Diagnosis and Management of Patent Ductus Arteriosus in Newborn: An Update
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Abstract
Patent ductus arteriosus is one of the common congenital acyanotic heart disease in neonates, especially in preterm. Patent ductus arteriosus (PDA) is a congenital condition, characterized by a persistent connection between the aorta and the pulmonary artery. Patency of Ductus Arteriosus is essential for fetal survival. Patent ductus arteriosus is one of the most common clinical findings and most frequent source of complications in premature infant. After birth, in term infants, the ductus usually closes within the first day of life, starting with functional closure followed by anatomical closure with vascular remodeling. The persistence of the PDA in preterm infant is inversely related to gestational age and birth weight. The incidence of Patent Ductus Arteriosus is 31% in preterm infant weighing 501 to 1500 gm and gestational age 29 weeks. The treatment options available are conservative medical management, pharmacological therapy or surgical ligation. Conservative medical management involves fluid restriction, watchful waiting and ventilator support.

Key words: Patent ductus arteriosus, newborn.

Introduction
The ductus arteriosus is a central vascular shunt connecting the pulmonary artery to the aorta, allowing oxygenated blood from the placenta to bypass the uninflated fetal lungs and enter the systemic circulation. Rapid closure of the ductus arteriosus after birth is essential for vascular transition to the mature, divided pattern of arteriovenous circulation. Failure of ductus arteriosus closure, termed patent ductus arteriosus (PDA), is primarily an affliction of prematurity, with the ductus remaining open at 7 days of age in up to 64% of infants born at 27 to 28 weeks’ gestation and 87% of infants born at 24 weeks.¹ Before the use of antenatal corticosteroids, PDA was frequently found in premature infants of all gestational ages and was associated with respiratory distress syndrome. Treatment with indomethacin was standard, and studies evaluated the benefits of early (or even prophylactic) PDA ligation.²

With advances in ventilation strategies, use of antenatal corticosteroids and exogenous surfactant, and increased willingness to wait for spontaneous ductus arteriosus closure, today’s more mature preterm infants rarely require intervention for a ductus arteriosus.³

This article is written with the view to explore the different modalities of investigations and treatment in home and abroad, which would be beneficial for the practicing doctors who deal with neonates.

Risk factors
The incidence of PDA is inversely associated with the degree of prematurity. Other factors associated

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with an increased risk of PDA in the premature
infant include respiratory distress syndrome, high
volume of intravenous fluids (>170 mL/kg per day)
in the first week, sepsis, prolonged rupture of
membranes, furosemide, male sex, and other
contributors. Evidence also shows that
aminoglycoside antibiotics and certain antacids,
frequently used in neonates, paradoxically increase
the risk of a PDA. Antenatal corticosteroids and
maternal hypertension decrease the incidence of
PDA.

Diagnosis
The diagnosis is often suspected clinically.
Continuous or systolic murmur occur may be
present. Murmur may be absent when shunt is large
enough that nonturbulent flow fails to generate a
detectable murmur. A low diastolic blood pressure
(due to runoff into the ductus during diastole, more
frequent in the most premature infants). A wide pulse
pressure (due to ductus runoff or steal), hypotension
(especially in the most premature infants), bounding
pulses, increased serum creatinine concentration or
oliguria, hepatomegaly, signs of pulmonary edema
are often seen, including tachypnea, decreased
oxygen saturation, and increasing respiratory
support. Chest radiography can show stigmata of
pulmonary edema.

Echocardiography is gold starndard for diagnosis.
Ductus size alone is inadequate to attribute
hemodynamic significance. Although an absolute
transductus diameter of more than 1.5 to 1.7 mm by
color doppler has been associated with increased
propensity for hypoperfusion. A large left-to-right
shunt suggests a hemodynamically significant shunt.
However, the degree of shunting depends in large
part on pulmonary vascular resistance.

Other echocardiographic criteria for determining
hemodynamic significance are the presence of
reversal of forward flow in the descending aorta
during diastole (indicating shunting through the
PDA), and left atrial or ventricular dilatation, which
are the consequence of overcirculation of the
pulmonary vascular bed and a chronic hyperdynamic
state. Left-to-right shunt across the intra-atrial
septum is indicative of a large shunt. The ratio of
the left ventricular output to superior vena cava flow
is directly proportional to the ductus flow and, when
greater than or equal to 4, may indicate
hemodynamic significance. A left atrial to aortic root
(LA/Ao) ratio is most sensitive when performed after
day 1, and is considered abnormal if >1.5.

Biomarkers
B-type natriuretic peptide (NT-proBNP) and mature
B-type natriuretic peptide (BNP) may be useful in
detecting a hemodynamically significant PDA. BNP
is secreted and released by the ventricular
myocardium when under stress from either increased
volume or pressure.

Biosensors
Bioengineering has also been developed to monitor
or detect PDA in preterm infants. Various approaches
include interpretation of pulse oximetry information
(perfusion index, plethys-mography),
interpretation of transthoracic electrical signals
(impedance, cardiometry, velocimetry,
bioreactance), regional oxygenation (near-infrared
spectroscopy), alterations in skin microcirculation
(side stream dark-field imaging, reflectance
spectropho-tometry), resonance Raman
spectroscopy.

Outcome
In healthy full-term infants, PDA closes within 48 to
72 hours. In premature infants born weighing more
than 1,000 gm, the ductus closes spontaneously in
67% by day 7 and in 94% by discharge. Only 3% of
infants weighing more than 1,000 gm may require
intervention for a PDA.

However, in extremely premature infants weight
<1,000 g at birth (extremely low birthweight), 57%
to 69% will still have a PDA at 7 to 10 days of age.
Of those 30% will reopen and may then reclose, or
go on to hemodynamically significant and require
pharmacologic or surgical closure.

Treatment
Patent ductus arteriosus (PDA) is treated with
medicines, catheter-based procedures, and surgery.
The goal of treatment is to close the PDA to prevent
complications and reverse the effects of increased
blood volume. There are prophylactic use of
indomethacin to prevent IVH, PDA, and the adverse
consequences of PDA in extremely low-birth weight
infants.

Pharmacological approach
Pharmacologic treatments are available to induce
constriction of a PDA: indomethacin, ibuprofen, and
acetaminophen (paracetamol). Indomethacin and
Ibuprofen are nonsteroidal anti-inflammatory drugs (NSAIDs), which nonselectively inhibit the cyclooxygenase enzymes, preventing the conversion of arachidonic acid to prostaglandins, which maintain ductal patency. Since 1976, indomethacin has been used to treat PDA in premature infants. Indomethacin is administered intravenously. Enteral and rectal preparations are also being used. In patients who receive a second course of indomethacin, only half will experience ductus closure. The odds of nonresponse to the second course of indomethacin are increased by 90% if there was nonresponse to the first course. Advancing gestational age appears to predict nonresponse to indomethacin.\textsuperscript{16}

Indomethacin and ibuprofen have a similar efficacy (70\%) for an initial course of 3 doses. Regardless of the treatment, there is about a 25\% rate of reopening, especially in the most premature infants. Because of this high rate of reopening, some advocate a fourth dose of indomethacin, given 24 hours after the third dose.

Acetaminophen decrease prostaglandin synthesis by interrupting prostaglandin synthesis at the peroxidase site of prostaglandin H2 synthetase (cyclooxygenase). Acetaminophen for treatment of PDA is associated with less elevation in serum creatinine concentration and oliguria compared to ibuprofen or indomethacin, and less elevation in bilirubin compared to ibuprofen.\textsuperscript{17} Acetaminophen has been used for rescue therapy after failed response to indomethacin in extremely premature infants, resulting in 46\% of infants having a smaller or closed ductus.\textsuperscript{18} When used as primary treatment, the efficacy ranges from 70\% to 81\%.\textsuperscript{19} Efficacy appears to be affected by both gestational age and postnatal age, with improved efficacy noted when treatment was started within the first week.\textsuperscript{20}

The range of reported treatment regimens for acetaminophen, from 7.5 mg to 10 or 15 mg/kg every 6 hours for 3 to 7 days. Acetaminophen can be given orally, at the same dosage and interval, with similar reported efficacy as the intravenous route.\textsuperscript{21}

A hemodynamically significant PDA can reduce forward blood flow to the superior mesenteric artery during diastole, and indomethacin acutely decreases gut blood flow. On the other hand, fasting is associated with intestinal mucosal atrophy which could increase the risk for NEC. So patients must have their oral feed during oral administration of indomethacin or ibuprofen.\textsuperscript{22}

**Ligation**

Candidates for surgical ligation hemodynamically significant PDA that results in cardiac dysfunction, renal failure, or respiratory failure. Ligation is typically performed with an open thoracic approach, and either using a metal clip or tying off the vessel. Intravascular approaches with placement of an occluding coil are available for patients weighing more than 5 kg.\textsuperscript{23} Adverse effects ligation are: vocal cord paralysis, postoperative hypotension, diaphragm paralysis,\textsuperscript{24} bronchopulmonary dysplasia, and worse neurodevelopment. Early PDA ligation is an independent risk factor for BPD and worse neurodevelopment compared with ligation at a later age.\textsuperscript{25}

Diagnosis and treatment option followed in some international institute:

**In National University Hospital (NUH) Singapore**

In their institute when they suspect PDA in a premature baby by clinical examination. An echocardiography of the heart (ultrasound scanning) done at the bedside can confirm the diagnosis. Treatment options include fluid restriction, medical treatment with drugs such as indomethacin and occasionally, surgical ligation (where the PDA is ligated in a surgical operation). In the majority of instances medical management is effective in closing a PDA. In the rare occasion of failure with medical therapy, surgical ligation is done by the cardiothoracic surgeons under general anesthesia. They have a support group (early starter club) for parents of premature babies that comprises doctors, nurses, medical social workers as well as parents of previous premature babies managed in NICU. In their VLBW cohort (2015-2019), 78 out of 268 (29\%) VLBW babies had a symptomatic PDA. 73\% of 78 VLBW babies with symptomatic PDA were successfully treated with medication and the remaining 27\% underwent surgical ligation. There were no deaths in babies who had ligation.\textsuperscript{26}

**In All India Institute of Medical Sciences (AIIMS)**

Patent ductus arteriosus (PDA) is a major morbidity in preterm infants, especially in extremely premature infants less than 28 weeks in NICU in AIIMS. The clinical signs and symptoms of PDA in preterm
infants are nonspecific 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, birthweight, serial echocardiography and clinical status to individualize the decision to treat.

**PDA with PPHN**

Persistant pulmonary hypertension (PPHN) is common association with PDA. Echocardiography remains the gold standard diagnosis of PPHN. Right-to-left or bidirectional shunting of blood at the foramen ovale and/or the ductus arteriosus is classically seen, as well as high pulmonary arterial/right ventricular systolic pressure estimated by Doppler velocity measurement of tricuspid regurgitation jet. The direction of the shunt at atrial and ductal level also provides clues to management. Left-to-right shunting at the foramen ovale and ductus arteriosus with marked hypoxemia suggests predominant intrapulmonary shunting, and interventions should focus on optimizing lung recruitment (increasing PEEP/mean airway pressure or intratracheal surfactant). The presence of right-to-left shunting at foramen ovale and/or ductus arteriosus is suggestive of extrapulmonary shunting and which may respond to pulmonary vasodilator therapy. Similarly, right-to-left shunting at the ductal level and left-to-right shunting at the atrial level suggest PPHN with left ventricular dysfunction with pulmonary venous hypertension as seen in CDH, asphyxia or sepsis. Ductal dependent systemic circulation syndromes may be associated with a similar shunt pattern. Adequate resuscitation, careful and intensive monitoring, careful fluid and electrolytes management, minimal handling prevent PPHN. Mechanical ventilation, surfactant therapy, pressor agent like dopamine is use to treat this condition. There are some other modalities of treatment like inhaled nitric oxide, Milrinone (a type 3 phosphodiesterase inhibitor), Sildenafil, Prostacyclin, inhaled/nebulized PGI2, Bosentan, Paralyzing agent like pancuronium, Magnesium sulphate. Extracorporial membrane oxiganation is indicated for term and near term infants with PPHN who fail to respond to conventional therapy.

**Treatment of PDA in full term baby**

PDA accounts for 10% of all congenital heart diseases in full term infants. The PDA in a full term infant is structurally different, so the sensitivity of the ductus to the relaxing effect of prostaglandin E2 is lost shortly after birth. That’s why it does not respond appropriately to the various stimuli for closure. Indomethacin is usually ineffective. The infant should monitored carefully, and surgical ligation should be considered at the earliest signs of significant congestion. Even without signs of failure, the PDA should be ligated before 1 year of age to prevent endocarditis and pulmonary hypertension.

**Conclusion**

PDA is a common condition among premature infants born at less than 28 weeks’ gestation. Recent advances include the addition of acetaminophen (paracetamol) to the arsenal of available treatments. Improvements are still needed regarding standardized echocardiographic criteria, optimal timing of treatment (when indicated), dosing regimens for acetaminophen, and development of endovascular occlusive devices for the smallest preterm infants.

**References**


