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*RESEARCH ARTICLE*

# MANAGEMENT STRATEGIES OF PATENT DUCTUS ARTERIOSUS IN PRETERM INFANTSREVIEW ARTICLE

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## *Abstract*

Patent ductus arteriosus (PDA) is a frequent congenital heart defect. It becomes even more common in preterm infants with a high burden of consequences and adverse effects. Recently, the emergence of a constellation of different management protocols urged for a comprehensive summery of the best evidence-based interventions. A detailed electronic search for evidence was carried out, including Cochrane, systemic and narrative reviews. Variable controversial aspects of PDA diagnosis and management were discussed. Brief echocardiographic and laboratory PDA diagnosis followed by a review of symptomatic and asymptomatic PDA Surgical and nonsurgical management strategies included. Early interventionfor asymptomatic PDA; depending on echo scoring, and grading all symptomatic PDAs clinically and echographically can guide management and decrease the need for surgical ligation.



## Introduction:-

DA (Ductus arteriosus) shunts blood from the high-pressure pulmonary circulation to the systemic circulation during fetal life. After birth, closure of the DA directs the entire right ventricular output to the lungs to facilitate its oxygenation.

Patent ductus arteriosus (PDA), defined as the failure of the DA to close within 72 hours after birth,is a common congenital heart defect.[1]Prevalence in term neonates is only 1 in 2000 births, which is about 5%–10% of all congenital heart diseases.[2] However, in preterm infants, DA remains open at day 4 of life in around 10% of preterm babies delivered between 30 and 37 weeks' gestation, up to 80% of those delivered between 25 and 28 weeks' gestation, and approximately 90% of those born at 24 weeks' gestation.[3] Recently, the explosion of diagnosis and treatment protocols urged for a comprehensive review to summarize the literature for the best diagnostic and therapeutic methods. Evidence-based practice and consistent guidelines will improve patient outcomes and decrease PDA associated complications.

## Methods:-

Extensive search was conducted through different databases including Medline, Embase, and CINAHL. Evidence from Cochrane reviews, randomized controlled trials, narrative and systemic literature reviews was

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scrutinized.While Animal and model studies were excluded. Studies on each PDA management method were included. An integrated approach was suggested based on the best current evidence.

## Results And Discussion:-

***Physiology***

As pulmonary vascular resistance declines after birth, blood typically flows left-to-right from the aorta though DA into the pulmonary arteries. Hence, a significant reduction in systemic blood flow with a concomitant increase in pulmonary blood flow ensues. Consequently, a cascade of numerous adverse outcomes emanates;like pulmonaryhemorrhage, bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), periventricular leukomalacia, cerebral palsy, necrotizing enterocolitis (NEC), and impaired renal function. [4]

***Diagnosis***

Since not all PDAs are hemodynamically significant, assessment of the hemodynamic impact of the PDA is imperative. In conjunction with clinical evaluation, echocardiogram remains the best investigation to assess the hemodynamic significance of PDA (HsPDA) and to rule out accompanying congenital heart disease. The main criteria for HsPDA are a ductal size of >1.5 mm, left to- right shunting of blood, LA:AO ratio of >1.5,[5] end-diastolic reversal of blood flow in the aorta and poor cardiac function.[6]

Additionally, Cardiac biomarkers recently showed a promising role in the evaluation of the hemodynamic significance of the ductal shunt. In comparison to echocardiography, BNP (brain-type natriuretic peptide) and the N-terminal fragment of pro-BNP (NT-pro-BNP) are reliable parameters for early prediction (2nd – 3rd day of life) of a PDA that becomes hemodynamically significant later.[7,8] Cardiac Troponin T is another blood test that may help in PDA screening. However, it is not in widespread use yet.[9]

***Management***

**General measures:**

General conservative PDA management includes a neutral thermal environment and prudentoxygen delivery to minimizes demand on the left ventricular function. Proper use of positive end-expiratory pressure (PEEP) reduces left-to-right ductal flow and improves systemic blood flow.[10]Hematocrit should be kept at 35-40% to raise pulmonary vascular resistance and decrease left-to-right shunting.[11]Conservative daily fluid intake between 110 and 130 ml/kg seems reasonable to avoid pulmonary fluid overload in neonates with HsPDA, as evidence for the fluid restriction is lacking.[12] Diuretics are not routinely recommended, as it stimulates the renal production of prostaglandin E2, that maintains DA patency.[13]

**Non-surgical definitive treatment:**

Non-surgical Definitive treatment for PDA includes Cyclooxygenase inhibitors (Indomethacin, Ibuprofen) and Paracetamol. At different stages, both inhibit the production of PGG2 and PGI2.

Indomethacin and Ibuprofen have similar closure rate at about 70%. [14,15] However, neonates withvery low birth weight or older than 10 days have lower response rates.[16]

The main difference between Ibuprofen and Indomethacin is toxicity. Ibuprofen has a safer renal profile with a lower risk of serum creatinine increment, or urine output reduction.[1] NEC link to Indomethacin is not proven even with larger doses and high concentrations, however, intestinal perforation could rarely occur with both Indomethacin and Ibuprofen.[17]

On the contrary, Indomethacin has a better long-term toxicity profile. In a recent systemic review, although PVL reported with brain ultrasound was not statistically different,[18]Ibuprofen was related to a higher risk of BPD in comparison with Indomethacin. Moreover, it was demonstrated that ibuprofen could displace bilirubin from albumin binding sites.[19]

Considering the similar toxicity profile, the choice of Indomethacin or Ibuprofen will depend on availability and cost. One factor that may counterbalance towards ibuprofen, is the oral administration that is safe and effective.[20]

Paracetamol is as effective, at doses of especially in late PDA after the second week. As well as, it may decrease the need for surgical ligation.[21]In a recent Cochrane review, Paracetamol showed similar response to Indomethacin and Ibuprofen with fewer adverse effects.[22]

**Timing of treatment:**
Therapy could be started prophylactically to all high-risk infants, therapeutically to asymptomatic HsPDA cases, diagnosed after screening echocardiography, therapeutically to symptomatic high-risk cases, or late after deterioration. Evidence for the best time to start treatment is still far from clear.

Prophylactic Indomethacin decreases the risk of HSPDA, the need for surgical ligation, severe IVH, and significant pulmonary hemorrhage.[23] Better Long-term outcome including decreases BPD and death was shown in a prospective double cohort-controlled study by Liebowitz.[24] However, no significant improvement in death, BPD, or severe neurosensory impairment could be replicated in other studies.[23,25] Similarly, prophylactic Ibuprofen reduces significant PDA and the requirement for surgical ligation but without considerable differences in mortality, BPD, IVH,[26]or NEC.[27]

Additionally, early rescue treatment did not result in any difference in mortality, BPD, or days on oxygen.[28]Although early indomethacin treatment increases PDA closure rate, it is associated with higher renal adverse effects and more severe complications without respiratory benefit over the delayed administration.[29] Furthermore, PDA has a high tendency for spontaneous closure, and medical treatment is fraught with serious side effects.

Conversely, delaying treatment decreases the response rate; as when the ductal tissue matures, it becomes less dependent on prostaglandins [30] and exposes the baby to the hemodynamic effects of the PDA in the early critical period of life. Additionally, Van Overmeire's study [29] is relatively old, less powered to detect the BPD difference (total recruited only 127cases), with probably more severe cases in the early treatment arm (higher LA/Ao).

The best available balance between these contradictory pieces of evidence could come from the grading system invented by McNamara and Sehgal [31] based on clinical severity and echocardiographic significance. It is a reasonable grading system, although it needs more studies to demonstrate its effects on treatment or outcome.

Alternatively, early echocardiographic screening for PDA with a targeted treatment for infants at a high risk of spontaneous early ductal constriction failure has been associated with reduced mortality and pulmonary hemorrhage.[32] El Khuffash et al. [33] suggested early PDA screening at the age of 2 days with severity scoring that can predict adverse outcomes such as BPD and death. Additionally, screening could limit the number of infants exposed to unnecessary PDA prophylaxis.

The best practice is to do echo screening for infants less than 28 weeks' gestation at the age of 2 days then following El Khuffash et al. severity scoring for the treatment decision.[21] However, all symptomatic PDAs should be echoed to confirm HsPDA and to exclude duct dependent congenital heart diseases. Management decision is taken according to the gestational age, hemodynamic state, and echocardiographic findings guided by McNamara and Sehgal's grading system.[31] However, if the first Ibuprofen course is not effective, Repeated courses are equally potent in decreasing the rate of treatment failure and the need for surgical ligation. [34]

**Surgical treatment:**
Surgical PDA ligation is considered for neonates who are persistently symptomatic after failure or contraindication to noninvasive treatment.[35] It is generally reserved for infants who are dependent on mechanical ventilation or with congestive heart failure. However, it could be performed either early on all PDAs that fail to close after pharmacologic therapy, or later only after cardiopulmonary compromise develops.[36]

The Selective late ligation approach resulted in the same incidence of BPD, ROP, sepsis, and neurologic insult with a significantly lower NEC rate [36] and lower incidence of abnormal Neurodevelopmental outcomes.[37] Hence, we follow selective ligation for the patient who remains on high ventilator settings or stays significantly symptomatic after failure or contraindication to medical therapy. This approach is less invasive, decreases the cost of early ligation, the burden of perioperative care, and the serious complications of PDA ligation.

Surgical ligation is effective for rapid and completeductal closure without significant increase in mortality during hospitalization compared to pharmacological closure.[38] However, serious complications are not uncommon. Namely, postoperative severe hemodynamic and respiratory collapse (post ligation collapse syndrome PLCS) which is the most serious complication that follows surgical ligation [39] and other complications including; pneumothorax, left vocal cord paralysis, lymphatic leak, injury to the left phrenic nerve,[40] chylothorax, [41] and scoliosis.[42]

On the Long term, surgical ligation is associated with a higher risk of BPD,[43,44] retinopathy of prematurity,[45] and neurodevelopmental impairment.[37,45 ,46]Therefore, extensive postoperative care and monitoring are needed. Cardiovascular support with volume and inotropic agents to achieve adequate blood pressure and perfusion is important to preserve postoperative infant stability.[47]

Tashiro et al. [48] have run a large study of 63,208 patients with PDA. Of these, surgical ligation was carried out in 6766 (10.7%). This ratio varies according to gestational age from 37% of fewer than 24 weeks to 12.5% for 27-28 weeks' infants.

## Conclusion:-

In conclusion, PDA is common in preterm infants. Nevertheless, not all PDAs require treatment. Early management of asymptomatic cases, depending on echo scoring, then echoing all symptomatic PDAs and grading them clinically and echocardiographically can guide treatment and cutback the number of cases who required surgical ligation. Infants who have a cardiopulmonary compromise should be referred for surgical ligation if not responding to medical therapy after the second course or if there is a contraindication to medical therapy.

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