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REVIEW ARTICLE

Systematic review on the persistence of the arterial pain in the premature newborn: a comparison between conservative, drug and surgical treatment

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Keywords:
Conservative treatment, Ductus arteriosus, Hypertension, pulmonary, Infant, premature, Pulmonary artery, Therapeutics.

Abstract

The ductus arteriosus is a vessel that communicates the pulmonary artery with the aorta in the fetus, being of great importance in this period of life, since a large part of the combined ventricular output passes through this communication to the descending aorta and the placenta. Functional closure of the ductus arteriosus in full-term newborns occurs at 12 to 15 hours of life, and permanent closure occurs at 5 to 7 days, and may reach up to the 21st day. In premature infants, the ductus arteriosus remains open for a longer time, and the frequency of patent ductus arteriosus is proportionally higher the more immature the NB is. The clinical picture varies with the gestational age, however, the symptomatic persistence of the ductus arteriosus is identified by the presence of heart murmur, tachycardia, hyperdynamic precordium and by the increase in pulse amplitude. PDA therapy can be clinical or surgical, the treatment decision still has great divergence. This research aims to compare the conservative, drug and surgical treatment of PDA in premature infants, in search of the best management. This is a systematic review that seeks to gather results from other studies through the PICO strategy, establishing a comparison between surgical, drug and conservative treatment of PDA, using renowned databases and interpreting the results obtained through the review.

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INTRODUCTION

The ductus arteriosus is a large vessel that connects the pulmonary artery to the aorta in the fetus. This musculoelastic vascular structure, essential for fetal life, functions as an arterial conduit, since it diverts more than half of the cardiac output to the systemic circulation, given that in the fetal period the lungs are constricted.[1] In the fetus, the duct remains open due to the intense blood flow and the presence of maternal prostaglandins.[2] Thus, because pulmonary vascular resistance is extremely high and the percentage of blood directed to the lungs is very small, most of the systemic cardiac output occurs through the ductus arteriosus, driven by the right ventricle. At birth, in response to the increase in blood oxygen pressure, the duct constricts while the pulmonary circulation dilates, establishing a new circulatory pattern in the newborn.[3]

Functional closure of the ductus arteriosus occurs within 48 hours after birth in term newborns (NB) and within 72 hours in 90% of infants over 30 weeks of gestational age (GA). Two events contribute to this closure: the direct action of oxygen and the reduction of Prostaglandin E_2 levels. When the duct remains open beyond 72 hours, it can be considered a patent ductus arteriosus (PDA), a condition associated with an anatomic defect caused by abnormal distribution of elastic material in the internal lamina and structural changes in the medial and subendothelial layers. Several factors interfere with the spontaneous closure of the ductus arteriosus, increasing the risk of PDA, such as: absence of antenatal corticosteroids, prenatal exposure to magnesium sulfate, sepsis, inflammation, rubella infection in the first four weeks of pregnancy, use of valproate during pregnancy, prematurity, maternal diabetes, and excessive intravenous fluids in the first days of life. This mechanism applies to term infants with PDA. However, in preterm infants (<37 weeks), PDA results from delayed occlusion due to morphofunctional immaturity of the vascular conduit, which did not complete its development because of early birth. The frequency of PDA increases with lower gestational age.[4]

While pulmonary arterial pressure remains high, PDA is asymptomatic. As pressure decreases, a left-to-right shunt develops, increasing blood flow to the lungs and leading to left ventricular overload. This rise in pulmonary vascular pressure can cause pulmonary capillary leakage, pulmonary edema, increased airway resistance, and, over time, worsening of the infant's condition. The lungs become stiffer, and systemic blood is "stolen," leading to arterial hypotension. This hypotension is mainly due to reduced diastolic pressure and impaired organ perfusion, particularly in the intestines and kidneys, increasing the risk of necrotizing enterocolitis and acute kidney injury. Reduced cerebral perfusion and altered cerebral blood flow may predispose to periventricular leukomalacia and intraventricular hemorrhage. Therefore, in cases of refractory hypotension, the possibility of a hemodynamically significant ductus arteriosus should be considered. Increased pulmonary blood flow may also cause hemorrhage with significant reduction in pulmonary compliance, secondary to capillary damage from excessive pulmonary blood flow.[5] Thus, acute repercussions of increased pulmonary blood flow and severe complications associated with PDA include necrotizing enterocolitis, renal failure, bronchopulmonary dysplasia, and intraventricular hemorrhage.[6]

Although not the focus of this study, it is worth mentioning that there are congenital heart diseases with pulmonary circulation dependent on the ductus arteriosus. This group of fetal malformations is represented by heart defects in which there is critical or complete obstruction of right ventricular outflow to the pulmonary artery. In such cases, all pulmonary blood flow after birth depends on ductal patency.[7]

From a clinical standpoint, diagnosis may be based on the presence of murmur, widened pulse pressure, or hyperdynamic precordium, in addition to tachycardia. These signs usually appear later (around 4–5 days of life) and are not very sensitive in the early days. Electrocardiogram is often normal or may show left axis deviation and left heart chamber overload. Echocardiography is considered the gold standard for diagnostic confirmation and assessment of hemodynamic repercussions.[4] Some laboratory tests may support the diagnostic hypothesis by demonstrating alterations associated with PDA, including metabolic acidosis, worsening of blood gases, elevated C-reactive protein, and increases in several biochemical markers such as B-type natriuretic peptide, cardiac troponin T, and N-terminal pro–B-type natriuretic peptide.[8]

Management of PDA differs between preterm and term infants. Moreover, preterm infants must be classified according to GA and weight (<1000 g, 1000–1500 g, and >1500 g). This distinction exists because in preterm infants, the ductus remains open for a longer period, altering therapeutic approaches.[4]

Clinical therapy for PDA is primarily based on the administration of nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit prostaglandin synthesis, in association with fluid restriction and diuretics. However, in cases where PDA is refractory to clinical management, surgical ligation is indicated to mitigate hemodynamic complications. Although this intervention yields satisfactory results, it is not free from complications.[3] Surgical intervention is therefore recommended when there is respiratory or systemic deterioration with echocardiographic evidence of hemodynamic repercussions after attempted pharmacological and conservative treatment. The decision for surgical treatment and the most appropriate timing remain the subject of much debate and controversy.[5] In children who continue to have symptomatic PDA with significant hemodynamic impact and high ventilatory and oxygen requirements despite pharmacologic therapy, corrective surgery is indicated.[9]

Given the wide variation in treatment strategies for PDA, the aim of this review is to compare the indications and effectiveness of conservative, pharmacological, and surgical treatments in preterm infants, in order to reduce biases and improve survival.

METHODS

A systematic literature review was conducted using the PRISMA methodology, which consists of a 27-item checklist designed to guide the development of systematic reviews and meta-analyses.[10]

The guiding question of this study, based on the PICO strategy for research question formulation, was: *What is the best management approach for the treatment of preterm infants with PDA: surgical, pharmacological, or conservative treatment?*

- **Population:** Preterm newborns and/or those weighing ≤1500 g with PDA.
- **Intervention:** Treatment (surgical or pharmacological).
- **Control:** Conservative and pharmacological therapy.
- **Outcomes evaluated:**
  - Failure to close PDA at the end of treatment.
  - Failure to close PDA after the 1st, 2nd, and 3rd treatment cycles.
  - Reopening of the ductus arteriosus.
  - Need for surgical closure of PDA.
  - Duration of supplemental oxygen requirement.
  - Surgical ligation rate.
  - Mental Development Index (MDI) and Psychomotor Development Index (PDI).
  - Neurodevelopmental impairment.
  - Moderate to severe cerebral palsy.
  - Blindness and deafness.
  - Intestinal perforation, gastrointestinal bleeding, or occult blood in stools.
  - Mucocutaneous bleeding.
  - Retinopathy of prematurity.
  - Intraventricular hemorrhage.
  - Oliguria, periventricular leukomalacia, necrotizing enterocolitis, feeding intolerance.
  - Bronchopulmonary dysplasia, pulmonary hemorrhage, pulmonary hypertension, chronic lung disease, sepsis, pneumothorax, elevated creatinine.
  - Mortality within the first 28 days and within the first year of life.
  - Respiratory data (FiO_2 at 24h postoperatively, days of intubation, and bronchopulmonary dysplasia).
  - Nutritional status (complete oral feeding and body weight).
  - Postoperative complications.
  - Infants with small PDA (<1.5 mm) without clinical sequelae and infants with large PDA (>1.5 mm) with echocardiographic signs of hemodynamic significance, including pulmonary hypertension and/or cardiac and pulmonary overload, as well as clinical symptoms associated with PDA, including worsening of respiratory failure.
  - Length of hospitalization, cost, procedure time, and adverse events (occluder migration, hemolysis, peripheral vascular complications, and residual shunt).
  - Use of postnatal corticosteroids, time to full enteral feeding, and time to regain birth weight.
  - Mortality by 36 weeks of postmenstrual age or presence of bronchopulmonary dysplasia or necrotizing enterocolitis (moderate or severe) at 36 weeks of postmenstrual age.
  - Better health outcomes at 2 years of corrected age, including survival without moderate/severe neurodevelopmental impairment and survival without respiratory morbidity.

Inclusion criteria: Full-text articles available online, including randomized clinical trials and systematic reviews (highest levels of evidence), restricted to studies on PDA in preterm infants with emphasis on treatment comparisons. Only articles published between 2017 and 2022 were considered.

Exclusion criteria: Studies conducted prior to the established timeframe, case reports, and articles mentioning descriptors only in the body of the text. Articles in languages other than English or Portuguese were excluded. Studies in which the primary outcome had not been completed at the time of publication were also excluded.

Databases and search strategy: The databases PUBMED and the Cochrane Central Register of Controlled Trials were searched electronically from the beginning of the present study until June 1, 2022. Outdated information was updated until November 30, 2022, before the final data analysis. The search strategy used was: *"treatment" AND "patent ductus arteriosus"*.

RESULTS

A total of 3,858 studies were identified in the PubMed database. These articles were screened according to the inclusion and exclusion criteria and assessed for eligibility by two reviewers, resulting in 79 articles. Based on title and abstract review, duplicate and similar articles were excluded, leaving only the most recent studies. Articles in which the descriptors of interest appeared only within the text but were not the main focus were also excluded, resulting in 14 studies selected for data extraction (Figure 1).

A summary table was prepared to present the findings and outcomes of each article included in this review, in order to support the description of the results reported herein (Table 1).

Studies on Conservative Treatment

Among the four studies analyzed on conservative management compared with other treatment approaches,

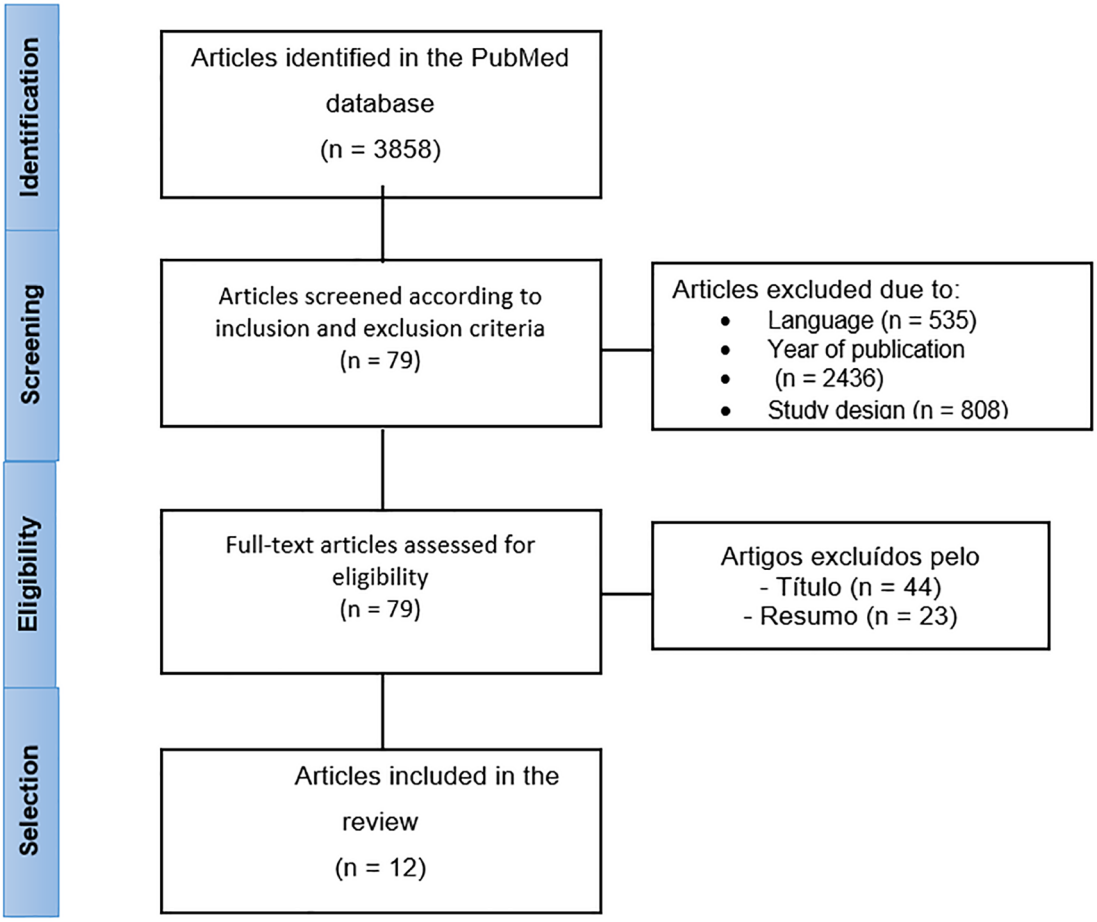


Figure 1. Study selection flowchart.

there were two systematic reviews with meta-analysis and two randomized clinical trials.

No significant difference was found between early treatment versus expectant management (no treatment initiated within the first seven days after birth) for hemodynamically significant PDA with respect to the primary outcome of *all-cause mortality* (moderate-certainty evidence) or other clinically relevant outcomes, such as surgical ligation of PDA (very low-certainty evidence) and chronic lung disease (moderate-certainty evidence).[11] This finding was also observed in another study, which reported no significant differences in the odds of mortality, necrotizing enterocolitis, or intraventricular hemorrhage when comparing placebo or no treatment with any of the other therapeutic modalities.[12]

On the other hand, in most hemodynamically stable infants, a PDA will eventually close spontaneously. Therefore, treatment potentially increases the risk of iatrogenic adverse effects. This was noted in the randomized clinical trial *"Multi-centre, randomised non-inferiority trial of early treatment versus expectant management of patent ductus arteriosus in preterm infants (the BeNeDuctus trial): statistical analysis plan,"* which explains why expectant management is gaining interest in the literature.[13] However, this study has not yet provided conclusive results to confirm such findings.

In addition to the observations on conservative treatment, statistical classification analyses indicated that high-dose oral ibuprofen is the best pharmacotherapeutic option for the closure of significant PDA and as a strategy to prevent surgical ligation.[12]

Some of these studies are still ongoing, but it is expected that the results will show a reduction in absolute risk for infants randomized to treatment compared with placebo, potentially yielding a clinically important difference.[14]

Studies on Pharmacological Treatment Comparison

Among the studies comparing pharmacological treatment, there are randomized clinical trials and systematic reviews with and without meta-analysis. The comparisons made in these studies include paracetamol and/or indomethacin and/or ibuprofen.

Table 1. Summary of findings, by article and year of publication.

Authors and Year	Study Design	Journal of Publication	Treatment	Sample	Evaluated Group	Outcomes Assessed
Oncel *et al.* (2017)[15]	Randomized Clinical Trial	American Journal of Perinatalogy	Oral Paracetamol vs. Oral Ibuprofen vs. Surgical Ligation.	80	Preterm infants ≤30 weeks of gestational age	Closure of the ductus arteriosus, reopening and closure after a second course, surgical ligation rate, MDI (Mental Development Index), PDI (Psychomotor Development Index), neurodevelopmental impairment, moderate to severe cerebral palsy, blindness, deafness.
Marconi *et al.* (2019)[16]	Systematic Review with Meta-analysis	Elsevier Ltd.	Indomethacin (oral, intravenous, or rectal) vs. Ibuprofen (oral, intravenous, or rectal) vs. Paracetamol (oral, intravenous, or rectal).	14.568	Preterm infants (<37 weeks), term infants (≥37 weeks), low birth weight (<2500 g), and normal weight infants (≥2500 g) with PDA diagnosed clinically or by echocardiographic (ECHO) criteria in the neonatal period (<28 days).	Failure to close the PDA at the end of treatment, failure to close the PDA after the 1st course, failure to close the PDA after the 2nd course, failure to close the PDA after the 3rd course, need for surgical closure of the patent ductus arteriosus, death, and occurrence of selected adverse events (defined as intestinal perforation, gastrointestinal hemorrhage, intraventricular hemorrhage, oliguria, periventricular leukomalacia, necrotizing enterocolitis, and bronchopulmonary dysplasia).
Dani C *et al.* (2020)[17]	Randomized Clinical Trial	European Journal of Pediatrics	Intravenous Paracetamol vs. Intravenous Ibuprofen vs. Surgical Ligation.	101	Preterm infants born between 25 weeks and 31 weeks + 6 days of gestational age.	Closure of the ductus arteriosus after the first treatment course, constriction of the PDA after the first treatment course, PDA closure and constriction rate after the second treatment course, reopening rate, and need for surgical closure 30 days after enrollment.
Ohlsson *et al.* (2020)[18]	Systematic Review	Cochrane	Paracetamol (oral or intravenous) vs. Ibuprofen (oral or intravenous) vs. Indomethacin (oral or intravenous).	916	Preterm infants <37 weeks or Low birth weight (<2500 g) or ECHO with PDA.	Failure to close the PDA after the 1st treatment course, neurodevelopmental impairment, in-hospital deaths, deaths within the first 28 days of life, deaths within the first year of life, reopening of the ductus arteriosus, surgical PDA closure after failure of medical treatment, duration of ventilatory support, pulmonary hemorrhage, pulmonary hypertension, duration of supplemental oxygen requirement, bronchopulmonary dysplasia, intraventricular hemorrhage (grades I–IV), periventricular leukomalacia, necrotizing enterocolitis, intestinal perforation, gastrointestinal bleeding or occult blood in stools, and retinopathy of prematurity.
Farooqui *et al.* (2018)[19]	Systematic Review	Jornal of Neonatal – Perinatal Medicine	Indomethacin vs. Ibuprofen vs. Placebo	466	Preterm infant <32 weeks and weighing less than 1500 g.	Pulmonary hemorrhage, chronic lung disease, intraventricular hemorrhage, feeding intolerance and necrotizing enterocolitis, retinopathy of prematurity, sepsis, and longer duration of hospitalization.

Evans *et al.* (2021)[20]	Systematic Review	Cochrane	Indomethacin	880	Symptomatic preterm infants <37 weeks and weighing less than 2500 g.	Failure of PDA closure, bronchopulmonary dysplasia, deaths, newborns who received medical rescue treatment, newborns requiring surgical ligation, pulmonary hemorrhage, sepsis, necrotizing enterocolitis, intraventricular hemorrhage (grades I–IV), periventricular leukomalacia, retinopathy of prematurity, infant mortality in the first year of life, use of inotropic agents, duration of assisted ventilation, length of hospitalization, intestinal perforation, mucocutaneous or gastrointestinal bleeding, and elevated creatinine.
Oboodi *et al.* (2019)[21]	Randomized Clinical Trial	Turkish Society of Cardiology	Intravenous Paracetamol vs. Oral Ibuprofen vs. Intravenous or Oral Ibuprofen + Oral Paracetamol.	224	Preterm infants <37 weeks of gestational age admitted to the NICU.	Overall PDA closure rate, PDA closure rate after the 1st course, and PDA closure rate after the 2nd course.
Scerbo *et al.* (2020)[22]	Systematic Review with Meta-analysis	NeoReviews	Percutaneous Closure	233	Very low birth weight preterm infants (<1500 g).	Infants with small PDA (<1.5 mm) without clinical sequelae, and infants with large PDA (>1.5 mm) with echocardiographic signs of hemodynamic significance, including pulmonary hypertension or cardiac and pulmonary overload, along with clinical symptoms associated with PDA, including worsening respiratory failure.
Yan *et al.* (2020)[23]	Systematic Review with Meta-analysis	Medicine (Baltimore)	Surgical Ligation	397	Preterm infants <37 weeks or <1500 g with diagnosed PDA.	Deaths, respiratory data (fraction of inspired oxygen at 24 hours postoperatively, days of intubation, and bronchopulmonary dysplasia), nutritional status (full oral feeding and body weight), and postoperative complications (necrotizing enterocolitis, retinopathy of prematurity, acute renal failure, intraventricular hemorrhage grade III or IV, and hospital stay).
Mitra *et al.* (2020)[11]	Systematic Review with Meta-analysis	Cochrane	Early Treatment vs. Expectant Management	910	Preterm infants <37 weeks or low birth weight (<2500 g) with hemodynamically significant PDA.	In-hospital deaths, PDA surgical ligation or transcatheter occlusion, pharmacological treatment for PDA, chronic lung disease, duration of ventilatory support, duration of supplemental oxygen requirement, use of postnatal corticosteroids, length of hospital stay, pneumothorax, intraventricular hemorrhage (grades I–IV), periventricular leukomalacia, necrotizing enterocolitis, spontaneous intestinal perforation, time to achieve full enteral feeding, time to regain birth weight, retinopathy of prematurity, sepsis, oliguria, and neurodevelopmental impairment.

Bell *et al.* (2021)[14]	Randomized Clinical Trial	Open Access	Intravenous Ibuprofen vs. Placebo	730	Preterm infants between 23 and 28 weeks + 6 days of gestational age, less than 72 hours old, with ECHO showing large PDA (>1.5 mm in diameter).	Death by 36 weeks of postmenstrual age or bronchopulmonary dysplasia (moderate or severe) at 36 weeks of postmenstrual age, better health outcomes at 2 years of corrected age including survival without moderate or severe neurodevelopmental impairment, and survival without respiratory morbidity.
Mitra *et al.* (2018)[12]	Systematic Review with Meta-analysis	JAMA	Placebo, Indomethacin (intravenous or oral), Ibuprofen (intravenous or oral), Paracetamol (intravenous or oral), and Surgical Ligation.	4.802	Preterm infants with gestational age less than 37 weeks at birth or infants with low birth weight (<2500 g) who were treated with intravenous or oral formulations of indomethacin, ibuprofen, or paracetamol compared with another drug, placebo, or no treatment for hemodynamically significant PDA diagnosed clinically or by echocardiography during the neonatal period (defined as <28 days of life).	Closure of the ductus arteriosus, surgical closure, mortality, necrotizing enterocolitis, and intraventricular hemorrhage.

The use of paracetamol is associated with fewer renal and gastrointestinal side effects compared with other drugs, thus offering a higher level of safety.[15,18] Some studies report similar treatment efficacy between paracetamol and ibuprofen for PDA closure, along with a reduced need for surgical intervention.[16] They also demonstrate that, due to its comparable constrictive effect and lower rate of adverse events, paracetamol may be considered the first-choice drug for the treatment of hemodynamically significant PDA.[23] Another therapeutic approach evaluated was the combination of paracetamol and ibuprofen, which showed good efficacy for each drug individually but improved effectiveness when used together. However, further studies with larger sample sizes are recommended to confirm these results.[21]

Pharmacological closure of the ductus arteriosus with COX inhibitors (ibuprofen or indomethacin) is effective in preterm infants. Indomethacin reduces the incidence of symptomatic PDA and decreases the duration of supplemental oxygen, but it does not reduce mortality.[19,25] Ibuprofen achieves a high closure rate and is associated with a lower risk of intraventricular hemorrhage (IVH), but likewise does not impact mortality. Nevertheless, there is a failure rate in ductal closure after two courses of COX inhibitors, particularly in low-birth-weight infants.[25]

One study also compared the efficacy of these drugs in terms of neonatal neurodevelopment and found no significant differences in neurodevelopment at 18 to 24 months of life between infants treated with paracetamol or ibuprofen. On the other hand, surgical ligation was associated with worse outcomes in this regard.[15]

Studies on Surgical Treatment

Non-surgical treatment with percutaneous PDA closure in very low birth weight (VLBW) infants is considered in one study as the procedure of choice outside the neonatal period. There is evidence regarding its feasibility, safety, and efficacy; however, no long-term risk-benefit has been identified.[22]

In addition to the percutaneous technique, there is the surgical method of transcatheter closure guided by transthoracic echocardiography (TTE). Although this approach was not part of the sample used in this systematic review, it is relevant to mention the study that evaluated this procedure, using as inclusion criteria a patient weight of ≥8 kg and the presence of clinical symptoms or echocardiographic evidence of cardiac overload, such as left ventricular enlargement. This procedure appeared safe and achieved a success rate comparable to fluoroscopy-guided surgery. That said, it may provide an alternative strategy, avoiding exposure to radiation and the use of contrast agents, although fluoroscopy remains 2% superior to TTE. Findings from the study revealed no deaths, cardiac perforation, pericardial tamponade, tricuspid regurgitation, occluder displacement or deformation, hemolysis, thrombosis, or infectious endocarditis in either group. In 7 cases (4 in the TTE group and 3 in the fluoroscopy group), residual shunts were observed immediately after the procedure, which resolved within 24 hours.[24]

Another technique for PDA closure is early or late surgical ligation, indicated when conservative or pharmacological treatment is contraindicated or fails. Early ligation is preferable for preterm or VLBW infants, as it is associated with better nutritional status and respiratory outcomes. On the other hand, late surgical ligation in very low birth weight preterm infants with hemodynamically significant PDA (hsPDA), where medical treatment has failed or is contraindicated, remains a necessary intervention with evidence of mortality reduction.[23]

DISCUSSION

The analysis of the studies selected in this literature review highlights differences in the choice of treatment for PDA depending on the general condition of the patient, the hemodynamic assessment of the duct, and the newborn's weight and gestational age.

Patients classified as preterm with hemodynamically stable PDA will eventually experience spontaneous closure. The studies showed that the adverse effects caused by early treatment with NSAIDs outweigh the benefits of treatment initiated within the first 7 days of life.

On the other hand, one randomized study demonstrated that extremely low birth weight infants at 36 weeks of gestational age had a lower incidence of death from BPD when randomized to treatment with ibuprofen compared to placebo.

When evaluating treatments in newborns with hsPDA, no significant difference was found between early treatment and expectant management regarding primary outcomes of mortality. However, the findings suggest cautious interpretation and application, since some benefits of early treatment were observed, such as shorter time to achieve full enteral feeding, faster recovery of birth weight, and significantly shorter hospitalization compared with expectant management. Thus, although early treatment does not reduce the overall mortality rate in newborns, it provides a more favorable recovery trajectory.

Intervention should be guided by echocardiographic results, with measurable hemodynamic effects leading to clinical stability. For instance, a 3 mm shunt in an asymptomatic 32-week-old newborn differs markedly from a duct of similar size in a 24-week-old newborn, 2 days old, with hemodynamic instability.

The studies that assessed pharmacological treatment revealed differences among the drugs of choice. Recent results support the use of intravenous paracetamol as the first-line drug for the treatment of hsPDA, since despite having similar efficacy to ibuprofen, it is associated with fewer renal and gastrointestinal adverse effects compared with intravenous indomethacin or oral/intravenous ibuprofen in preterm or low-birth-weight infants.

On the other hand, a randomized study evaluated the use of paracetamol combined with ibuprofen and demonstrated that it was the most effective option compared with either drug used alone. However, larger studies are still needed to confirm this combined therapy approach.

When comparing treatment failure rates, paracetamol and ibuprofen showed similar results, meaning both carry the same risk of requiring surgical intervention. Nevertheless, pharmacological treatment remains the preferred approach before surgery, as it avoids postoperative risks and complications.

In cases where PDA does not resolve with conservative or pharmacological treatment, the decision to proceed with surgical intervention must be made by the medical team. Early ligation is preferable for preterm or very low birth weight (VLBW) infants, as it is associated with better nutritional status and respiratory outcomes. Late surgical ligation in VLBW preterm infants with hemodynamically significant PDA, in whom medical treatment has failed or is contraindicated, remains a necessary option and has been shown to reduce mortality. Therefore, compared with pharmacological treatment, surgical ligation significantly reduced mortality in preterm infants.

Percutaneous closure of the patent ductus arteriosus is considered a safe procedure for PDA closure outside the neonatal period, as it is feasible, effective, and associated with few adverse events. However, the complications of the procedure (vascular injury and device embolization) are greater in device closure compared with surgical ligation. In preterm infants, although percutaneous closure is safe, there is still no conclusive evidence regarding its effectiveness.

CONCLUSION

Thus, we can conclude that in the presence of PDA, treatment should be individualized for each case, taking into

account the clinical condition of the preterm newborn and selecting the best management based on a risk–benefit assessment. In cases of hemodynamic stability, the ideal approach is to begin with conservative treatment; if there is no improvement, pharmacological treatment may be initiated, prioritizing the use of paracetamol due to its lower incidence of side effects compared with other drugs. Finally, if no improvement is observed, surgical treatment should be considered. In cases of severe hemodynamic instability, however, the indications for surgical treatment must be carefully assessed.

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