

Patent Ductus Arteriosus in Preterm Neonates

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Abstract

Failure of the ductus arteriosus to close within 48-96 hours of postnatal age results in a left to right shunt across the ductus and overloading of the pulmonary circulation. This is more likely to happen in premature neonates with respiratory distress syndrome. Deterioration in the respiratory status on day 3-4 in a ventilated neonate and unexplained metabolic acidosis may be the earliest indicators of a patent ductus arteriosus (PDA). Indomethacin is the main stay of medical management of PDA in preterm neonates. Guidelines for administration of indomethacin have been described in the protocol. Restricted fluid therapy may be beneficial in the prevention of PDA in preterm neonates. Presence of PDA in a term neonate should be investigated to rule out an underlying congenital heart disease.

Key words: Preterm, patent ductus arteriosus, indomethacin, ibuprofen

1. Introduction

During intrauterine life, 10% of the cardiac output passes through the lungs. The remaining 90% is shunted via the ductus arteriosus (DA) to the aorta and systemic circulation. After birth, most of the right ventricular output should pass through the lungs to facilitate proper gas exchange. In order to make this possible, the ductus undergoes constriction and functional closure soon after birth in term neonates. Eighty percent (80%) of the DA in term infants close by 48 hours and nearly 100% by 96 hours. Failure of this normal closure results in problems especially in preterm neonates.

2. Physiology

Oxygen and endothelin are very strong vasoconstrictors and prostaglandins E₂ and I₂ are strong vasodilators of the DA. Lower oxygen concentrations in utero and high circulating PgE₂ and PgI₂ levels help in keeping the ductus patent. Sudden elevation in circulating oxygen tension and fall in prostaglandin levels soon after delivery results in strong vasoconstriction and functional closure of the DA soon after delivery. It is believed that this action of oxygen is mediated via the formation of the endothelin molecule. This functional closure is followed by anatomical closure in the next 1-3 months.

3. Ductus arteriosus in preterm neonates

The normal mechanisms of ductal closure fail to work in preterm neonates. The various factors contributing to an increased incidence of PDA in preterms include: (a) Increased sensitivity of the ductus to prostaglandins as compared to term neonates (b) Sensitivity to

prostaglandins is sustained for a longer period (c) Higher incidence of hypoxia and acidosis (d) Defective smooth muscle migration resulting in compromised anatomical closure.

4. Hemodynamic consequences of PDA

Shunting of blood from the systemic circulation to the pulmonary circulation results in congestive cardiac failure, which manifests clinically with wide pulse pressure and bounding pulses. Overloading of the pulmonary vasculature leads to pulmonary edema/hemorrhage which predisposes the neonate to chronic lung disease. Blood flow to the kidney and gastrointestinal tract is compromised predisposing to acute renal failure (ARF) and necrotizing enterocolitis (NEC). Hypo-perfusion followed by reperfusion increases the risk of intraventricular hemorrhage (IVH).

5. Risk factors for PDA in preterm neonates

The incidence of PDA is inversely related to gestational age and birth weight. A hemodynamically significant shunt due to PDA has been reported in 40% of infants less than 1000 grams and 20% of infants between 1000-1500 grams.¹⁻³ Respiratory distress syndrome (RDS) in preterm neonates needing ventilation and surfactant is an additional risk factor for PDA. Prophylactic use of synthetic surfactant has been associated with an increased risk of PDA. Lack of antenatal steroids, presence of sepsis, and liberal fluid therapy are other risk factors for developing PDA.

6. Clinical features:

6.a. Hyperdynamic circulation

A wide pulse pressure (>25 mm Hg), prominent precordial pulsations & bounding pulses and an ejection systolic murmur (occasionally pan systolic and continuous murmur) heard best at the 2nd left parasternal area⁴ are usually present on clinical examination.

6.b. Indicators of ductus opening on a ventilated baby

Metabolic acidosis not attributable to hypoperfusion and sepsis, deteriorating respiratory status on day 3-4 after a period of relative stability, increasing ventilatory requirements on day 3-4, unexplained CO₂ retention, fluctuating FiO₂ requirements and recurrent apneas in a ventilated baby should raise clinical suspicions of a symptomatic PDA.

Studies have revealed that echocardiographic criteria of a significant left to right shunt usually precede clinical symptoms by an interval of 2-3 days. However, clinical features have a better correlation with long-term morbidity and available evidence does not recommend routine screening with echocardiography for at-risk neonates³.

7. Differential Diagnosis

- AV fistula
- Ruptured sinus of valsalva
- Aorto-pulmonary window.

8. Investigations

8.a. Chest Xray: Radiographic findings are non-specific for diagnosis of PDA. They include cardiomegaly, upturned left bronchus due to left atrial enlargement and pulmonary plethora.

8.b. Echocardiography

Echocardiography is not recommended routinely for all preterm neonates. A clinical diagnosis of PDA should preferably be confirmed by echo prior to starting medical therapy. Echocardiographic criteria include (a) Left atrial dilatation (Left atrial: Aortic root > 1.6) (b) Diastolic turbulence (backflow) on doppler in the pulmonary artery and (c) Direct imaging to measure the diameter of PDA.

A hemodynamically significant PDA is diagnosed in the presence of a ductus diameter > 1.5mm and absent/ retrograde diastolic flow in the post-ductal aorta. Doppler echo is more specific and sensitive for the diagnosis of PDA while an M mode echo is useful for assessing the severity of the shunt across the PDA.

9. Strategies of management⁵

9.a. Prophylactic treatment: In this strategy, treatment is started before the appearance of PDA, usually within the first 24 hours of birth. Indomethacin has been tried as prophylactic treatment in very preterm neonates, especially < 1000 grams. Although it was found to decrease symptomatic PDA and IVH, it was not associated with any change in long-term morbidity and neuro-developmental outcome. More over, indomethacin has also been found to decrease cerebral and renal blood flow and hence is not recommended as a prophylactic agent in the prevention of PDA⁶. Trials with prophylactic ibuprofen are still going on⁷.

9.b. Early Symptomatic: In this strategy, treatment is started as soon as the PDA is detected even if it is not hemodynamically significant.

- **Weight <1000 grams:** Among neonates detected to have a PDA, 80% of neonates would progress to develop a hemodynamically significant shunt. Hence, it is recommended to treat PDA in this group early even though it may not be hemodynamically significant. However, in view of the recent evidence, the risks and benefits of such treatment must be weighed before treating asymptomatic babies.⁸
- **Weight >1000 grams:** Early treatment is not recommended in this group as progression to symptomatic PDA is less common and spontaneous closure are known to occur in this group⁸.

9.c. Late Symptomatic

Only hemodynamically significant PDA is treated in this strategy and it is the recommended approach for neonates >1000 grams.

10. Management

10.a. General measures

- Fluid restriction: 60% of maintenance fluids
- Avoid hypoxia and acidosis
- High peak end expiratory pressure (PEEP) and lower inspiratory time (Ti), if otherwise appropriate⁹.
- Furosemide is generally not required. Furosemide increases prostaglandin levels, which may interfere with the therapeutic effect of indomethacin. However enough evidence for this concern is not yet available¹⁰. In intractable CHF, we occasionally use furosemide in a dose of 1 mg/kg/dose 12 hourly. Careful evaluation of hydration status is essential before and during treatment with furosemide.
- Digoxin has no role in management of PDA.

10.b. Medical Management

10.b.i. Indomethacin

Mechanism of action

The postulated mechanism of action is an inhibition of cyclo-oxygenase (COX) enzyme in the prostaglandin pathway. Indomethacin has a greater affinity for COX 1 (renal) as against COX 2 (extra-renal). Due to this greater affinity for renal COX1, the incidence of renal complications is higher with indomethacin as compared to other inhibitors of prostaglandin synthesis.

Indications for indomethacin use:

- Early symptomatic treatment of PDA in <1000 grams
- Late symptomatic treatment of PDA in > 1000 grams
- Re-treatment after failure of the first course of Indomethacin.
- Recurrence of PDA after the first course of indomethacin.

Oral medication

Due to non-availability of the IV formulation, we have been using oral indomethacin for closure of PDA. Oral indomethacin is available as 25 mg tablets and it can be broken into lower doses. We usually mix the dose with 2-5 ml expressed breast milk and administer it through the oro-gastric tube.

Side effects and monitoring

Adverse effects 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. Decreased cerebral blood flow associated with the use of indomethacin may be associated with poor neuro-developmental outcome. Various parameters that should be monitored

include (a) Urine output: If urine output falls below 1 ml/kg/hr low dose dopamine at 1-2 $\mu\text{g/kg/min}$ for its renal effect may be used¹¹ (b) Renal function (alternate days) and (c) Platelet counts (daily)

Contraindications

Renal: Urine output < 0.6 ml/kg/h, blood urea > 30 mg/dl, creatinine > 1.8 mg/dl

Bleeding: Bleeding from IV sites; gastrointestinal bleeding, enlarging or evolving intraventricular hemorrhage (IVH); platelet count < 60,000/mm³

Gastrointestinal: necrotizing enterocolitis; blood in stool

Efficacy

The closure rate with indomethacin is 80%. The efficacy is unaffected by gestation or birth weight. The full course should be completed even if closure is achieved before the third dose. Longer treatment with lower doses (0.1 mg/kg/dose for 6 doses) has similar toxicity and efficacy and are not recommended¹²

10.b.ii. Ibuprofen

Ibuprofen is also an inhibitor of prostaglandin synthesis and is effective in closing the ductus. It has an equal efficacy as compared to indomethacin with fewer side effects¹³. Its use is associated with a lower incidence of oliguria and renal compromise. It has been found to have a lesser effect on mesenteric and cerebral blood flow as compared to indomethacin. The dose is 10 mg/kg stat followed by 5 mg/kg/dose x 2 doses at 24 hour intervals given orally.

10.c. Surgical ligation

The indications for surgical therapy include a contraindication to medical therapy and failure of a second course of indomethacin. Surgical ligation may be carried out by Thoracotomy or Video assisted thoracoscopy¹⁴.

11. Restricted fluid intake for prevention of PDA

Bell et al¹⁵ have conducted a meta-analysis on studies evaluating fluid therapy and have shown that restricted fluid intake in the initial 4-5 days of life is associated with a lower incidence of PDA. In our unit, we usually start with 60 ml/kg in babies weighing between 1000-1500 grams and 80 ml/kg for babies between 750-1000 grams. We try to maintain serum sodium of 135-145 meq/L, urine output of 1-3 ml/kg/hr and a urine specific gravity of 1.005 to 1.012. We use thin transparent plastic barriers (clingwrap) to create a microenvironment around the baby in order to decrease insensible water losses. We would allow a weight loss of at least 2-3% per day and generally do not exceed a fluid intake of 150-160 ml/kg/day by day 5-7 day of life. Using this scheme of fluid therapy, we have achieved a low incidence of PDA in our unit.

12. Guidelines for treatment

- Preterm babies are at risk of developing hemodynamically significant PDA.
- Prematurity, lack of antenatal steroids, RDS and sepsis increase the risk of PDA.
- At-risk preterm neonates should be monitored for clinical features suggestive of PDA.
- Echocardiography should be used to confirm a clinical suspicion of PDA. In the absence of an echo, treatment may be started with a clinical diagnosis.

- Babies <1000 grams with a diagnosis of PDA (irrespective of hemodynamic effect) should be treated. However, the risk-benefit ratio must be carefully weighed especially in growth retarded babies with absent or reverse diastolic blood flow.
- Babies >1000 grams with a diagnosis of PDA should be treated only if a hemodynamically significant left to right shunt is present.
- Prophylactic treatment with indomethacin is not recommended.
- Platelet counts and renal parameters should be checked prior to starting therapy with indomethacin and repeated after 24 hours.
- A second course of indomethacin should be tried after failure of the first course or recurrence after the first course.
- Preliminary studies seem to suggest that ibuprofen is a safe alternative to indomethacin in the treatment of PDA.
- Surgical ligation should be considered if PDA recurs after the second course or if contraindications to indomethacin/ ibuprofen exist.
- Both ibuprofen and indomethacin may be used orally.

These recommendations do not apply to PDA in term neonates. Term neonates with PDA should not be treated with indomethacin/ ibuprofen and should have a detailed echo to rule out an underlying congenital heart defect. They would require surgery for closure of an isolated patent ductus arteriosus.

AIMS Protocols

Table- Dosage of indomethacin and ibuprofen for closure of patent ductus arteriosus

<p>Indomethacin <i>Initial Dose</i> 0.2 mg/kg stat followed by age adjusted doses: <i>Subsequent dose</i> < 2 day- 0.1 mg/kg/dose 12 hourly for 2 doses 2-7 day- 0.2 mg/kg/dose 12 hourly for 2 doses > 7 day- 0.25 mg/kg/dose 12 hourly for 2 doses</p>
<p>Ibuprofen 10 mg/kg stat followed by 5 mg/kg/dose 24 hourly for 2 doses</p>

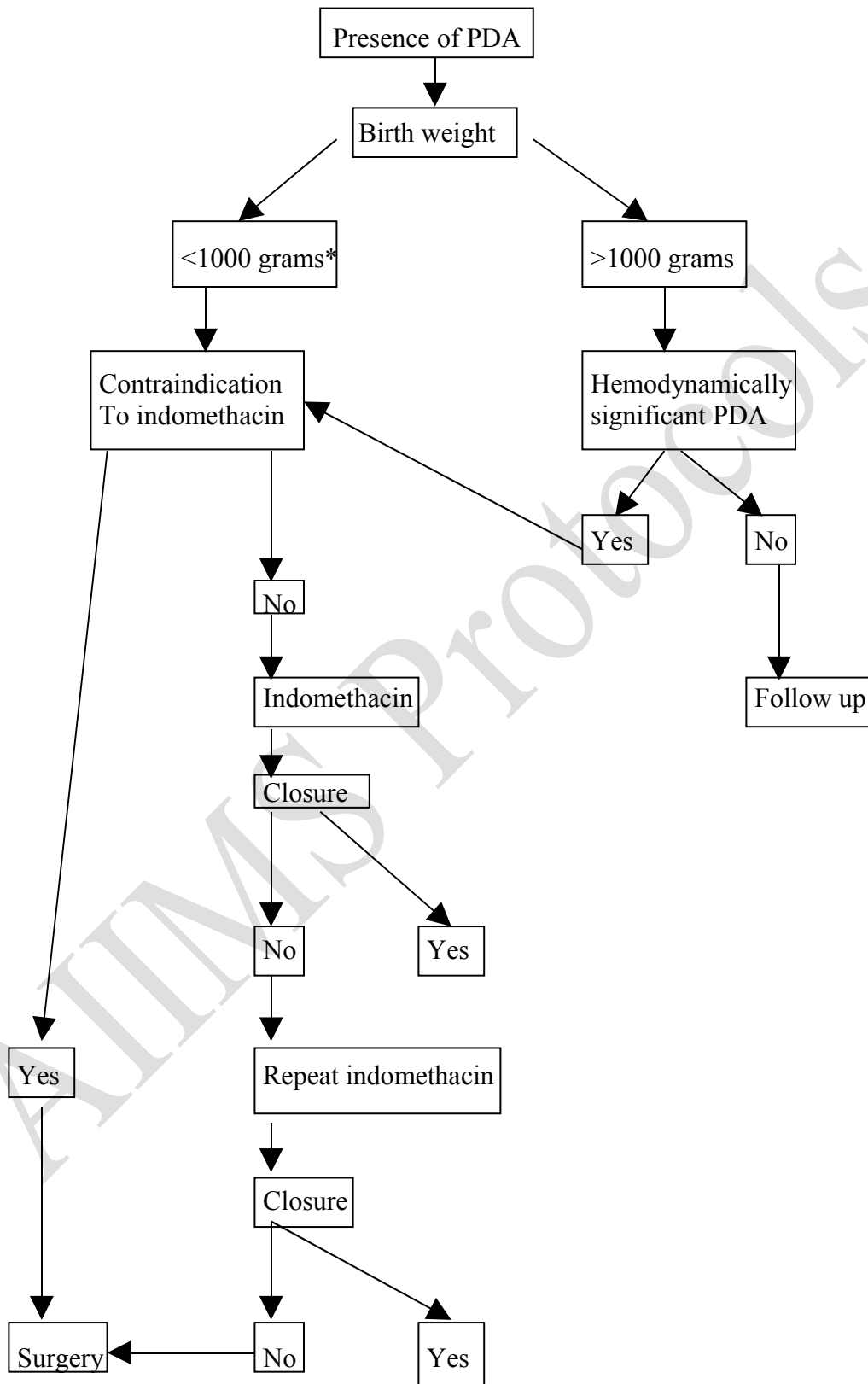
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References

1. Wechsler SB, Wernovsky G. Cardiac disorders. In Manual on neonatal care. Eds Cloherty JP, Stark AR. 4th Edn pp 430-432.
2. Archer N. Cardiac diseases. In Textbook of neonatal care. Eds- Rennie JM, Robertson NRC. 3rd Edn pp 687-689.
3. 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.
4. Zahaka KG, Patel CR. Congenital cardiac defects. In Neonatal perinatal medicine – Disorders of the fetus and infants. Eds- Fanaroff AA, Martin RJ. 6th Edn. 1997 pp1155-1157.
5. Clyman RI. Treatment of premature neonates with patent ductus arteriosus: analysis of four treatment strategies. J Pediatr 1996;128 :601-607.
6. Foulie WP. Prophylactic Indomethacin - systematic review and meta-analysis. Arch Dis Child 1996; 74: F81-F87.
7. De Carolis MP, Romagnoli C, Polimeni V, Piersigilli F, Zecca E, Pappacci P et al. Prophylactic ibuprofen therapy of patent ductus arteriosus in preterm infants. Eur J Pediatr 2000; 159:364-368.
8. Bose CL, Laughan MM. Patent ductus arteriosus: Lack of evidence for common treatments. Arch Dis Child Fetal Neonatal Ed 2007;92 :F 498-502 .
9. Vanhaesebrouck S, Zonnenberg I, Vandervoot P, et l .Conservative treatment for patent ductus arteriosus in the preterm . Arch Dis Child Fetal Neonatal Ed 2007;92 :F 244-247 .

10. Brion LP, Campbell DE. Furosemide in indomethacin treated infants - systematic review and meta-analysis. *Pediatr Nephrol* 1999;13: 212-218.
11. Fajardo CA, Whyte RK, Stele BT. Effect of dopamine on failure of indomethacin to close patent ductus arteriosus. *J Pediatr* 1992;121:771-775
12. Tammela O, Ojala R, Livainen T, Lautamatti V, Pokela ML, Janas M et al. Short versus prolonged indomethacin therapy for patent ductus arteriosus in preterm infants. *J Pediatr* 1999; 134: 552-557.
13. Van Overmeire B, Smets K, Lecoutere D, Van de Broek H, Weyler J, Degroote K et al. A comparison of ibuprofen & indomethacin for closure of patent ductus arteriosus. *N Engl J Med* 2000;343: 674-681.
14. Burke RP, Jacobs JP, Cheng W, Trento A, Fontana GP. Video-assisted thoracoscopic surgery for patent ductus arteriosus in low birth weight neonates and infants. *Pediatrics* 1999;104: 227-230.
15. Bell EF, Acarregui MJ. Restricted versus liberal water intake for preventing morbidity and mortality in preterm infants. *Cochrane Database Syst Rev* 2000; (2):CD000503
16. McNamara, Sehgal A. Towards rational management of the patent ductus arteriosus: the need for disease staging. *Arch Dis Child Fetal Neonatal* 2007;92:F 425-27.

Management of PDA in preterm neonates



* - Risk-benefit ratio must be weighed for asymptomatic growth retarded baby