedside Doppler ultrasonography. The indications for testing were based on clinical factors including a murmur, bounding pulse, hyperdynamic precordium, tachycardia and a need for increased ventilatory support associated with radiographic evidence of cardiomegaly or pulmonary congestion. When PDA was diagnosed, a short trial of indomethacin therapy was instituted. The protocol for indomethacin treatment was the usual 0.2 mg/kg intravenously, every 12–24 hours for three doses, as a full course, if there was no contraindication. Contraindications for indomethacin treatment included: serum creatinine > 1.7 mg/dL, active bleeding, sepsis, NEC, or oliguria. If the PDA remained open according to clinical or echocardiographic evaluation after the first course of indomethacin, a second course was given if there were no contraindications. The criteria for PDA ligation included a hemodynamically significant PDA by echocardiography, ventilator dependence, and failure of indomethacin treatment or a contraindication to its use. Contraindications for PDA ligation included severe pulmonary hypertension with predominant right-to-left or bidirectional shunt, life-threatening infection, and septic shock. Surgical ligation was performed in the NICU operating room under general anesthesia. The duct was approached through a left lateral thoracotomy, and suture ligation or hemoclipping was performed.

**Procedure**

The premature infants with symptomatic PDA refractory to or contraindicated for medical closure, who underwent surgical ligation, were our target population. They were divided into two groups: early ligation (EL; age ≤ 14 days) and late ligation (LL; age > 14 days). The groups were compared with regard to gestational age, birth weight, Apgar score, antenatal steroids, respiratory distress syndrome (RDS), surfactant use, mean airway pressure, first day of symptomatic PDA, and mean age at surgery (Table 1). Outcome assessed included BPD (defined as need for oxygen or

**Table 1. Population characteristics**

<table>
<thead>
<tr>
<th></th>
<th>EL (n = 13)</th>
<th>LL (n = 43)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (wk)</td>
<td>24.8 ± 1.1</td>
<td>25.3 ± 1.6</td>
<td>0.298</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>694 ± 199</td>
<td>714 ± 183</td>
<td>0.736</td>
</tr>
<tr>
<td>Male gender</td>
<td>7 (53.8)</td>
<td>22 (51.2)</td>
<td>0.862</td>
</tr>
<tr>
<td>Apgar at 1 min</td>
<td>4.3 ± 2.8</td>
<td>4.83 ± 2.1</td>
<td>0.490</td>
</tr>
<tr>
<td>Apgar at 5 min</td>
<td>7.33 ± 1.2</td>
<td>7.23 ± 1.2</td>
<td>0.793</td>
</tr>
<tr>
<td>Antenatal steroid</td>
<td>7 (53.8)</td>
<td>27 (62.8)</td>
<td>0.977</td>
</tr>
<tr>
<td>Respiratory distress syndrome</td>
<td>10 (76.9)</td>
<td>39 (90.7)</td>
<td>0.912</td>
</tr>
<tr>
<td>Surfactant use</td>
<td>4 (30.7)</td>
<td>16 (37.2)</td>
<td>0.987</td>
</tr>
<tr>
<td>Airway pressure (cmH2O)</td>
<td>8.4 ± 2.1</td>
<td>8.7 ± 2.4</td>
<td>0.687</td>
</tr>
<tr>
<td>First day of symptomatic PDA</td>
<td>5.7 ± 1.6</td>
<td>8.1 ± 3.6</td>
<td>0.024†</td>
</tr>
<tr>
<td>Age at surgery</td>
<td>11.2 ± 2.5</td>
<td>20.3 ± 4.3</td>
<td>0.001†</td>
</tr>
</tbody>
</table>

*Data presented as mean ± standard deviation or n (%); †significant difference. EL = early ligation (age ≤ 14 d); LL = late ligation (age > 14 d); PDA = patent ductus arteriosus.
respiratory support at 36 weeks of postconceptual age), grade III and IV intraventricular hemorrhage (IVH), stage 3 and 4 retinopathy of prematurity (ROP), NEC, acute renal failure (ARF; creatinine > 1.7 mg/dL), pneumothorax, and mortality (Table 2). Nasal continuous positive airway pressure (CPAP), ventilator use, duration of total parenteral nutrition (TPN), and length of hospital stay were compared.

**Statistical analysis**

Statistical analysis was performed using a two-tailed Student’s t test for continuous variables and Fisher’s two-tailed exact test for dichotomous variables. Continuous variables were reported as mean ± standard deviation. A value of $p < 0.05$ was considered significant.

**Results**

A total of 448 infants with <1500 g body weight were born at CHONY and admitted to the NICU between 1 January 2001 and 31 December 2003. Thirty-two infants who had major congenital anomalies or complex CHD were excluded. A total of 167 cases (40.1%) developed symptomatic PDA, and 111 infants (66.5%) were successfully closed by medical treatment, which was confirmed by Doppler ultrasonography. A total of 56 cases (33.5%) underwent surgical ligation of symptomatic PDA, and were divided into the EL (age ≤ 14 days, $n = 13$) and LL (age > 14 days, $n = 43$) groups (Figure 1). The gestational age of the study infants was 23–31 weeks and birth weight was 430–1310 g. There were no significant differences between the groups for gestational age, birth weight, Apgar score, antenatal steroid use, RDS, surfactant use, and mean airway pressure. The significant differences were first days of symptomatic PDA and mean age at surgery (Table 1). The two groups were clinically similar and cared for in the same fashion.

Major morbidity and mortality are summarized in Table 2. Patient outcomes were similar. BPD requiring oxygen therapy beyond 36 weeks postconceptual age occurred in two surviving infants in the EL group and 10 in the LL group ($p = 1.000$). NEC was noted in one infant in the EL group and in eight patients in the LL group, although this was not a significant difference ($p = 0.670$). Two infants in the EL and seven in the LL group died, but the difference was not significant ($p = 1.00$). Other morbidities that were common in premature infants, including ARF, grade III and IV IVH, stage 3 and 4 ROP, and pneumothorax, did not differ significantly between the two groups.

The EL group received nasal CPAP for 59.4 ± 25.6 days, similar to the 63.2 ± 28.4 days in the LL group ($p = 0.668$). The EL group received mechanical ventilation for 11.1 ± 6.7 days, which was significantly shorter than the 18.6 ± 10.5 days in the LL group ($p = 0.019$). The EL group received TPN for 39.6 ± 13.9 days, which was significantly shorter than the 60.4 ± 31.4 days in the LL group ($p = 0.025$). The mean length of hospital stay in the EL group was 92.3 ± 47.1 days, which did not differ significantly from the 111.6 ± 51.9 days in the LL group ($p = 1.00$).
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**Discussion**

Our results indicated that the days of ventilator use and duration of TPN use were significantly shorter in premature infants with early surgical ligation (age ≤ 14 days) of symptomatic PDA that was refractory to medical treatment. We found no evidence that delayed duct closure was associated with BPD, NEC, IVH, ARF, ROP, length of hospital stay, or death.

The patency of the ductus arteriosus makes a “diastolic steal” of blood flow from the abdominal organs to the pulmonary artery and causes impaired intestinal blood flow. Cassady et al confirmed that impaired intestinal blood flow may cause feeding intolerance and NEC in premature infants, and that early prophylactic ligation of PDA in extremely-low-birth-weight infants reduces the incidence of NEC. This can explain why early ligation of PDA led to a shorter duration of TPN use and was able to meet most of the patients’ nutritional needs at an earlier age, as well as sparing certain serious complications of TPN.

Jaillard et al have also shown that early surgical closure of the ductus arteriosus (< 3 weeks old) is associated with a shorter delay in full oral feeding and improved body growth, when compared with late surgical closure (> 3 weeks old). NEC occurred in one of 13 infants in our EL group, but was noted in eight of 43 infants in the LL group. Early ligation of symptomatic PDA seemed to have a trend towards reducing NEC, but did not make a significant difference in our study.

We found that infants in the EL group had fewer days of mechanical ventilation (11.1 ± 6.7 days vs. 18.6 ± 10.5 days in LL, p = 0.019), but BPD incidence did not differ. Early ligation of PDA...
improves pulmonary edema in premature infants, thus we can wean infants off ventilation earlier, but many factors are considered to contribute to the occurrence of BPD in premature infants. The evidence of PDA and its closure on respiratory status in premature neonates is not clear. Gerhardt and Bancalari and Szymankiewicz et al reported improved lung function after surgical closure of PDA. Farstad and Bratlid, however, found no difference in compliance with ductal closure in infants with RDS. We did not find in our series or any published report that early ligation of PDA reduced BPD in premature infants.

Yeh and associates have suggested that the development of BPD is linked to the severity of RDS and the high inspired oxygen concentrations delivered within 4 hours of age. For this reason, they proposed that any therapeutic regimen should be instituted very early to have any effect on reducing the development of BPD.

The results of this study provide a rational solution to an important management dilemma. Even though CHF and pulmonary edema is satisfactorily controlled, we believe that the infant with symptomatic PDA who has failed treatment with indomethacin will benefit from early surgical closure of the ductus. The incidence of surgical complications in the present study was minimal and consistent with the 4–10% morbidity reported in the literature. Any infants with progressive, uncontrolled CHF or pulmonary edema should undergo immediate ductus closure as a lifesaving measure, unless the shunting in the ductus is right-to-left or bidirectional.

Our study was not a randomized controlled trial. The number of subjects was limited by the fact that the occurrence of symptomatic PDA in very-low-birth-weight infants refractory to medical closure was infrequent, and patients transferred from or referred to other hospitals were excluded because of follow-up difficulties and possible differences in treatment strategy. The long-term outcomes of PDA ligation were not followed in our study. Kabra et al reported that surgical PDA closure was a risk factor for neurosensory impairment at 18 months in children who were enrolled in the Trial of Indomethacin Prophylaxis in Preterms. Controlled trials with long-term follow-up are urgently needed to better delineate the role of surgical closure of PDA in the care of premature infants.

In conclusion, early ligation of medical refractory PDA in very-low-birth-weight premature infants improves enteral feeding tolerance and reduces TPN and ventilator use, but it does not improve the major outcomes of premature infants. The long-term benefits or harms need to be further evaluated.

Acknowledgments

We thank Tara Randis M.D. for help with the chart reviews at CHONY, Columbia Presbyterian Medical Center, New York, and Chin-Yi Huang for the statistical analysis.

References