REVIEW ARTICLE

Patent Ductus Arteriosus in Preterm Infants

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Patent ductus arteriosus (PDA) is a major morbidity in preterm infants, especially in extremely premature infants less than 28 weeks. The clinical signs and symptoms of PDA in preterm infants are non specific and insensitive for making an early diagnosis of significant ductal shunting. Functional echocardiography is emerging as a new valuable bedside tool for early diagnosis of hemodynamically significant ductus, even though there are no universally accepted criteria for grading the hemodynamic significance. Echocardiography has also been used for early targeted treatment of ductus arteriosus, though the long term benefits of such strategy are debatable. The biomarkers like BNP and N- terminal pro–BNP are currently under research as diagnostic marker of PDA. The primary mode of treatment for PDA is pharmacological closure using cyclo-oxygenase inhibitors with closure rate of 70-80%. Oral ibuprofen is emerging as a better alternative especially in Indian scenario where parenteral preparations of indomethacin are unavailable and side effects are comparatively lesser. Though pharmacological closure of PDA is an established treatment modality, there is still lack of evidence for long term benefits of such therapy as well as there is some evidence for the possible adverse effects like increased ROP and BPD rates, especially if treated prophylactically. Hence, it is prudent to reserve treatment of PDA to infants with clinically significant ductus on the basis of gestation, birth weight, serial echocardiography and clinical status to individualize the decision to treat.

Key words: *Functional echocardiography, Ibuprofen, Indomethacin, Patent ductus arteriosus, Preterm infant.*

Patent ductus arteriosus (PDA) is a major morbidity encountered in preterm neonates, especially in babies less than 28 weeks gestation or 1000g. Natural ductal closure is inversely related to gestational age and birth weight. The incidence ranges from 15% to 37% in newborn babies less than 1750 grams [1-3]. This is very high compared to incidence of 2/1000 in term newborns. However, this does not mean that all PDA in preterm infants are hemodynamically significant warranting treatment. Spontaneous closure of the ductus has been noticed by various researchers in up to two-third of the preterm neonates [4]. The spontaneous closure rate of ductus arteriosus is less, as well as delayed with decreasing gestation and birth weight, especially in extremely low birth weight infants [1,5].

In addition, fetal growth restriction may be associated with PDA though the evidence for the same is very limited. In a study by Rakza, *et al* in preterm infants of 26-32 weeks gestation, more ductus arteriosus became significant within 48 hours of birth in growth restricted as compared to eutrophic infants [11/17(65%) *vs* 12/31(40%); $P<0.05$] [6]. The role of genetic variation i.e. single nucleotide polymorphism in transcription factor AP-2β, tumor necrosis factor receptor-associated factor 1, and prostacyclin synthesis may play a role in persistent patency of ductus arteriosus in preterm neonates [7].

PHYSIOLOGIC EFFECTS OF PDA

The presence of PDA has significant effects on myocardial functions as well as systemic and pulmonary blood flow. Preterm newborns adapt, by increasing the left ventricular contractility, and thereby maintaining the effective systemic blood flow even when the left to right shunts equals 50% of the left ventricular output. This is mainly accomplished by an increase in stroke volume (SV)

rather than heart rate [8]. This increase in stroke volume is primarily due to reduction in afterload and simultaneous increase in left ventricular preload.

Despite the increased left ventricular output, there is significant redistribution of blood flow to major organ systems, with the presence of *ductal steal* seen in PDA due to left to right shunt. There is flow across the ductus all throughout the cardiac cycle, the direction of which depends on the difference between systemic and pulmonary pressures. Usually there is shunting from systemic to pulmonary circulation called *ductal steal*, the maximum of which occurs at the beginning of the cardiac systole when the pressure gradient is maximum [9]. Contrary to the belief that ductal run off occurs only in diastole, it is present all throughout the cardiac cycle. However, its effect on systemic circulation is best demonstrated on echocardiogram during diastole, as a retrograde flow in the descending aorta, or other systemic vessels on Doppler, instead of the normal low velocity forward flow. This steal phenomenon may lead to systemic hypoperfusion, despite increased cardiac output. Hence hemodynamically significant PDA has negative effect on cerebral circulation and oxygenation, which may lead to injury to the immature brain [10,11].

DIAGNOSIS

Echocardiography

Echocardiography is the gold standard for diagnosis as well as for assessing severity of PDA. The features suggestive of patent ductus arteriosus include (*a*) turbulence in main pulmonary artery (MPA) due to left to right shunt jet flowing into MPA, detected by pulsed Doppler; and (*b*) direct visualization of the ductus by 2-D and color Doppler in short axis view (high parasternal and low parasternal view). In 2-D short axis view in the presence of a patent ductus, the appearance is classically described as 'three-legged stool' appearance. However these signs only establish the presence of a patent ductus and do not reflect the hemodynamic significance of the ductus [12].

Though the term hemodynamically significant PDA(hs-PDA) is very popular, it is best to avoid this terminology, due to lack of uniform definitions and poor correlation between features of significant ductus and need for treatment or associated morbidities. Hence the question, "whether the ductus is clinically significant?" cannot be answered by echocardiography. What is possible by echocardiogram is to characterize the size of the ductus, the direction of the shunt, volume of shunting as well as hemodynamic effects of the shunt on systemic and pulmonary circulations , so as to use this information in conjunction with overall clinical picture to guide the clinical decision making [13]. The echocardiographic markers of hs-PDA have been well described in a recent review by Sehgal, *et al*. [14] (***Table* 1**). The ductal flow pattern which is dependent on systemic and pulmonary vascular resistance has been described by Su, *et al*. [15] to determine the direction of shunting as well as its significance, using high parasternal color Doppler. The sequence of pattern change progressed from pulmonary hypertension pattern to growing pattern or pulsatile pattern in those with clinically significant PDA. Pulsatile pattern had sensitivity of 93.5% and specificity of 100% in predicting significant PDA. Longitudinal echocardiographic assessment of PDA shunt flow pattern can reflect the hemodynamic changes in PDA and predict the need for treatment with accuracy, as shown by the same group in a subsequent study [16].

Biomarkers

An increasing number of biological substances like hormones, enzymes which are markers of cardiac stress, dysfunction or myocardial injury-collectively called biomarkers–are emerging as diagnostic and prognostic markers especially in the setting of heart failure or ischemic injury [17]. One such marker emerging in the diagnosis of hs-PDA is brain natriuretic peptide (BNP). Natriuretic peptides are hormones, produced either by atria (atrial natriuretic peptide-ANP) or by ventricles (BNP) in response to myocardial stress, secondary to dilatation, hypertrophy or increased wall tension. They result in natriuresis, diuresis, arterial vasodilatation and suppression of renin-angiotensin-aldosterone system. In adults, extensive research has been conducted on the use of BNP and its precursor, the N-terminal pro-BNP, in the diagnosis of congestive heart failure as

TABLE I ECHOCARDIGRAPHIC MARKERS OF HEMODYNAMICALLY SIGNIFICANT PDA.

Echocardiography parameter	No PDA	Mild	Moderate	Large
Features of ductus arteriosus				
Transductal diameter (mm)	–	<1.5	1.5-3.0	>3.0
Ductal velocity Vmax (cm/sec)	–	>2	1.5-2.0	<1.5
Antegrade PA diastolic flow (cm/sec)	–	>30	30-50	>50
Pulmonary overcirculation				
Left atrial /aortic root width ratio	1.1 ± 0.2	<1.4:1	1.4-1.6	>1.6:1
Left ventricular/aortic root width ratio	1.9 ± 0.3	–	2.2 ± 0.4	2.27 ± 0.27
E wave/A wave ratio	<1	<1	1-1.5	>1.5
IVRT(ms)	<55	46-54	36-45	<35
LVSTI	0.34 ± 0.09	–	0.26 ± 0.03	0.24 ± 0.07
Systemic hypoperfusion				
Retrograde diastolic flow (%)	10	< 30	30-50	>50
Aortic stroke volume (mL/kg)	≤2.25	–	–	≤2.34
Left ventricular output (mL/kg/min)	190-310	–	–	>314
LVO/SVC flow ratio	2.4 ± 0.3	–	–	4.5 ± 0.6

LVO = left ventricular output, SVC = superior vena cava, LVSTI = left ventricular stroke volume index, IVRT = isovolumic *relaxation time, PWD = pulse wave Doppler, CWD = continuous wave Doppler, PA =pulmonary artery. (Empty boxes implies data not available).*

well as in predicting survival.

BNP and N- terminal pro-BNP are emerging as markers of hs-PDA with good sensitivity and specificity. The normal levels of these hormone markers both for term and preterm newborns are already established [18]. In a study by Choi, *et al*. [19] bedside assay of plasma BNP levels using BNP kits were done in preterm neonates, ranging from 25 to 34 weeks of gestation age from day 3 of life onwards, to evaluate the utility of rapid assay of BNP in diagnosis of hs-PDA. Mean BNP concentration was significantly higher in those with hs-PDA (2896 ± 1627 pg/mL) as compared to controls, *i.e.* infants with asymptomatic PDA or no closed ductus (208 ± 313 pg/mL). The BNP levels also directly correlated with the magnitude of ductal shunt, with sensitivity of 100% and specificity of 95.3%, at a cut off of 1100 pg/mL. The N-terminal pro-BNP also has similar sensitivity and specificity as compared to echocardiogram in diagnosis of hs-PDA and also had longer half life than BNP, making it even more promising. However, the use of biomarkers are still in research phase and has not yet become a routine clinical tool in the management of preterm PDA, unlike in the management of congestive heart failure in adults.

MEDICAL TREATMENT

The pharmacological basis for medical therapy is the use of non selective cyclo-oxygenase (COX) inhibitors, which inhibits prostaglandin synthesis and causes ductal constriction. The two most widely studied and used non selective COX inhibitors are indomethacin and ibuprofen. The future of pharmacological treatment of PDA could be with the use of nitric oxide inhibitors and prostaglandin receptor antagonists [20].

Indomethacin

Indomethacin is the most widely used nonselective COX inhibitor for the pharmacological closure of ductus arteriosus. In a large national collaborative trial involving 421 preterm infants with significant patent ductus arteriosus, with birth weight <1750gm indomethacin given concurrently with usual medical therapy at the time of diagnosis, resulted in ductal closure in 79% *vs* 35% with placebo (*P*<0.001) [3].

The effectiveness of indomethacin for ductal closure has been further proven in a number of randomized control trials evaluating the prophylactic use of indomethacin in preterm infants. A Cochrane meta-analysis (19 randomized controlled trials, 2872 infants) has shown that prophylactic indomethacin in preterm babies <37 weeks provides short term benefits, which does not translate to significant long term outcome of increased survival without neuro-developmental impairment [21]. Further, indomethacin therapy initiated after 24 hours of life in preterm babies <37 weeks, with asymptomatic PDA diagnosed either clinically or with echocardiogram, has shown significant reduction in incidence of symptomatic PDA (RR= 0.36, 95%; CI 0.19-0.68), as well as reduction in duration of supplemental oxygen (WMD -12.5, CI -23.8,-1.26). However, this meta-analysis failed to show significant difference in mortality, chronic lung disease, intraventricular hemorrhage (IVH), retinopathy of prematurity (ROP) or duration of ventilation. No long term outcomes were reported [22].

The two most commonly followed dosing schedules for indomethacin are the short course (3 intravenous doses at 12 hourly intervals with starting dose of 0.2 mg/kg followed by 0.1 mg/kg for babies less than 2days of age, 0.2 mg/kg for 2-7 days and 0.25 mg/kg for >7 days old infants) and the long course (0.1mg/kg per day for 6 doses) therapy. The basis for the long course therapy is that indomethacin induced prostaglandin inhibition is a transient phenomenon and the prostaglandin levels normalizes within 6-7 days after the short course therapy, which increases the chance for reopening of the duct. In case there is persistence of PDA following the first course of indomethacin therapy, a second course is tried before surgical ligation. The closure rate of PDA with indomethacin is 80% [20]. A Cochrane meta-analysis, comparing short course (0.3 to 0.6 mg/kg, 3 doses) *vs* the long course (0.6 to 1.6 mg/kg, 6 to 8 doses) indomethacin therapy for PDA included 431 preterm low birth weight infants from 5 randomized controlled trials. It failed to reveal significant difference between the two groups for PDA closure rate, need for surgical ligation or re-opening rates. The prolonged course group had nearly two times more risk of necrotizing enterocolitis (NEC) compared to the conventional dose group (RR=1.87, 95% CI 1.07,3.27). The Cochrane review conclude that the prolonged long course treatment cannot be recommended for routine treatment of PDA [23].

Studies have also evaluated higher doses of indomethacin in the event of failure with conventional dose. The higher doses have little effect on duct closure and are associated with more adverse effects, so cannot be recommended for practice [24].

Continuous versus bolus administration: There have been concerns about effect of continuous versus bolus administration of indomethacin on the efficacy of therapy as well as side effect profile, especially reduced blood flow to various organ systems, particularly reduced cerebral circulation when bolus administration was given. The recent Cochrane meta-analysis involving two trials comparing the continuous (indomethacin given after 24 hours of life as slow intravenous infusion over 36 hours) *vs* bolus dose (indomethacin given after 24 hours of life as intravenous infusion over 20 min) concludes the evidence to be insufficient to draw conclusion regarding the efficacy for the treatment of PDA. There was an insignificant trend towards increased rates of PDA closure rate on day 2 and day 5 in the bolus administration group. There was no significant difference in secondary outcomes like reopening of PDA, neonatal mortality, IVH or NEC. The review demonstrated that there was a decrease in cerebral blood flow velocity, after bolus injections which persisted even at 12-24 hours compared to the continuous infusion group. However, the clinical impact of this reduced blood flow to organ systems, especially brain is unclear and definite recommendation regarding preferred method of indomethacin administration cannot be made [25]. This concern of reduced cerebral blood flow is questioned by recent studies. In a randomized controlled trial evaluating the effect of early indomethacin *vs* placebo on blood flow to brain and upper part of the body, in preterm infants <30 weeks gestation, with large PDA (ductal diameter >1.6 mm), Osborn, *et al.* [26] showed that superior vena cava (SVC) flow, a marker of blood flow to upper part of the body, did not change much with intravenous indomethacin. Infants with failed ductal constriction had lower SVC flow and

developed late grade 3 or 4 peri/intraventricular hemorrhage. Similarly an improvement in mean blood pressure and cerebral oxygenation has been shown by Lemmers, *et al*. [11] using near infrared spectroscopy, in infants with PDA after indomethacin therapy.

Ibuprofen

Due to the concern of adverse effect of indomethacin on systemic circulation as well as transient renal side effects, other COX inhibitors have been investigated. The most commonly used one is ibuprofen [20]. In the Cochrane meta-analysis comparing ibuprofen with indomethacin in preterm <37 weeks gestation or low birth weight (<2500 g), involving 20 trials enrolling 1092 infants, there was no difference in the failure of duct closure (RR=0.94; 95% CI 0.76, 1.17) [27]. Oral ibuprofen was used in 3 trials, while intravenous preparation was used in the rest. The ibuprofen group had significantly lower serum creatinine levels and decreased incidence of oliguria. There was 32% reduction in NEC in ibuprofen group (RR=0.68; 95% CI 0.47, 0.99). There was no difference in other outcomes like mortality, reopening rate of PDA, need for surgical ligation of PDA, duration of ventilator support, chronic lung disease (CLD), IVH or ROP. Studies have shown a closure rate of 70-80% with either indomethacin or ibuprofen in preterm babies ≤32 weeks [28]. Hence both are equally effective in closing PDA; however, ibuprofen currently appears to be the superior option with its better safety profile, especially reduced NEC rates. The question of which drug confers better long term intact survival is as yet unanswered. Pulmonary hypertension, increased risk of unconjugated hyperbilirubinemia and lack of short term neuroprotective effect have been reported as the drawbacks of ibuprofen [20,29].

Oral Ibuprofen: Considering the fact that intravenous indomethacin or ibuprofen is not available in Indian market and the high cost for imported injections, oral ibuprofen is a promising alternative. In randomized controlled trial of oral *vs* intravenous ibuprofen for VLBW infants with PDA, the rate of ductal closure was more (oral=84.3% *vs* IV=62.5%; *P*=0.04) and renal side effects were less in the oral ibuprofen group. Hence oral ibuprofen may be a safe and easily available cheap option for treatment of PDA [30].

Early Targeted Treatment

With the emergence of functional echocardiography as an important tool in the management of preterm infants, especially those <1000g or <28 weeks gestation, the identification of PDA with hemodynamic significance is made well before the clinical manifestations set in. This emerging practice of identifying significant ductus early in life, often within first 24 hours, by in house echocardiography and instituting treatment is called early targeted treatment. Osborn, *et al.* [26], in a double-blinded RCT of indomethacin *vs* placebo, in preterm babies <30weeks and <12 hours of life, used serial echocardiography at 3 hours and 10 hours to detect significant PDA (>1.6 mm) [26]. Infants with failed ductal constriction had lower SVC flow as well as more grade 3 or 4 IVH, but the indomethacin treated group did not show improvement in SVC flow. Similarly O' Rourke, *et al*. [31] in a cohort of very low birth weight (VLBW) infants, performed serial echocardiography resulting in earlier identifi-cation and treatment of ductus. They have shown a reduction in IVH as well as number of ventilator days, in comparison to a historical cohort. In a randomized control trial of ibuprofen *vs* indomethacin in preterm infants <28 weeks, Su, *et al*. [16] using ductal Doppler flow pattern, administered early targeted treatment within 24 hours with closure rate of nearly 90% in both the groups. However, there is a need to generate more evidence for the clinical benefits of echocardiographically guided early targeted treatment of PDA on neonatal outcomes.

Role of Furosemide and Dopamine

There has been concern of furosemide adversely affecting the efficacy of indomethacin therapy by increasing the clearance of indomethacin, resulting in failure of therapy [32]. However, the latest Cochrane meta-analysis involving 70 patients enrolled in 3 trials, failed to show any increase in treatment failure (RR=1.25; 95% CI 0.62, 2.52) or reduction in toxicity of indomethacin therapy in PDA [33]. Hence routine use of furosemide in indomethacin treated symptomatic PDA is not

KEY MESSAGES

- Patent ductus arteriosus, is a major morbidity in preterm infants, with incidence inversely related to gestation and birth weight. Antenatal steroids and judicious fluid therapy seems to be protective against PDA, whereas RDS requiring mechanical ventilation, delay spontaneous closure of the ductus arteriosus.
- Bedside functional echocardiography is a valuable tool for early diagnosis, assessment of hemodynamic effects and response to therapy. It may emerge as a valuable tool in all tertiary level NICUs.
- Ibuprofen with its superior safety profile, especially reduced risk of NEC and comparable efficacy to indomethacin, is currently the drug of choice. Oral ibuprofen is emerging as safe and effective alternative to intravenous indomethacin in treatment of PDA.
- There is increasing advocacy for reserving pharmacological treatment of PDA for compelling indications like refractory hypotension or congestive heart failure as early medical treatment is not associated with proven long term benefits and in nearly one half of the infants, PDA spontaneously closes.

recommended and is contraindicated in presence of dehydration.

Low dose dopamine is considered to be beneficial in reversing indomethacin induced oliguria in preterm babies with PDA. However, there is no evidence to support this notion. In the Cochrane meta-analysis [34], use of dopamine in indomethacin treated symptomatic PDA showed improvement in urine output but there was no effect on serum creatinine or incidence of oliguria [34]. The use of dopamine had no effect on the rate of failure for ductal closure. The evidence for effect of dopamine on cerebral circulation, IVH or death before discharge is insufficient. Hence use of dopamine for prevention of renal dysfunction induced by COX inhibitors cannot be recommended.

TO TREAT OR NOT TO TREAT PDA

Despite three decades of intense research enrolling thousands of preterm infants, evidence for the long term benefits of pharmacological closure of PDA is inconclusive and debatable. There is an emerging school of thought advocating conservative approach, with medical therapy reserved for compelling indications like refractory hypotension or congestive heart failure attributed to large ductal shunt [35]. The decision to treat PDA depends on there 3 factors - the spontaneous closure rate, adverse effect of ductal patency, and risk benefit of treatment. In a recent systematic review, Benitz, *et al*., [36] evaluated the effect of medical and surgical treatment- either prophylactic or therapeutic on various outcomes. Although all modes of interventions effectively closed the ductus, there was little beneficial effect on the outcomes. Indomethacin treatment for PDA increased the rates of IVH while prophylaxis regimen reduced IVH >grade 2 with no beneficial effect on long term neurodevelopmental outcome. More concerning was the observation that prophylactic surgical or medical treatment resulted in higher rates of ROP (≥grade 3) as well as CLD. Also the requirement of ventilator support, contrary to the popular notion, is increased in the post ductal ligation phase and prophylactic medical treatment with increase in oxygen requirement and mean air way pressures.

There is also emerging evidence for conservative approach in the management of PDA. Vanhaesebruock, *et al.* [37] in a prospective observational study, in 30 preterm infants ≤30 weeks gestation with RDS requiring surfactant replacement therapy and mecha-nical ventilation, showed 100% ductal closure rate with conservative treatment i.e. restricted fluid (130 mL/kg/day) with low inspiratory time (Ti=0.35) and high positive end expiratory pressure (PEEP= 4.5mbar). Complication rates were lesser com-pared to Vermont Oxford network data.

Hence the therapeutic decision to treat ductus arteriosus is complex and there is a hot debate for conservative approach, especially in preterm infants more than 1000g in whom the spontaneous closure rate is high.

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