Patent Ductus Arteriosus in Premature Neonates

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Abstract

Persistent patency of the ductus arteriosus is a major cause of morbidity and mortality in premature infants. In infants born prior to 28 weeks of gestation, a haemodynamically significant patent ductus arteriosus (PDA) can cause cardiovascular instability, exacerbate respiratory distress syndrome, prolong the need for assisted ventilation and increase the risk of bronchopulmonary dysplasia, intraventricular haemorrhage, renal dysfunction, cerebral palsy and mortality. We review the pathophysiology, clinical features and assessment of haemodynamic significance, and provide a rigorous appraisal of the quality of evidence to support current medical and surgical management of PDA of prematurity. Cyclo-oxygenase inhibitors such as indomethacin and ibuprofen remain the mainstay of medical therapy for PDA, and can be used both for prophylaxis as well as for rescue therapy to achieve PDA closure. Surgical ligation is also effective and is used in infants who do not respond to medical management. Although both medical and surgical treatment have proven efficacy in closing the ductus, both modalities are associated with significant adverse effects. Because the ductus does un-
dergo spontaneous closure in some premature infants, improved and early identification of infants most likely to develop a symptomatic PDA could help in directing treatment to the at-risk infants and allow others to receive expectant management.

1. Introduction

In the developing fetus, the pulmonary artery and the aortic arch are connected via the ductus arteriosus, a vascular shunt that diverts the right ventricular output away from the fetus’s fluid-filled lungs and into the systemic circulation. Whereas this ductal shunt closes spontaneously within a few hours of birth in full-term infants, this process is frequently delayed/interrupted in premature infants and is associated with increased risk of clinical complications. In this article, we review the clinical features and management of persistent patent ductus arteriosus (PDA) in premature infants.

2. Epidemiology

The incidence of persistent PDA correlates inversely with birth weight and gestational age, seen in about 30% of infants born with a birth weight less than 1500 grams, 40% of infants weighing 751–1000 grams, and more than 50% of those weighing 501–750 grams. Although spontaneous ductal closure occurs eventually in nearly a third of extremely premature neonates, more than 60% of all preterm infants born prior to 28 weeks’ gestation receive medical or surgical treatment to prevent complications associated with persistent PDA such as exacerbation of respiratory distress syndrome (RDS), pulmonary haemorrhage, prolonged use of assisted ventilation, bronchopulmonary dysplasia (BPD), intraventricular haemorrhage (IVH), renal dysfunction, necrotizing enterocolitis (NEC), periventricular leukomalacia (PVL), cerebral palsy and mortality.

3. Pathophysiology of Patent Ductus Arteriosus (PDA)

The ductus arteriosus undergoes functional closure within a few hours after birth due to constriction of the medial smooth muscle layer. A more definitive anatomical closure occurs over the next several days, with intimal remodeling and loss of smooth muscle cells from the media. With the cessation of the ductal shunt between the systemic and pulmonary circulation, the right ventricular output is no longer diverted to the aorta and flows directly into the pulmonary circulation. The consequent increase in venous return from the lungs raises the left atrial pressures, closing the other right-to-left shunt of fetal life across the foramen ovale in the inter-atrial septum. With the closure of these two right-to-left shunts, the pulmonary and systemic circuits carry equal volumes of blood flow in ‘series’ instead of the ‘parallel’ configuration of fetal life. Although the physiological mechanisms involved in ductal closure are still being elucidated, postnatal changes in the systemic and pulmonary vascular resistance, sudden increase in tissue oxygenation after birth, decreased levels of prostaglandins, and increased expression of endothelin and its cognate receptors are known to play an important role.

In premature infants, the normal process of ductal closure is often delayed or interrupted. Very low birth weight (<1500 grams), acute perinatal stress, moderate-severe RDS with a need for assisted ventilation within 24 hours of birth, neonatal sepsis, and higher total fluid administration during the initial few days after birth are some of the factors associated with persistent PDA. As the pulmonary vascular resistance falls after birth, blood is increasingly shunted away from the aorta into the pulmonary artery, resulting in pulmonary over-circulation, with frequent exacerbation of lung disease and increased risk of pulmonary haemorrhage and BPD. Left-to-right ductal shunting can also ‘steal’ blood from the systemic circulation and reduce end-organ perfusion, placing the preterm infant at increased risk of complications such as renal dysfunction, NEC, IVH and PVL.
4. Clinical Manifestations and Diagnosis of PDA

PDA can be ‘asymptomatic’ (where no heart murmur is detected), ‘symptomatic’ (associated with a murmur), ‘haemodynamically non-significant’ (no cardiovascular dysfunction) or ‘haemodynamically significant’ (with cardiovascular dysfunction).\[37\] Most infants with PDA have a characteristic systolic or systolo-diastolic murmur at the upper left sternal border.\[37\] A haemodynamically significant PDA is frequently marked by additional clinical signs such as an active precordium, bounding pulses, wide pulse pressure\[28\] and radiological signs such as cardiomegaly, prominent pulmonary vascular markings, dilatation of the left atrium and a horizontalized left main bronchus.\[6,37\] As the shunt size increases, the electrocardiogram may also show signs of left ventricular hypertrophy and left atrial enlargement.\[6\] To assess the haemodynamic impact of the PDA, a clinical cardiovascular distress scoring system can be useful (table I).\[38\] This score evaluates five variables (heart rate, peripheral arterial pulses, precordial pulsations, duration of murmur and cardiothoracic ratio on chest x-ray); a score ≥3 is strongly associated with a haemodynamically significant PDA.

Echocardiography is the mainstay of diagnosis and assessment of PDA. It allows direct visual assessment of the ductus originating from the descending aorta distal to the left subclavian artery and connecting to the main pulmonary artery.\[34\] The ratio of the smallest ductal diameter to the ostium of the left pulmonary artery (LPA) \[PDA : LPA ratio\] is a useful indicator of the ductal size, where ratios of ≥1, 0.5–1 and <0.5 indicate a large, medium and small PDA, respectively.\[39\] Doppler flow studies can confirm ductal patency and help assess the direction of ductal flow, cardiac anatomy, ventricular function, the ratio of estimated pulmonary to systemic blood flow\[40\] and pulmonary artery pressures.\[6\] Echocardiography can also be useful in predicting the clinical course; the ductal size on day 3–4 (PDA : LPA ratio) is a useful predictor of a haemodynamically significant PDA, antedating the onset of clinical signs by up to 2–3 days.\[41\]

Although no laboratory tests can reliably indicate the presence of a PDA, circulating levels of B-type natriuretic peptide (BNP), a hormone secreted by the ventricles under haemodynamic stress and congestive heart failure, can be both sensitive and specific for detecting a haemodynamically significant PDA and for monitoring response to therapy.\[42,43\] Plasma concentrations of BNP between 70 and 100 pg/mL have been used to determine a symptomatic PDA.\[34\] In a prospective blinded study, Sanjeev et al.\[42\] showed that a cut-off of 72 pg/mL was useful as a screening tool for a haemodynamically significant PDA. BNP levels were higher in infants with a haemodynamically significant PDA \((n = 14)\) than in those without \((n = 15); \ 508.5 ± 618.2 \text{ vs } 59.5 ± 69.9 \text{ pg/mL}; \ p < 0.005\), and concentrations decreased after successful medical/surgical treatment of PDA \((n = 12; \ 404.9 ± 159.2 \text{ to } 25.1 ± 4.1 \text{ pg/mL}; \ p < 0.03)\).\[42\] Further study is needed in larger cohorts to determine whether BNP levels in the early neonatal period can help differentiate between candidates for expectant versus aggressive management.\[34\]

5. Management of Neonatal PDA

5.1 Medical Treatment of PDA

Medical management of PDA in a premature infant comprises fluid restriction, cyclo-oxygenase

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Table 1. Cardiovascular distress score in premature infants with patent ductus arteriosus\[38\]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>&lt;160</td>
</tr>
<tr>
<td>Heart murmur</td>
<td>None</td>
</tr>
<tr>
<td>Peripheral pulse</td>
<td>Normal</td>
</tr>
<tr>
<td>Precordial pulsation</td>
<td>None</td>
</tr>
<tr>
<td>Cardiothoracic ratio</td>
<td>&lt;0.60</td>
</tr>
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</table>
COX inhibitors such as indomethacin and ibuprofen, and, occasionally, cautious use of diuretics in symptomatic infants.\[44,45\] COX inhibitors promote the constriction and eventual closure of the ductus\[46\] by inhibiting the synthesis and release of prostaglandins, which play a major role in maintaining ductal patency during fetal life.\[31\] While indomethacin has been the traditional ‘drug of choice’ for treatment of PDA, the US FDA approved the use of intravenous ibuprofen in April 2006 for closure of clinically significant PDA in premature infants <32 weeks and weighing 500–1500 grams. There has been considerable variability in the dosing regimens for the two drugs; table II summarizes dosing regimens for indomethacin and ibuprofen used for prophylactic and rescue therapy.

### 5.2 Surgical Treatment of PDA

Surgical ligation of a symptomatic PDA in preterm neonates is successful in closing the ductal shunt in 98–100% of cases.\[53,54\] The procedure is generally well tolerated and is considered by some as a preferred first line of treatment in preterm infants who are less likely to respond to indomethacin, such as those weighing less than 800 grams with a large left atrial-aortic root ratio on echocardiography.\[53-56\] Surgical ligation of a haemodynamically significant PDA can improve haemodynamics and lung compliance, and reduce the duration of mechanical ventilation.\[47,59\] Offered as a prophylactic therapy, surgical ligation was effective in preventing NEC (relative risk [RR] 0.25, 95% CI 0.08, 0.83; p=0.02, number needed to treat [NNT] 5) but did not reduce mortality, severe IVH, BPD or retinopathy of prematurity (ROP).\[60\] Complications of PDA ligation include pneumothorax, hypothermia, intra-operative bleeding, phrenic nerve palsy, wound infection, vocal cord palsy and thoracic scoliosis.\[53,61,62\]

### 5.3 Medical vs Surgical Therapy for PDA

Although the efficacy of both COX inhibitors and surgery in ensuring ductal closure is well established, a consensus on the choice of medical versus surgical treatment remains elusive. Gerwes et al.\[63\] compared clinical outcomes in 154 preterm infants who received either surgical ligation or medical treatment with COX inhibitors for a symptomatic PDA. There was no difference in mortality, BPD, bleeding, NEC, sepsis, renal insufficiency or IVH. The surgical group had a higher incidence of pneumothorax (RR 2.68, 95% CI 1.45, 4.93; risk difference [RD] 0.25, 95% CI 0.11, 0.38; number needed to harm [NNH] 4, 95% CI 3, 9) and severe ROP (RR 3.80, 95% CI 1.12, 12.93; RD 0.11, 95% CI 0.02, 0.20; NNH 9, 95% CI 5, 50) than the indomethacin group.

Three recent observational studies have reported that infants receiving surgical ligation of PDA may be at increased risk of adverse outcomes such as chronic lung disease, ROP and neurosensory impairment.\[64-66\] In some studies, surgical ligation was also associated with in-

| Table II. Pharmacotherapeutic options for neonatal patent ductus arteriosus |
|-----------------------------|-----------------------------|
| Drug                        | Dosing regimen              |
| Indomethacin prophylaxis\[12,47-50\] | I. Short three-dose course of prophylactic indomethacin (0.2, 0.1, 0.1 mg/kg, administered at 24 h intervals) OR |
|                            | II. Extended six-dose course (0.2, 0.1, 0.1, 0.1, 0.1 mg/kg, at 24 h intervals) starting within 15 h of birth OR |
|                            | III. Three-dose course of 0.1 mg/kg IV at 24 h intervals |
| Indomethacin treatment\[51\] | I. 1st dose: 0.2–0.3 mg/kg IV |
|                            | 2nd dose: 0.2 mg/kg IV every 12–24 h after first dose if PDA persists |
|                            | 3rd dose: 0.2 mg/kg IV 12–24 h after second dose if PDA persists OR |
|                            | II. 0.2 mg/kg/dose PO/IV for three doses given at 12 h intervals |
| Ibuprofen prophylaxis\[46\] | I. Oral suspension 10 mg/kg; 5 mg/kg, 5 mg/kg PO every 24 h for symptomatic PDA |
| Ibuprofen treatment\[5,52\] | I. Loading dose of 10 mg/kg IV/PO on d 1, followed by 5 mg/kg/dose at 24 h and 48 h subsequently OR |
|                            | II. Ibuprofen 10 mg/kg/dose PO for three doses given at 24 h intervals |

IV = intravenous; PDA = patent ductus arteriosus; PO = orally.
creased cardiorespiratory morbidity in the immediate post-operative period.\[64,67\] Because of these concerns, surgical ligation is generally considered as a ‘rescue’ strategy in infants who have a contraindication to treatment with COX inhibitors or in whom medical therapy has failed.\[28,68\] In a study of 3779 infants weighing less than 1500 grams, Lee et al.[69] noted that 28% of infants were treated for PDA. In this group, 75% were treated with indomethacin alone, 8% with surgical ligation alone, and 17% received both indomethacin and surgical ligation.

5.4 Prophylactic vs Therapeutic Use of Indomethacin

Randomized controlled trials (RCTs) of indomethacin for prophylaxis against IVH and PDA were first published in the 1980s. Indomethacin prophylaxis, which was primarily directed against IVH, effectively closed the ductus in about 70% and reduced the incidence of a symptomatic PDA by 50%.[70-72] Fowlie et al.[12] reviewed 19 RCTs (n = 2872) of prophylactic indomethacin in preterm infants <37 weeks and showed a reduction in the incidence of symptomatic PDA (RR 0.44, 95% CI 0.38, 0.50) and the need for surgical ligation (RR 0.51, 95% CI 0.37, 0.71). The benefit of prophylactic indomethacin in reducing pulmonary haemorrhage, a known association of PDA,[13,14] remains unclear. Data from Bandstra et al.,[73] Couser et al.[74] and the TIPP (Trial of Indomethacin Prophylaxis in Preterm Infants) study[75] showed no benefit despite reducing the incidence of symptomatic PDA. In a study published in abstract form only, Domanico et al.[76] reported a strong trend towards prevention of pulmonary haemorrhage (5/52 in treated group vs 12/48 in control; RR 0.38, 95% CI 0.15, 1.01). In a study of 1202 infants, Alfaleh et al.[77] noted that prophylactic indomethacin reduced the risk for serious pulmonary haemorrhage by 35% in the first week and by 23% over the course of the neonatal intensive care unit (NICU) stay. Prophylactic indomethacin did not change respiratory outcomes or the incidence of pulmonary haemorrhage, gastrointestinal perforations, NEC, severe bleeding or sepsis. Treated infants had a higher incidence of oliguria (RR 1.90; 95% CI 1.45, 2.47) but did not have major renal impairment.

In an effort to restrict the use of indomethacin and limit the possibility of adverse effects to patients with greater chance of benefit, some studies have targeted infants with an asymptomatic PDA (instead of treating all premature infants prophylactically). In a meta-analysis[78] of three RCTs\[48-50\] (n = 97), indomethacin treatment of asymptomatic PDA (vs placebo/no intervention) reduced the frequency of symptomatic PDA (RR 0.36, 95% CI 0.19, 0.68) and duration of supplemental oxygen (weighted mean difference −12.5, 95% CI −23.8, −1.26). There was no evidence of effect on mortality, BPD, IVH, ROP or the total duration of ventilation.

5.5 Dosing Regimens for Indomethacin

Several dosing regimens of indomethacin have been used for prophylaxis and treatment of PDA (table II). The most commonly used prophylactic regimen includes three intravenous doses of 0.1 mg/kg every 24 hours, whereas treatment usually involves an initial dose of 0.2 mg/kg followed by two doses of 0.1–0.2 mg/kg every 12 hours.[48-50] In cases with no success with an initial course, or if the ductus reopens after initial closure, a second course may successfully close the PDA in up to 44% of cases.[79] The rate of clinical reopening of ductus may be higher in infants with a birth weight less than 1000 grams and if echocardiography shows residual luminal flow.[80,81] Although most clinicians will try more than one course of indomethacin before opting for surgical ligation, multiple courses have not been evaluated in controlled trials.

The choice of the 12-hour dosing intervals in indomethacin therapy is largely empirical. In a retrospective study, Rosito et al.[82] compared indomethacin infusions over a 4-hour period every 24 hours with a new regimen where indomethacin was infused over 30 minutes at a 12-hour dosing interval. Although there was a trend towards a higher rate of PDA closure and a lower need for surgical ligation of the ductus with the 12-hour dosing regimen, the differences did not reach statistical significance. The study also did not
evaluate for the frequency of adverse effects in the two treatment groups.

Several studies have evaluated continuous infusions of indomethacin as a strategy to minimize adverse effects. Yoshimoto et al.\(^{[83]}\) administered prophylactic indomethacin (within 6 hours of birth in 30 infants born between 23 and 24 weeks gestation at a continuous infusion of 0.01 mg/kg/hour for 12 hours. None of the treated infants developed a symptomatic PDA, compared with 11/15 controls (p < 0.001). There was no difference in mortality and early neonatal morbidities in the two groups. Similarly, in meta-analysis\(^{[84]}\) of data from two trials,\(^{[50,85]}\) there was no difference in the efficacy or safety of continuous versus bolus infusion of indomethacin for treatment of PDA. The frequency of ductal reopening and of adverse effects such as oliguria, azotemia, IVH, NEC or mortality was also similar between the two groups.

5.6 Ibuprofen Therapy for PDA

In a study of 160 infants weighing less than 1000 grams with a clinically symptomatic PDA, Richards et al.\(^{[5]}\) showed that 70 (44%) infants had PDA closure after a single course of ibuprofen, and 32/80 (40%) following a second course. Infants born prior to 26 weeks of gestation (n = 83) were less likely to respond after both the first (27.7% vs 63.6%; p < 0.001) or second (30.9% vs 60.0%; p = 0.026) courses. In other studies, oral and intravenous ibuprofen may achieve a similar efficacy in ductal closure. Gokmen et al.\(^{[52]}\) randomized 102 infants born with a birth weight less than 1500 grams to receive either oral or intravenous ibuprofen for closure of PDA. All infants received an initial dose of 10 mg/kg, followed by 5 mg/kg at 24 and 48 hours. The investigators detected a higher rate of PDA closure in the oral ibuprofen group than in the intravenous ibuprofen group (84.6% vs 62%) after the first course of the treatment (p = 0.01). Although clinical renal injury was not detected, infants receiving oral ibuprofen showed a rise in cystatin-C levels (a marker of renal function that reflects glomerular filtration rate better than serum creatinine) after treatment (p = 0.001), indicating that infants with borderline renal function may need careful monitoring. Infants receiving intravenous ibuprofen did not show these changes.

Ibuprofen has also been used for prophylaxis against PDA. Ohlsson and Shah\(^{[46]}\) performed a meta-analysis on seven studies (n = 931) comparing prophylactic ibuprofen with placebo/no intervention. Ibuprofen decreased the incidence of PDA (RR 0.36, 95% CI 0.29, 0.46; RD = −0.27, 95% CI −0.32, −0.21; NNT 4, 95% CI 3, 5) and reduced the need for surgical ligation. Results from two studies administering oral ibuprofen had similar results, but showed an increased risk of gastrointestinal bleeding (NNH 4, 95% CI 2, 17).\(^{[86,87]}\) Ibuprofen also negatively affected renal function. There was no difference in mortality, IVH and BPD.

5.7 Indomethacin vs Ibuprofen for Treatment of PDA

Jones et al.\(^{[88]}\) reviewed evidence from ten randomized trials to evaluate the effects of indomethacin or ibuprofen compared with placebo on PDA closure, morbidity and mortality in preterm infants with an echocardiographically or clinically significant PDA beyond 24 hours after birth. Included studies\(^{[44,48-50,63,89-98]}\) compared intravenous indomethacin versus intravenous ibuprofen (ten trials), intravenous indomethacin versus placebo (nine trials) and intravenous ibuprofen versus placebo (one trial). Both intravenous indomethacin (RR 2.39, 95% CI 2.05, 2.78) and intravenous ibuprofen (RR 2.40, 95% CI 2.03, 2.84) closed a PDA more effectively than placebo. Other studies\(^{[99,100]}\) have shown a similar efficacy of the two drugs. The two drugs also had a similar failure rate for PDA closure, ranging between 0% and 50%; Ohlsson et al.\(^{[51]}\) performed a meta-analysis on data from 19 trials (n = 956 infants) for failure rates after 1–3 doses of ibuprofen compared with indomethacin. They did not find a significant difference between the two groups (RR 0.94, 95% CI 0.76, 1.17; RD −0.02, 95% CI −0.07, 0.04).

5.8 Adverse Effects of Indomethacin vs Ibuprofen during Treatment of PDA

Little et al.\(^{[81]}\) reviewed the clinical course of 167 infants treated with indomethacin for a
symptomatic PDA, and noted adverse effects in 73% of patients. Indomethacin therapy was associated with thrombocytopenia (36%), azotaemia (31%), sepsis (30%), oliguria (25%), hyponatraemia (25%), IVH (16%), pulmonary interstitial emphysema (11%), NEC (8%), intestinal perforation (4%) and bleeding (3%).

In a systematic review of 19 studies (n = 956) comparing ibuprofen and indomethacin with placebo in preterm infants aged <37 weeks and with birth weight <2500 grams, Ohlsson et al.[51] detected a reduced risk of developing NEC with ibuprofen (RR 0.68, 95% CI 0.47, 0.99; RD −0.04, 95% CI −0.08, −0.00; p = 0.04). The proportion of infants with oliguria was also significantly lower in the ibuprofen group (RR 0.28, 95% CI 0.14, 0.54; RD −0.09, 95% CI −0.14, −0.05) than in those treated with indomethacin. Infants in the ibuprofen group also had lower serum/plasma creatinine levels 72 hours after initiation of treatment (weighted mean difference −4.70 mmol/L, 95% CI −8.88, −0.53). These differences in renal toxicity are consistent with physiological studies that show greater impairment of renal perfusion when exposed to indomethacin as compared with ibuprofen.[92,93,101,102] There were no differences in infants treated with indomethacin or ibuprofen in bilirubin levels, IVH, NEC, ROP, sepsis, rate of surgical ligation, length of hospital stay or mortality.

**6. Limitations of Pharmacotherapy for PDA**

Pharmacotherapy for PDA has been shown to be efficacious in achieving ductal closure but is associated with notable side effects. Studies evaluating COX inhibitors for treatment of neonatal PDA are frequently limited by small sample size and lack of precision, making it difficult to draw strong conclusions regarding dosing regimens, comparative efficacy and safety profiles of the drugs. Although both COX inhibitors and surgery are highly effective in closing the ductus, the routine use of COX inhibitors in preterm infants is now being increasingly questioned: RCTs show little evidence of benefit when used for the treatment of PDA; prophylactic COX inhibitor therapy has not improved neurodevelopmental outcome; COX inhibitors are associated with significant side effects; and there is a high potential for spontaneous ductal closure.[103-105] The ductus may close spontaneously by postnatal day 8 in up to 40% of infants born with a birth weight less than 1000 grams.[34]

**7. Conclusions**

Persistent patency of the ductus arteriosus is a major cause of morbidity and mortality in premature infants. Medical management of PDA in premature infants comprises fluid restriction and COX inhibitors such as indomethacin and ibuprofen. In selected cases, surgical ligation of the ductus is also an option. There is a need for novel clinical/laboratory markers for early identification of infants at risk of developing a persistent and symptomatic PDA. Such an approach could potentially allow most premature infants to receive expectant management and limit active treatment to a few selected patients.[103]

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