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REVIEW ARTICLE

Pharmacological Closure of Patent Ductus Arteriosus: Selecting the Agent and Route of Administration

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Abstract Opinions are divided regarding the management of a persistently patent ductus arteriosus (PDA). Some of the adverse effects associated with a large hemodynamically significant duct, including prolonged ventilation, pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and mortality, indicate that active management of infants with large ductal shunts may sometimes be necessary. Indomethacin and ibuprofen are the two US FDA-approved cyclooxygenase (COX) inhibitors used for the closure of a ductus in preterm babies. Both these drugs are effective in 70–80 % of extremely low birthweight infants. Treatment with COX inhibitors may be associated with renal impairment, gastrointestinal hemorrhage, NEC, and spontaneous intestinal perforation when given concurrently with steroids, as well as changes in cerebrovascular auto-regulation. Ibuprofen appears to be a better choice for PDA closure, with a better side effect profile and efficacy that equals that of indomethacin. However, long-term outcome studies of ibuprofen are lacking, and prophylactic ibuprofen is ineffective in decreasing severe IVH. The choice of one drug over the other also depends on local availability of both drugs and the intravenous or enteral preparation. The oral preparation of ibuprofen appears as effective as the intravenous preparation. The use of paracetamol to close a hemodynamically significant PDA has increased in recent years. Paracetamol also decreases prostacyclin synthesis; however, unlike COX inhibitors, it does not have a peripheral vaso-constrictive effect and can be given to infants with contraindications to non-steroidal anti-inflammatory drugs. It appears to have similar efficacy based on limited data available from randomized trials. Until more data are available on efficacy, safety, and long-term outcomes, it cannot be recommended as the first choice.

Key Points

Indomethacin and ibuprofen are the two most commonly used drugs for closing a hemodynamically significant ductus in the neonate.

Prophylactic indomethacin reduces the risk of patent ductus arteriosus, intraventricular hemorrhage, and pulmonary hemorrhage but does not improve the rate of survival without neurosensory impairment at 18 months.

Ibuprofen is as equally effective as indomethacin and causes less oliguria and necrotizing enterocolitis. Oral formulations are equally efficacious and can be considered if locally available.

Paracetamol has fewer side effects and similar efficacy, but more data on safety and long-term outcomes are needed.

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1 Introduction

The ductus arteriosus is an essential vascular connection between the fetal aorta and pulmonary artery that allows the majority of the right ventricular output to bypass the high-resistance pulmonary circulation. After birth, with placental separation and initiation of breathing, the ductus usually closes within the first 48 h of life in full-term infants [1]. In preterm infants, the closure of ductus arteriosus may be delayed or fail to occur [2]. In about one-third of low birthweight preterm infants, the ductus can remain open in the first few days of life [3]. In preterm infants <1000 grams and <29 weeks' gestation, the incidence of ductus arteriosus that is still open beyond 72 h of life is 70 % [4].

2 Pathophysiology

Factors that induce closure of ductus arteriosus after birth in a term infant include the postnatal increase in PaO_2 and a decrease in circulating vasodilators such as prostaglandin (PGE2) and prostacyclin (PGI2) [5]. The oxygen-sensing mechanism of ductal smooth muscle cells causes depolarization, calcium entry, and ductal constriction. Platelets also promote ductal closure by causing thrombotic closure of constricted ductus and luminal remodeling [6]. In preterm infants, the sensitivity of ductus to oxygen is decreased, and sensitivity to vasodilator mediators like nitric oxide and PGE2 is increased [1]. Studies in preterm rabbits have shown that the calcium and potassium channels in the ductal smooth muscles are immature in preterm animals [7, 8]. These factors contribute to the delayed closure or persistence of ductus arteriosus in preterm infants. Risk factors associated with persistence of ductus in the preterm population include birthweight <1500 g [9], a diagnosis of hyaline membrane disease, intrauterine growth retardation, acute perinatal stress [10], and excessive fluid intake in the first week of life [11, 12]. The pathological consequences of patent duct are related to the hemodynamic effects of significant left-to-right shunting of blood and redistribution of systemic blood flow. Although left ventricular output increases, the splanchnic and renal blood flows are decreased, and these alterations are reversed after closure of patent ductus arteriosus (PDA) [13]. Thus, significant shunting through PDA can lead to heart failure, pulmonary hemorrhage [14], increased ventilatory requirements, and chronic lung disease (CLD) [15]. PDA is also associated with intraventricular hemorrhage (IVH) [16], decreased gut perfusion [17], and death [15].

3 Management of Patent Ductus Arteriosus (PDA)

The treatment options for a significant PDA include conservative management, pharmacological therapy, and surgical ligation.

3.1 Conservative Management

Conservative management of PDA is based on the premise that most PDA spontaneously close without drugs or ligation. It includes interventions such as fluid restriction, ventilator support, and optimal use of positive end expiratory pressure (PEEP) [18] and vasopressors. Digoxin [19] and furosemide [20] are not useful in the management of ductus arteriosus. Data on the outcomes of babies with PDA managed conservatively are scarce. None of the randomized trials in PDA included a control group that was managed with conservative therapy while an intervention group received drugs or ligation. Observational studies suggest a persistently patent ductus in extremely preterm infants is not benign. Symptomatic PDA that remains patent after failed medical management (conservative and a course of indomethacin) in neonates with gestational age <29 weeks is associated with higher mortality [15, 21, 22]. In a before-and-after study, Kaempf et al. [22] compared era 1, where indomethacin and ligation were used early to close moderate and large PDAs in infants receiving respiratory support, versus era 2, where a conservative strategy of fluid restriction and watchful waiting were attempted first and indomethacin/ligation were reserved for those infants with large PDAs who met certain cardiorespiratory distress criteria [22]. In era 2, indomethacin use declined from 79 to 26 %. There was no difference in the use of supplemental oxygen or duration of mechanical ventilation, but the combined outcome of CLD or mortality after day 7 increased significantly in the less aggressive treatment group.

One can probably wait for a spontaneous closure if the PDA is small to moderate and still patent at the time of discharge if the neonate is at least 28 weeks of gestation, as a great majority of these are noted to close spontaneously during infancy [23]. Although tolerance of the PDA with a conservative treatment approach is a reasonable treatment strategy in small PDA and in mature babies, the safety and long-term outcomes of persistent patency of large ductus in the extremely low birthweight (ELBW) population is not known. Observational data do suggest that such an approach may be harmful. We need more data from randomized trials that compare conservative versus drug therapy on short- and long-term outcomes in preterm neonates with PDA [24].

3.2 Pharmacological Treatment

Indomethacin and ibuprofen are the two US FDA-approved cyclooxygenase (COX) inhibitors used for the closure of a ductus in preterm babies. Both these drugs are effective in 70–80 % of ELBW infants [25, 26]. Indomethacin and ibuprofen reduce prostaglandin-mediated vasodilatation via inhibition of the COX site on prostaglandin H2 synthetase (PGHS) enzyme complex. The use of paracetamol (acetaminophen) to close a hemodynamically significant PDA has increased in recent years, but its use is still off label. It appears to have similar efficacy without side effects [27–29]. Paracetamol acts on the peroxidase site of prostaglandin H2 synthetase. This article focusses on the drugs used for medical closure of PDA.

3.3 Surgical Ligation

Ligation of ductus involves thoracotomy and is associated with significant morbidities such as pneumothorax, chylothorax, infection, laryngeal nerve paralysis, respiratory compromise, and blood pressure fluctuations [30]. In a recent systematic review and meta-analyses [31] of 39 cohort studies and one randomized trial, surgical ligation was associated with increased risk of CLD, retinopathy of prematurity (ROP) and neurodevelopmental impairment (NDI) but with reduced mortality when compared with medical therapy. There was no difference in the composite outcome of death or NDI in early childhood. The increased morbidity associated with ligation could be because of both the surgical procedure and the illness severity of the babies who underwent ligation. Nearly all included studies failed to adjust for postnatal confounders such as IVH, duration and intensity of mechanical ventilation, necrotizing enterocolitis (NEC), and sepsis that existed prior to ligation. Large ductus in preterm neonates that fail medical therapy and continue to cause persistent symptoms (need for mechanical ventilation or inotrope support) and those situations where drug therapy may be contraindicated (NEC, intestinal perforation, pulmonary hemorrhage, or renal impairment) are managed surgically.

4 Bibliographic Search

The bibliographic search was performed electronically using PubMed and Embase using the following key words and their combinations: ‘patent ductus arteriosus OR PDA OR ductus’; ‘indomethacin’; ‘ibuprofen’; ‘paracetamol OR acetaminophen’; ‘infant OR neonate’. The search time line included 1966 to December 2015 and was restricted to articles (and or abstracts) in the English language. We considered all relevant articles, regardless of publication type. The full text of all relevant articles was read and the bibliography was examined. We conducted a manual search of the reference lists of all eligible articles.

5 Indomethacin

Indomethacin is a non-selective COX inhibitor and causes ductal closure by inhibition of prostaglandin E synthesis [32]. Indomethacin is available as a sodium trihydrate salt for intravenous use and is reconstituted in preservative-free normal saline or sterile water for injection. There is no commercially available oral formulation of indomethacin for use in neonates. In studies where an oral preparation of indomethacin was used, the authors prepared a suspension of the drug powder from capsules in saline–dextrose solution or water [33–35].

5.1 Pharmacokinetics and Pharmacodynamics

Indomethacin can be administered orally or intravenously. Food delays oral absorption without interfering with the amount absorbed. There are varying reports of the oral bioavailability of indomethacin. Bhat et al. [33] and Evans et al. [36] reported a poor oral bioavailability of 13 and 20 %, respectively, based on the area under the indomethacin concentration time curve. However, Al Za’abi et al. [34] noted that the oral suspension achieved almost complete bioavailability of 98.6 % without the need for dosage adjustment. Al Za’abi et al. [34] argue that the similar ductal closure rates of oral and intravenous indomethacin preparations reported in studies [37–39] imply a good systemic absorption, albeit not supported by pharmacokinetic evidence. Hence, preterm infants can be treated with either oral or intravenous preparations based on availability of preparation and enteral feeding status without the need for dosage adjustment [34].

Oral and intravenous administration of indomethacin resulted in similar drug concentrations in serum (0.15 vs. 0.19 μg/ml, respectively) [34]. Following either route, the mean drug clearance in serum was 20.7 ± 10.8 ml/kg/h, the mean volume of distribution was 0.55 ± 0.18 L/kg, and mean half-life was 20.4 ± 4.9 h. In preterm infants, the half-life of the drug in plasma is longer compared with that of adults and is inversely related to the gestational age. Bhat et al. [33] studied the pharmacokinetic profile of indomethacin administered either orally or intravenously in 13 preterm infants with significant PDA. They noted that the mean serum half-life of indomethacin was longer in neonates aged <32 weeks’ gestation compared with those >32 weeks’ gestation (17.2 h [standard deviation; SD 0.8] vs. 12.5 h [SD 0.5]). Because of the longer half-life in serum and lesser elimination in preterm infants of smaller

gestational ages, these infants are at higher risk of cumulative toxicity with extended treatment regimens [40, 41].

In plasma, 90 % of indomethacin is bound to albumin at therapeutic plasma concentrations. The drug is metabolized by cytochrome P450 (CYP) 2C9 and 60 % of the drug is excreted in the urine, predominantly in glucuronidated form, while about 40 % is excreted in the feces after biliary secretion. A large amount of the dose undergoes biliary recycling. The biotransformation is independent of the route of administration [42].

5.2 Treatment Strategies with Indomethacin

Indomethacin can be administered as three broad treatment strategies [43]: (1) prophylactic therapy refers to initiation of therapy within the first 24 h of life to all high-risk preterm infants without assessment of ductal patency or shunt size, (2) treatment of asymptomatic PDA in high-risk infants where a ductal patency is suspected based on clinical signs or demonstrated by echocardiography but before the onset of symptoms of congestive cardiac failure or significant left-to-right shunt, (3) treatment of symptomatic PDA that causes clinical symptoms of congestive cardiac failure or demonstration of hemodynamically significant left-to-right shunt.

5.2.1 Prophylactic Treatment of PDA with Indomethacin

The data on prophylactic treatment of PDA comes from the meta-analyses of 19 randomized or quasi-randomized trials [44, 45] where prophylactic indomethacin was used either for prevention of IVH or for PDA. A total of 2872 preterm infants were included, with the largest trial [46] contributing 1202 infants with birthweight <1000 g. In all the trials, the first dose of indomethacin was administered within the first 24 h of birth. Most trials used 0.1–0.2 mg/kg indomethacin administered every 24 h for a total of 3 doses, except three studies that used a different dosing regimen: Krueger et al. [47] used a single dose of 0.2 mg indomethacin at 24 h after birth; Couser et al. [48] used 0.1 mg/kg indomethacin every 24 h for 6 doses; and Ment et al. [49] used 0.1 mg/kg indomethacin every 12 h for 5 doses.

The results of the meta-analyses [44, 45] showed that the rate of PDA (relative risk [RR] 0.44; 95 % confidence interval [CI] 0.38–0.50) and particularly the rate of surgical ligation for PDA (RR 0.51; 95 % CI 0.37–0.71) were reduced in the prophylactic indomethacin group. They found that 20 infants would need to be treated with prophylactic indomethacin to prevent one surgical ligation and four infants would need to be treated to prevent a later symptomatic PDA. There was also a reduction in the incidence of any IVH (RR 0.88; 95 % CI 0.80–0.96) and severe (grades 3 and 4) IVH (RR 0.66; 95 % CI 0.53–0.82). No differences were noted in other short-term outcomes such as NEC and bronchopulmonary dysplasia (BPD). Of note, the reduction in the incidence of symptomatic PDA or severe IVH did not translate into improved mortality or long-term neurodevelopmental outcomes. The use of prophylactic indomethacin for the prevention of IVH has declined following the publication of TIPP (Trial of Indomethacin Prophylaxis in Preterm Infants), which failed to show an improvement in the primary outcome of improved survival or neurosensory outcome [46, 50].

5.2.2 Treatment of Asymptomatic PDA with Indomethacin

This treatment strategy targets high-risk infants with a patent ductus but without clinical symptoms or echocardiographic evidence of significant left-to-right shunt. Here again, there is unnecessary exposure to a drug therapy in a number of babies who can otherwise achieve a spontaneous closure of PDA. Cooke et al. [51] conducted a meta-analysis of three randomized trials involving a total of 97 babies where indomethacin was used 24 h after birth for asymptomatic ductus. Each of the included studies utilized 3 doses of indomethacin or placebo given intravenously, with doses of 0.1–0.3 mg/kg/dose at intervals of 12–24 h. The meta-analyses showed a reduction in the incidence of symptomatic PDA (RR 0.36; 95 % CI 0.19–0.68) and duration of supplemental oxygen (weighted mean difference [WMD] −12.5 days; 95 % CI −23.8 to −1.26). There was no evidence of effect on mortality, CLD, IVH, ROP, or length of ventilation. Long-term neurodevelopmental outcomes were not reported.

5.2.3 Early Targeted Treatment of PDA

Combining the above two approaches, Kluckow et al. [52] from Australia designed a double-blind randomized multicenter trial of early echocardiography-targeted treatment of large PDA. High-risk neonates (<29 weeks' gestation) underwent echocardiographic evaluation at 3–12 h of age and—if diagnosed has having a large duct (based on age-specific norms [53])—received indomethacin or placebo within 12 h of age. Infants received placebo or a loading dose of 0.2 mg/kg indomethacin followed by 0.1 mg/kg for 2 further doses at 24-h intervals administered via 30-min infusion. The study stopped recruitment after randomizing 92 neonates (44 indomethacin and 48 placebo) due to unavailability of indomethacin. There was no difference in the primary outcome of death or abnormal cranial ultrasound between groups. Infants receiving early indomethacin had significantly less pulmonary hemorrhage (2 vs. 21 %), a trend towards less periventricular hemorrhage/IVH (4.5 vs. 12.5 %), and were less likely to receive later

open-label treatment for a PDA (20 vs. 40 %). Among the 72 non-randomized infants with a small PDA, 80 % had spontaneous closure.

5.2.4 *Early and Late Symptomatic Treatment of PDA with Indomethacin*

'Early symptomatic' refers to treatment between 2 and 5 days of age when signs of PDA first appear; 'late therapy' involves waiting until the 2nd week of life (days 10–14) [54]. In a meta-analyses, Clyman [55] found that patients who received early symptomatic treatment had both a significant reduction in BPD (odds ratio [OR] 0.39; 95 % CI 0.21–0.76; $p < 0.005$) and a significant reduction in the duration of mechanical ventilation ($p < 0.025$). The included studies were conducted in the 1980s and the relevance of the results is unclear in the current era of antenatal steroids, surfactant, minimal mechanical ventilation, and non-invasive ventilatory strategies.

Van Overmeire et al. [56] conducted a prospective randomized multicenter trial of early (day 3) versus late (day 7) symptomatic treatment of PDA in ventilated, surfactant-treated preterm infants <32 weeks' gestation. Both the early and late treatment group received the same dose: 3 doses of 0.2 mg/kg indomethacin, each given over a 15-min infusion at 12-h intervals on either day 3 or day 7 of life. The authors reported that the PDA closure rate was higher in the early treatment group when assessed at both 6 (73 vs. 44 %, $p = 0.0008$) and 9 (91 vs. 78 %, $p = 0.047$) days of age. However, there was no significant difference in PDA ligation. The early treatment group had lower urine output and higher serum creatinine levels and required more indomethacin courses. The incidence of major adverse events (death, NEC, and/or localized perforation, extension of hemorrhage, or cystic leukomalacia) occurred more frequently in the early treatment group ($p = 0.017$). Although early indomethacin treatment improved PDA closure, it was associated with more severe complications and had no respiratory advantage over late indomethacin therapy. Delaying drug therapy in infants with mild signs of PDA (metabolic acidosis, murmur, bounding pulses) may decrease the need for drugs or ligation by 50 % when compared with early treatment without increasing adverse effects [57]. Kaempf et al. [22] conducted an observational study, wherein early indomethacin or ligation was used in era 1 versus waiting until a conservative strategy failed in era 2 in moderate to large PDA in infants receiving respiratory support. The authors suggested that the combined outcome of CLD or mortality after day 7 increased significantly in the less aggressive treatment group. Patient selection and the severity of ductal symptoms can help guide individualize the timing of therapy.

In summary, indomethacin prophylaxis in small preterm neonates (at highest risk for IVH) reduces the risk of IVH and PDA and prevents both pulmonary hemorrhage and the need for surgical ligation [45]. In such ELBW infants, indomethacin prophylaxis does not improve the rate of survival without neurosensory impairment at 18 months [46]. When used after the diagnosis of an asymptomatic PDA (pre-symptomatic treatment), it achieves ductal closure but does not produce any respiratory benefits. The long-term effects are not known [51]. When used after the diagnosis of hemodynamically significant PDA, indomethacin is efficacious in closing the PDA [58]. Kluckow et al. [52] showed that an early targeted therapy based on echocardiographic parameters between 3 and 12 h of life in high-risk preterm neonates is feasible and reduced the incidence of pulmonary hemorrhage and the need for later pharmacological closure. Table 1 shows the dosage and regimens of indomethacin. The benefits of treatment should always be weighed against the side effects that these drugs produce (discussed below along with those for ibuprofen). We need more data regarding the benefits or harms of early versus late drug therapy and conservative versus early drug therapy. Opinions are still divided regarding the closure of PDA because of the relatively high rates of spontaneous closure, failure of randomized controlled trials (RCTs) to show improved outcomes after PDA closure, failure of prophylactic indomethacin to improve neurodevelopmental outcome, and the potentially significant side effects of indomethacin and ibuprofen [59].

5.3 Impact of Different Indomethacin Administration Regimes on Closure of PDA and Side Effects

5.3.1 *Bolus Versus Continuous Infusion for the Treatment of PDA*

Two RCTs [60, 61] and a meta-analysis [62] of the two studies compared the effects of a 36-h infusion of indomethacin versus a course of rapid bolus administration. In these two studies, both groups (bolus and continuous) received the same total dose of indomethacin and neither showed a difference in the rate of PDA closure. Both studies showed a decrease in the cerebral mean blood flow velocities after the bolus injections until 24 h post-administration compared with no decrease in the continuous infusion groups. A similar decrease in renal and mesenteric blood flow was noted following bolus administration in one study. Although the available data are insufficient to draw conclusions regarding the efficacy of continuous indomethacin infusion versus bolus injections, it is evident that rapid boluses are associated with short-term decrease in cerebral, renal, and mesenteric flows. In most other studies,

Table 1 Dosage and regimens of indomethacin and ibuprofen for ductal closure

	Indomethacin	Ibuprofen
Preparations available	IV preparation is available as sodium trihydrate salt, which is reconstituted in sterile water for injection. Oral preparations are not routinely available. The powder content of an IND 25-mg capsule can be freshly prepared by dissolving in 25 ml distilled water [93]	Available as a sterile solution for injection and as a suspension for oral use. The IV preparation should be diluted in saline or dextrose prior to infusion
Drug administration	Administered as an infusion by a syringe pump over 30 min or as a continuous infusion over 36 h	Administered as an infusion by a syringe pump over 30 min
Contraindications	Thrombocytopenia (<60,000/mm^3), clinical bleeding tendency (bloody gastric aspirates, bloody stools, pulmonary hemorrhage, oozing from puncture sites), raised serum creatinine >140 μmol/l (1.6 mg/dl), urine output <1 ml/kg/h during the preceding 8 h, severe grades of IVH and NEC	Thrombocytopenia (<60,000/mm^3), clinical bleeding tendency (bloody gastric aspirates, bloody stools, pulmonary hemorrhage, oozing from puncture sites), raised serum creatinine >140 μmol/l (1.6 mg/dl), urine output <1 ml/kg/h during the preceding 8 h, severe grades of IVH and NEC
Regimens		
1. Prophylactic therapy	Three-dose IV course of 0.1 mg/kg at 24-h intervals beginning at 6–12 h of age [46]	Can precipitate PDA closure, although generally not recommended
2. Early or late symptomatic therapy	If treatment is started <48 h of age with a diagnosis of PDA: first dose is 0.2 mg/kg followed by 0.1 mg/kg at 24-h interval for a total of 3 doses [22, 52]	Three-dose course of 10 mg/kg followed by 5 mg/kg/dose at 24-h interval (10–5–5). Higher doses (20–10–10) may achieve greater closure rates in preterm neonates <28 weeks gestation
	Therapy started between 2 and 7 days of age: three-dose IV course of 0.2 mg/kg at 24-h interval [58]. An often-used dosage is 0.2 mg/kg for 3 doses, 12 h apart. Acceptable doses range from 0.1 to 0.25 mg/kg given at 12- to 24-h intervals	
	The dosage is same for oral formulation [93]	
Repeat course of NSAID	A repeat course (3 doses) of IND can be considered if ductus fails to close after the first course or reopens after initial constriction and continues to be hemodynamically significant. A maximum of 2 courses is used	A repeat course of 3 doses can be considered if ductus continues to be hemodynamically significant. Surgery should be considered if the PDA is hemodynamically significant and has not responded to 2 courses
Prolonged course of NSAID	If the duct remains open at the end of a course of IND, 2 more doses can be given at 0.1 mg/kg every 24 h and consider it part of the first course. However, if the ductus fails to respond, it is unlikely to respond to further courses	If the duct remains open at the end of a course of IBU, 2 more doses can be given at 5 mg/kg every 24 h and consider it part of the first course. However, if the ductus fails to respond, it is unlikely to respond to further courses
Monitoring during therapy	Monitor urine output, serum creatinine, blood glucose and platelet counts. Observe for bleeding from gut and puncture sites. If case of oliguria or elevation of creatinine, further doses are delayed or withheld until renal functions normalize. Neonates can continue to receive trophic feeds while on IND	Same as for IND. Renal and gastrointestinal side effects are less versus IND. However, they need to be monitored as for IND therapy. Neonates can continue to receive trophic feeds while on IBU

IBU ibuprofen, *IND* indomethacin, *IV* intravenous, *IVH* intraventricular hemorrhage, *NEC* necrotizing enterocolitis, *NSAID* non-steroidal anti-inflammatory drug, *PDA* patent ductus arteriosus

intravenous indomethacin was administered as a short infusion over 15–30 min [46, 52, 56, 63].

5.3.2 *Prolonged Versus Short Course of Indomethacin for the Treatment of PDA*

A Cochrane meta-analysis [41] identified five trials [64–68] ($n = 431$) comparing prolonged versus short-course indomethacin treatment and did not find a statistically significant difference in PDA closure, re-treatment, re-opening, or ligation rates. The short intravenous course consisted of 3 doses of indomethacin 0.2 mg/kg administered every 12 h for 3 doses [64–66] or 0.2 mg/kg for the first dose and 0.1 mg/kg every 12 h for 2 more doses [68]. The prolonged course consisted of 0.1 mg/kg every 24 h for 6 or 7 days. One study used intravenous indomethacin 0.2 mg/kg every 24 h for 5 days in addition to the short course in the prolonged treatment arm [64], and one study used oral indomethacin for both short and long courses [67]. The prolonged course was associated with an increased risk of NEC (typical RR 1.87; 95 % CI 1.07–3.27) and a decreased incidence of renal function impairment. Hence a prolonged course of indomethacin is not recommended

for routine treatment of PDA in preterm neonates. If one short course of therapy fails to close the PDA and it remains hemodynamically significant, one can consider prolonging the course with 2 more doses or consider another short course. Adverse effects can be decreased if echocardiogram is used to follow ductal closure and extra doses are withheld if the ductus closes.

6 Ibuprofen for the Treatment of PDA

The complications associated with the use of indomethacin encouraged the search for an alternative drug to treat PDA. Ibuprofen is another non-steroidal anti-inflammatory drug (NSAID) that causes rapid and reversible non-selective competitive inhibition of both COX-1 and COX-2 iso-enzymes. Ibuprofen has been reported to close a PDA, but without many gastrointestinal and renal side effects [69, 70].

6.1 Pharmacokinetics and Pharmacodynamics of Ibuprofen

Ibuprofen is a chiral drug with R and S enantiomers and a unidirectional conversion of the R to the S enantiomer. It is available as two preparations: ibuprofen THAM (trishydroxyamino-methane) and ibuprofen lysine. Ibuprofen is administered at a loading dose of 10 mg/kg followed by 5 mg/kg/day every 24 h twice (total of 3 doses in 3 days) [71]. A dose-finding study [72] confirmed that the dose regimen (10–5–5 mg/kg) of ibuprofen recommended by Aranda et al. [71] was associated with a high closure rate (80 %) and few adverse effects in premature infants with a post-menstrual age of 27–29 weeks. Ibuprofen injection is administered as a slow infusion over 15 min.

Sharma et al. [73] studied the pharmacokinetics of a single dose of enteral ibuprofen 10 mg/kg administered between 4 and 72 h after birth in 20 preterm infants (gestational age 26–32 weeks). The mean peak serum concentration of enteral ibuprofen was 20 μg/ml, the time to reach peak plasma levels (mean t_{max}) was 3 h, and the mean plasma elimination half-life was 16 h. Aranda et al. [71] studied the pharmacokinetic kinetic profile of intravenous ibuprofen lysine (10 mg/kg bolus) given within the first 3 h after birth in 21 premature neonates (mean gestational age 26.8 weeks) and noted higher plasma concentration at 1 h (180.6 ± 11.1 μg/ml and longer half-life of 30.5 ± 4.2 h. These data suggest that the dosage regimen for the oral route required to generate similar plasma concentrations might be higher than the intravenous route. However, most studies in preterm neonates used the same dosage for the oral as for the intravenous regimen [58]. It is possible that the slower and adequate rate of absorption, the longer t_{max} compared with the intravenous route, and the prolonged time of contact with ductal tissue might explain the similar clinical effect of the oral and the intravenous preparations [74, 75]. Ibuprofen is eliminated following extensive biotransformation to glucuronide metabolites that are excreted in urine. Hepatic and renal dysfunction can alter the disposition kinetics of ibuprofen [76].

6.2 Ibuprofen Versus Indomethacin for the Treatment of PDA

The Cochrane review [58] on the use of ibuprofen for the treatment of PDA included 20 studies ($n = 1019$) that compared ibuprofen (oral or intravenous) with indomethacin (oral or intravenous) and found no significant difference between the two drugs with respect to failure to close a PDA (RR 0.98; 95 % CI 0.80–1.20). The meta-analysis also noted less risk of NEC at any stage (15 studies, $n = 865$; RR 0.68; 95 % CI 0.47–0.99), less risk of oliguria (RR 0.28; 95 % CI 0.14–0.54), and lower serum creatinine level 72 h after initiation of therapy (WMD −4.70 mmol/l; 95 % CI −8.88 to −0.53). The Cochrane review concluded that ibuprofen is as effective as indomethacin in closing a PDA and reduces the risk of NEC and transient renal insufficiency.

Studies show that much of the side effect profile related to indomethacin could be attributed to the bolus administration of the drug. The decreases in cerebral blood flow as demonstrated by reduction in middle cerebral artery flow velocity [61], and decreases in renal and mesenteric blood flow velocities, were noted with bolus injections but not when indomethacin was administered as a continuous infusion over 36 h [60, 77].

6.3 Oral Versus Intravenous Ibuprofen for the Treatment of PDA

Among the 20 studies that investigated ibuprofen compared with indomethacin, 14 used an intravenous preparation of ibuprofen and six used an oral preparation. The oral dosing regimen used in the majority was 10 mg/kg loading followed by 5 mg/kg doses every 24 h for 2 days, which is similar to the intravenous dosing (10–5–5). One study used an oral dose of 10 mg/kg/dose for all 3 doses given every 24 h [78]. Three RCTs ($n = 236$) compared safety and efficacy between intravenous and oral ibuprofen [79–81]. All studies showed a higher rate of closure with the oral formulation, and the meta-analysis [58] showed a statistically significant difference in failure to close a PDA (typical RR 0.37; 95 % CI 0.23–0.61), with oral ibuprofen performing better than intravenous.

6.4 Intravenous Ibuprofen Lysine Versus Intravenous Ibuprofen THAM for the Treatment of PDA

Two preparations of intravenous ibuprofen are available: ibuprofen lysine is the most commonly available; the other is ibuprofen THAM. THAM is a biologically inert amino alcohol that solubilizes the ibuprofen in the preparation. THAM is considered an alternative to sodium bicarbonate and is well tolerated at a dose of 3–5 mmol/kg to correct acidosis. The usual three doses of an ibuprofen course with THAM preparation in a 1-kg infant would provide 0.12 mmol of THAM well within the tolerable dose. A double-blind RCT [82] that used ibuprofen THAM for prophylactic treatment of PDA was prematurely terminated as three cases of severe persistent pulmonary hypertension of the newborn (PPHN) were noted in the intervention arm. This could have been due to the early use of ibuprofen (within 6 h of birth) or attributed to the specific preparation of ibuprofen used in the trial. In the same study, the rates of NEC and decreased urine output were higher in the intervention arm [82, 83]. These findings suggest that the two preparations may have a different safety profile.

6.5 Considerations in Choosing Oral Versus Intravenous Formulation of Ibuprofen

The scarcity of intravenous ibuprofen in certain regions of the world and the easy availability of inexpensive oral preparations has led to off-label enteral administration of ibuprofen in preterm infants with PDA. A survey of 44 neonatal intensive care units (NICUs) in Europe found that 13 NICUs (29 %) used oral ibuprofen and 16 (36 %) used intravenous ibuprofen; the choice was influenced by economics in ten (22 %) [84]. Gouyon and Kibleur [85] reviewed the literature on the use of oral ibuprofen for PDA and identified 12 clinical efficacy studies (excluding Cherif et al. [81], an RCT). The majority of the studies were small, uncontrolled, and had methodological limitations such as a lack of blinding, or use of a variable dosage or interval of ibuprofen. When the results of all studies were pooled, the authors noted an efficacy benefit for enteral ibuprofen over indomethacin, with PDA closure rates of 88 and 77 %, respectively. Similarly, the Cochrane meta-analysis of three RCTs that compared the oral versus intravenous formulations indicated the oral formulation was more efficacious.

The higher osmolality of currently available oral ibuprofen formulations [86] and the risk of COX inhibition in the kidneys and in the gut [87] are major concerns with the oral preparation. The Cochrane meta-analysis [58] of three studies [79–81] did not find any statistically significant difference in the incidence of NEC, bowel perforation or gastrointestinal bleeding between oral and enteral ibuprofen. Although renal impairment characterized by oliguria or elevation of serum creatinine were not observed with oral ibuprofen in the above three studies [79–81], there have been reports of transient renal impairment with its use [88, 89]. Oral ibuprofen is easy to administer, cheap, and an efficacious alternative to the intravenous preparation. We should monitor for side effects with equal vigilance while using oral ibuprofen.

6.6 High-Dose Versus Standard-Dose Ibuprofen

The clearance of ibuprofen depends on postnatal age. The dose-finding study by Hirt et al. [90] suggested that to achieve optimal therapeutic concentrations, the ibuprofen dosage recommended is 3 doses of 10–5–5 mg/kg at 24-h intervals for neonates <70 h of age. However, the dose is increased to 14–7–7 mg/kg for neonates between 70 and 108 h and 18–9–9 mg/kg for neonates between 108 and 180 h. In infants <27 weeks' gestation, the success of ductal closure was only 30 % with the 10–5–5 regimen, and a higher dose regimen (20–10–10 mg/kg) achieved a higher closure rate. However, in those aged <27 weeks, even the 10–5–5 regimen resulted in higher minor renal adverse effects, and the safety of higher doses needs to be investigated in this population [72].

Two randomized trials compared a high dose of intravenous ibuprofen (20–10–10) by Dani et al. [91] and (15–7.5–7.5 mg/kg/day) by Fesharaki et al. [92] versus the standard dose of 10–5–5 mg/kg/day. In the study by Dani et al. [91] (70 preterm infants <29 weeks' gestation), the rates of successful closure between standard and high-dose arms were 63 versus 86 %, respectively ($p = 0.03$). No differences in the occurrence of adverse effects were observed between the two groups. In the study by Fesharaki et al. [92], the success rates were 75 % (23/30) versus 100 % (30/30), respectively. Both the studies favored high-dose ibuprofen. Pourarian et al. [93] compared high-dose oral ibuprofen (20–10–10 mg/kg/day) with the standard regimen. The high dose was associated with more success: 70 versus 37 % without an associated increase in adverse effects. These studies make a point for high-dose ibuprofen therapy; but patients should be closely monitored for side effects.

6.7 Role of Prophylactic Ibuprofen

6.7.1 Role of Prophylactic Ibuprofen in the Prevention of Intraventricular Hemorrhage

A double-blind, randomized, multicenter trial [94] investigated whether ibuprofen would prevent the development of severe IVH when given within 6 h of birth to preterm neonates with a gestation of 24–30 weeks as compared with placebo. Infants in both groups were eligible to

receive rescue treatment with either indomethacin or ibuprofen if they had a persisting ductus and continued to be on mechanical ventilation. There was no significant difference in the number of infants developing severe IVH: 8 % in the ibuprofen group and 9 % in the placebo group (RR 0.97; 95 % CI 0.51–1.82). More infants in the ibuprofen group than in the placebo group had their ductus closed on day 3 (84 vs. 60 %) and fewer infants in the ibuprofen group required rescue therapy (20 vs. 6 %, $p < 0.001$). However, administration of ibuprofen was associated with a higher incidence of transient renal abnormalities. Another double-blind, RCT [95] in which preterm infants with gestational ages of <28 weeks received ibuprofen or placebo within the first 6 h of birth also showed that prophylactic ibuprofen is ineffective in preventing severe grades of IVH. This is in contrast to a significant reduction in the frequency of severe IVH after prophylactic indomethacin (pooled RR 0.66; 95 % CI 0.53–0.82) [45, 46]. Although both ibuprofen and indomethacin are non-selective COX inhibitors, they seem have different effects on cerebral hemodynamics. These effects are probably explained by other mechanisms not yet elucidated and may not be related to inhibition of prostaglandin synthesis alone.

6.7.2 Role of Prophylactic Ibuprofen on the Prevention of PDA

In various RCTs, intravenous ibuprofen prophylaxis compared with placebo resulted in a significant decrease in PDA by 72 h after treatment [70, 82, 94–96]. All studies used intravenous ibuprofen-lysine except Gournay et al. [82], who compared ibuprofen THAM versus placebo. This trial was prematurely aborted after three infants in the ibuprofen arm developed severe pulmonary hypertension. Possible but not proven causes for pulmonary hypertension include the prophylactic use (<6 h of age) of the drug when pulmonary pressures are still high; the use of ibuprofen solution (buffered with tromethamine or THAM), which might have caused precipitation and micro-embolization in the lungs; or just individual patient susceptibility [83]. This side of pulmonary hypertension was later also reported by studies that used ibuprofen lysine [97–100]. Clinicians using either preparation of ibuprofen (THAM or lysine) should keep in mind the potential serious complication of pulmonary hypertension when using ibuprofen in a prophylactic mode.

7 Side Effects of Cyclooxygenase Inhibitors

The side effects of COX inhibitors pertain to the cerebral, renal and gastrointestinal systems and effects secondary to displacement of bilirubin from albumin. Many of these adverse effects have been discussed in context with the specific drugs in the earlier sections. These adverse effects may be greater with indomethacin than ibuprofen [58]. Some adverse effects that merit discussion are mentioned below.

7.1 Gastrointestinal Effects

Mucosal injury to the gut occurs via various mechanisms, of which inhibition of gut prostaglandin synthesis is predominant [87]. Indomethacin given in close proximity to corticosteroids (dexamethasone or hydrocortisone) can lead to spontaneous intestinal perforation (SIP) in neonates [101, 102]. Concurrent usage of indomethacin and steroids should be avoided as it is associated with a higher risk of SIP [103]. Wadhawan et al. [104] showed that indomethacin given as treatment for PDA and not prophylactic use of indomethacin (within 24 h of age) was associated with increased risk of SIP. In the Cochrane meta-analysis comparing ibuprofen versus indomethacin, two trials ($n = 62$) reported intestinal perforation and three trials ($n = 85$) reported gastrointestinal bleeding; no statistically significant differences were found between them.

7.2 Necrotizing Enterocolitis

The presence of a hemodynamically significant PDA can increase the risk of NEC due to the ductal steal phenomenon [105]. Indomethacin is also known to produce decreased blood flow velocity in the superior mesenteric artery [106]. This combined with already compromised gut blood flow with a hemodynamically significant PDA can explain the increased risk of NEC associated with the use of indomethacin. Christmann et al. [60] observed that superior mesenteric blood flow velocity decreased significantly when indomethacin was given as a bolus compared with continuous infusion. However, unlike indomethacin, ibuprofen does not significantly reduce mesenteric blood flow [107]. In the Cochrane meta-analysis of RCTs [58], 15 studies ($n = 865$) reported on this outcome, and the incidence of any stage of NEC was 12.5 % in the indomethacin group and 8.1 % in the ibuprofen group (typical RR 0.68; 95 % CI 0.47–0.99). Given the reduction in NEC, the authors recommended ibuprofen as the drug of choice for PDA closure. Continuous indomethacin is another treatment option that does not increase the risk of NEC [61]. Despite the known associations between PDA, indomethacin, and NEC, there is no clear evidence that either treatment of PDA protects against NEC or that indomethacin is causally related to the incidence or severity of NEC [108]. Some reports indicate gastrointestinal bleeding may be higher with oral than with intravenous ibuprofen because of higher osmolality and greater local effects on the gut [86].

Infants started on either indomethacin or ibuprofen need not be kept 'nil by mouth' during therapy unless there are contraindications. Giving trophic enteral feeds during indomethacin or ibuprofen therapy treatment appears to have no detrimental effects compared with fasting and may decrease the time needed for infants to achieve full enteral feedings [109, 110].

7.3 Renal Effects

Animal studies have shown that both indomethacin and ibuprofen cause similar decreases in renal blood flow and increased vascular resistance [111, 112]. These effects can manifest as increased blood urea nitrogen and creatinine, oliguria, and renal failure. Pezatti et al. [107] observed that mechanically ventilated preterm neonates with PDA exposed to indomethacin had a greater reduction in renal blood flow velocity 30 min after drug administration, which did not return to the pretreatment values by 120 min. This adverse effect was not noted when indomethacin was administered as an infusion [77]. Ibuprofen did not alter blood flow 30 min after treatment, and blood flow increased 120 min after treatment. Although treatment with ibuprofen results in a lower incidence of oliguria [58, 113] than indomethacin, it is not completely free of negative effects on the kidney [94, 114].

7.4 Hyperbilirubinemia

As ibuprofen is bound to the protein albumin, it is theoretically possible that high doses of ibuprofen could displace bilirubin from albumin, thus increasing the risk of kernicterus in sick preterm neonates with PDA. Clinical studies have shown that the risk—if any—of hyperbilirubinemia is limited [115]. One retrospective study showed that although the peak serum bilirubin levels were higher with indomethacin, the duration of phototherapy and neurodevelopmental outcome at 2 years of age did not differ between the ibuprofen and indomethacin groups [116].

7.5 Cerebral Blood Flow

Studies performed in preterm neonates using near infrared spectroscopy showed significant reductions in cerebral blood flow, cerebral blood volume, and cerebral oxygen delivery after intravenous indomethacin, but there were no significant changes after the use of intravenous ibuprofen [117, 118]. This might be one reason why indomethacin prophylaxis did not improve the long-term outcome of survival without neurosensory impairment at 18 months [46].

8 Contraindications for Indomethacin or Ibuprofen Use

Contraindications to the use of indomethacin or ibuprofen treatment include thrombocytopenia (<60,000/mm^3); clinical bleeding tendency as revealed by hematuria or blood in the endotracheal aspirate, gastric aspirate, or stools; oozing from venous or capillary puncture sites; grade III or grade IV IVH; raised serum creatinine >140 μmol/l (1.6 mg/dl), urine output <1 ml/kg/h during the preceding 8 h; hyperbilirubinemia with impending exchange transfusion; liver failure; concurrent use of postnatal corticosteroids; NEC; life-threatening infection and persistent pulmonary hypertension [52, 56, 79, 80, 119]. Some authors have also avoided the use of indomethacin in babies with severe growth restriction (<3rd centile) with abnormal umbilical Doppler arterial flows [52].

9 Paracetamol for the Closure of PDA

Although both indomethacin and ibuprofen have similar efficacy in ductal closure (70–85 %) [58, 79, 80], the side effects associated with their use led to the felt need for alternative medications with the same efficacy but without side effects. An incidental observation of closure of ductus after the use of paracetamol in a preterm neonate with two previously failed ibuprofen therapies led Hammerman et al. [27] to consider off-label use of the drug to close PDA. They published their experience as a case series of five babies: gestational age 26–29 weeks, age of treatment 3–35 days, infants treated with paracetamol if they had a failed response or had contraindications to ibuprofen use. All the infants closed/constricted their ductus within 3 days of therapy, and no adverse effects were documented.

Paracetamol inhibits the peroxidase site of the enzyme PGHS enzyme, inhibiting the conversion of PGG2 to PGH2. Including the first case series by Hammerman et al. [27], a total of 116 infants have been reported in 14 observational studies on the use of paracetamol for ductal closure [28, 120–129]. Table 2 shows the only two randomized studies conducted thus far on paracetamol for ductal closure. The dosage that has been used for ductal closure is oral or intravenous paracetamol 15 mg/kg given every 6 h for 3 days. However, no dose-response studies have been conducted in this population.

A meta-analysis of the two RCTs shows that the efficacy of oral paracetamol in achieving ductal closure is similar to that of ibuprofen [130, 131]. Pooled data from uncontrolled studies indicated a significant improvement in efficacy when paracetamol was used in subjects with a

Table 2 Randomized studies on paracetamol for closure of PDA

Study #	Study	Study type	Participants	Intervention	Closure rates	Comments
1	Oncel et al. [119]	RCT	90 infants (≤30 weeks, BW ≤1250 g) and postnatal age 48–96 h with ECG confirmed significant PDA	Oral PCM (15 mg/kg every 6 h for 3 days) or oral IBU (initial dose of 10 mg/kg, followed by 5 mg/kg at 24 and 48 h)	IBU group 31/40 (77.5 %) vs. PCM group 29/40 (72.5 %) $p = 0.6$	Rates of surgical closure similar
2	Dang et al. [29]	RCT	160 infants <34 weeks gestation with ECG confirmed PDA	Oral PCM, 15 mg/kg every 6 h for 3 days ($n = 80$) or IBU 10 mg/kg followed by 5 mg/kg after 24 and 48 h	IBU group, 63/80 (78.8 %) vs. PCM group 65/80 (81.2 %) $p = 0.69$	PCM showed a decreased incidence of hyperbilirubinemia and GI bleeding and equal efficacy to IBU

BW birthweight, *ECG* electrocardiographically, *IBU* ibuprofen, *PCM* paracetamol, *PDA* patent ductus arteriosus, *RCT* randomized controlled trial

gestational age of ≥28 weeks, a postnatal age of <7 days, and when it was used as first-line therapy rather than after failed NSAIDs [130]. The pharmacokinetics and safety of the higher doses of paracetamol used for PDA closure (15 mg/kg every 6 h, 60 mg/kg every 24 h for 2–7 days) in extreme preterm neonates have not been studied comprehensively. This dosage is higher than the usual dosage of (7.5 mg/kg every 6 h, maximum of 30 mg/kg every 24 h and maximum 48 h) used in term neonates for pain relief and fever control [132]. At higher dosages, neonates may be at higher risk of hepatotoxicity. An intermediate of paracetamol metabolism by CYP450 enzyme in the liver is N-acetyl-p-benzoquinone-imine (NAPQI), which is toxic to the liver. This metabolite is conjugated by glutathione, and this mechanism may be premature in preterm neonates. However, no evidence of hepatotoxicity has been observed to date with the use of paracetamol for ductal closure. More data are needed from prospective randomized trials of the efficacy and safety of paracetamol compared with ibuprofen and indomethacin. Long-term outcomes such as BPD and neurodevelopment compared with standard treatments should also be assessed in future trials.

10 Discussion

The management of ductus arteriosus in the preterm neonate remains controversial. The treatment options include (1) prevention of ductus in the extreme preterm population via prophylactic drug therapy; (2) early detection and closure of significant ductus in asymptomatic neonates; (3) early or late closure of ductus after it becomes symptomatic; (4) simply tolerating a small to moderate ductus with the presumption that it will spontaneously close. With the so-called conservative therapy, one can delay or decrease the manifestations of the ductus by early restriction of fluid intake and judicious use of ventilatory strategies such as PEEP. Diuretics and digoxin have no role and should be avoided [19, 20]. The literature is scarce on the safety and efficacy of conservative measures alone to allow ductal closure. While conservative measures can be successful if the ductal size is small and the neonate is at least 28 weeks old [23], these measures often fail in large hemodynamically significant PDA and in extremely preterm neonates. A case to consider drug therapy to close a hemodynamically significant ductus in very low birth weight neonates comes from observational studies where the persistence of ductus was associated with increased mortality [15, 21, 22].

The second challenge is when, how, and whom to treat. The timing of treatment can be prophylactic, early targeted, early symptomatic, and late symptomatic. While prophylactic therapy in ELBW neonates reduces the incidence of symptomatic PDA, the need for surgical ligation (by approximately 50 %), the incidence of pulmonary hemorrhage and severe IVH/periventricular hemorrhage (by 40 %), there was no benefit in such long-term outcomes as BPD, hydrocephalus, and neurosensory impairment at 18 months. There would be unnecessary drug exposure to 25 % of neonates to avoid a PDA becoming symptomatic. Hence, this approach is not recommended. Early symptomatic treatment refers to treatment between 2 and 5 days of age when signs of PDA first appear, and late therapy is waiting until the 2nd week of life (days 10–14). Delaying drug therapy in infants with mild signs of PDA (metabolic acidosis, murmur, bounding pulses) may decrease the need for drugs or ligation by 50 % when compared with early treatment without increasing adverse effects [57]. Van Overmeire et al. [56] noted that the success of closure of

symptomatic PDA in ventilated, surfactant-treated, preterm infants was higher if treatment was started on day 3 of life as compared with day 7. The early treatment group had more adverse events (death, intestinal perforation, extension of IVH, or cystic leukomalacia) as well as more renal impairment. The benefits and hazards of early treatment must be balanced with delaying therapy once PDA becomes symptomatic. While the latter approach seems reasonable in stable infants with small to moderate PDA and mild symptoms, it may be unreasonable to delay treatment if infants have severe manifestation such as pulmonary hemorrhage, hypotension or rapid respiratory deterioration due to a large ductus. At the same time, waiting longer can incur losing a therapeutic window of pharmacological closure, as ducts might not respond well to drugs beyond 2 weeks of age, and the irreversible hemodynamic consequences on the lung and other organs might have already occurred.

As the early signs of PDA may be subtle and unreliable in extremely preterm neonates, Kluckow et al. [52] suggested an early targeted therapy based on echocardiographic parameters between 3 and 12 h of birth. In their randomized trial (which ceased early due to unavailability of indomethacin), the authors showed that early targeted therapy is feasible and reduces the incidence of pulmonary hemorrhage and the need for later pharmacological closure. This option is promising and needs to be explored further. Future studies should investigate the use of echocardiographic tools [133, 134] or biomarkers [135] for early prediction and guided therapy of persistent PDAs that lead to cardiorespiratory compromise.

As discussed earlier, the chances of spontaneous PDA closure is higher in more mature preterm infants (>28 weeks gestational age) and restraint is justified, especially if they are stable and requiring minimal ventilatory support. Regarding the choice of drugs, both indomethacin and ibuprofen have equal efficacy; ibuprofen has a better side effect profile and is generally the preferred drug. Oral formulations of both dugs are effective and can be considered in place of intravenous formulations if locally available. Paracetamol is emerging as a new therapy for PDA that has equal efficacy and a wider therapeutic range without many of the side effects of NSAIDS, but more data regarding its safety and long-term outcome are needed. Future studies should include moderate and long-term outcomes such as BPD, duration of hospitalization, and mortality in addition to the usual outcome measure of successful rates of PDA closure.

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