Controversies in the Management of Patent Ductus Arteriosus

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Controversies in the Management of Patent Ductus Arteriosus

Jason Gien, MD*

Abstract
Exposure to a chronic persistent patent ductus arteriosus (PDA) is associated with several neonatal morbidities, but whether such outcomes are as a result of a persistent left-to-right shunt across the PDA or as a consequence of prematurity remains in question. Animal studies have shown significant benefit to early PDA closure, but such findings have not been replicated in any human trial. Both pharmacologic and surgical treatment options exist for closing a PDA, both of which have their own morbidities. Although the incidence of PDA is high in preterm infants, there also is a high rate of spontaneous PDA closure. Treatment of a PDA is not benign and has not been shown to prevent any morbidities associated with prematurity. For this reason, there has been much debate in recent years as to when a PDA is pathologic and when closure is indicated. This discussion focuses on the debate, treatment options for PDA, and outcomes associated with PDA and its treatment.

Introduction
Patent ductus arteriosus (PDA) is a connection between the pulmonary artery and aorta that, during fetal life, diverts blood from the pulmonary vascular bed to the body. In utero, 90% of fetal right ventricular output shunts blood via the PDA. In the term infant, functional closure occurs by 12 to 15 hours after birth. If the PDA remains functionally open beyond 72 hours, it is considered persistent. PDA persists in fewer than 1% of term infants, but the incidence in preterm infants is as high as 50%. (1) PDA may be present in up to 65% of infants who have respiratory distress syndrome (RDS). (2) Inhibition of prostaglandin production with indomethacin has been the mainstay of therapy to date, although the question still remains as to when a PDA is pathologic. Many randomized trials have evaluated different treatment strategies for PDA as well as the effect of a PDA on short- and long-term outcomes, but the timing and method by which to close a PDA in the neonatal period remains unclear.

Development of Pulmonary Edema
The earliest and only trial evaluating the effect of an untreated PDA on pulmonary morbidity was published 30 years ago and clearly demonstrated adverse outcomes with prolonged exposure to a symptomatic PDA. (3) Infants were randomized to surgical closure of the PDA (10 infants) and medical treatment (15 infants), which, at the time, was limited to diuretics and digoxin. Infants treated surgically weaned more quickly from the ventilator, had less need for furosemide and digoxin, and reached full enteral feedings faster. This trial, although small, clearly demonstrated adverse pulmonary outcomes with prolonged exposure to a symptomatic PDA. Multiple subsequent studies have confirmed the finding that long-term exposure to a symptomatic PDA worsens pulmonary morbidity. (4)(5)(6)(7)(8)(9)

A PDA that involves left-to-right shunting increases fluid and protein efflux from the pulmonary vasculature into the lung parenchyma. The increased fluid and protein in the lung interstitium increases pulmonary microvascular filtration pressure, and increased lung lymph flow eliminates

Abbreviations
BPD: bronchopulmonary dysplasia
CLD: chronic lung disease
NEC: necrotizing enterocolitis
PDA: patent ductus arteriosus
RDS: respiratory distress syndrome

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excess fluid and protein from the lung. This compensatory increase in lung lymph inhibits fluid accumulation in the lung. (2) With persistent ductal patency, this compensatory mechanism is overloaded, and pulmonary edema develops. The mechanism is overwhelmed more easily in the presence of sepsis and RDS. (2)(9)(10)(11)(12) Once pulmonary edema ensues, infants often require increasing respiratory support. This mechanism is believed to be responsible for the subsequent development of bronchopulmonary dysplasia (BPD) after prolonged exposure to a symptomatic PDA.

Although exposure to a widely patent, symptomatic ductus worsens the pulmonary sequelae of preterm birth, its contribution to other neonatal morbidities is less well established. There is clearly an association between PDA and many of the common neonatal morbidities, but it is unclear if these morbidities are related to the PDA itself, are due to its treatment, or are consequences of prematurity. (13)

**Pharmacologic Closure and Pulmonary Outcome**

**Indomethacin**

Animal studies have demonstrated significant benefit to early closure of the PDA. (14) Early pharmacologic closure of the PDA in preterm baboons improved pulmonary mechanics and decreased the detrimental effects of preterm birth on alveolarization. To date, no studies in preterm infants have shown a similar benefit. The Trial of Indomethacin Prophylaxis in Preterms (TIPP) evaluating the long-term effects of indomethacin prophylaxis (0.1 mg/kg per dose every 24 hours for three doses) in extremely low-birthweight infants failed to show a reduction in the rates of BPD despite a significant decrease in both the incidence of PDA and the need for surgical ligation. (15) Although PDA rates decreased from 49% in the placebo group to 21% in the treatment group, there was no effect on the incidence of BPD, with BPD rates of 45% and 43% in the treatment and placebo groups, respectively (Table 1). However, fewer adverse effects were reported with indomethacin treatment in infants who did not have PDA. The rate of BPD in the group that did not have PDA exposed to indomethacin was 43% compared with 30% in the placebo group. Although highly effective in closing the PDA and decreasing the need for PDA ligation, indomethacin prophylaxis cannot be recommended for all infants who have PDA without addressing potential reasons why the TIPP trial failed to show benefit in terms of decreasing rates of BPD.

If prolonged exposure to a symptomatic PDA worsens pulmonary outcomes, early closure of the PDA with indomethacin prophylaxis should improve pulmonary outcomes unless adverse outcomes are related to indomethacin. Infants treated with indomethacin in the Schmidt investigation had increased needs for supplemental oxygen from postnatal days 3 to 7, decreased urine volumes in the first 4 days after birth, and reduced weight loss by 7 days after birth. (1) These effects were related to the decreased renal perfusion and urine output seen with indomethacin exposure. The authors concluded that the early adverse effects of indomethacin treatment on oxygenation and net weight loss might have offset any potential pulmonary benefit from early drug-induced PDA closure. Because the adverse effects of indomethacin treatment may have been related to fluid retention, aggressive fluid restriction in the presence of indomethacin treatment has the potential to offset the harmful effects of this therapy. If fluid balance can be maintained, true benefit may be seen from early ductal closure, as demonstrated in animal studies. Other studies evaluating the effects of early ductal closure with indomethacin have demonstrated similar results. (16)

**Ibuprofen**

An alternative approach is the use of a therapy associated with fewer renal adverse effects. To date, studies performed to evaluate the effects of ibuprofen prophylaxis on PDA closure have shown similar results to indomethacin. Although ibuprofen prophylaxis is effective in reducing the incidence of PDA and the need for surgical ligation, early ductal closure has failed to reduce the incidence of BPD or any other relevant neonatal morbidities. (17) Treatment of symptomatic PDA with ibuprofen has less effect on serum creatinine and urine output than indomethacin treatment, (18)(19)(20) but results in a statistically higher incidence of chronic lung disease (CLD), as defined by an oxygen requirement at 28 days

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**Table 1. Risk of Bronchopulmonary Dysplasia (BPD) by Patent Ductus Arteriosus (PDA)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of PDA</td>
<td>21%</td>
<td>49%</td>
</tr>
<tr>
<td>Incidence of BPD</td>
<td>43%</td>
<td>45%</td>
</tr>
<tr>
<td>Risk of BPD by PDA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDA</td>
<td>52%</td>
<td>56%</td>
</tr>
<tr>
<td>No PDA</td>
<td>43%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Modified from Schmidt et al (15).
after delivery, (19)(20) further complicating the issue. Although early PDA closure with ibuprofen in the baboon model of BPD prevented the detrimental effects of preterm birth on alveolarization, the same effect has not been demonstrated in human infants.

Because of the risk of exposing infants who have closed PDAs to indomethacin/ibuprofen prophylaxis and the potential adverse effects of these medications, an alternative approach is to treat only infants who have echocardiographically confirmed PDA. Treatment of echocardiographically confirmed PDA with ibuprofen (10 mg/kg loading dose followed by 5 mg/kg per dose every 24 hours for two more doses)/indomethacin (0.2 mg/kg per dose every 12 hours for three doses) is effective in closing the PDA, but such therapy has had no effect on preventing BPD or CLD. (19)(20) In addition, ibuprofen treatment is associated with a statistically significant higher incidence of CLD. (18)(20) A reasonable approach may be to institute treatment only when a PDA becomes symptomatic. However, such an approach exposes infants to a symptomatic PDA for a duration of time that exceeds the ability of the pulmonary lymph system to compensate for the pulmonary overcirculation. As a result, pulmonary edema occurs, with increasing respiratory requirements and subsequent development of BPD.

### Surgical Closure

Surgical ligation of the PDA is associated with thoracotomy, pneumothorax, chylothorax, and vocal cord paralysis, among other complications. It also often requires transfer to a tertiary center for the procedure. However, the benefit of early surgical ductal closure may outweigh such detrimental effects. Surgical ligation in preterm baboons improved cardiopulmonary function, (14) but failed to prevent the histologic evolution of BPD. PDA ligation in preterm baboons on postnatal day 6 failed to improve pulmonary function, concentrations of inflammatory cytokines, lung compliance, and lung histology. (14) In contrast, pharmacologic closure of the PDA with ibuprofen in preterm baboons improved pulmonary mechanics and decreased the detrimental effects of preterm birth on alveolarization, with significant improvement in alveolarization following early ductal closure. (14)

Failure to demonstrate benefit may be related to delayed surgical closure on day 6 rather than surgical closure itself. Surgical closure employed as an initial therapy for PDA has been compared with medical treatment with cyclooxygenase inhibitors. (21)(22) Babies weighing less than 1,000 g were randomized to either PDA ligation on the day of birth or standard treatment. Closure of the PDA surgically as early as the day of birth failed to show benefit in terms of mortality, CLD, sepsis, retinopathy, or intraventricular hemorrhage, although there was a reduced incidence in stage II and III necrotizing enterocolitis (NEC) (Table 2). (21)(22) Further analysis of data from earlier randomized trials has shown possible detrimental effects from PDA ligation. (1)(23) In the TIPP trial, infants exposed to PDA ligation had statistically increased incidences of cognitive delay and neurosensory impairment at 18 months of age. (23)

Other studies also have suggested that early surgical ligation of the PDA contributes to long-term adverse neurodevelopmental outcomes. (24)(25) The detrimental effects of PDA ligation are not confined to the brain. Surgical ligation also has been shown to be significantly

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Event Rate</th>
<th>Adjusted Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No surgery</td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>67%</td>
<td>P=0.023</td>
</tr>
<tr>
<td>Severe retinopathy of prematurity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No surgery</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>27%</td>
<td>P=0.012</td>
</tr>
<tr>
<td>Death or neurosensory impairment at 18 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No surgery</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>59%</td>
<td>P=0.069</td>
</tr>
<tr>
<td>Death before 18 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No surgery</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>14%</td>
<td>P=0.095</td>
</tr>
<tr>
<td>Neurosensory impairment at 18 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No surgery</td>
<td>34%</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>53%</td>
<td>P=0.0093</td>
</tr>
<tr>
<td>Cognitive delay</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No surgery</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>45%</td>
<td>P=0.015</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No surgery</td>
<td>14%</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>19%</td>
<td>P=0.55</td>
</tr>
</tbody>
</table>

associated with the development of CLD, independent of immature gestation. (24) Furthermore, an asymptomatic PDA still patent at discharge closes in 85% of cases without further treatment. (26) Due to the presence of safer and more efficacious options for ductal closure as well as the high rates of spontaneous ductal closure, surgical ligation should be reserved only for infants who have failed cyclooxygenase inhibitor therapy and continue to have a symptomatic PDA.

Echocardiography and Natriuretic Peptide

Reserving PDA ligation for infants who have symptomatic PDA requires differentiation of symptomatic from asymptomatic PDA. Echocardiographic evidence of symptomatic ductal patency includes ductal diameter of more than 1.5 mm in the first 30 hours after delivery, left atrial/aortic root ratio more than 1.5, and pulsatile transducatal flow ($V_{max}$) less than 1.8 m/sec (Table 3). (27)(28)(29) Although no study to date has shown a correlation between PDA and NEC, reverse end-diastolic flow in the descending aorta is a definite risk factor for NEC. (30)(31)(32) Therefore, feeding in the presence of this finding cannot be recommended, and PDA ligation is recommended to allow for enteral feeding. In the absence of any of the previously noted echocardiographic findings, PDA ligation cannot be recommended.

Data are emerging on the utility of B-type natriuretic peptide for evaluation of symptomatic PDA. (33)(34)(35)(36) Despite the correlation between increased B-type natriuretic peptide and symptomatic PDA, no clear cutoff value has been established for differentiating symptomatic from asymptomatic PDA using this measure. Values between 70 and 100 pg/mL have been used to determine symptomatic PDA. Monitoring B-type natriuretic peptides in infants who have PDA that meet echocardiographic criteria for being symptomatic may have some utility in helping to decide which infant should have the PDA ligated versus being followed clinically.

Table 3. Echocardiographic Criteria for Symptomatic Patent Ductus Arteriosus

1. Ductal diameter >1.5 mm in the first 30 hours after delivery.
2. Left atrial/aortic root ratio >1.5.
3. Pulsatile transducatal flow ($V_{max}$) <1.8 m/sec.
4. Reverse end-diastolic flow in the descending aorta/mesenteric artery.

Recommendations

Pharmacologic treatment of a PDA in the newborn period offers measurable benefits without an increase in clinically significant adverse effects. If pharmacologic treatment is to be used, early treatment is more likely to result in successful ductus closure and prevent adverse pulmonary outcomes. For this reason, indomethacin prophylaxis is the preferred alternative (Figure). Although equally effective in closing the PDA, ibuprofen failed to demonstrate the same neuroprotective effect in terms of preventing grade III and IV intraventricular hemorrhage and may be associated with an increased risk
for BPD. The adverse effects of indomethacin treatment seem to be related to decreased renal blood flow and urine output, which may be offset by aggressive fluid restriction until urine output improves. For infants who continue to have a symptomatic PDA after prophylaxis, treatment options include a course of indomethacin or ligation. Ligation is associated with adverse pulmonary and neurodeveloped outcomes, and multiple repeated courses of indomethacin (more than three doses) are associated with an increased incidence of NEC. (37) In institutions where the rate of NEC is high, ligation may be a better alternative; otherwise, a treatment course of indomethacin is recommended prior to proceeding to ligation. Ligation should be reserved only for infants who fail pharmacologic treatment and continue to have a symptomatic PDA by echocardiographic criteria. As we gain more experience with B-type natriuretic peptides, their utility in differentiating symptomatic from asymptomatic PDA will become evident.

Further studies clearly are needed to help clarify many issues, the most pressing being which infants will benefit from surgical ligation and which infants might best be left untreated when pharmacologic approaches no longer are an option.

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