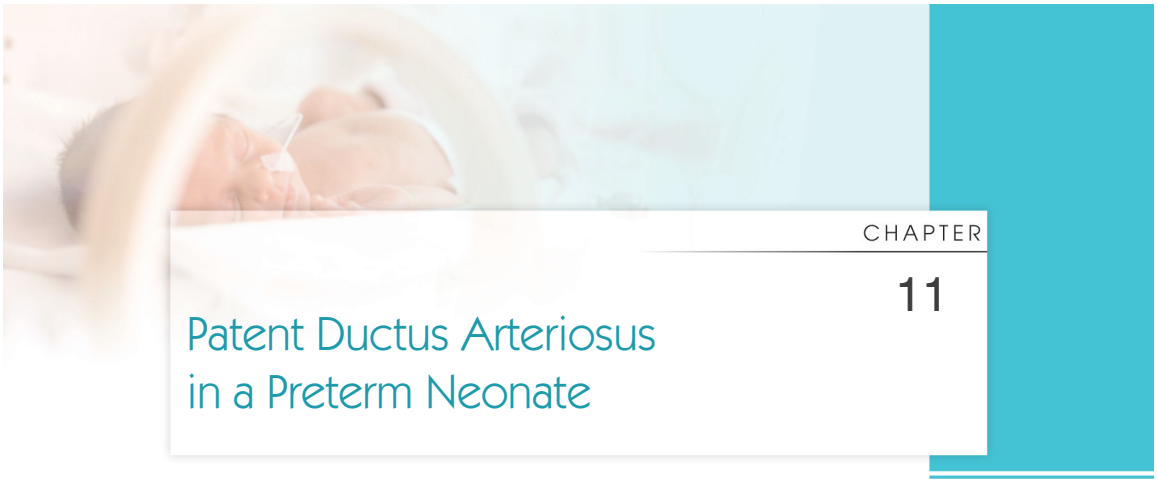

CHAPTER

11

Patent Ductus Arteriosus in a Preterm Neonate

The ductus arteriosus that connects the pulmonary artery to the descending aorta is an essential conduit of fetal circulation and diverts a large portion of combined ventricular output away from the lungs. After birth at term, the ductus constricts within the first 24–48 hours of life, aided by the expansion of the lungs, an increase in oxygenation, and a fall in vasodilatory prostaglandins (*functional closure*). Subsequently, medial and intimal connective tissue proliferation and muscle atrophy convert this muscular structure into a thin ligamentum arteriosum, typically over the next three weeks (*anatomical closure*). In a preterm infant, the ductus tissue has a lower intrinsic tone, less smooth muscle fiber, fewer sub-endothelial cushions, and a high concentration of vasodilatory prostaglandins that predispose to a delay or failure of the ductus to close postnatally.

The incidence of patent ductus arteriosus (PDA) varies inversely with gestation. About 15–40% of very low birth weight infants (<1500 g) have a PDA. In extremely preterm infants (<28 weeks), the incidence is as high as 70–80%.[1–3]

HEMODYNAMIC CONSEQUENCES AND CLINICAL SIGNS

Significant shunting of blood from left-to-right circulation through the ductus can lead to complications related to pulmonary over circulation and systemic hypoperfusion. The clinical signs and complications associated with PDA depend on the magnitude of the left-to-right shunt, the ability of the neonate to initiate compensatory mechanisms, and the presence of co-morbid conditions, such as sepsis and respiratory distress syndrome.

Pulmonary over circulation can cause a reduction in lung compliance and ineffective gas exchange, leading to a prolonged need for respiratory support. Alveolar flooding can lead to protein leakage and surfactant inactivation, further accelerating the

development of bronchopulmonary dysplasia (BPD).[4] An increased volume load to the left ventricular (LV) is also poorly tolerated, as preterm neonates have a poorly compliant LV with a limited capacity to increase stroke volume. Therefore, they compensate by increasing the heart rate. LV remodels in response to volume overload and assumes a larger, spherical shape.

Ductal 'steal' implies significant retrograde blood flow from the thoracic and abdominal aorta to the pulmonary circulation. A large ductus can steal up to 50% of the total aortic flow in neonates resulting in *systemic hypoperfusion*, especially in the 'non-vital' renal and mesenteric circulation. Contrary to the belief, ductal steal is present throughout the cardiac cycle but is best demonstrated during diastole on an echocardiogram as a retrograde flow in the descending aorta. Low diastolic aortic pressure can compromise coronary perfusion and aggravate myocardial dysfunction. Thus, a large PDA can contribute to significant morbidities, including renal insufficiency, necrotizing enterocolitis, intraventricular hemorrhage, myocardial ischemia, BPD, and mortality.[4,5]

DIAGNOSIS

A. Clinical

As outlined above, the clinical signs of a hemodynamically significant PDA (hsPDA) are due to hyperdynamic circulation resulting in bounding pulses (easily palpable dorsalis pedis), wide pulse pressure (>25 mm of Hg), a hyperactive precordium (visible pulsations in more than two rib spaces), systolic murmur (ejection systolic; rarely pansystolic or continuous), and persistent tachycardia, and are generally noted on day 3 or 4 of life. In a ventilated neonate, PDA can present with increased ventilatory settings, higher FiO_2 requirement, hypercarbia, metabolic acidosis, and recurrent apnea. Although these signs are reasonably specific, they lack sensitivity; a large hemodynamically significant PDA can remain clinically silent, causing a delay of 1–4 days in diagnosis if one were to rely on clinical signs alone.[6] A high index of suspicion is therefore required, particularly in extremely preterm neonates, to aid in early diagnosis and treatment.

B. Role of Echocardiography

Echocardiography is the gold standard for the diagnosis of PDA. It can assist in the evaluation of the presence of PDA; the direction

and velocity of the ductal shunt ductal steal; and to rule out duct-dependent systemic or pulmonary circulation, where the closure of ductus is contraindicated (Table 11.1).[7,8]

These echocardiographic parameters are not specific for PDA in isolation, but their presence as a constellation, especially with clinical signs, significantly increases the likelihood of a hsPDA. The most common parameter used is the La/Ao ratio, where a value >1.5 has a sensitivity of 79% and a specificity of 95% after 24 hours of birth.[9] Presence of atrial shunting at the foramen ovale decreases the performance of La/Ao, E/A, and IVRT to detect a PDA. Diastolic reversal at the descending aorta and increased LPA diastolic velocity are more specific markers.[10]

While echocardiography is indicated in all preterm infants with suspected PDA, its role as a routine screening tool in all preterm neonates is being questioned as it does not offer clear benefits in terms of diagnosis or management. In extremely preterm neonates, however, routine screening for hsPDA is advisable to ensure early targeted treatment. Echocardiography can also be used to follow up spontaneous or therapeutic closure of a PDA. A practical approach for the timing of screening echocardiography can be found in Table 11.2.

Limitations of echocardiography: Although the criteria for assessment of hsPDA are established, there is no uniform agreement on the threshold to initiate treatment. Many neonatal units lack ready access to echocardiography, and it is still a consultative tool, making initial and serial assessments practically challenging. Moreover, echocardiography is highly operator dependent, and the findings should always be supplemented with clinical information.

C. Other Diagnostic Tests

Chest radiograph findings are nonspecific. Features like cardiomegaly, pulmonary plethora, and left atrial enlargement to appear late on a radiograph when significant PDA leads to congestive heart failure.

D. Role of Biomarkers

Three biomarkers [atrial natriuretic peptide (ANP), cardiac troponin T (TnT), and brain natriuretic peptide (BNP)] have been investigated as predictive and diagnostic tools for PDA. BNP, the most widely studied biomarker, correlates well with echocardiographic markers

Table 11.1: Echocardiographic findings used to evaluate ductus arteriosus and its hemodynamic significance

Parameter	*Echo view and mode*	*Echocardiographic findings*	*Parameters indicating the hemodynamic significance of DA8*
Ductal patency and size	High parasternal ductal view, 2D mode	**Ductal patency:** Two-dimensional (2D) imaging of the ductus in the high parasternal view can reveal a widely open ductus, but confirmation of its patency requires a color Doppler to indicate the direction of the shunt. A duct shunting blood from left to right produces a red signal which appears strongly contrasted against the blue signal in the left pulmonary artery (LPA) and descending aorta (DA). (Fig. 11.1a) However, a pure right-to-left shunting ductus (blue color on Doppler) will likely be missed. **Ductal size:** Measure the duct diameter at the narrowest portion of the ductal length (isthmus) in mm. (Fig. 11.1b)	Transductal diameter of >1.5 mm
Direction, velocity, and flow pattern shunt	High parasternal ductal view, color/PW mode	The direction and velocity of the shunt depend on the pressure difference between pulmonary and systemic circulation; the shunt will be left-to-right if the pulmonary pressure is lower and vice versa. In almost equal pressures, the shunt can occur in both directions.	• Ductal velocity <2 meters/sec • Pulsatile left-to-right flow • Right to left shunt less than 30% of total time of cardiac cycle.

(*Contd.*)

Table 11.1: Echocardiographic findings used to evaluate ductus arteriosus and its hemodynamic significance (*Contd.*)			
Parameter	*Echo view and mode*	*Echocardiographic findings*	*Parameters indicating the hemodynamic significance of DA8*
Assessing the hemodynamic significance of a shunt	Parasternal long axis view (PLAX)/Ductal view/Suprasternal aortic arch view	**Signs of pulmonary overcirculation:** A significant left-to-right shunt causes LV volume overload. This leads to an increase in left atrial and left ventricular size. **Signs of systemic hypoperfusion:** With increasing ductal shunt size, the normal low-velocity antegrade diastolic flow in the descending aorta decreases progressively and becomes absent, followed by retrograde in direction.	• LA: Ao root diameter ratio ≥1.4 (PLAX, M mode) • Left ventricular/ aortic root width ratio >2.2 (PLAX, M mode) • Antegrade left pulmonary artery diastolic flow >40 cm/sec (Ductal view, PW) • Descending aorta diastolic flow absence or reversal (subcostal view for flow in celiac or superior mesenteric artery, PW)
		Myocardial performance: Due to an increased left-to-right shunt and LV overload, the left ventricular stroke volume and left ventricular output also increase.	• LV output >320 ml/kg/min • E/A ratio >1 • Isovolumetric relaxation time (IVRT) <45 msec • Myocardial performance index (MPI)

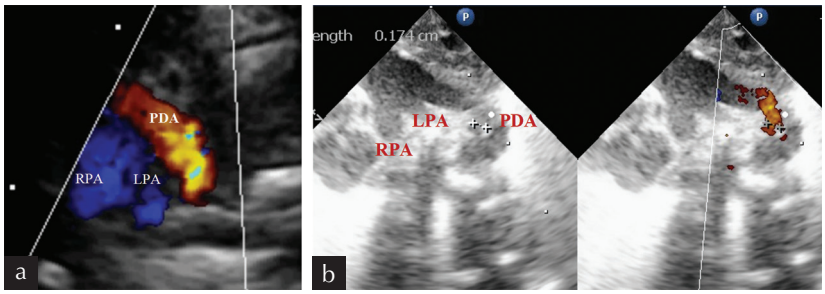

Fig. 11.1: Echocardiographic diagnosis of a PDA on the ductal view ('three-legged stool' appearance)

Table 11.2: Recommended timing of echocardiographic screening for PDA in preterm neonates[11]

Type of screening	*Gestation*	*Timing of screening for hsPDA*
Early targeted (Asymptomatic)	≤28 weeks	36 ± 6 hours, 72 ± 6 hours, and day 7
	29–30 weeks	36 ± 6 hours and 72 ± 6 hours
Symptomatic	<32 weeks	At the onset of symptoms

of PDA and can be assayed at the bedside using commercially available kits. BNP levels are higher in significant PDA and decline after therapeutic closure. The good sensitivity and specificity of BNP assay (88% and 92%, respectively), the easy availability of bedside kits, the lesser cost compared to echocardiography, and its decline in treatment response makes it an attractive biomarker.[11] However, BNP levels in preterm neonates vary with gestational age (higher in preterm), postnatal age (highest in the first three days and gradually declines with age), renal function, and the type of kit used. The test becomes accurate from day 3 of life and hence cannot be used within the first 48 hours of life. Therefore, BNP can be used only as an add-on test and cannot replace echocardiography for diagnosis or management. Due to the variability of assays across various settings, universal recommendations for standard thresholds of the biomarkers remain challenging.

MANAGEMENT

Despite a large number of studies done to ascertain the optimal treatment strategy for PDA, the management remains controversial. There has yet to be a clear consensus on whether PDA should be closed and, if so, when, how, and in whom? A lack of proven benefit

after PDA closure can possibly be explained by the following reasons:[12]

1. There is no causal association between hsPDA and short- and long-term morbidities. Most PDAs in preterm neonates are known to close spontaneously with time; up to 90% of PDA close spontaneously among 30 weeks gestation, while it is around 65% among those <30 weeks' gestation.[13]
2. Studies have used variable definitions of 'hemodynamic significance,' The overall results have been diluted by some 'non-hemodynamically significant' PDAs.
3. In randomized trials focused on medical or surgical treatment of PDA in the intervention arm, up to one-third of the controls receiving rescue treatment to close a PDA. This overlap introduces bias in our ability to interpret the studies.[1,2] The frequent need for rescue treatment in placebo groups has led to contamination of the intervention, introducing bias.[2,14] Emerging evidence suggests that treatments that close the patent ductus may be detrimental. Neither individual trials, pooled data from groups of randomized-controlled trials, nor critical examination of the immediate consequences of treatment provide evidence that medical or surgical closure of the ductus is beneficial in preterm infants. These conclusions are supported by sufficient evidence. Neither continued routine use of these treatments nor additional clinical trials using similar designs seems to be justified. A definitive trial, comparing current standard management with novel strategies not primarily intended to achieve ductal closure, may be necessary to resolve doubts regarding the quality or conduct of prior studies.
4. Although hsPDA has been associated with significant neonatal morbidities such as BPD and necrotizing enterocolitis, the evidence that treatment improves either short-term or long-term outcomes is bleak.[15,16] Moreover, PDA closure alone might be insufficient to improve the associated morbidities or mortality.

Further, non-steroidal anti-inflammatory agents, the mainstay of PDA's pharmacological closure, are associated with significant side effects. Conversely, observational studies have also pointed out that persistent exposure to a PDA is not without harm and can be associated with a higher risk of mortality in preterm neonates <29 weeks' gestation.[2,17]

While considering these nuances in the existing literature, the clinician often must decide which neonates one can await

spontaneous closure of PDA. Such a 'wait and watch' strategy seems reasonable in a more mature infant (>28 weeks' GA) who is stable, tolerating feeds, and on minimal or noninvasive respiratory support.[2] In such cases, fluid restriction and appropriate ventilatory titration can be coupled with watchful waiting. Although recent evidence in extremely preterm neonates reveals expectant management as a non-inferior approach to early treatment in terms of BPD, NEC, and mortality,[18] it may be unadvisable to wait watchfully, and early treatment is usually recommended.

A. Nonpharmacological Strategies

1. **Fluid restriction:** Although evidence for this approach is lacking, a careful attention to fluid balance is recommended for management of PDA. In a restricted regime, fluid intake is at most 120 to 130 mL/kg beyond day 3 of life. Ensuring adequate urine output and monitoring serum sodium levels during fluid restriction is important. Fluid restriction should be discontinued if serum sodium exceeds 147 mEq/L or increases by >4 mEq/L every 8 hours.[13] In neonates beyond the first week and on full enteral feeds, a fluid intake of up to 150 ml/kg/day may be permitted, with calorie-dense feeds to ensure optimal weight gain.
2. **Ventilatory strategies:** If neonates require invasive ventilation, higher PEEP (at least 4.5–5 cm H_2O) and lower Ti (0.35 s) may be helpful, though data is limited.[13,19] Conservative treatment may result in similar outcome, but without exposure to the harmful side effects of medication. A retrospective analysis revealed a ductal closure rate of 94% after conservative treatment with adjustment of ventilation. There is no role for the use of diuretics in the management of PDA.[20]

Observational studies have noted that conservative therapy is a feasible option with closure rates as reasonable as pharmacological therapy and may decrease the need for pharmacotherapy and ligation. However, if the neonate does not show clinical improvement or worsens, one should consider therapeutic closure.

B. Pharmacological Closure of PDA

Pharmacotherapy should be used in a select group of neonates in whom PDA might be actively contributing to hemodynamic

compromise, and the risk of non-closure may be associated with morbidities. Examples include:

- Extreme preterm neonate with echocardiographically proven hemodynamically significant ductus arteriosus. We define hsPDA as a PDA with ductal diameter >1.5 mm with one of the following: LA/Ao ratio >1.5, LV/Ao ratio >2.2, a retrograde diastolic flow in descending aorta, celiac or cerebral arteries (>30% of antegrade flow), and left ventricular output >320 mL/kg/min.
- Preterm neonates with severe symptoms related to PDA like congestive cardiac failure, pulmonary hemorrhage, pulmonary edema, and inability to be weaned from mechanical ventilation.

The most widely studied and used drugs in the closure of PDA are the non-steroidal anti-inflammatory agents, namely indomethacin and ibuprofen, which are non-selective cyclo-oxygenase inhibitors. Both indomethacin and ibuprofen are equally efficacious, with a closure rate of 70–80%. However, there are concerns regarding their safety in neonates, especially in necrotizing enterocolitis, intestinal perforation, active bleeding, and concomitant use of corticosteroids, where they are contraindicated. The publication of case reports and further randomized trials has created increased interest in paracetamol as a lucrative and efficacious agent for ductal closure. Paracetamol inhibits prostaglandin production through inhibition of the peroxidase enzyme. Moreover, paracetamol has been shown efficacious in various situations where NSAIDs are either contraindicated or have failed to achieve PDA closure. A comparison of the three commonly used drugs, dosage, and regimens are shown in Table 11.3.

Monitoring during drug therapy: Monitor for side effects of therapy (Table 11.4) during medical closure of PDA, mainly if an NSAID is used.

Essential Considerations when Treating a PDA

1. **Choice of medication:** A recent network meta-analysis in 2018 revealed that high-dose oral ibuprofen had the highest efficacy regarding PDA closure and need for surgical ligation, with 3.6 times higher odds of closure than intravenous ibuprofen.[21] Another metanalysis in 2022, which included 70 trials, concluded that high-dose ibuprofen had the highest net clinical benefit in terms of closure and adverse events, followed by standard

Table 11.3: Drugs for medical management of PDA

	Indomethacin	*Ibuprofen*	*Paracetamol (PCM)*
Preparation	Intravenous preparation requires reconstitution. Oral suspension is not available but can be prepared by dissolving the powder content of a 25 mg indomethacin capsule in 25 ml of distilled water.	IV Ibuprofen is not available in India. The oral formulation is the most common and readily available form in India.	Available both as an injection (10 mg/ml) and oral suspension
Dosage (same for intravenous and oral formulation)	Loading dose: 0.2 mg/kg/dose Subsequent dose (adjusted as per postnatal age): • <2 days: 0.1 mg/kg/dose 12 hourly × 2 doses • 2–7 days: 0.2 mg/kg/dose 12 hourly × 2 doses • >7 days: 0.25 mg/kg/dose 12 hourly × 2 doses	Loading dose: 10 mg/kg/dose Subsequent dose: 5 mg/kg/dose 24 hourly × 2 doses (High dose Ibuprofen: 20 mg/kg/dose followed by 10 mg/kg/dose 24 hourly for two doses)[21]	• 15 mg/kg every 6 hours for three days
Drug administration	Administered as an infusion over 30 minutes or as a continuous infusion over 36 hours	Administered as an infusion over 30 minutes	• Administered as an infusion over 15–30 min
Contraindications	Thrombocytopenia (< 60 000/mm^3), the clinical bleeding tendency (bloody gastric aspirates, bloody stools, pulmonary hemorrhage, oozing from puncture sites), raised serum creatinine >1.6 mg/dl, urine output <1 ml/kg/h during the preceding 8 hours, severe IVH, and NEC.	Same as Indomethacin	• Elevated liver enzymes or hepatic failure.

(*Contd.*)

Table 11.3: Drugs for medical management of PDA (*Contd.*)			
Side effects	Transient or permanent renal impairment, NEC, gastrointestinal hemorrhage or perforation, alteration of platelet function, and impairment of cerebral blood flow or cerebral blood flow velocity	Lesser risk of NEC and transient renal insufficiency	• No known renal adverse effects. Lower antiplatelet activity.
Persistence of a hemodynamically significant ductus at the end of 1st course	A repeat course (3 doses) of indomethacin can be considered (maximum of 2 courses). The first course can be prolonged by giving two more doses of 0.1 mg/kg Q 24 hourly. However, if the ductus fails to respond, it is unlikely to respond to further courses.	A repeat course (3 doses) for a maximum of 2 courses can be considered. Extension of the initial course by giving two more doses of 5 mg/kg Q 24 hourly can be considered. However, if the ductus fails to respond, it is unlikely to respond to further courses.	• A longer course of 15 mg/kg 6 hourly for 6–7 days can be considered based on echocardiography to guide treatment.

Table 11.4: Parameters to be monitored during therapeutic closure of PDA with NSAIDs	
Baseline	Urine output, RFT, platelet count
Monitoring during therapy	
Daily	Urine output
Alternate day	RFT, platelet counts (daily if baseline counts are <150,000/mm^3)

dose oral PCM in neonates >28 weeks. Although the evidence is lacking in those less than 28 weeks, the best option was deemed to be oral PCM in terms of net clinical benefit.[22] IV Ibuprofen is not available in India.

Indomethacin versus ibuprofen: Both indomethacin and ibuprofen are equally efficacious, with a PDA closure rate of 70–80% in preterm babies 32 weeks. No difference was noted in treatment failure rates when ibuprofen (oral or IV) was compared with indomethacin (oral or IV). However, ibuprofen has a better safety profile (lesser renal impairment and NEC) and may be preferred.[23]

Oral paracetamol (PCM) versus ibuprofen/indomethacin: In several case reports, the efficacy of paracetamol for PDA closure was around 70–80%. Paracetamol is now preferred because it lacks the significant side effects of other NSAIDs and its applicability when contraindicated. In a Cochrane review including 27 trials and 2278 neonates, there was low- to moderate-quality evidence that there is little or no difference in the effectiveness of PCM compared to indomethacin or ibuprofen.[24] There are a few concerns with PCM, including its adverse effects on the developing brain in neonatal mice and the later development of autism in human children after prenatal exposure been reported. Hence, further studies are needed before paracetamol can be recommended as the universal drug of choice for medical closure.

2. **Route of medication:** Randomized studies comparing oral versus IV ibuprofen showed a higher closure rate with oral than IV formulation.[25] One can use IV formulation if the neonate is not on oral feeds.

3. **Feeding during medical closure:** Most neonatologists refrain from feed advancement and often withhold enteral feeds while using ibuprofen or indomethacin for PDA. A randomized trial showed that a neonate in whom feeds have just been initiated will achieve full enteral feeds earlier if they continue receiving trophic feedings rather than kept nil orally. Continued enteral feeding did not increase the risk of infection, necrotizing enterocolitis, or spontaneous intestinal perforation.[26] In our unit, we continue the same volume of feeds if the neonate is already on oral feeds and advance once the course is completed or allow trophic feeds unless there is feed intolerance or other contraindications of feeding.

4. **Timing of therapy:** The timing of treatment can be prophylactic, early targeted, and symptomatic (early and late).[8]
   a. **Prophylactic therapy** refers to the closure of PDA in high-risk preterm neonates even before it produces any symptoms. While prophylactic ibuprofen decreases the incidence of symptomatic PDA, the need for surgical ligation, and the incidence of pulmonary hemorrhage, it does not alter long-term outcomes. There is a trend toward decreased risk of IVH with an increased incidence of oliguria, questioning its overall benefit.[25] prophylactic indomethacin significantly reduced the incidence of severe grades of IVH with no translation of the effect to improved long-term neurodevelopment.[27] Prophylactic therapy is not recommended due to an unclear risk versus benefit.
   b. **Symptomatic treatment** is when signs of PDA first appear between 2–5 days of age (**early**) or until the second week of life (days 10–14, **late**). Whether to close early vs. late depends on the severity of symptoms and the neonate's gestational age. Late treatment may be justified in mature neonates with mild signs of PDA (metabolic acidosis, murmur, bounding pulses). Still, an early closure would be reasonable in very preterm neonates with symptomatic ductus and those with life-threatening manifestations like pulmonary hemorrhage, hypotension, or rapid respiratory deterioration. Ductus that remains patent beyond two weeks of age may not respond to drug therapy well, and adverse hemodynamic consequences might have already occurred.
   c. In extremely preterm neonates, Kluckow et al. showed that an **early-targeted therapy** based on echocardiographic parameters between 3–12 hours of life reduces the incidence of pulmonary hemorrhage and the need for later pharmacological closure.[28] However, the investigators stopped enrollment early due to the non-availability of Indomethacin. However, a recent trial of 273 extreme preterm neonates failed to demonstrate any benefit of early targeted treatment with Ibuprofen in terms of mortality or major complications (severe NEC or moderate to severe BPD).[29] Authors speculated that it may be due to adverse effects of Ibuprofen negating any benefit achieved with PDA treatment. Despite this many advanced centers hold the view that in neonates <26 weeks, the early targeted treatment is beneficial, especially in those with large shunts and needing respiratory support.[30]

5. **Surgical ligation:** Surgery should be considered if medical management fails (after two courses of pharmacotherapy) or if there are contraindications to medical therapy like NEC, gastrointestinal perforation, or renal impairment. Meta-analyses of studies comparing surgical vs. medical treatment noted that neonates undergoing surgery are at an increased risk of neurodevelopmental impairment, chronic lung disease, and ROP but lesser mortality risk.[31] However, surgery is more likely to have been performed on a sicker ventilator-dependent infant with other comorbidities.

   Surgical closure, although definite, is associated with complications like pneumothorax, chylothorax, infection, and vocal cord palsy. A peculiar hemodynamic complication of surgical ligation called the post ligation cardiac syndrome (PLCS) appears in one-third of the extremely low birth weight neonates undergoing surgery for PDA. Typically starting 4–12 hours post-operative, profound hypotension ensues due to a sudden increase in afterload (increased peripheral vascular resistance) to the left ventricle and decreased preload (less blood return from a pulmonary vein), leading to ventricular dysfunction.[13,32] The neonate presents with an increasing need for inotropes, oxygen lability, and worsening ventilatory requirements. Risk factors for post-ligation syndrome include surgery before four weeks of age, gestational age <26 weeks, birth weight <1000 grams, and need for inotropes before ligation. Management is supportive, including inotropes, optimal ventilation, and hydrocortisone for refractory cases.

6. **Transcatheter device closure:** Device closure is increasingly used for PDA closure. The device is delivered inside the PDA through a venous approach. It can be done bedside or in a catheterization laboratory. The success rate was >95% in a recent trial on 200 infants and more than 99% in 700–2000 g, with an effect sustained till six months.[33] Emerging evidence reveals a lower risk of hemodynamic complications compared to surgical ligation, with a high success rate. However, concerns still need to be addressed regarding long-term outcomes, optimal timing, and the type of device.

OUTCOMES

Many infants discharged with a PDA will have spontaneous closure by one year of age. It, therefore, appears safe to leave a small PDA

open at discharge but with regular follow-up. The exact timing of post-discharge closure rates and their association with coexisting severe BPD requires further exploration.

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