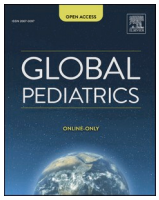
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Patent ductus arteriosus (PDA): Recent recommendations for to close or not to close

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ABSTRACT

Ductus arteriosus which is a physiological necessity for intrauterine life, when is not capable of closing in the preterm infant due to the anatomical characteristics of the tissue, results in a number of hemodynamic alterations. Hemodynamically significant patent ductus arteriosus (hsPDA) is still an elusive condition that challenges neonatologists and pediatric cardiologists due to recent advances in the field of neonatology. The short- and long-term effects of hsPDA have been the focus of several research, reports, reviews, and meta-analyses. The current research question at new era is to treat PDA or not, and if to treat who is the target patient that may benefit from the treatment. Nowadays, more interoceptive approach among NICUs is rising depending on the outcomes of recently published studies concerning expectant management. Therefore, it would be best to make decisions about PDA management and follow-up on an individual basis, considering the balance of benefits and harms of both medical and surgical treatments. It is also essential to design scoring and prediction models to support these decisions and to identify patients who require and will benefit from treatment.

1. Introduction

Patent ductus arteriosus (PDA) is the most common cardiovascular condition in preterm infants. While the ductus arteriosus (DA), a physiological necessity for intrauterine life, is not capable of closing in the preterm infant due to the anatomical characteristics of the DA tissue, results in a number of hemodynamic alterations and an increase in preterm morbidity. The vascular structure as vasa vasorum supplies the muscular layer of the ductus arteriosus. In premature infants, these vasa vasorum are depleted and smooth muscle cells (SMCs) receive oxygen by diffusing from the lumen. To achieve a similar degree of constriction, a greater level of hypoxia is required compared to more mature infants. PDA is still an elusive condition that challenges neonatologists and pediatric cardiologists due to recent advances in the field of neonatology. Preterm babies with respiratory distress syndrome (RDS) have high pulmonary vascular resistance (PVR). After surfactant treatment, PVR decreases, and a left-to-right shunt occurs in the DA. Exposure to a left-to-right shunt across the PDA may cause pulmonary hyperperfusion and systemic hypoperfusion. The evaluation of PDA and left-to-right shunt includes physical examination findings and echocardiography. A PDA shunt have an impact on premature morbidities such as bronchopulmonary dysplasia (BPD), pulmonary and intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and ultimately mortality.[1]

Neonatologists have been encouraged to treat PDA to reduce its association with prematurity-related morbidity and mortality. In spite of the many studies on this issue, it is still debated on the relationship between the morbidities and the characteristics of the PDA. There has been considerable uncertainty about when and how to close ductus arteriosus in preterm infants in recent years. Up to date, most of the research was about comparison of the treatment modalities, comparison of the drugs, comparison of the drug dosages, and comparison of the treatment timing. In recent years, the question of to treat or not to treat PDA has been the most puzzling question in PDA management.[2-6]

2. Clinical impacts of PDA

During the intrauterine period, pulmonary vascular resistance (PVR) is high while systemic vascular resistance is low, resulting in a right-to-left current direction in DA. Postnatally, PVR decreases due to lung ventilation, whereas systemic vascular resistance increases. As a result, systemic arterial blood pressure rises above pulmonary artery pressure and determines the direction of flow in the DA from left to right. PVR is elevated in preterm infants when respiratory distress syndrome (RDS) is

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present. Following surfactant treatment, PVR decreases, and a left-to-right shunt is observed in DA. In addition to the changes of vascular resistance, the size and shape of the PDA, gestational and postnatal age, underlying medical risk factors, blood viscosity, chemical mediators, and medications all play a significant role in the clinical deterioration that leads to either acute or chronic organ damage.[1, 7, 8]

Stealing blood flow from the systemic to the pulmonary circulation, particularly during the diastolic phase, can alter the flow to the organs, resulting in compromised organ function.[1, 7] This circulatory alteration results in organ involvement with two distinct pathophysiology. As the lung over-circulates, pulmonary venous pressure increases, capillary permeability increases at both the arterial and venous ends, and pulmonary edema may develop. Pulmonary edema can reduce lung compliance and increase the need for mechanical ventilation (MV), oxygen (O_2) and pulmonary hemorrhage.[9] The infiltration of fluid into the pulmonary interstitium disrupts the mechanics and development of the alveoli and prolongs the duration of MV. Studies examining the impact of PDA on BPD have found correlations between PDA and BPD, but the existence of a direct causal relationship is still controversial.[10, 11]

The immature myocardium and vascular system do not respond effectively to the increased volume load created by the shunt. Although the stroke volume of the left ventricle rises, there is no consequent increase in systemic blood flow, which leads to heart failure. This cardiac overload stimulates the neurohumoral and renin-angiotensin systems. A decrease in blood flow to the abdominal aorta results in decreased flow to the liver, intestines, and kidneys. These conditions can lead to liver or kidney failure (presents with oliguria, elevated creatinine levels and hyponatremia) and increase risk of NEC.[12] In contrast to that, there has been no reduction in the risk of NEC with treatment for PDA.[1]

Lack of autoregulation causes pressure fluctuations that results in hypo-hyper perfusion and a probable association between the development of IVH and white matter damage that compromises neurodevelopment. However, randomized controlled trials (RCTs) have not demonstrated improvement with either prophylaxis or treatment of PDA, either.[10, 13]

Most studies that have evaluated PDA and morbidity have focused on the associations rather than the pathophysiologic mechanism. Therefore, we think that dynamic echocardiographic, clinical, and biochemical studies of organ systems may provide more detailed information on PDA and treatment strategies.

3. Decision of hemodynamically significant PDA

3.1. Clinical findings

Clinical features of hemodynamically significant PDA (hsPDA) include oliguria, mean or diastolic hypotension, metabolic acidosis, use of cardiotropic or vasopressor medications, increased number and severity of apneas and desaturations, feeding intolerance, radiographic evidence of cardiomegaly, and pulmonary edema. The clinical symptoms of PDA are usually not very sensitive in the first few days of life, so it may take a long time to make a clinical diagnosis of PDA. Echocardiography remains the gold standard for assessing PDA.[14, 15]

3.2. Echocardiographic evaluation

Echocardiography is used to diagnose PDA, determine the shunt volume, and assess its hemodynamic significance, and identify or exclude associated congenital heart defects. A comprehensive echocardiographic evaluation should include ductal features, pulmonary over-circulation parameters, and indicators of systemic hypoperfusion.[15] In this context, several echocardiographic parameters and detailed staging and scoring systems have been described recently.[16] Table 1 provides a summary of the essential echocardiographic measures that clinicians may use to make clinical decisions.[15]

The hemodynamic significance of a PDA is dependent on the volume of shunt across the DA, which is primarily a result of systemic and pulmonary vascular resistance, the capacity of the myocardium to adapt to the increased shunt volume, and the size of the DA. This means that a large PDA detected by echocardiogram may not be a clinically significant PDA.[15]

Table 1
Essential Echocardiography Parameters for Assessment of hsPDA.

PDA evaluation criteria	Essential echocardiographic parameters for assessment of PDA and hemodynamic evaluation
Ductal characteristics	PDA size (small <1.5 mm, moderate 1.5 to 1–2 mm, large >2 mm), and Flow direction (left to right, right to left, or bi-directional), and Doppler assessment with maximum velocity (Vmax) in systole and end-diastole
Assessment of pulmonary over circulation	Dilated left side of the heart on visual inspection "eyeballing" and LA/Ao ratio (mild <1.4, moderate 1.41–1.6, severe >1.6), or LVEDD (correlate with z-scores), or LPA diastolic velocity—mean velocity >0.42 m/s, end-diastolic velocity >0.2 m/s, or Reversal of mitral E/A ratio*Document presence or absence and magnitude of intra-atrial shunt
Assessment of systemic hypoperfusion	Retrograde or absent blood flow during diastole in: - descending aorta, or - coeliac trunk or superior mesenteric artery, or - anterior or middle cerebral arter

A comprehensive echocardiographic assessment should be performed to rule out any underlying congenital heart defect or pulmonary hypertension and delineate the orientation of arch (left- or right-sidedness) before any intervention to close the PDA.
Abbreviations: E/A ratio, the ratio of the velocity of the early (E) diastolic phase of ventricular filling vs. the late atrial (A) contraction component; LA/Ao, left atrium/aorta; LPA, left pulmonary artery; LVEDD, left ventricular end-diastolic diameter; PDA, patent ductus arteriosus.

The diagnosis and management of PDA is still a challenge for neonatologists and pediatric cardiologists. The question of who should perform echocardiography for the evaluation of PDA remains controversial worldwide. Point-of-care ultrasound (POCUS) has recently received gained attention due to the widespread use of ultrasound equipment in neonatal intensive care units (NICU). The POCUS in the NICU, also known as functional echocardiography, neonatologist-performed echocardiography, and targeted neonatal echocardiography, is used to assess myocardial function, systemic and pulmonary blood flow, and intracardiac and extracardiac shunts.[17-20]

POCUS is used to help diagnose PDA, confirm normal structural cardiac anatomy, and identify patients who may benefit from treatment by estimating the hemodynamic consequences of PDA to predict spontaneous closure and risk of morbidity. Functional echocardiography is not intended to replace detailed structural evaluation by the pediatric cardiology specialist. According to consensus recommendations, the initial echocardiogram must evaluate the complete anatomy of the heart to rule out major congenital defects by a pediatric cardiologist.[21]

3.3. Clinical scoring systems

The scoring systems were developed for PDA with the target of early prediction and reduction of the number of echocardiographic examinations. These scoring systems depend on patient characteristics, prenatal and perinatal history, physical examination, and other clinical and vital signs. They could not be used instead of echocardiographic evaluation, but they would help the clinician to predict patients who need early echocardiographic assessment, and to provide objective follow-up for hsPDA.[22-25] Table 2 summarizes few of these clinical scoring systems for PDA.

Table 2
Clinical Scoring Systems For PDA.

Clinical score	Aim	Including parameters	Scoring	Reference	Sensitivity	Specificity
Cotton et al.[22] *(1981)*	Prediction of symptomatic PDA early	Birth weight Hyaline membrane disease IUGR Acute perinatal stress Treatment with distending airway pressure	Birth weight as gram The others scored as 0–1		80 %	NA
Yeh et al.[23] *(1981)* Cardiovascular dysfunction score	Prediction of hsPDA	Heart rate Heart murmur Peripheral pulse Precordial pulsation Cardiothoracic ratio	Points between 0–2 And equations for each reference test $\geq$ 3 associated with La/Ao$\geq$1.3	La/Ao ratio LVEDD Blood pH, PCO_2	NA	NA
Kindler et al.[24] *(2017)* The new short clinical PDA score	Detection and follow up hsPDA	Pulsations of precordium Increased femoral pulses. Acidosis Respiratory deterioration	Scored as 0–1 Score should be calculated every day		84 % (For day 4)	80 % (For day 4)
Gonen et al[25] *(2021)* SIMPLE A Novel Scoring System for Predicting Hemodynamically Significant Patent Ductus Arteriosus	Detection and follow up hsPDA	Maternal chorioamnionitis Antenatal steroid exposure Birth weight Cord blood base deficit Presence of hypotension Presence of tachycardia Need of invasive MV Presence of metabolic acidosis Presence of respiratory acidosis Maximum PIP PIP reduction FiO_2 at admission FiO_2 reduction Number of surfactant administration	Scored each item between 0–3	Echo evaluation	90–100 % (Differs according to postnatal age)	85–94 % (Differs according to postnatal age)

Abbreviations: hsPDA: hemodynamically significant patent ductus arteriosus, IUGR: intrauterine growth restriction, LA/Ao, left atrium/aorta, LVEDD, left ventricular end-diastolic diameter, MV: *mechanical ventilation PDA: patent ductus arteriosus, PCO_2: Partial carbon dioxide pressure, PIP: positive inspiratory pressure*

3.4. Echocardiographic scoring systems for PDA

Echocardiography is considered the standard of care for the diagnosis of PDA; however, the findings from echocardiograms are not standardized when making treatment decisions for hsPDA. To address this, PDA severity scoring systems using echocardiographic parameters have been developed to estimate significant morbidity and mortality in patients with PDA.[26-28] These echocardiographic scoring systems are listed in Table 3.

3.5. Other methods for PDA assessment

Although echocardiography is considered the gold standard diagnostic method for PDA, several methods have been evaluated to improve the assessment. Biomarkers and continuous monitoring techniques have been evaluated to determine hsPDA, but most do not have reference values for preterm infants.[7]

3.5.1. Platelet count and indices

Platelet count and other platelet indices such as platelet distribution width (PDW), mean platelet volume (MPV) have also been evaluated for association with PDA. Two meta-analyses provide strong evidence of an association between hsPDA, and low platelet counts. It is currently unclear whether it contributes to the pathogenesis of PDA or is secondary to immaturity and clinical instability.[29, 30] PDW, MPV, platelet crit (PCT), and platelet mass were also probably related to hsPDA.[31, 32] Platelet count, PCT and platelet mass in the first 3 postnatal days, have been found to be helpful in determining hsPDA in a systematic review.[33] Platelets may regulate ductal closure by playing a role in hemostasis, secretion of various signaling molecules, and modulation of specific platelet-endothelial interactions. Evidence suggests that low platelet counts, and platelet dysfunction are associated with ductus arteriosus patency and potential failure of pharmacologic treatment of PDA.[34]

3.5.2. Cardiac peptides

Pressure and volume loading in the cardiac ventricles cause the release of pro-brain natriuretic peptide (proBNP), which turns out to be cleaved into physiologically active BNP and inactive N-terminal proBNP (NT-proBNP).[35] The most recent review included 13 studies that evaluated BNP for the diagnosis of hsPDA in preterm infants and found better diagnostic accuracy with lower cutoffs (<250 pg/mL versus ≥250 pg/mL), testing at <30 weeks' gestation, and chronological age at testing at one to three days of age.[36] This review included 21 studies that evaluated NT-proBNP and there was no difference by threshold (<6000 pg/ml and ≥6000 pg/ml). Similar to BNP, gestational age less than 30 weeks and chronological age at testing (postnatal 1–3 days vs >3 days) had better accuracy. However, even in this largest review, the strength of the evidence was low. Due to the different characteristics of the test and the infants, generalization between centers is not possible. The recommendation is local validation for specific populations and its use for treatment response monitoring. Other than BNP/proBNP, there are a few studies on the relationship between cardiac troponin T and hsPDA. El-Khuffash et al. found that the levels of cardiac troponin T were correlated with the echocardiographic findings of PDA.[37]

Table 3
Echocardiographic Scoring Systems For PDA.

Clinical score	Aim	Including parameters	Scoring	Reference	Sensitivity	Specificity
EL-Khuffash et al.[26] *(2015)* PDA severity score (PDAsc)	Prediction of chronic lung disease or death before discharge	PDA diameter PDA mx flow velocity LV output Diastolic flow in the descending aorta and celiac trunk Variables of LV function	On the day 2 Equation for scoring = [GA(w) x -1.304] + [PDA diameter (mm) x 0.781] + [LVO (ml/kg/min) x 0.008] + [max PDA velocity (m/s) x - 1.605)] + [LV a' wave(cm/s) x -0.470) + 41 Score between 0–13 (Low to high risk)	CLD (Oxygen need at 36 w PMA) Death before discharge	PDAsc >5 92 %	PDAsc >5 87 %
Fink et al.[43] *(2017)* Shaare Zedek Medical Center PDA severity score (SZMC)	Prediction of long-term morbidities	PDA diameter La/Ao ratio Retrograde diastolic flow in the abdominal aorta Ductus arteriosus shunt flow pattern	Scores for each between 0–2 Closed ductus 0 0–2 hemodynamically insignificant 3–5 borderline significance ≥6 hsPDA	CLD/death Correlation with PDAsc (El-Khuffash)	NA	NA
Giesinger et al.[28] *(2023)* Iowa Score	Evaluation of hsPDA	Pulmonary vein D wave (cm/s) Mitral valve E wave (cm/s) Isovolumetric relaxation time (ms) La/Ao Left to right ventricular output ratio Aortic/peripheral doppler flow reversal Ductus diameter indexed to weigh (mm/kg)	Scores for each between 0–2 ≥6 hsPDA	NA	NA	NA

CLD: chronic lung disease, GA: gestational age, hsPDA: hemodynamically significant PDA, LA/Ao, left atrium/aorta LV: left ventricle, LVO: left ventricle output, PDA: patent ductus arteriosus.

3.5.3. Near infrared spectroscopy, perfusion index

Near-infrared spectroscopy continuously measures regional tissue oxygenation non-invasively. It could help identify impaired cerebral, renal, and mesenteric circulation for early diagnosis of hsPDA.[38, 39] The perfusion index (PI) is a simple, continuous parameter provided by the pulse oximetry to access the peripheral perfusion, and it could help to predict a significant PDA.[38, 40]

3.5.4. New insights

Proteomics analysis and various cytokines have been studied in neonates, and large PDA in extremely preterm neonates has been found to be associated with differences in angiotensinogen, periostin, immune and complement systems. There are few studies on proteomics in PDA; however, these developments may improve understanding of pathogenesis, early diagnosis, drug development, and monitoring of disease severity in the future.[41]

Machine learning prediction models have been used in most areas of medicine. Recently, a model was developed to predict the efficacy of treatment for hsPDA closure. In this model, the authors found a 60.2 % success rate and a 48.4 % failure rate. To improve the accuracy of models, prospective studies with large samples should be conducted. Such models may help clinicians predict infants who will benefit from medical treatment.[42]

4. Management of PDA

4.1. Medical treatment

The drugs used to close PDA react by inhibiting cyclooxygenase and peroxidase, thus preventing the production of prostaglandins. The resulting reduction in prostaglandins causes the DA muscles to contract, and the ductal vasa vasorum undergoes severe hypoxia. These processes cause the PDA to become restricted, fibrotic, and anatomically closed, with the addition of platelet recruitment. Three drugs (indomethacin, ibuprofen, and paracetamol) have been demonstrated to be effective in placebo-controlled randomized trials.[44] No significant differences in effectiveness have been reported among these medications. However, there are significant variations in dosage and the effects on cerebral and renal perfusion. For the treatment of symptomatic PDA, all available prostaglandin inhibitor drugs appear to be more effective in closing a PDA than placebo or no treatment in symptomatic cases.[45]

4.1.1. Timing of treatment

Randomized controlled trials comparing prophylactic PDA treatment initiated within 12 hours of birth with delayed treatment later in the first postnatal week have reported a reduction in several short-term morbidities, including severe early pulmonary hemorrhage, dopamine-dependent hypotension, the need for higher ventilator support, and the need for surgical PDA ligation, but no difference in the long-term morbidities such as BPD, NEC, or neurodevelopmental impairment. Currently, prophylactic treatment is not recommended as most premature infants without hsPDA are exposed to potential drug side effects, with no positive effect on long-term neurodevelopmental prognosis or sequela-free survival. If medical treatment is an option, an early targeted treatment strategy is recommended in last reviews.[46-52]

4.1.2. Non-steroidal anti-inflammatory drugs

■ ***Indomethacin* vs. *Ibuprofen***

Similar efficacy in rates of PDA closure and reopening were reported in the systematic review comparing ibuprofen and indomethacin.[53] Five of 13 RCTs comparing nonsteroidal anti-inflammatory drugs (NSAIDs) suggested improved urine output and another study reported reduced mortality in neonates treated with ibuprofen.[53-55]

■ ***Ibuprofen* vs. *Paracetamol***

In some studies, comparing two drugs, neonates given paracetamol had a lower rate of PDA closure compared to neonates given ibuprofen. However, when PDA constriction was taken into consideration, there was no significant difference in the closure rates between two groups.[56,

[57] The most recent systematic review showed that for failure of ductal closure after the first course, there was almost no difference between paracetamol and ibuprofen. There was little to no difference between paracetamol and ibuprofen for in-hospital mortality and NEC in favor paracetamol.[58]

■ ***Indomethacin* vs. *Paracetamol***

Paracetamol and indomethacin both revealed comparable efficacy, according to Dash et al.[59] In a recent systematic review of the four randomized controlled trials comparing the efficacy and safety of paracetamol with indomethacin, no difference was found for the outcome of PDA closure after one or two courses of treatment or for the outcome of PDA ligation. Infants who received paracetamol had lower rates of NEC, and there were no significant differences in other clinical outcomes (IVH, BPD, ROP requiring treatment, and mortality). Two of these studies found significant elevations in serum creatinine and blood urea after treatment with indomethacin, compared to none with paracetamol.[60]

■ ***Different Drug Dose Scheme***

There are some studies that provide conflicting results when high doses of ibuprofen are compared with standard doses. In the network meta-analysis by Mitra et al, high-dose ibuprofen (defined as 15–20 mg/kg followed by 7.5–10 mg/kg administered every 12–24 hours for a total of 3 doses) was associated with significantly higher rates of PDA closure compared with standard-dose ibuprofen, without an increase in NEC rate.[44] In a retrospective study, the effect of dose escalation according to postnatal age was evaluated (10–5–5 mg/kg/dose regimen for before the 70th h of postnatal age, 14–7–7 mg/kg/dose regimen for the 70th-108th h of postnatal age, and 18–9–9 mg/kg/dose regimen for after the 108th h of postnatal age). The authors concluded that increasing ibuprofen doses with postnatal age was not as effective as earlier treatment.[61] This may be associated with early drug efficacy independent of dose or time-accelerated spontaneous closure rates.

■ ***Administration route (Oral* vs. *Intravenous)***

In the network meta-analysis evaluating the effectiveness of oral ibuprofen administration to intravenous treatment, the oral route proved to be more effective. High dose oral ibuprofen was found to be associated with the best efficacy on hsPDA closure among all available pharmacotherapeutic options without an increased incidence of NEC.[44]

■ ***Combined treatment (Paracetamol and Ibuprofen)***

Given the different mechanisms of the two drugs, combining paracetamol and ibuprofen might have a synergistic effect on closing the PDA. With this knowledge, few studies were conducted to evaluate the effect of combination therapy. The meta-analysis of 5 trials that evaluated combination therapy as first-line treatment suggested that combination therapy was more effective than monotherapy. However, in this analysis, most studies were not randomized, sample sizes were small, dosages and duration of therapy varied, and toxicity information was limited. Randomized controlled trials are needed to recommend combination therapies as first-line treatment.[62] There is only one report that evaluates combined therapy for those who failed to complete with monotherapy and in this report successful treatment with combined therapy was reported in the monotherapy resistant PDA group.[63]

The literature suggests that the timing, dose, route, and duration of treatment, as well as the maturity of the infant being treated, all impact the efficacy of the treatment.[64, 65] The results of studies conducted in the past ten years provided that oral ibuprofen appears to be more effective in PDA closure than intravenous ibuprofen. High-dose ibuprofen appears to be more effective in PDA closure than standard-dose regimen. With respect to adverse outcomes, compared to indomethacin administration, NEC appears to be lower with ibuprofen, oral ibuprofen, and acetaminophen.[45]

4.1.3. Medical vs conservative management

Currently, it is not clear which is preferable, to close the PDA (either pharmacologically or surgically) in the newborn period, or to deal with the PDA-induced pulmonary edema and hypotension more "conservatively" (with inotropes, diuretics, fluid restriction, and increased end-expiratory pressure) while awaiting spontaneous PDA closure. Comparison of "prophylactic" PDA treatment (starting within 12 hours of birth) with delayed treatment later in the first postnatal week, resulted just a decrease in several short-term morbidities (severe early pulmonary hemorrhage, dopamine-dependent hypotension, need for higher levels of ventilator support, and need for surgical PDA ligation) but no difference in the incidence of long-term morbidities like BPD, NEC, or neurodevelopmental impairment. Additionally, analyses showed that 40–50 % of the prophylactically treated infants were treated unnecessarily since their PDA would have closed spontaneously by 7 days.[66]

Few randomized controlled trials attempted to determine whether exposure to moderate-sized PDA shunts that persist for more than one week affected morbidity in preterm infants whose GA was <28–29 weeks.[2, 4, 67] Two of them compared early routine treatment beginning at 8 days of age with a conservative, expectant management approach. PDA-Tolerate study by Clyman et al. concluded that in preterm infants age <28 weeks with moderate-to-large PDAs who were receiving respiratory support after the first week, early treatment did not reduce PDA ligations or the presence of a PDA at discharge and did not improve any of the prespecified secondary outcomes, but delayed full feeding and was associated with higher rates of late-onset sepsis and death in infants born at ≥26 weeks of gestation.[2] Including the study by Sung et al., both studies demonstrated that the closure rates of PDA were unsatisfactory in the early intervention groups. There were no changes in BPD, NEC, or mortality between groups in either study.[2, 4] In another randomized, non-inferiority trial of expectant management versus early treatment of PDA in preterm infants less than 32 weeks' gestation, there was no difference between groups for PDA closure at discharge. In addition, no significant difference was observed for BPD/death.[3] A recent study known as BeNeDuctus,[5] enrolled a total of 273 infants with the median gestational age of 26 weeks, and the median birth weight of 845 g. This study showed that expectant management for PDA in extremely premature infants was noninferior to early ibuprofen treatment with respect to NEC, BPD, or death at 36 weeks' postmenstrual age.

Our group conducted Inter-PDA Study, a prospective, multicenter, cohort study to compare the effects of conservative approaches and medical treatment options on ductal closure at discharge, surgical ligation, prematurity-related morbidities, and mortality.[68] Among the 1193 enrolled infants (26.7 ± 1.4 weeks and 926 ± 243 g), 130 infants with moderate-to-large PDA were managed conservatively, in contrast to 414 who received medical treatment. Eighty (62 %) of 130 infants who were managed conservatively did not receive any rescue treatment and the PDA closure rate was 53 % at discharge. There were no differences in the rates of late-onset sepsis, NEC, ROP, IVH (≥Grade 3), surgical ligation, and presence of PDA at discharge between conservatively-managed and medically treated infants ($p > 0.05$). Infants treated before postnatal day 7 had higher rates of mortality and BPD/death than infants who were conservatively managed or treated beyond day 7 ($p = 0.009$ and 0.007, respectively). In preterm infants born at <29 weeks of gestation with moderate-to-large PDA, medical treatment did not show any reduction in the rates of open PDA at discharge, surgical or prematurity-related secondary outcomes. In addition to the high incidence of spontaneous closure of PDA in the first week of life, early treatment (<7 days) was associated with higher rates of mortality and BPD/death.

The association of prolonged exposure to PDA and BPD is the new focus of research in the new era. Recent studies have indicated that a

correlation between PDA and BPD is present only in infants with moderate-to-large PDA shunts that last more than 7–14 days and need MV or tracheal intubation for at least 10 days.[41, 69-74] This implies that early closure of PDA may not be necessary for infants who require intubation for less than 10 days. What we do know is that neither a delay of 2 to 5 days before starting PDA treatment during the first week nor routine treatment that starts only after infants have been exposed to a moderate-to-large shunt for more than 2 weeks appear to affect the incidence of BPD. Whether exposure to a moderate-to-large PDA shunt for more than the first 7–14 days actually contributes to the development of BPD is a question that awaits testing in appropriately designed RCTs. Future trials should be designed to determine which infants are most likely to benefit from PDA treatment and which infants might best be left untreated.[66]

The trials that evaluated early treatment and conservative management are summarized in Table 4.

4.2. Surgical ligation and transcatheter closure

Transcatheter PDA closure or surgical ligation are considered as options if medical treatment is unsuccessful. Both methods carry significant risks, particularly regarding transportation within or between hospitals. These risks include securing the airway, extubation, hypothermia, hemodynamic instability, and loss of vascular access.[76-78] The latest trend involves transcatheter PDA closure being performed in the NICU to eliminate the risks of transport.[79-82] Few researchers suggest it as an alternative to surgical ligation or even to medical treatment. Recently, FDA and CE approved the Amplatzer Piccolo Occluder® device for the transcatheter closure of PDA in premature infants weighing over 700 gs and over 3 days old.[83] Several cohort studies have shown favorable results, including extremely low birth weight infants as small as 640 g. Better pulmonary outcome reported compared to surgical ligation.[83, 84] But as a common approach, this procedure is currently used for medical treatment failure or contraindications. .[84-88] Now, surgical operations are carried in NICUs, too. In a large multicenter study comparing PDA ligation performed in the operating room and in the NICU, no differences in mortality or sepsis were observed, except for increased postoperative hemodynamic instability in the operating room group.[89]

The latest meta-analysis of percutaneous PDA closure in infants weighing less than 1500 g evaluated technical success and safety profile of the procedure.[90] In this study, technical success was found to be 96 %, overall incidence of adverse events was 27 % and major adverse events was 8 %. Five of 373 patients died and 4 of them were <800 g. The probability of technical failure was found to be inversely related to age at the time of the procedure. Reported technical failures were cardiac perforation, hemopericardium, inferior vena cava dissection, cardiac tamponade, aortic coarctation, device embolization to the left pulmonary artery.

In a recent small study, authors suggested that surgical ligation may be associated with increased severity of BPD compared with transcatheter closure in extremely preterm infants.[91] Surgical ligation may be related to the effects of pulmonary or thoracic manipulation during surgery, although we could not make a precise suggestion based on this low certainty evidence.

Currently, there is no strong evidence to suggest transcutaneous PDA closure as a first-line treatment approach. It is still reserved for infants in whom medical therapy has failed or is contraindicated. Long-term randomized controlled trials are also needed in this area to explain the effects on long-term morbidity such as BPD.

5. Conclusion

The short- and long-term effects of hsPDA have been the focus of

Table 4
The Studies Comparing Early Targeted PDA Treatment with Conservative Management.

	BeNeDuctus[5] (2022)	PDA-Tolerate[2] (2019)	Inter PDA[68] (2020)	Sung et al. Nonintervention vs oral ibuprofen[4] (2020)	Baby Oscar[6] (2022)	TRIOCAPI[75] (2021)
Sample size	273	202	544	146	646	228
Gestational age (w)						
	26.1	25.9	26.5	26.7	26.1	25.8
■ **Conservative**	26	25.7	26.5	26.8		
■ **Early treatment**						
Birth weight (g)	863	809	924	915		
	825	790	877	893		
Echocardiographic assessment time (d)	2.3	7–10	3	8.4		
Treatment groups						
	50	49	24	49		
■ **Conservative**	50	51	76	51		
■ **Early treatment**						
In conservative management (%)						
		49	38	0	0	
■ **Rescue treatment**		?	62			
■ **Spontan closure**						
PDA ligation/transcatheter (%)						
	0	12	6	6		
■ **Conservative**	2.2	12	7	4		
■ **Early treatment**						
Open PDA at discharge (%)						
		27	19	12		
■ **Conservative**		19	19	7		
■ **Early treatment**						
BPD (%)						
	33.3	53	47	40	59	40
■ **Conservative**	50.9	49	49	45	64	34
■ **Medical**						
Mortality (%)						
	14	10	22	8		
■ **Conservative**	18.2	19	35	9		
■ **Early treatment**						
Other morbidity	NS	NS	NS	Sepsis rate higher in the treatment group		

several research, reports, reviews, and meta-analyses. The primary research questions at this point are about medical treatment or conservative management of hsPDA. In recent years, several studies have attempted to answer this question, and the results have shown that medical treatment is not superior to conservative management in terms of long-term morbidity, need for PDA ligation, or mortality. However, all of the randomized controlled trials (RCTs) were confounded by infants who had little or no effect of continuing to have PDA. There is a significant challenge at present regarding preterm neonates born before 26 weeks of gestational age. Identifying the appropriate population to enroll, particularly those at risk for increased morbidity from PDA, is another challenge for future randomized controlled trials.

If there is a hsPDA, it would be inappropriate to make a definitive statement that it should be closed. With current knowledge, such a recommendation may potentially cause delays in the treatment of infants who may be affected by PDA or result in unnecessary treatments of PDA that will undergo spontaneous closure. For this reason, it would be best to make decisions about PDA follow-up and treatment on an individual basis, considering the balance of benefits and harms. It is also essential to design scoring and prediction models to support these decisions and to identify patients who require and would benefit from treatment.

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CRediT authorship contribution statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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