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REVIEW

Patent ductus arteriosus in the preterm infant: to treat or not to treat?

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Pharmacological and/or surgical closure of a hemodynamically significant patent ductus arteriosus (PDA) in the very preterm infant has been the standard of care over the past few decades. However, the rationale for closure of PDA has recently been challenged. In this article, the factors that have fueled the controversy of the approach to the management of PDA and the gap in our knowledge are reviewed in detail. In addition, the pros and cons of the different treatment strategies applied in clinical care are evaluated with a focus on discussing the available evidence in the literature. *Journal of Perinatology* (2010) **30,** S31–S37; doi:10.1038/jp.2010.97

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Introduction

The ductus arteriosus is a vital structure in fetal life where the systemic and pulmonary circulations function in parallel and thus cardiovascular function is dependent on the presence of shunts, such as the foramen ovale and the ductus arteriosus, between the two circulations.[1] However, after birth and transition to postnatal circulation, where the systemic and pulmonary circulations are in series, the presence of shunts between the two circulations is nonphysiological and, if sustained and significant, may lead to hemodynamic compromise. Indeed, the ductus arteriosus closes in the vast majority of term infants within the first 48 h after delivery. However, in about 50 to 70% of the extremely low birth weight (ELBW) infants (birth weight <1000 g), the ductus arteriosus remains patent.[2,3] For the past several decades, concerns over the increase in pulmonary blood flow and decrease in systemic perfusion have made the management of patent ductus arteriosus (PDA) a major focus in the care of preterm infants. Although closing the PDA by using a cycloxygenase (COX) inhibitor is the most common approach in addressing these concerns, other strategies such as fluid restriction and administration of diuretics have also been used often in addition to the use of COX inhibitors.

One of the most frequently asked and controversial questions in neonatal medicine is 'When should one consider closing the PDA by using a COX inhibitor?' It is generally accepted that a tiny (<1 mm) PDA in a hemodynamically stable 29-week-gestation preterm infant receiving no respiratory support does not warrant treatment at 24 h of age. On the other hand, a hypotensive 5-day-old 25-week gestation premature infant with a left-to-right shunt through a large (~ 3 mm) PDA who is receiving high ventilatory support is, in general, believed to benefit from closure of the PDA. Although the decision how to manage the PDA may be less controversial in these two extreme scenarios, this is not the case in most clinical situations. Indeed, among neonatologists in various institutions and even within the same center, there are significant differences in the approach to treat a PDA as far as timing, duration, dosing schedule and choice of the COX inhibitors are concerned.[4] Although there have always been differences in the treatment approach, the standard of care has been to close the PDA early on during the initial hospital stay. The main reason for this strategy is the physiological plausibility that systemic hypoperfusion and pulmonary overcirculation resulting from left-to-right shunting through the PDA could have long-lasting adverse effects on major organ systems. Epidemiological data showing associations between the presence of a PDA and some of the major complications of prematurity (see below) have strengthened the widely held belief that PDA is harmful. However, the wisdom of closing a PDA has recently been challenged.[5–10]

Potential role of PDA in complications of prematurity

There is an association between PDA and the development of bronchopulmonary dysplasia (BPD). Initially, the increase in fluid filtration into the lungs as a result of high blood flow is cleared by an increase in lymphatic flow.[11] However, persistence of left-to-right shunting through the PDA exhausts this compensatory mechanism, leading to pulmonary edema and an increased need of ventilatory support. Indeed, in the very low birth weight (<1500 g) infants with PDA, epidemiological data show a 1.9-fold increase in the odds of developing BPD.[12] This association is even

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more prominent in the extremely preterm infants with mild or no respiratory distress syndrome.[13]

With regard to the central nervous system, although some investigators have reported no change in cerebral blood flow (CBF) as a result of compensatory increase in cardiac output,[14] most studies have found CBF to be impaired in preterm infants with a PDA.[15–19] Doppler studies have shown that the negative effect of PDA on CBF mainly affects the blood flow during diastole, as evidenced by a decrease in flow velocity and increase in pulsatility or resistance index. Similarly, near-infrared spectroscopy and superior vena cava flow studies have demonstrated and suggested, respectively, a reduced CBF in the presence of a hemodynamically significant PDA.[20,21] A recent study found that the high cerebral oxygen extraction in preterm infants with a PDA returns to the suggested normal range 24 h after starting indomethacin treatment.[21] As oxygen extraction is inversely related to blood flow, this study indicates that babies with a PDA have low CBF but the flow normalizes following closure of the ductus arteriosus. These adverse effects of PDA on cerebral hemodynamics are believed but not proven to have a role in the pathogenesis of intraventricular hemorrhage (IVH).[22,23] However, this notion is strengthened by the fact that prophylactic use of indomethacin significantly decreases the incidence of IVH.[24]

As far as gastrointestinal system is concerned, studies have consistently shown a reduction in intestinal blood flow in the presence of a PDA as evidenced by reduced abdominal aorta and superior mesenteric artery (SMA) blood flow assessed by Doppler ultrasonography.[14,17,25,26] The decrease in blood flow occurs despite the increase in left ventricular output.[14] Observations in animal experiments support the findings of Doppler studies in humans.[27–29] In the preterm lamb, presence of even a small PDA defined by a shunt equal to 40% of the left ventricular output reduced the intestinal blood flow, and the magnitude of reduction in blood flow was inversely related to PDA size.[28] A recent study found that SMA mean velocity does not increase after feeding in preterm baboons with a PDA.[30] Therefore, both the baseline intestinal blood flow and the normal postprandial increase in intestinal blood flow are decreased in the presence of a PDA. As compromised intestinal blood flow is believed to have a major role in pathogenesis of necrotizing enterocolitis (NEC), presence of a PDA might put preterm infants at a higher risk for developing NEC.[31,32]

Controversy with regard to treatment of PDA

In the last few years, the controversy with regard to treatment of PDA has increased.[5–10] Some authors have raised the question whether PDA in an extremely preterm neonate is pathological at all and therefore whether one should be treating it.[5] Others have questioned the extent of treatment.[8] The main reasons for this controversy include that there is little evidence of a benefit of treatment of PDA from randomized controlled trials (RCTs), the failure of prophylactic indomethacin to improve neurodevelopmental outcome, the potentially significant side effects of COX inhibitors, and the relatively high incidence of spontaneous closure. Here we address these issues from the literature point of view and using our understanding of developmental hemodynamics.

As for the lack of convincing evidence for a benefit of treatment of the PDA, except for a few studies from several decades ago, all RCTs compared PDA treatment starting at a different postnatal age and allowed for rescue treatment of PDA in the control group if the ductus arteriosus remained open.[9] As the initial insult and the pathogenesis of comorbidities of interest such as NEC or BPD likely expand over many days and perhaps weeks, the available RCTs cannot evaluate the impact of PDA on these common complications of prematurity. On the other hand, the role of PDA in the development of complications that mainly occur in the first 1 to 3 postnatal days, such as pulmonary hemorrhage and IVH, might be ascertained by analysis of the findings of the RCT on the use of prophylactic indomethacin. However, even then it is not clear whether the beneficial effect of indomethacin prophylaxis in reducing IVH is mediated through ductal closure or through a direct stabilizing effect of indomethacin on brain blood flow that is believed to be independent of the drug's action on COX inhibition.

The second reason for the controversy is the failure of prophylactic indomethacin to improve the long-term outcome. Indeed, in the Trial of Indomethacin Prophylaxis in Preterm Infants (TIPP), ELBW infants were randomized to receive either a 3-day course of prophylactic indomethacin or placebo with the primary composite outcome of death, cerebral palsy, cognitive delay, deafness and blindness at corrected age of 18 months.[33] Although the study did show a decrease in the incidence of severe IVH and PDA, the primary composite outcome was not different between the two groups. The reason for the lack of long-term beneficial effects despite a decrease in the incidence of severe IVH is not clear, but has, among others, been attributed to an excessively large anticipated effect size.[34]

The third reason for the controversy is that the medications most commonly used to close the PDA are not without significant side effects. Fortunately, the adverse renal side effects and inhibition of platelet aggregation are, in the vast majority of the cases, transient. Although the clinical relevance of transient decrease in CBF following indomethacin administration is not known, the impairment of intestinal blood flow, especially with concomitant use of steroids, has been implicated in the pathogenesis of spontaneous intestinal perforation.[35–37] Although ibuprofen appears to have a better profile with regard to renal side effects and organ blood flows, the drug's effect on bilirubin metabolism and displacement of albumin binding, and the possible but recently debated association with pulmonary hypertension, have raised concerns.[38–40] Ibuprofen is thought to impair biliary excretion of bilirubin and therefore it raises serum bilirubin

level.[41,42] In addition, at higher serum concentration ibuprofen can displace bilirubin from its binding to albumin.[38] Indeed, a recent study showed that ibuprofen augments bilirubin toxicity in rat cortical neuronal culture.[43] The clinical significance of this potential neurotoxicity remains unknown. Data on the long-term outcome of preterm infants randomized to ibuprofen would be helpful in clarifying these concerns.

The fourth reason for the controversy is the relatively high rate of spontaneous closure. In the placebo arm of the prophylactic COX inhibitor studies, about 50% of the very preterm infants closed their ductus spontaneously or never developed evidence of a hemodynamically significant PDA.[33,39,44]

Watchful waiting approach

Given the high rate of spontaneous closure at least in the more mature very low birth weight infants and the concern over side effects of the COX inhibitors, it may appear reasonable to wait and see whether the ductus arteriosus closes on its own before considering treatment. In evaluating this approach, one needs to examine whether there is any drawback to not treating PDA until it declares itself. However, there are several concerns with this approach. By the time the ductus arteriosus declares itself, it may already be too late and it may have already contributed to the development of one of the feared complications of prematurity. Indeed, it is clearly not known how long the ductus arteriosus can be left open without worrying about its potential harmful effect. However, the individual patient's vulnerability likely depends on many factors, including the level of immaturity, postnatal age, existing comorbidities and the overall condition of the patient, as well as the adequacy of compensatory mechanisms and the vulnerability of the affected organ and the process of postnatal cardiovascular adaptation. For example, with regard to the brain, the highest vulnerability period seems to be during the first 12 h after birth, during which a larger ductus arteriosus is an independent predictor of low superior vena cava flow.[21] The second concern with the watchful waiting approach is the delay in initiation of feeding and reaching full enteral feeds.[45] Although clear evidence is absent, because of the increased risk for NEC, many neonatologists do not start enteral feeds in the presence of a significant PDA. Finally, the longer one waits, the less effective the COX inhibitor becomes at closing the ductus arteriosus. Indeed, prophylactic treatment is more effective than early symptomatic treatment, which in turn is more effective than late symptomatic treatment in closing the PDA.[46]

Management of a persistent PDA

Although the watchful waiting approach in initiating the first course of COX inhibitor described above will certainly decrease the number of preterm infants exposed to COX inhibitor, it will also result in more failure of ductal closure. If the ductus arteriosus remains open and the infant has documented or suspected cardiorespiratory complications, the persistent PDA may be managed by either a conservative approach or surgical closure.

Conservative management

Conservative management includes interventions such as strategies to elevate pulmonary vascular resistance, fluid restriction, diuretics and vasopressors—inotropes or inotropes. Data on the outcomes of conservative management in preterm infants are scarce. In a study from Western Australia, where surgical ligation was not a practical option as the nearest cardiac surgical center was >2000 miles away, the mortality rate was noted to be much higher in patients with an open ductus arteriosus compared with neonates with a ductus arteriosus closed either spontaneously or in response to exposure to a COX inhibitor.[47] After adjustment for initial disease severity, gestational age and other perinatal factors, there was still a fourfold increase in mortality in patients with a persistent PDA. Our group has studied preterm infants (gestational age $\leqslant$29 weeks and birth weight $<$1500 g, $n = 329$) to evaluate the impact of a persistent PDA on mortality.[48] We found that the mortality rate was significantly higher in those with a persistent PDA as compared with those with a closed ductus arteriosus. The difference in mortality rate persisted even when babies who died in the first week or first 2 weeks after birth were excluded. Next, adjustments were made for the factors that might affect mortality as identified by univariate regression analysis. We took into account the effect of gestational age, exposure to antenatal steroids, Apgar score at 5 min, initial disease severity (Critical Risk Index for Babies score), severe IVH, NEC, sepsis, exposure to a COX inhibitor and time to death using Cox proportional hazard regression analysis. After adjustments, we still found an eightfold increase in mortality in patients with a persistent PDA. Therefore, a persistent PDA appears to significantly increase the risk for mortality during the initial hospital stay. On the other hand, preterm infants with a small PDA at the time of initial hospital discharge have been shown to have a low rate of morbidity after discharge.[49] In this subset of patients, there is a high chance of spontaneous closure of the PDA after discharge.

Surgical closure

The second option for the treatment of a persistent PDA is surgical ligation of the ductus arteriosus. Although the procedure is generally considered to be safe, recent reports indicate that procedural complications such as left vocal cord paralysis may be more frequent than previously thought.[50,51] In addition, there are growing concerns about the immediate short-term and possible long-term effects of surgical ligation. The immediate adverse effects of concern include systemic hypotension, myocardial dysfunction and possible respiratory deterioration in the immediate

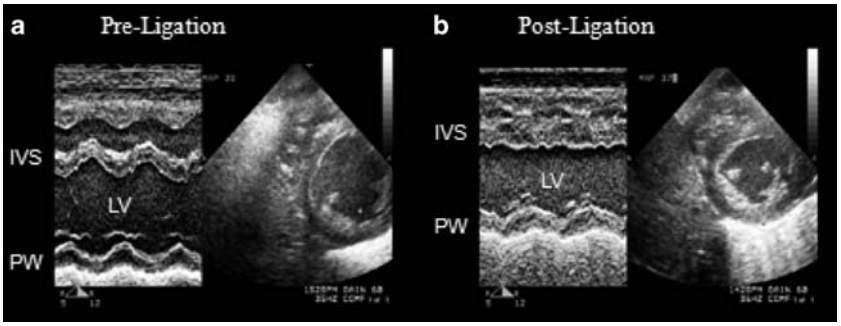

Figure 1 Some preterm infants develop a dramatic decrease in ventricular septal motion after ligation. This is a short-axis view of the heart with M-mode tracing. (**a**) Before ligation, the left ventricle (LV) is dilated and a good motion of the interventricular septum (IVS) and posterior wall (PW) is visible. (**b**) After ligation, the LV diameter is smaller and IVS is essentially motionless.

postoperative period. In about 30% of preterm infants undergoing PDA ligation, there is some degree of cardiovascular compromise as evidenced by the need for initiation or escalation of vasopressor–inotrope or inotrope treatment.[52–54] The reason for this deterioration is not known. In one study, lower gestational age, and higher respiratory support and, interestingly, exposure to antenatal steroids were associated with post-ligation hypotension.[52] Age at ligation might be another factor having a role in the development of postoperative morbidities, although the studies show conflicting results.[52–54] The sudden change in the preload and systemic vascular resistance at the time of surgical ligation is also thought to result in subtle myocardial dysfunction.[53] This transient deterioration in myocardial function in turn contributes to an exaggerated drop in left ventricular output.[53] In a subset of these babies, there is a significant deterioration in contractility of intraventricular septum (Figure 1). These deleterious hemodynamic effects may in turn contribute to the recently described long-term adverse outcome associated with surgical ligation.

Several studies have evaluated the effect of surgical ligation on long-term outcome. In the TIPP trial, 426 subjects had symptomatic PDA; 74% were treated with COX inhibitors; and 26% were treated with ligation after medical treatment had failed.[55] After adjustment for antenatal steroid exposure, gestational age, gender, multiple birth, mother's level of education and total dose of indomethacin, patients who had undergone surgical ligation had a twofold increase in the incidence of severe retinopathy of prematurity (ROP), BPD, neurosensory impairment and cognitive delay. But it is important to note that adjustment for the duration of exposure to PDA was not made in this study. As PDA ligations were performed mostly in the second or third week, the impact of prolonged cerebral and other organ blood flow disturbances could not be ruled out. The second large study looking at long-term outcome evaluated 446 preterm infants (<28-week gestation) who received prophylactic indomethacin.[56] In this study, the effects of PDA, PDA-related treatments and prenatal–neonatal factors were assessed by using four logistic regression models. Except for about twofold increase in the odds of developing BPD in the ligation group, there was no association of ligation or any PDA treatment factor with ROP, NEC, death, death or neurodevelopmental impairment (NDI), cerebral palsy or cognitive delay. It is interesting that most of the predictive effects a PDA and its treatment had on neonatal morbidity could be accounted for by the infants' level of immaturity. The third large study looking at the long-term effects of PDA treatment analyzed data from a large database.[57] ELBW infants ($n = 2838$) were divided into four groups: supportive treatment only, indomethacin only, surgical closure as primary treatment and surgical ligation after failure of indomethacin treatment. Comparing supportive treatment with indomethacin treatment, there was no difference in the incidence of NEC, BPD, NDI or death. However, both primary surgical ligation and ligation after indomethacin treatment increased the odds of developing BPD and having NDI at 18 months as compared to indomethacin group. However, when compared with the indomethacin group, ligation was protective against death. In this analysis, adjustments were made for several factors, including severe respiratory distress syndrome as a surrogate for disease severity. However, there was no adjustment made for the PDA characteristics such as size of the ductus and length of exposure to left-to-right shunting, or for factors with known impact on mortality and long-term outcome, such as IVH.

Obviously, these studies were not designed to evaluate the effect of ligation on long-term outcome. As such, the observed adverse outcomes can only be considered as associations. However, several animal studies have recently shed some light on this interesting topic. To investigate the effect of ligation on short-term brain development, preterm baboons were ventilated for 14 days, and on day 6, the ductus arteriosus was either ligated or left untreated.[58] The growth and developmental index scores were decreased in both the unligated and ligated groups compared with gestational-age matched controls. However, there was some evidence of brain growth sparing in the ligated group that was lacking in the unligated group. The unligated group had more brain injury as evidenced by the increase in astrocyte density and reduction in

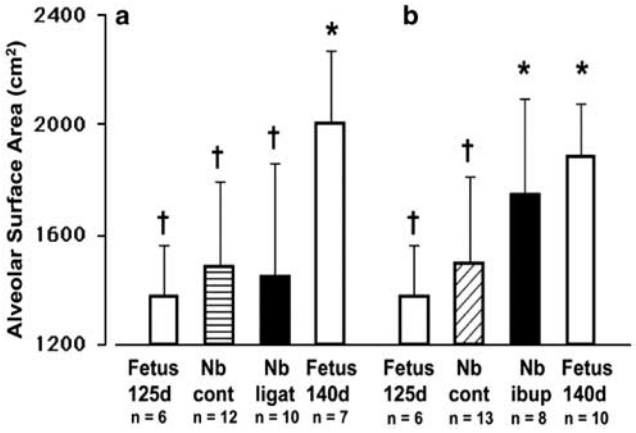

Figure 2 Digital image analysis of the total alveolar surface area of the right lower lobe in fetuses (125- and 140-day gestation) and in 14-day-old premature newborn baboons. Values are mean ± s.d.; *n*, number of animals. **P*<0.05, groups compared with the 125-day gestation fetus. †*P*<0.05, groups compared with the 140-day gestation fetus. (**a**) Total alveolar surface area in fetuses (125- and 140-day gestation) and in 14-day-old premature newborns (with an open ductus (Nb cont) or a ligated ductus (Nb ligat)). Total alveolar surface area increased with advancing gestation (comparing 125-day fetus with 140-day fetus). There was no increase in surface area after 14 days in preterm newborns with either an open ductus or a ligated ductus. (**b**) There was an increase in surface area (compared with 125-day gestation fetuses) when ibuprofen was used to close the preterm newborn ductus (Nb ibup), but no such increase was seen with an open ductus (Nb cont).[62]

oligodendrocyte density and surface folding index (gyrification). Therefore, as far as the brain is concerned, this study shows that ligation actually might provide some benefit over leaving a persistent PDA untreated. Yet, it is clear that caution should be exercised when attempting to apply these data obtained in a primate model to the human neonate.

In the only randomized trial of early ligation, ELBW infants were randomized to ligation on the first day versus ligation when symptomatic.[59] The incidence of NEC was lower in the ligation group, but there was no difference in the incidence of BPD as defined by oxygen requirement at 28 days. Recently, the data from this trial have been reanalyzed.[60] When BPD was defined as oxygen requirement at 36 weeks postmenstrual age, it was found that the ligation group had a higher rate of BPD. Other than the fact that the data are from the 1980s, one of the limitations of the study is that half of the patients in the control group were also ligated. Nevertheless, this study does support a possible role of ligation in the development of BPD. Findings from animal studies are also in agreement with the results of this study. Figure 2 shows the alveolar growth in preterm baboons ventilated for 14 days in two studies: the first study compared the effects of ductal closure with ibuprofen on the first postnatal day with those of no treatment, and the second study compared ligation on postnatal day 6 with no treatment.[61,62] Subjects exposed to ibuprofen maintained alveolar growth, whereas, in the control group with the ductus untreated, alveolar growth was retarded. In contrast, when the ductus was closed by ligation, the growth of alveolar surface area was also stunned just similar to the open-ductus group. Therefore, it appears that the beneficial effect of closure of the ductus on alveolar growth might be cancelled out by the procedure of ligation.

Conclusions

The current state of knowledge about PDA supports several conclusions. First, due to a lack of RCTs comparing common PDA treatment strategies (that is, COX inhibitor prophylaxis, early presymptomatic, early symptomatic, late symptomatic and surgical closure) with no treatment, a firm recommendation on a particular treatment strategy cannot be made. Second, a persistent PDA is not harmless and is associated with increased mortality. Third, surgical ligation of the ductus arteriosus is associated with significant short- and long-term complications, and it is an independent risk factor for developing BPD. Fourth, a strategy of decreasing the incidence of persistent PDA and therefore reducing the ligation dilemma is clearly desirable. The approach may entail initiation of an early presymptomatic treatment based on echocardiographic identification of significant PDA. Finally, progress in the following areas can improve treatment strategy of PDA: development of a measure of more accurate prediction of the ductus arteriosus that will spontaneously close and an accurate tool to differentiate between 'hemodynamically' significant and nonsignificant PDA. The increased use of functional echocardiography may help in identifying PDAs that have low chances of spontaneous closure earlier, as well as aid in limiting unnecessary exposure to a COX inhibitor to the minimum necessary doses required to permanently close the ductus arteriosus.[4,63,64] Similarly, advances in monitoring systemic hemodynamics and cerebral and renal–intestinal oxygenation by a combination of the use of echocardiography, electrical impedance and near-infrared spectroscopy may aid in early identification of the 'hostile' ductus arteriosus that deserves aggressive treatment.

Conflict of interest

The author declares no conflict of interest.

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