Patent Ductus Arteriosus in Preterm Neonates

Introduction

Patent ductus arteriosus (PDA) is a major morbidity seen in premature infants, with its incidence being inversely related to gestational age and birth weight. Studies report incidence of 15-40% in very low birth weight infants (<1500g) where as in premature extremely low birth weight infants (<28weeks; < 1000g) it's as high as 50-65%.[1,2]

The closure of ductus arteriosus (DA) following birth is an important component of transitional circulation, thereby directing the entire right ventricular output to the lungs to facilitate its oxygenation. Contrary to this the ductus arteriosus acts as conduit for diverting the partially oxygenated blood to support systemic circulation in fetus. The closure of DA is mediated by a shift in balance of vasoconstricting (endothelin) and dilating (PGE2) mediators, which in turn is mediated by increased oxygenation and reduced flow through the DA. Premature infants are at increased risk of PDA due to elevated levels of PGE_2, increased PGE_2 receptor levels and reduced intrinsic vascular tone as a result of weak actin myosin complex formation. Generally the ductus arteriosus functionally close in term infants by 12-24 hrs, whereas the closure may be delayed by 3-5 days in preterm neonates.[3]

Hemodynamic consequences of PDA

The presence of PDA has significant effects on myocardial functions as well as systemic and pulmonary blood flow. Preterm newborns adapts, 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.[4] This is mainly accomplished by increase in stroke volume (SV) rather than heart rate.

Despite the increased left ventricular output, there is significant redistribution of blood flow to major organ systems, with the presence of *ductal steal* 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. 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 hypo perfusion, despite increased cardiac output. Hence hemodynamically significant PDA has negative effect on cerebral circulation and oxygenation, which may lead to injury of the immature brain.

Diagnosis of PDA

Clinical diagnosis of PDA and its pitfalls

The clinical features of a PDA are mainly because of the hyperdynamic circulatory effects caused by the shunt, resulting in bounding peripheral pulses (diagnosed clinically by easily palpable dorsalis pedis), wide pulse pressure (>25 mm of Hg), hyperactive precordium (visible precordial pulsations in more than 2 rib spaces), systolic murmur (usually ejection systolic; rarely pansystolic or continous), persistant tachycardia etc.

In a ventilated infant, fluctuating FiO_2, increasing pressure requirements, unexplained CO_2 retention or metabolic acidosis, recurrent apnea etc suggests a symptomatic ductus. However diagnosis of PDA based on clinical features alone has mainly two pitfalls i.e. low sensitivity and delay in detection. In studies comparing clinical examination vs echocardiography, there was a delay of 1-4 days in diagnosis of PDA based on clinical findings alone.[5] More over these signs were insensitive (sensitivity of 30-40%) and had poor predictive value (60%).

Role of echocardiography

Echocardiography is the gold standard, for diagnosis as well as for assessing severity of PDA.[6] The features suggestive of patent ductus arteriosus include

(a) 2-D and color Doppler- short axis view: Direct visualization of the ductus. In 2-D short axis view, in the presence of a patent ductus, the appearance is classically described as 'three-legged stool' appearance. In color Doppler, there is continuous flare in the MPA.
(b) Short axis view, Pulsed Doppler: Turbulence in main pulmonary artery (MPA) due to left to right shunt jet flowing into MPA.
(c) Four chamber view: Bowing of interatrial septum to right with enlarged left atrium and left ventricle
(d) Long axis view: LA/Ao ratio > 1.5:1
(e) Raised left ventricular stroke volume

However these signs only establish the presence of a patent ductus and do not reflect the hemodynamic significance of the ductus. The echocardiographic markers indicating the hemodynamic significance and degree of shunting have been well described in a recent review by Sehgal, et al (**Table** 1).[7]

Table 1: Echocardiographic markers of hemodynamically significant PDA

Echocardiography parameter*	No PDA	Mild	Moderate	Large
Features of ductus arteriosus				
Trans ductal diameter (mm)	0	<1.5	1.5-3.0	>3.0
Ductal velocity Vmax (cm/sec)	0	>2	1.5-2.0	< 1.5
Antegrade PA diastolic flow (cm/sec)	0	>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 (as % of forward 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)*

Echocardiography also helps in ruling out other structural heart diseases and facility for in-house echocardiography enables serial monitoring as well as determines treatment responses.

Limitations of echocardiography

Even though echocardiography is the gold standard for diagnosis of PDA, it has its own limitations especially with regard to decisions on treatment.[8]

a) There is limited data prove that functional echocardiography alters the neonatal outcomes.
b) Though the criteria for assessment of degree of shunting are established, there is lack of universal consensus regarding the best criteria for initiating treatment of PDA. No data till date supports decision to treat PDA based of echocardiography criteria alone.
c) Many neonatal units lack ready access to echocardiography and it is still a consultative tool, making serial assessments practically difficult.
d) Last but not least, the echocardiography is highly operator dependent and hence it needs to be always used in conjunction with clinical findings.

Recommendations on use of echocardiography in PDA

a) Though early screening echocardiography could predict possible significant PDA, there is no data to support routine screening in all preterm infants, as it does not seem to change the long term outcomes.
b) Echocardiography establishes presence of ducts and its hemodynamic significance, but it cannot be used in isolation to decide on treatment. Treatment decision should be in conjunction with clinical symptoms.
c) In all infants in whom treatment of PDA is considered, echocardiography before treatment is essential to establish the diagnosis as well as to rule out other structural heart disease (e.g. duct dependent condition in which closure of PDA is contraindicated)
d) Post treatment echocardiography is required to document the response to treatment and assess the ductus.
e) Early targeted treatment based on echocardiographic criteria alone cannot be recommended at this point of time even though some large RCT (DETECT Trial , Australia) is currently evaluating the same

Other diagnostic tests

The other diagnostic tests have very limited role, especially in preterm babies with PDA. Chest radiograph findings are non-specific and features like cardiomegaly and pulmonary plethora occurs late when significant PDA leads to congestive heart failure.

An emerging newer diagnostic modality is biomarkers like brain natriuretic peptide (BNP) and N-terminal-pro- BNP which has shown good sensitivity and specificity. Though these markers are promising, there widespread clinical use is yet to emerge.[9]

Management of PDA

The management of PDA could be broadly divided into three aspects- pharmacological closure of ductus, general supportive measures and surgical ligation of the PDA.

To treat or not to treat a PDA

Despite three decades of intense research enrolling thousands of preterm infants, yet evidence for the long term benefits of pharmacological closure of PDA is inconclusive and debatable.[9] The decision to treat PDA depends on the 3 factors- the spontaneous closure rate, adverse effect of ductal patency and risk benefit of treatment.

In a recent systematic review, Benitz et al evaluated the effect of medical and surgical treatment- either prophylactic or therapeutic on various outcomes.[10] Although all modes of interventions effectively closed the ductus, there was little beneficial effect on the outcomes. 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.

Pharmacological closure of PDA

Indications for treatment*

Treatment should be considered in preterm infants with echocardiographically proven hemodynamically significant ductus arteriosus with one of the following conditions

1. Features of congestive heart failure
2. Requiring prolonged respiratory support (invasive or non invasive) unlikely to be due to other reasons
3. Unexplained oxygen requirement(FiO2 ≥ 30%) or rising O2 requirement on respiratory support
4. Recurrent apnea requiring respiratory support (CPAP/Nasal IMV/invasive ventilation) attributed to PDA

** These indications are based on pragmatic clinical decision and not based on high quality evidence*
** Treatment of all infants otherwise clinically asymptomatic, based on echocardiography findings of hs-PDA alone is not warranted*
**Definition of hs-PDA: Presence of PDA >1.5mm with one of the following LA/Ao ratio >1.5:1, LV/Ao ratio >2.2:1, retrograde flow diastolic flow in descending aorta, celiac or cerebral arteries > 30% of ante grade flow; Left ventricular output >320mL/kg/min.*

Mechanism and agents of pharmacological closure

The pharmacological basis for medical therapy is the use of non selective cyclo-oxygenase (COX) inhibitors, which inhibits prostaglandin synthesis and causes ductal constriction.[11] The two most widely studied and used non selective COX inhibitors are

- Indomethacin
- Ibuprofen

Indomethacin versus Ibuprofen

The Cochrane meta-analysis comparing ibuprofen with indomethacin in preterm <37 weeks gestation or low birth weight (<2500 gm), 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).[12] 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.

Oral Iboprufen

Considering the fact that intravenous ibuprofen is not available in Indian market and the high cost for imported indomethacin 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 higher (oral=84.3% vs. IV=62.5%; P=0.04) and renal side effects were lesser in the oral ibuprofen group. Hence oral ibuprofen may be a safe and easily available cheap option for treatment of PDA.[13] The though concerns of pulmonary hypertension, increased risk of unconjugated hyperbilirubinemia, lack of short term neuroprotective effect were reported with iboprufen, it seems to be of little clinical significance.

There is very limited data on use of oral indomethacin and it's not generally recommended especially with oral iboprufen being easily available.

Recommendation

1. Both Indomethacin and Iboprufen are equally effective in closing PDA with closure arte of 70-80%.
2. Iboprufen currently appears to be the superior option with its better safety profile, especially reduced NEC rates.
3. Infants
    a. On full enteral feeds (atleast 120ml/kg/day) – Oral Iboprufen
    b. On parentral fluids, partial feeds – IV Indomethacin*

4. The question of which drug confers better long term intact survival is yet unanswered

**IV iboprufen is not available in Indian market*

Dosage and Duration of treatment

Indomethacin

Short versus Long course

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 2 days of age, 0.2 mg/kg for 2-7 days and 0.25 mg/kg for > 7 days old infants) and the long course (0.1 mg/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.

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 infants from 5 randomized controlled trials, failed to reveal significant difference between the two groups as regards to 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). Hence prolonged long course treatment cannot be recommended for routine treatment of PDA.[14]

Continuous vs intermittent bolus administration of Indomethacin

There have been concerns of 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 2 trials comparing the continuous i.e. indomethacin given after 24 hours of life as slow intravenous infusion over 36 hours vs. bolus dose i.e. indomethacin given after 24 hours of life as intravenous infusion over 20 min concluded that the evidence was insufficient to draw conclusion regarding the efficacy for the treatment of PDA. There is 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.[15]

Recommendation on dosage

Dosage of Indomethacin and Iboprufen for pharmacological treatment of a PDA[16]		
Indomethacin	IV Infusion over 30 min	▪ Loading dose: 0.2 mg/kg/dose ▪ Subsequent doses (adjusted as per postnatal age) • <2 days: 0.1 mg/kg/dose 12 hourly x 2 doses • 2-7 days: 0.2 mg/kg/dose 12 hourly x 2 doses • >7 days: 0.25 mg/kg/dose 12 hourly x 2 doses
Iboprufen	IV or oral	▪ Loading dose: 10 mg/kg/dose ▪ Subsequent dose: 5mg/kg/dose 24 hourly x 2 doses
• *Following the first course, a second course with same dosage could be used in case of persistent PDA needing treatment or re-opening of the ductus with symptoms.* • *Failure of medical treatment: Persistence of hemodynamically significant ductus or reopening despite two courses of treatment defines failure of medical treatment*.		

Side effects and monitoring

Adverse effects of treatment with NSAIDS include

- Renal compromise due to its effect on COX 1,
- Bleeding tendency due to its effect on platelet function and
- Increased risk of necrotizing enterocolitis.

Monitoring during therapy

Baseline	Urine output, RFT, platelet count
Daily	Urine output
Alternate day	RFT, Platelet counts (daily if baseline counts are <150,000/mm^3

Contraindications

- Renal: Urine output< 0.6 ml/kg/h, blood urea > 40 mg/dL, creatinine >1.8 mg/dL
- Bleeding: Bleeding from IV sites, skin bleeds, gastrointestinal bleeding, enlarging or evolving intraventricular hemorrhage (IVH), platelet count < 60,000/mm3
- Gastrointestinal: necrotizing enterocolitis; blood in stool

General measures

1. Fluid restriction

In Cochrane metaanalysis, restriction of fluid intake to mean of 120 ml/kg/day as compared to 160 ml/kg/day in the initial few weeks of life is found to be beneficial with lower incidence of PDA, CLD and mortality.[17] Similarly Vanhaesebruock et al in a prospective observational study, in 30 preterm infants ≤30 weeks gestation with RDS requiring surfactant replacement therapy and mechanical 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), with no increase in complication rates.[18]

2. Role of furosemide and dopamine in medical management of PDA

There has been concern of furosemide adversely affecting the efficacy of indomethacin therapy, by increasing the clearance of indomethacin, resulting in failure of therapy.[19] However, the latest Cochrane meta-analysis involving 70 patients enrolled in 3 trials, fails 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.[20] Hence routine use of furosemide in indomethacin treated symptomatic PDA is not 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 by Barrington, et al[21] 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. 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

3. Mechanical ventilation strategy

In infants on ventilator support with hs-PDA, using slightly higher PEEP and lower Ti might be helpful, though data is very limited.[18]

Recommendations

1. In clinically symptomatic or echocardiographically diagnosed PDA, it is recommended to restrict parenteral fluid intake to 120 mL/kg/day, provided other parameters like urine output, serum Na, urine specific gravity etc are within normal limits
2. Infants on full enteral feeds with hs-PDA a fluid intake of up to 150 ml/kg/day may be used and calorie density may be increased in case of inadequate weight gain
3. No role for routine use of dopamine in treating NSAID induced oliguria
4. No role for routine use of frusomide in treatment of PDA except in case of established congestive heart failure

Surgical ligation

It is reserved for infants with symptomatic hs-PDA with

1. Failure of medical therapy
2. Contraindications to medical therapy

Studies have also shown in preterm <28 weeks gestation that need for surgical ligation of PDA is an independent risk factor for increased rates of CLD, ROP and adverse neurodevelopmental outcome.[22]

PDA and Neonatal Outcomes

The presence of PDA has been associated with adverse neonatal outcomes like CLD and NEC. [23,24] However none of the studies have shown cause-effect relationship, and studies have failed to consistently show association between symptomatic PDA and adverse outcomes like cerebral palsy, cognitive delay, ROP, NEC or CLD once adjusted for prematurity and perinatal factors.[22]

References

1) Van Overmeire B, Van de Broek H, Van Laer P, Weyler J, Vanhaesebrouck P. Early versus late indomethacin treatment for patent ductus arteriosus inpremature infants with respiratory distress syndrome. J Pediatr 2001; 138:205-11.
2) Fanaroff AA, Stoll BJ, Wright LL, et al. Trends in neonatal morbidity and mortality for very low birth weight infants. Am J Obstet Gynecol. 2007; 196:147e1–e8.
3) Clyman R I. Mechanisms regulating the ductus arteriosus. Biol Neonate 2006; 89: 330–335.
4) Shimada S, Kasai T, Konishi M, Fujiwara T. Effects of patent ductus arteriosus on left ventricular output and organ blood flows in preterm infants with respiratory distress syndrome treated with surfactant. J Pediatr 1994; 125: 270-277.
5) Skelton R, Evans N, Smythe J. A blinded comparison of clinical and echocardiographic evaluation of the preterm infant for patent ductus arteriosus. J Paediatr Child Health. 1994;30:406–411.
6) Evans N, Malcolm G, Osborn D, Kluckow M· Diagnosis of patent ductus arteriosus in preterm infants. NeoReviews 2004; 5: 86-97.
7) Sehgal A, McNamara PJ. Does echocardiography facilitate determination of hemodynamic significance attributable to the ductus arteriosus. Eur J Pediatr 2009; 168: 907–914.

8) Kluckow M, Seri I, Evans N· Functional Echocardiography: An emerging clinical tool for the Neonatologist· J Pediatr. 2007 Feb;150(2):125-30.
9) Sasi A**,** Deorari AK. Patent ductus arteriosus in preterm infants. Indian Peditr 2011; 48: 301-308.
10) Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis. Journal of Perinatology 2010; 30: 241–252.
11) Narayanan-Sankar M, Clyman RI. Pharmacologic closure of patent ductus arteriosus in the neonate. NeoReviews 2003; 4: 215-221.
12) Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm and/or low birth weight infants. Cochrane Database Syst Revs. 2010; 4: CD003481.
13) 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: e1256-e1261.
14) Herrera C, Holberton J, Davis PG. Prolonged versus short course of indomethacin for the treatment of patent ductus arteriosus in preterm infants. Cochrane Database Syst Rev. 2007; 2: CD003480.
15) Gork AS, Ehrenkranz RA, Bracken MB. Continuous versus intermittent bolus doses of indomethacin for patent ductus arteriosus closure in symptomatic preterm infants. Cochrane Database Syst Rev. 2008; 1: CD006071.
16) Clyman RI. Patent ductus arteriosus in preterm neonates. In Avery's diseases of the new born. Eds: Taeush HW, Ballard RA. 7th edn WB Saunders pp 699-710.
17) Bell EF, Acarregui MJ. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2000;(2):CD000503.
18) Vanhaesebrouck S, Zonnenberg I, Vandervoort P, Bruneel E, Van Hoestenberghe M, Theyskens C. Conservative treatment for patent ductus arteriosus in the preterm Arch. Dis. Child Fetal Neonatal Ed 2007; 92:F244–F247.
19) Green TP, Thompson TR, Johnson De, Lock JE. Furosemide promotes patent ductus arteriosus in premature infants with respiratory distress syndrome. N Engl J Med 1983; 308: 743-8.
20) Brion LP, Campbell DE. Furosemide for prevention of morbidity in indomethacin treated infants with patent ductus arteriosus. Cochrane Database Syst Rev. 2001; 3: CD001148.
21) Barrington KJ, Brion LP. Dopamine versus no treatment to prevent renal dysfunction in indomethacin treated preterm newborn infants. Cochrane Database Syst Rev. 2002; 3: CD003213.
22) Chrone N, Leonard C, Piecuch R, Clyman R I. Patent ductus arteriosus and its treatment as risk factors for neonatal and neurodevelopmental morbidity Pediatrics 2007; 119:1165-1174.
23) Rojas MA, Gonzalez A, Bancalari E, Claure N, Poole C, Silva-Neto G: Changing trends in the epidemiology and pathogenesis of neonatal chronic lung disease. J Pediatr 1995; 126: 605– 610.
24) Dollberg S, Lusky A, Reichman B. Patent ductus arteriosus, indomethacin and necrotizing enterocolitis in very low birth weight infants: a population-based study. J Pediatr Gastroenterol Nutr 2005; 40:184–8.