Review Article

Patent ductus arteriosus in preterm infant: Basic pathology and when to treat

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ABSTRACT

The incidence of patent ductus arteriosus (PDA) in premature neonates varies according to the gestational age and respiratory status. Failure of PDA closure in preterm infants with respiratory distress syndrome results in a left to right shunt across the duct which may lead to pulmonary congestion and deterioration in respiratory status. Although indomethacin and ibuprofen are the main stay of medical treatment, conservative approach by restricted fluid and applying continuous positive airway pressure (CPAP) may be effective in prevention of PDA without complication. The daily clinical round debate on how to diagnose, when, and how to treat PDA in preterm neonates will be discussed with details in this review.

Key words:
Patent ductus arteriosus; Preterm infant; Indomethacin; Ibuprofen; Surgical closure.

INTRODUCTION

Patent ductus arteriosus (PDA) is an old problem with present clinical dilemma. It has been described by Galen in the first century with the description of postnatal circular adaptation [1]. However, it was not until 1888 that Munro conducted the dissection and ligation of the ductus arteriosus in an infant cadaver, and it took another 50 years before Robert E. Gross, in 1938, successfully ligated a patent ductus arteriosus (PDA) in a young child in Boston [1]. It is largely unknown that in the same year and before Gross, Emil Karl Frey, a Surgeon at the Medizinische Akademie in Dusseldorf, Germany, already ligated a PDA successfully. Assuming that he would soon perform more ligations, Frey did not publish his findings, and accordingly this historic ductal operation escaped attention [1]. In fetal life the ductus arteriosus (DA) serves to divert ventricular output toward the placenta and away from the lungs by connecting the main pulmonary artery to the descending aorta.

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Fetal duct patency is regulated by low oxygen tension and prostanoids, mainly prostaglandin E2 (PGE2) and prostacyclin (PGI2). These substances produced by placenta and were not cleared by fetal lungs [2]. In post natal life the duct closes anatomically within three days in full term infant, because of increase systemic blood flow, gradual decline in pulmonary pressure, increase arterial oxygen tension and decreased in prostaglandin and its receptors which lead to duct remodling (Table 1) [3,4]. In contrast, preterm infants fail this remolding mechanism which leads to persistent DA, that have clinical consequences depending on the degree of left-to-right shunting known as stealing phenomena. With the increase in pulmonary blood flow it can lead to hemorrhagic pulmonary edema, loss of lung compliance, and deterioration of respiratory status, which ultimately leads to chronic lung disease (CLD) [4].

Table 1- Factors controlling the duct closure after birth

Factors which constrict DA	Factors which prevent DA constriction
Increase in arterial oxygenation (PaO2)	Hypoxia
Decrease in pulmonary blood pressure flow	Increased pulmonary pressure
Decrease in circulating PGE2	Increased sensitivity to vasodilating effect of PGE2 and NO coupling with down regulation of the receptors
Decrease in PGE2 receptors	Fluid

DA - Ductus arteriosus, NO - Nitric oxide, PGE2 - Prostaglandin E2

Despite being a focus of neonatal research for many years, controversy still surrounds the role of PDA in adverse neonatal outcome and the best method and appropriate timing of treatment. Some of the uncertainty over the importance of PDA to the preterm infant relates to common misconceptions about the natural history of preterm ductal shunting and about the best method for diagnosis. The objective of this review article is to provide the best evidence of diagnosis, treatment and outcome of preterm infant with PDA.

Incidence

The incidence of PDA in term infants has been estimated to be 55% if screened in the first 24 hours after birth and 57 per 100 000 live births after the second week of life [5,6].

Whereas, in preterm infant the incidence depend on how small is the infant and the respiratory condition after birth, every third preterm infant with a birth weight (BW) of 501 to 1500 g (very low birth weight -VLBW) is expected to have a persistent PDA [3]. Furthermore, 55% of infants who weigh <1000 g (extremely low birth weight, ELBW) have been described to have a symptomatic PDA that needs medical treatment (Table 2) [7].

In a hospital based study at King Khalid university hospital, Saudi Arabia, the prevalence of PDA varies according to the gestational age and found to be 25%, at < 28 weeks gestation, and 12% at 28-32 weeks.

Although spontaneous permanent DA closure occurs in variable percentages, Koch, et al reported closure in up to 34% of ELBW neonates at 2 to 6 days postnatal age, and in the majority of VLBW neonates within the first year of life [8]. The majority of preterm infants (60% to 70%) of less than 28 weeks gestation receive medical or surgical therapy for a PDA, usually with the intention to prevent respiratory decompensation, heart failure, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and death.

Table 2- Incidence of spontaneous permanent closure of DA in ELBW neonates [7]

Gestational age (weeks)	Patients (No)	% of patients
<25	3	2.1
25-26	20	1.05
27-28	8	0.7
>29	11	0.53

DA - Ductus arteriosus, ELBW - Extremely low birth weight

Clinical assessment

The clinical manifestations of PDA depend on the magnitude of the left to right shunt, which lead to increase pulmonary venous pressure and pulmonary congestion. In the setting of preterm respiratory distress with low plasma oncotic pressure and increased capillary permeability, PDA can result in interstitial and alveolar pulmonary edema and decreased lung compliance, which, in turn, will lead to higher ventilator settings, prolonged ventilation with potentially high oxygen load, and probably to all preterm morbidities [9]. In ELBW and VLBW infants, lung injury is often combined with myocardial dysfunction due to left-sided volume overload that, together with a ductal steal phenomenon, will worsen systemic perfusion especially when severe hemorrhagic edema had developed. Therefore, preterm infants born at < 1000 g are susceptible to hypo-perfusion of vital organs and resultant additional co-morbidities such as IVH, PVL, NEC, and (pre) renal failure. However, all these morbidities can developed in preterm infant without hemodynamic significant PDA [10].

Clinical diagnosis

The patency of the duct is suspected when the ventilation support is difficult to wean, along with the presence of systolic murmur at the left upper sternal edge radiating to the back, active pericardial impulses, widened pulse pressure and prominent or bounding peripheral pulses. However, these clinical signs have very low sensitivity for the diagnosis, and most of the significant patent ducts do not produce clinical signs. Davis and colleagues reported that high percentage of patients with PDA had no murmur, and observed that bounding pulses were also a poor independent predictor factor for the presence of PDA [11]. In line with these findings, Skelton and colleagues evaluated clinical signs over a period of several days and demonstrated that relying on clinical signs led to a mean diagnostic delay of 2 days, with a range of 1 to 4 days [12]. These authors also found that clinical signs of PDA were specific but insensitive. Hence, a murmur heard in a preterm infant is likely to be due to patent ductus arteriosus; however, absence of a murmur does not exclude a PDA [12]. Therefore Doppler flow echocardiography is required to confidently confirm the diagnosis of PDA [13]. However, the main challenge would be that pediatric cardiologists or their team members are not always available to perform echocardiography and assist with a timely diagnosis of PDA. Therefore, neonatologist or neonatal fellows are required to develop the skills and training in performing echocardiogram.

The primary questions that can be answered by neonatal Doppler flow echocardiography are:

1. Is the heart and great vessel are structurally normal?
2. Is the ductus arteriosus patent?

3. Is the ductal shunting hemodynamically significant?
4. What is the volume of ductal shunting (by calculating pulmonary to the systemic blood flow (QP:QS) ratio)?

Echocardiographic evidence of symptomatic ductal patency includes ductal diameter of more than 1.5 mm in the first 30 hours after delivery, left atrial/aortic root ratio more than 1.5 and pulsatile transductal flow (Vmax) less than 1.8 m/second [14,15].

Treatment

Before the decision to treat is taken, it is important to distinguish between a clinically significant and non-significant PDA. The hemodynamically significant PDA causes deterioration in the respiratory status of the preterm infants by increasing ventilator support and oxygen requirement in a previously weanable infants. In non-hemodynamically significant duct, conservative management is the first option, which include fluid restriction (not more than 130ml/kg) after the third day of life, and adjustment of ventilation by lowering inspiratory time to as low as 0.35 seconds, and applying higher peak end expiratory pressure (PEEP) of 6 to7. In a retrospective analysis of 109 preterm infant <30 weeks gestation with respiratory distress syndrome required mechanical ventilation and surfactant replacement, PDA was diagnosed in 31 infants (28%), all of them treated conservatively with a successful closure of up to 80%, only 6 neonates required medical treatment and surgical ligation. There were no significant complications in conservatively treated neonates [16].

If treatment with drugs is to be used, early treatment is more likely to result in successful ductal closure and prevent adverse pulmonary outcomes. For this reason, indomethacin prophylaxis is the preferred regimen. The Trial of indomethacin prophylaxis (0.1 mg/kg per dose every 24 hours for three doses) in extremely low-birth weight infants showed a significant decrease in both the incidence of PDA and the need for surgical ligation. However, there was no significant benefit in reducing BPD, other prematurity related complication (like retinopathy of prematurity (ROP) and NEC) and long term neurological morbitidies [17]. An important positive remark of this trial was the significant reduction in severe pulmonary hemorrhage in the first week of life [18].

The other alternative regimen is the rescue treatment with either indomethacin or Ibuprofen. Both agents are equally efficacious, achieving successful closure of a PDA in 75–93% of cases [19]. In a Cochrane systematic review by Olsson, there was no statistically significant difference in the effectiveness of ibuprofen compared to indomethacin in closing PDA [19]. Ibuprofen reduces the risk of oliguria, but may increase the risk for chronic lung disease (CLD), and pulmonary hypertension [19].

The standard dose of rescue treatment with indomethacin is 0.1mg/kg/dose at 24 hours interval and to repeat the course if the duct clinically or by repeated Echocardiography persists. There is no practical advantage in prolonging the course for 6 days. The reduction of transient renal impairment in short course does not outweigh the increased risk of NEC [20]. Another alternative regimen is intravenous or oral Ibuprofen in the dose of 10mg/kg then 5mg/kg at 24hour and 5mg/kg at 48 hour. In very low birth weight infants, the rate of early ductal closure with oral ibuprofen is at least as good as with the intravenous route [21].

If the medical therapy in appropriate dose and time failed to close the duct, the choice of repeating the course or surgical closure is controversial, ligation is associated with adverse pulmonary and neurodevelopmental outcomes, and multiple repeated courses of indomethacin (more than three doses) are associated with an increased incidence of NEC. In

institutions where the rate of NEC is high, ligation may be a better alternative; otherwise, a repeated course of indomethacin is recommended prior to proceeding to ligation. Ligation should be reserved only for infants who failed pharmacologic treatment and continue to have a symptomatic PDA by echocardiographic criteria [20,22].

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

REFERENCES

1. Kaemmerer H, Meisner H, Hess J, Perloff JK. Surgical treatment of patent ductus arteriosus: a new historical perspective. Am J Cardiol 2004; 94:1153-54.
2. Schneider DJ, Moore JW. Patent ductus arteriosus. Circulation 2006; 114:1873-1882. doi: 10.1161/CIRCULATIONAHA.105.592063.
3. Bouayad A, Kajino H, Waleh N, Fouron JC, Andelfinger G, Varma DR, et al. Characterization of PGE(2) receptors in fetal and newborn lamb ductusarteriosus. Am J Physiol Heart Circ Physiol 2001; 280:H2342-2349.
4. Edward M, Dzialowski, Henry G. Maturation of the contractile response of the Emu ductus arteriosus. J Comp Physiol B 2008; 178:401-412.
5. Hoffman JI, Kaplan S. The incidence of congenital heart disease. J Am Coll Cardiol 2002; 39:1890-1900.
6. Clyman RI. Mechanisms regulating the ductus arteriosus. Biol Neonate. 2006; 89:330-335.
7. Investigators of the Vermont-Oxford Trials Network Database Project. The Vermont- Oxford Trials Network: very low birth weight outcomes for 1990. Pediatrics 1993; 91:540-545.
8. Koch J, Hensley G, Roy L, Brown S, Ramaciotti C, Rosenfeld CR. Prevalence of spontaneous closure of the ductus arteriosus in neonates at a birth weight of 1000 grams or less. Pediatrics 2006; 117:1113-11121.
9. De Felice C, Bechelli S, Tonni G, Hansmann G. Systematic underestimation of oxygen delivery in ventilated preterm infants. Neonatology 2010; 98:18-22. doi: 10.1159/000262482.
10. Clyman RI, Chorne N. Patent ductus arteriosus: evidence for and against treatment. J Pediatr 2007; 150:216-219.
11. Davis P, Turner-Gomes S, Cunningham K, Way C, Roberts R, Schmidt B. Precision and accuracy of clinical and radiological signs in premature infants at risk of patent ductus arteriosus. Arch Pediatr Adolesc Med 1995; 149:1136-1141.
12. Skelton R, Evans N, Smythe J. A blinded comparison of clinical and echocardiographic evaluation of the preterm infant for patent ductus arteriosus. J Pediatr Child Health 1994; 30:406-411.
13. Alagarsamy S, Chhabra M, Gudavalli M, Nadroo AM, Sutija VG, Yugrakh D. Comparison of clinical criteria with echocardiographic findings in diagnosing PDA in preterm infants. J Perinat Med 2005; 33:161-4.
14. Evans N, Malcolm G, Osborn D, Kluckow M. Diagnosis of PDA in preterm infant. Neo Reviews 2004; 5: 86-96.
15. Gien J. Controversies in the management of Patent Ductus Arteriosus. Neo Reviews 2008; 9:477-482.
16. Noori S, McCoy M, Friedlich P, Bright B, Gottipati V, Seri I. Failure of ductus arteriosus closure is associated with increased mortality in preterm infants. Pediatrics 2009; 123:e138-144. doi: 10.1542/peds.2008-2418.
17. Schmidt B, Roberts RS, Fanaroff A, Davis P, Kirpalani HM, Nwaesei C, et al. Indomethacin prophylaxis, patent ductus arteriosus, and the risk of bronchopulmonary dysplasia: further analyses from the Trial of Indomethacin Prophylaxis in Preterms (TIPP). J Pediatr 2006; 148:730-734.
18. Al Faleh K, Smyth JA, Roberts RS, Solimano A, Asztalos EV, Schmidt B et al. Prevention and 18-Month Outcomes of Serious Pulmonary Hemorrhage in Extremely Low Birth Weight Infants: Results From the Trial of Indomethacin Prophylaxis in Preterms. Pediatrics 2008; 121:e233-238. doi: 10.1542/peds.2007-0028.

19. Ohlsson A, Walia R, Shah S. Ibuprofen for the treatment of a patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Rev 2007; 3:CD003481.
20. Herrera C, Helberton J, Davis P. Prolong versus short course of indomethacin for the treatment of PDA in preterm infant. Cochrane Database Syst Rev 2007; 2:CD003480.
21. Cherif A, Khrouf N, Jabnoun S, Mokrani C, Amara MB, Guellouze N, et al. Randomized Pilot Study Comparing Oral Ibuprofen With Intravenous Ibuprofen in Very Low Birth Weight Infants With Patent Ductus Arteriosus. Pediatrics 2008; 122:1256-1261.
22. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol 2010; 30:241-52.