

Controversies in Management of Patent Ductus Arteriosus in the Preterm Infant

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Abstract

The management of patent ductus arteriosus in the preterm infant is one of the areas of clinical care that is subjected to great practice variation. This is sadly one of the consequences of widespread adoption of closure of the patent ductus arteriosus by pharmacological or surgical means without subjecting the treatment approaches to rigorous randomized control trials. The diverse approaches to treatment currently range from early and aggressive closure of the ductus arteriosus to a conservative approach of watchful waiting for spontaneous closure. This review reviews the complex management strategies of the ductus arteriosus highlighting the areas of greatest controversy that need to be addressed in future trials to provide greatest benefit to the vulnerable preterm infant.

Keywords: Patent ductus arteriosus; PDA; Preterm; Indomethacin; Ibuprofen; Ligation

Introduction

Patent Ductus Arteriosus (PDA) is the most common cardiovascular abnormality in preterm neonates with a reported incidence as high as 60% in Extremely-Low-Birth-Weight (ELBW) newborns less than 28 weeks gestation [1]. While the Ductus Arteriosus (DA) is important for prenatal and immediate postnatal circulation, its persistence beyond the transitional period is associated with neonatal morbidity and mortality [2]. However, there is little evidence of consistent effect of treatment of PDA on major preterm morbidities and aggressive attempts to close the DA is now being questioned [3,4]. The exact population of preterm babies that benefit from PDA treatment is unknown. Whether or not PDA should be treated, the timing of PDA treatment, mode, dose and duration of therapy is increasingly becoming a subject of great controversy.

Historical Perspective

The DA is uniquely positioned in the history of medicine. Its presence was originally recognized by Galen in the 2nd century AD and recorded in his anatomic compendia [5]. However, Galen and other early anatomists formed erroneous conclusions about the fetal and adult circulation and it was not until the 16th century that the DA was more accurately described [6,7]. The first surgical ligation of PDA performed in 1938 by Robert E. Gross of Boston Childrens Hospital heralded the true beginning of the field of congenital heart surgery [8]. The knowledge that prostaglandins were responsible for ductal patency, lead to the widespread use of cyclooxygenase inhibitors since the first trials published in 1976 [9,10].

Morphogenesis

The DA is a vascular connection between the proximal descending aorta and the main pulmonary artery near the origin of the left branch pulmonary artery. During fetal life, DA diverts placental oxygenated blood from the pulmonary artery into the aorta by-passing the lungs. The factors responsible for maintaining ductal patency in the fetus include: exposure to low partial pressure of oxygen, circulating or locally produced prostaglandins, especially prostaglandin E2 (PGE2), and local nitric oxide production [11].

Closure of the DA occurs in 2 steps: smooth muscle constriction resulting in “functional” closure of the lumen of the DA within a few hours of birth and “anatomical” occlusion of the lumen that occurs over the next few days or weeks. The functional closure is facilitated by physiological rise in blood oxygen tension and cessation of

placental function leading to loss of a major source for prostaglandin E2 (PGE2) [12]. Furthermore PGE2 levels also fall due to active metabolic clearance by the lungs. Histologically, the ductal wall contains a thick layer of smooth muscle, arranged in a spiral helix, which encircles the DA in both clockwise and counter clockwise directions and therefore suited for postnatal DA closure. Remodeling of the DA for its permanent anatomical closure is a complex process encompassing various mechanisms including development of intimal cushions and platelet plug with subsequent necrosis and fibrosis [13].

The immature DA has high threshold of response to oxygen, produces more prostaglandin and is also more sensitive to the relaxant effect of PGE2 and nitric oxide [14]. Even when the premature ductus does constrict, it remains relatively resistant to developing profound subendothelial hypoxia that stimulates cell death and remodeling. Delayed ductal closure is related to prematurity and exaggerated by comorbidities such as respiratory distress syndrome and sepsis. A genetic basis for ductal patency has also been suggested by mutations and polymorphisms within genes interfering with remodeling of vascular smooth muscle cells of ductal media [15].

Natural History of PDA

With the widespread use of medical and surgical strategies to close the DA since the 1970s, the natural history of DA is less well known. Historical observational studies in the 1960s have reported spontaneous delayed closure in premature infants [16,17]. In a prospective observational study of 65 infants with BW<1500 g, spontaneous DA closure occurred by 1 week of age in approximately one-third of preterm babies with BW of <1000 g and two third of babies >1000g [18]. In this study, in babies >1000g, 94% of DA closed prior to discharge. The median time to spontaneous closure was 7 days for infants >1000 g versus 56 days for infants ≤1000 g. Among a select group of VLBW

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infants with a persistent PDA at initial hospital discharge either from non-treatment or re-opening following initial treatment, spontaneous closure was common, occurring in the majority of infants, and usually occurring within several months of discharge [19]. After adopting a “conservative” approach to treatment of PDA, a cohort-controlled study in preterm infants <28 weeks gestation showed that of the 1/3rd of the conservatively treated infants where PDA remained opened, 2/3rd of these infants ultimately closed their duct either prior to discharge or before 6 months of life while 1/3rd needed closure in infancy via transcatheter coil embolization [20].

The spontaneous closure of PDA can be affected adversely by several perinatal and postnatal events, including growth restriction [21], late onset septicemia [22], low platelets [23] and excessive fluid administration during the first days of life [24]. Although surfactant itself has no direct effect on ductal hemodynamics [25], it may alter the pulmonary vascular resistance and lead to an earlier clinical presentation of the left-to-right shunt through the PDA [26].

Diagnosis of PDA

PDA presents clinically in the preterm infant as systolic murmur, bounding peripheral pulses, hyperactive precordium and wide pulse pressure. Echocardiography is used as the gold standard for diagnosis of PDA. The PDA is often clinically silent in the first 24 hours of birth. A blinded comparison of clinical and echocardiographic parameters in a cohort of preterm infants showed that the signs of bounding pulses, active precordium, and systolic murmur were of reasonable specificity but very low sensitivity in the first 3 to 4 days of birth for diagnosis of an echocardiographically defined significant PDA [27]. The study also showed that relying on clinical signs alone led to a mean diagnostic delay of 2 days. Other studies have similarly reported that precision and accuracy of clinical and radiological signs of a PDA with left-to-right shunting are unsatisfactory [28] highlighting the importance of echocardiography for a reliable early diagnosis of PDA. Repeated clinical examinations combined with serial echocardiography is an important practice for early detection and management of the PDA.

Clinical Consequences of PDA

A significant left-to-right shunting through the PDA may result in pulmonary overcirculation leading to clinical outcomes like pulmonary hemorrhage [29,30], RDS [31], and chronic lung disease [32]. It also steals blood away from the systemic circulation resulting in adverse consequences of necrotizing enterocolitis [33] intraventricular hemorrhage [34] periventricular leukomalacia [35], cerebral palsy [36] and death [37]. Although observational studies have consistently shown an association with the above adverse outcomes, there is lack of evidence whether PDA is truly causal or simply an association. Meta-analysis of trials assessing benefits of treatment have depicted no detectable reduction in neonatal morbidities [2]. This may be partly because the treatment themselves have adverse effects and added morbidities. Moreover some of the physiological explanations to the outcomes may be an oversimplification and do not take the adaptive mechanisms into account. For instance even in the presence of high ductal shunt volume, upper body blood flow may be relatively well maintained in infants outside the transitional period [38].

Clinical Versus Hemodynamic Significance

There is no consensus over the criteria to quantify the hemodynamic significance of the duct or appropriate treatment. The size of the ductus, the pattern of left to right shunt, volume of shunting causing left atrial dilatation and flow pattern in descending aorta are among

the few parameters quantifying the hemodynamically significant PDA (hsPDA) [39]. Harling et al. [40] found that among a range of echocardiographic criteria studied the ductus diameter appears to be the most important variable in determining the need for therapeutic intervention. Su et al. [41] described a sequence of pattern changes from pulmonary hypertension pattern to growing pattern or pulsatile pattern in those with clinically significant PDA. Pulsatile pattern had a sensitivity of 93.5% and specificity of 100% in predicting hsPDA. An increasing number of biomarkers representing cardiac stress, dysfunction or myocardial injury like Brain Natriuretic Peptide (BNP) are also emerging as diagnostic and prognostic markers for hsPDA [42] but they lack the sensitivity and diagnostic specificity to be clinically useful.

How much of this hemodynamic significance of PDA translates to clinical significance is currently unknown. Ductal shunting has been shown to be independently related to short term but not long term respiratory outcomes [43]. Similarly, a strong association was noted between early ductal size and Intraventricular Haemorrhage (IVH), probably mediated through low SBF [44]. More studies are needed to demonstrate hemodynamic consequence of hsPDA on long term neonatal outcomes. McNamara and Sehgal have proposed an individualistic and rational approach to treatment that combines echocardiographic assessment with clinical parameters [45].

Management of PDA

Treatment modalities

Watchful waiting for spontaneous closure: This has recently emerged as an option following emergence of evidence that current medical and surgical therapy does not improve the outcome that was intended by treatment. In older preterm infant with BW>1000 g with uncomplicated respiratory course where the likelihood of spontaneous closure is high, this may be the most prudent approach. While awaiting spontaneous closure, a strategy applied to infants with left to right shunt associated with congenital cardiac malformations has been proposed by some investigators [3]. This includes judicious fluid restriction and diuretics for congestive heart failure; use of minimal supplemental oxygen, permissive hypercapnia, avoidance or correction of metabolic alkalosis to minimize pulmonary vasodilation and application of continuous distending airway pressure to reduce pulmonary blood flow and increase systemic perfusion.

Medical therapy

Choice of drug: Cyclo-oxygenase inhibitors such as indomethacin and ibuprofen remain the mainstay of medical therapy. Indomethacin is most widely used but Ibuprofen is now being recommended as the drug of choice owing to reduction in the risk of NEC and transient renal insufficiency [46]. Success of PDA closure by paracetamol in a limited number of extreme preterm neonates have been reported [47], but further studies are needed to confirm its effectiveness and safety when used for this indication.

Adverse effects: Unfortunately the medical therapy of PDA is not without side effects. Little et al. [48] 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%). Similar adverse effects have been reported in other studies and it has been additionally shown that Ibuprofen may be associated with

lower serum creatinine values, higher urine outputs and less adverse peripheral vasoconstrictive effects compared to Indomethacin [49].

Dose and administration: Indomethacin is classically administered as 3 bolus doses at 12 h intervals although several different regimens for both Indomethacin and Ibuprofen have been described [50]. Indomethacin mediated reduction in systemic blood flow may be ameliorated by slowing the infusion rate to 20-30 minutes [51] or by continuous administration [52]. Rather than following a fixed dosing schedule, an indomethacin treatment strategy based on serial echocardiographic measurements of PDA flow pattern is associated with reduction in total doses of drug while being equally effective [41].

Number of courses: Studies using more than 2 courses of indomethacin are few with some evidence of increasing renal toxicity with increased doses. In a retrospective study, Sangem et al. [53,54] observed a 42% response rate after a second course of indomethacin and a 43%, with the third course of indomethacin, yielding a cumulative response rate to 3 courses of indomethacin of 90%. However, a higher increase of periventricular leukomalacia in those who received a 3rd course of indomethacin does raise some concern. Like Indomethacin, the closure rate of PDA after a second or third course of ibuprofen was similar to the closure rate after the first course but not associated with an increase in adverse effects [54].

Clinical factors that have been associated with permanent ductal closure in response to pharmacologic therapy include exposure to antenatal steroids, the absence of significant respiratory distress, reduced fluid intake, postnatal age at the time of treatment, and a longer duration of indomethacin treatment.

Surgical treatment: Surgical ligation is commonly used if medical therapy fails to close a significant PDA or contraindications exist to medical therapy. There is a high rate of variation in the rates of surgical ligation across the world with up to 24% of babies less than 27 weeks of gestation subjected to ligation in North America compared to 10% ligation rate in Australian units [55]. Surgical closure of the PDA involves either placement of suture ligatures or application of vascular clips. Clip application is a shorter procedure, requires less extensive dissection and therefore may be the preferred method of surgical closure [56]. Postoperative morbidities of PDA ligation include thoracotomy, NEC, IVH, wound infection, chylothorax, pleural effusion and vocal cord dysfunction [57]. Although the overall morbidity due to the procedure itself is low, it may entail transfer to another facility or operating room posing a significant burden to the fragile ELBW infant. Moreover, surgical ligation is often associated with impaired left ventricular systolic function, sometimes resulting in circulatory and respiratory collapse requiring marked escalation in intensive care support [58]. The postoperative cardiorespiratory instability may be reduced when ligation is delayed [59].

Timing of treatment

Timing of PDA treatment can be grouped as (1) Prophylactic (2) Presymptomatic (3) Early Symptomatic (4) Late symptomatic.

Prophylactic treatment

This involves giving treatment prophylactically within the first 24 h according to defined gestation or weight-based criteria. Indomethacin is the best studied with 2872 babies randomised in 19 trials [60]. This meta-analysis showed that prophylactic indomethacin reduced the incidence of major IVH and PVL but did not affect mortality or long-term neurodevelopmental outcome. Prophylactic PDA ligation may reduce NEC [61] but increases the incidence of BPD [62]. Given the

lack of effect on long term outcomes, evidence of spontaneous closure of DA in almost 1/3rd of VLBWs, potential vasoconstrictive effects of Indomethacin in other peripheral vascular beds, prophylactic therapy cannot be universally recommended.

Pre-symptomatic treatment

This relies on echocardiography for diagnosis of PDA before it is clinically apparent. Investigators have also used biochemical markers like B-type atrial natriuretic peptide (BNP) levels at 24 h of age to guide for early targeted treatment of hsPDA and avoid the unnecessary use of cyclooxygenase inhibitors in ELBW infants [63]. A comparison of early (day 3) with late (day 7) intravenous indomethacin in a prospective multicenter trial improved PDA closure rates but was associated with increased renal side effects and more severe complications in early treatment group while offering no respiratory advantage over late indomethacin administration in ventilated, surfactant-treated infants [64]. Similarly, Aranda et al. [65] did not show a difference in outcome with treatment of non-symptomatic PDA within 72 h of life in ELBW infants with ibuprofen or placebo based on echocardiographic criteria. Champions of early treatment of PDA have argued that day 3 may still be too late as the hemodynamic consequences of large duct are apparent within a few hours of birth. However, Indomethacin given to premature infants with a large ductus in the first hours of life detected by echocardiography showed no positive or negative effects on blood flow to the brain and upper body [66]. The results of the DETECT (Ductal Echocardiographic Targeting & Early Closure Trial) trial; targeting treatment to large ducts within the first 12 h of life are awaited [67].

Symptomatic treatment

The symptomatic approach, although most commonly used, is most difficult to classify due to variation in attributing clinical significance to presence of murmur to varying degrees of ventilator dependency or cardiovascular compromise. The evidence for this approach is mostly from a large historical trial that recommended administration of indomethacin only when non pharmacological supportive treatment fails as this was associated with fewer side effects [67]. With advancing postnatal age, dilator prostaglandins play less of a role in maintaining ductus patency, and indomethacin becomes less effective in closing PDA [68]. In infants who failed indomethacin treatment, an “aggressive approach” of early surgical ligation (within 2 days) compared with “conservative approach” of delaying ligation till development of significant cardiorespiratory compromise showed no significant differences in the rates of BPD, sepsis, ROP, neurologic injury, or mortality in a cohort controlled study [20]. The risk for NEC was significantly less in the conservatively treated infants, even though they received enteral feedings in the presence of a PDA.

Conclusion and Future Directions

The variation in management of PDA due to conflicting evidence that it truly impacts the long-term outcome brings a sense of urgency to conduct robust trials that could identify which group of preterm infants benefit most from early treatment of PDA and which group can be managed expectantly with watchful waiting or delayed treatment. Lack of benefit of PDA treatment on major neonatal outcomes may relate to the lack of standardization of diagnosis of hemodynamic significance, variability in timing of intervention and diagnosis, difference in therapeutic regime, and failure of consideration of co-morbidities. A scoring system that combines echocardiographic, clinical and lab criteria of PDA that correlate with adverse outcome and is subsequently validated in a well designed trial will go a long way in standardizing care and improving outcomes in this vulnerable population. Until more

evidence comes up, the risk of treatment has to be carefully weighed against benefit offered.

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