

Controversies in the Management of Patent Ductus Arteriosus in Preterm Infants

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Abstract

Patent Ductus Arteriosus (PDA) is present in 40-60 percent of preterm infants with its incidence inversely proportional to the gestational age. Management of PDA in extreme prematurity and extremely low birth weight infants is controversial specially with newer literature showing no significant benefits in long term outcomes in infants who were treated as compared to those who were not treated. Further the mortality and morbidities in preterm infants may not be entirely related to PDA as previously ascribed. Hence there is controversy as to which preterm infants benefit from treatment, when should they be treated and which treatment modalities should be used. We have reviewed the current literature to bring out the controversies in the answer to these questions.

Keywords: PDA; Hemodynamic Significant; Outcomes; COX inhibitors

Introduction

Persistent patent ductus arteriosus (PDA) was first described in 1757 but it was given attention as a congenital cardiac malformation in mid nineteenth century. The classic Gibson's murmur heard in PDA was named after Dr. Gibson, who first described it. First surgical ligation was successfully performed in a 7 year old child and published in 1938 by Dr. Gross. Catheter based ductal closure was first performed in 1971 [1].

PDA is present in 40-60 percent of preterms with its incidence inversely proportional to the gestational age [2]. The ductus arteriosus serves as an important physiological communication in prenatal life but its persistence in postnatal life is considered pathological due to its associated morbidity and mortality. Failure of closure of ductus leads to over circulation of pulmonary and hypoperfusion of systemic circulation. It is associated with higher incidence of mortality and morbidities such as bronchopulmonary dysplasia (BPD), pulmonary hemorrhage, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) and renal impairment leading to interventions to close the PDA [3-5].

Functional closure in term infants occurs within few hours after birth and anatomical closure takes about 18-21 days. In older preterm infants with birth weight more than 1500 g ductus closes within first four days of life in 95% of the infants [6]. Spontaneous ductal closure in less than 1500 g (ELBW) infants is seen in about 34% of the cases and is dependent on gestational age and severity of presence of respiratory distress syndrome (Figures 1 and 2) [6]. The patency of PDA is primarily dependent on oxygen tension and levels of circulating prostaglandins. High postnatal oxygen tension leads to depression of voltage-dependent potassium channels that increases the influx of calcium in smooth muscle cells lining the duct leading to vasoconstriction and ductal closure. For anatomical closure, smooth muscle hypoxia associated with vasoconstriction leads to apoptosis and remodeling [7,8]. Further, prostaglandin (PG) E2 binds to its receptor on the smooth muscle cell around the duct and leads to increased cyclic adenosine monophosphate, protein kinase A and decreased myosin light chain kinase causes vasodilatation of the duct. Prematurity is associated to increased sensitivity of the smooth muscle cells to the circulating PG [9].

Management of PDA in extreme prematurity and ELBW infants

is controversial specially with newer literature showing no significant benefits in long term outcomes in infants who were treated as compared to those who were not treated. Further the mortality and morbidities in preterms may not be entirely related to PDA [10]. Hence presently there is controversy as to which preterm infants should be treated, when should they be treated and which treatment modalities should be used? To answer these questions extensive search was performed in PubMed from 2005 onwards using terms as preterm, PDA, ductus arteriosus, hemodynamically significant, treatment, surgery, indomethacin, ibuprofen, acetaminophen, heart failure, outcomes and mortality.

Types of Treatment Approaches

The various treatment approaches for the preterm infants are related to the timing of their treatment - prophylactically, asymptomatic but after confirming presence of PDA or only those PDA which are symptomatic.

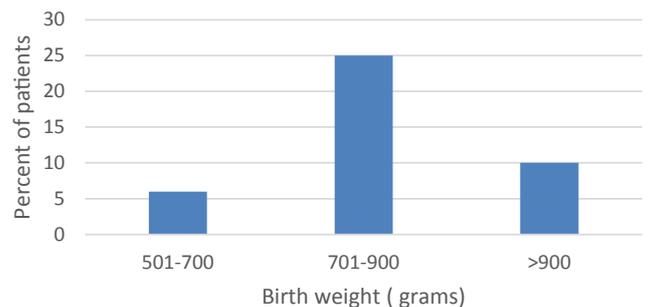


Figure 1: Relationship between birth weight and incidence of PDA.

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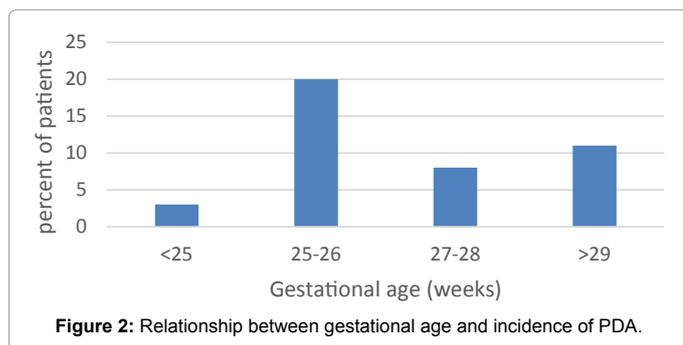


Figure 2: Relationship between gestational age and incidence of PDA.

Prophylactic treatment

Prophylactic treatment is defined as when the infants are treated within 24 h of life. Pulmonary vascular resistance and pulmonary artery pressure decrease after birth and PDA manifests by 2-3 days, hence prophylaxis window is before that period [11]. Maony et al. reported that this approach was more beneficial in infants less than 1000 g. It was related to decreased incidence of symptomatic PDA, need for future surgery for ductal closure and associated IVH [12]. But studies performed later did not confirm these findings and showed no decrease in morbidity and mortality. Rather prophylactic treatment was associated with increased incidence of hypoperfusion to cerebral, gastrointestinal and renal vascular beds, and associated gastrointestinal bleeds. Hence this approach has fallen out of favor [12].

Treatment of all infants after diagnosis of PDA is confirmed

This method offers advantage as it spares preterm infants without PDA from unnecessary treatment. Metanalysis from three trials showed this approach was associated with decrease in duration of supplemental oxygen along with decreased number of symptomatic PDA but it was not associated with decreased incidence of mortality, BPD, IVH, ROP or time on ventilator. Multiple studies showed no benefit in long term outcomes. Hence this treatment approach is being used less often by the clinicians [13].

Treatment of symptomatic infants

This method is used only to treat all the infants who are diagnosed with “hemodynamically significant (hs) PDA”. But the definition of hemodynamic significant PDA is variable [2]. It is essentially a clinical diagnosis corroborated with laboratory and echocardiographic variables. Clinical presentation associated with hs PDA commonly include gestational age, weight, clinical presentation such as bounding pulses and wide pulse pressure, sepsis [14], associated with laboratory findings of organ dysfunction (abnormal kidney and liver function tests), increased natriuretic peptide (BNP or NT-proBNP) and cardiac troponin T (cTnT) [15]. Echocardiographic findings such as the size of PDA, left atrium/aorta ratio, internal diameter of ductus to body surface area ratio, reversed diastolic flow in descending aorta, left sided heart dilatation and associated mitral regurgitation also help in quantification of clinical and laboratory parameters [14]. Decision making in individual clinical scenario can be extremely challenging, subjective and dependent on the provider. Despite few reports where hs PDA are defined [16], there is lack of agreement among the providers on the definition of hs PDA. Echocardiographic parameters are not completely reliable due to the variability in the experience of the performer and process of performing echocardiography. Also, a given ductal size may be insignificant for a higher weight/ gestational infant when compared to smaller infant as the presentation is related to the shunt size rather than anatomical size. Furthermore depending

solely on clinical diagnosis is usually related to delay in treatment of hs PDA by two or more days. This delay can be associated with increased refractoriness to the pharmacological therapy and may be related to higher rate of surgical ligation [2].

Modalities of Treatment

Treatment for PDA has evolved from surgery to pharmacological treatment to conservative management or a combination depending on the clinical scenario and the provider’s preference and availability of the surgical support. After successful trials of prostaglandins for closure of PDA, pharmacological treatment with cyclo-oxygenase inhibitors became mainstay [17]. Surgery is reserved for refractory cases. The use of prospective studies has shown no benefit in the incidence of mortality and morbidity between the infants treated with prophylactic surgery as compared to prophylactic medical therapy [18]. Cochrane review also reported no statistical benefit in long term outcomes for those treated initially with surgery as compared to those treated with cyclooxygenase (COX) inhibitors [19]. Table 1 shows the comparison of various treatment modalities [20]. Pharmacological treatment is preferred over surgical intervention as latter is associated with short and long term side effects related to surgery and anesthesia. These complications include higher incidence of death, left vocal cord and diaphragmatic paresis, intraoperative bleeding, chylothorax and pneumothorax [2]. Recently, post-surgical ligation syndrome has been described which entails ionotrope refractory hypotension and adrenal insufficiency that develops after surgical ligation and is related to myocardial dysfunction and respiratory worsening in the immediate postoperative period [21]. It is seen in half of the babies undergoing ligation [22]. Preterm myocardium is inefficient to compensate for sudden changes in afterload related to closure of the hs PDA and its associated decreased preload. As the myocardial of the preterm infants is mainly dependent on L-type calcium channels for contraction and there is paucity of T-tubule system the preterm infants are not able to respond to the sudden increase in afterload due to inability to increase their myocardial contractility [23]. Furthermore, their myocardium has less elastin fibers and more non-contractile collagen. Hence there is decreased diastolic filling related to decreased preload due to the sudden decrease in left to right shunting after ligation [24]. Preterms are at increased risk of hemodynamic instability which can be increased with surgery and associated anesthesia leading to decreased perfusion in brain and associated poor neurodevelopmental outcome [25]. NEC is another short term complication which could be related to surgery, though it is controversial [2]. Long term outcomes of surgery demonstrate no pulmonary benefit and may even have increased incidence of BPD due to arrest in alveolarization in the lungs. There are reports of increased incidence of retinopathy of prematurity (ROP),

Treatment Option	Advantage	Disadvantage	Cost	Complications
Fluid restriction and expectant management	No exposure to drugs	Lower success rate	Less expensive	Delays treatment Decreased response to COX inhibitors
Pharmacological	High success rate Non invasive	May require multiple courses	Expensive	Drug side effects
Surgical	High success rate Good option where drugs contraindicated	Invasive	Expensive due to post-operative costs	Surgery related complications and BPD, ROP and neurosensory impairment.

Table 1: Comparison of various PDA treatment modalities.

risk of neurosensory impairment and cognitive delay at 18 months, especially if surgery was performed within 10 days of life [26].

Methods used in surgery for closure of PDA include use of coils, vascular clips and suture ligation by traditional intercostal incision or by video-assisted thoracoscopic approach. Coils were used for small PDA residual shunts that commonly resolve on their own. Device occlusion is preferred with children in moderate to large PDA. Even though invasive it is generally considered to be safe. Percutaneous closure is an alternate option with the advantage of leaving no scar but may not be as effective in infants less than 1000 g [27,28]. Surgical ligation has also evolved into two basic approaches- early ligation and selective ligation. Early ligation is defined as closing the duct when medical treatment has failed irrespective of the degree of shunting or ventilator requirement. Selective ligation is done only if there are hs PDA. Selective ligation has been shown to be associated with improved neurodevelopmental outcome as compared to early ligation [29].

Pharmacological treatment includes use of COX inhibitors and paracetamol. Indomethacin and ibuprofen are the COX inhibitors used for treatment of PDA. Both have almost equal success in closure rates with ibuprofen having the advantage of lower risk of NEC and transient renal insufficiency [30]. Potentially serious side effects exist with medical management which may vary in incidence depending on the agent used. Indomethacin is associated with adverse effects such as renal circulation insufficiency and decreased platelet function due to inhibition of platelet aggregation though these are usually transient. One adverse effect clinically of concern is related to diminish intestinal blood flow, especially with concomitant use of steroids, and is a significant risk factor for spontaneous intestinal perforation. Fortunately, ibuprofen has decreased incidence of renal side effects and less decrease in organ blood flow [31], but its role in neurotoxicity due to its effect in bilirubin metabolism is debatable. Recent studies have shown that it displaces bilirubin decreasing its binding to albumin and releasing unconjugated bilirubin in the serum making it more likely to cross blood brain barrier [32]. Recently, pulmonary hypertension has been reported with ibuprofen use [33]. More recently paracetamol has been used for ductal closure as first line therapy because of its low cost and safety profile. It can be safely used in infants who have intestinal issues and noted to have success in closing PDA between 80-100% in infants born between 24-32 weeks [34].

Failure of treatment or relapse after initial success in closing the duct with indomethacin is between 13-53%. Ibuprofen also has variable success between 45-92% after the first course. In extremely preterm infants the second course of indomethacin showed successful closure in 44% patients [35]. The closure rate declines to almost 20% as observed in a study following multiple courses. Persistence of PDA following medical management and not followed by surgical ligation was a significant risk factor for death compared to children with closed PDA [36].

Conservative therapy is another modality used and requires watchful monitoring in anticipation of spontaneous closure. It is important to consider the rate of spontaneous PDA closure before starting treatment. It is estimated that in majority of infants with more than 30 weeks' gestational age will close by day four of life and in infants less than 30 weeks with severe respiratory distress ductus shall close in 60% by day four of life [3]. About 70% of infants with gestational age more than 28 weeks will have spontaneous closure in first 10 days of life. In less than 27 weeks gestational age babies 75% infants will have spontaneous closure by end of first year. Hence it is important to wait and give adequate chance for the ductus to close as medical or surgical interventions are associated with side effects [3]. In a metaanalysis, restriction of fluids to decrease total blood volume and decrease pulmonary overload had shown that it has no effect on oxygen requirement, ductus size, flow velocity in ductus, systemic blood pressure [37]. It does decrease blood flow in superior vena cava and superior mesenteric artery. Furosemide is used with same intentions but is no longer recommended as it increases COX inhibitor therapy failure by increasing prostaglandin release and hence keeping the duct patent [38].

Is PDA Even Pathological in Preterm?

Randomized controlled trials performed to evaluate the associations between PDA and development of NEC and BPD have shown positive association but the contribution of PDA in their causation is still not clear. These comorbidities that co-exist with prematurity which could be more important in their pathogenesis than presence of PDA which is also associated with prematurity. Further, decreased incidence of short term complications associated with PDA like IVH and pulmonary hemorrhage after prophylactic indomethacin use for closure of ductus does not imply causation [39]. The benefits of indomethacin prophylaxis in reducing IVH is not solely through ductal closure and maybe related to direct stabilizing effect of indomethacin on brain blood flow independent of the drug's action on COX inhibition.

In the Trial of Indomethacin Prophylaxis in Preterm Infants (TIPP) study, ELBW infants were randomized to receive prophylactic indomethacin or placebo and primary outcomes that were evaluated were death, cerebral palsy, cognitive delay, deafness and blindness at corrected age of 18 months. Decreased incidence of severe IVH and PDA were observed in the indomethacin group but the composite outcomes were the same in both groups [40]. Metaanalysis have shown that early PDA closure has no effect on neonatal morbidity including BPD, NEC neurosensory impairment, and mortality or even combined outcomes [41]. Even decreased incidence of moderate to severe IVH associated with early closure does not translate into better neurodevelopmental outcome [42]. Table 2 details various trials reported to evaluate the management of PDA.

Study	Year/Location	Study design	Summary of Outcomes
DETECT Trial	2013/Australia	Randomized placebo-controlled trial	Early ultrasound targeted treatment of large PDA resulted in decreased incidence of pulmonary hemorrhage and medical treatment but no effect on mortality and abnormal cranial USG.
TIPP Trial	1993-2001/Multicenter involving 32 NICUs in United States, Australia, Canada and Hong Kong	Randomized double blinded trial	Indomethacin prophylaxis decreases severe IVH need for surgery but no improvement in death or disability at 18 months.
National Collaborative Trial	1983	Randomized control trial	Infants randomized to surgical ligation had higher incidence of pneumothorax and ROP vs. medical management; no difference in other outcomes.
Hammerman et al.	In progress/Australia	Clinical trial	Testing paracetamol vs. placebo

Table 2: Clinical trials for treatment of PDA.

In conclusion there is lack of consensus regarding definition of PDA. Though, there are some parameters that can be used but are not universally applicable in all infants and acceptable by the medical providers. Further, identification of group of infants that benefit from treatment needs to be better defined. Furthermore, there is evidence that not only the type of modality but the age when it is used may have different results. More studies are needed to define which infants need treatment and how and when should they be treated. Large multicenter studies with long term follow up is needed to see if the treatment of PDA is associated with better short and long term patient outcomes.

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