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SYSTEMATIC REVIEW

# Efficacy of pharmacological treatment for closure of patent ductus arteriosus in preterm infants: a systematic review

## Eficacia del tratamiento farmacológico para el cierre del ductus arterioso persistente en recién nacidos pretérmino: una revisión sistemática

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## ABSTRACT

**Introduction:** patent ductus arteriosus (PDA) represents a relevant clinical problem due to its hemodynamic implications, especially in premature newborns, which has motivated multiple studies on its management. Currently, pharmacological treatment is one way to solve this problem, but there is no clear consensus as to which treatment is the most effective and least risky.
**Objective:** the aim of this study was to find the drug with the highest rate of efficacy in PDA closure and with the least adverse effects.
**Method:** a descriptive systematic review was carried out following PRISMA guidelines. The search was carried out in SCOPUS, PUBMED, SCIELO, COCHRANE and LILACS databases.
**Results:** after applying certain inclusion criteria, we obtained a total of 20 studies, most of which were systematic reviews and cohort studies. Among the studies reviewed, drugs such as indomethacin, ibuprofen, paracetamol and betamethasone have been used, finding that among the first three there is no statistically significant difference in efficacy. Closure rates and adverse effects vary considerably in the different studies, depending on factors such as dose, route of administration and gestational age of the neonate.
**Conclusions:** the studies reviewed show that both ibuprofen and indomethacin have similar efficacy in PDA closure in preterm infants. Indomethacin is associated with higher risks of adverse effects. Acetaminophen appears to be a safe and effective alternative, with a superior safety profile compared to NSAIDs.

**Keywords:** Patent Ductus Arteriosus; Pharmacological Treatment; Prematurity; Efficacy; Adverse Effects.

## RESUMEN

**Introducción:** el ductus arterioso persistente (DAP) representa un problema clínico relevante por sus implicaciones hemodinámicas, especialmente en recién nacidos prematuros, lo que ha motivado múltiples estudios sobre su manejo. Actualmente, el tratamiento farmacológico es una vía para solucionar este problema, pero no hay un consenso claro de que tratamiento es el más eficaz y con menos riesgos.
**Objetivo:** se plantea como objetivo hallar el fármaco con mayores tasas de eficacia de cierre del DAP y con menos efectos adversos.
**Método:** se realizó una revisión sistemática descriptiva siguiendo los lineamientos PRISMA. La búsqueda se llevó a cabo en las bases de datos SCOPUS, PUBMED, SCIELO, COCHRANE y LILACS.
**Resultados:** luego de aplicar ciertos criterios de inclusión obtuvimos un total de 20 estudios, la mayoría fueron revisiones sistemáticas y estudios de cohorte. Dentro de los estudios revisados, se han empleado fármacos como la indometacina, ibuprofeno, paracetamol y betametasona, encontrando que entre los tres primeros no hay una diferencia en su eficacia que haya sido estadísticamente significativa. Las tasas de cierre y los efectos adversos varían considerablemente en los diferentes estudios, dependiendo de factores

como la dosis, la vía de administración y la edad gestacional del neonato.
**Conclusiones:** los estudios revisados muestran que tanto el ibuprofeno como la indometacina tienen una eficacia similar en el cierre DAP en recién nacidos prematuros. La indometacina se asocia con mayores riesgos de efectos adversos. El paracetamol parece ser una alternativa segura y eficaz, con un perfil de seguridad superior en comparación con los AINEs.

**Palabras clave:** Ductus Arterioso Persistente; Tratamiento Farmacológico; Prematuro; Eficacia; Efectos Adversos.

## INTRODUCTION

The ductus arteriosus (DA) is a structure formed in the intrauterine stage that connects the aorta to the pulmonary artery. This communication is vital because during this stage the lungs are filled with fluid and air, preventing them from participating in gas exchange. As a result, all the oxygen used by the fetus comes from the placenta, entering the circulation through the umbilical vein and then passing to the left side of the heart through the foramen ovale (FO) and the ductus arteriosus.[1] After the umbilical cord is clamped, and with the first breaths, the fluid is absorbed from the alveoli, allowing them to fill with air, causing vasodilation in the pulmonary circulation so that blood can reach the alveoli and gas exchange can occur.[2]

This change in fetal-neonatal circulation increases pulmonary arterial blood flow, reducing hypoxia and increasing systemic pressure, while promoting the closure of right-to-left shunts, such as the FO and CA.[3]

In the case of the ductus arteriosus, its postnatal closure occurs in two phases: a functional phase, which occurs between 12 and 24 hours and is characterized by vasoconstriction of the ductus (achieving almost complete closure in 100 % of cases at 72 hours), and an anatomical phase, in which the ductus is transformed into the arterial ligament through fibrosis. Generally, this last phase occurs during the first 2 to 3 weeks of life, although sometimes it can last for months.[4]

In addition, closure of the ductus arteriosus also depends on a decrease in prostaglandin E1 and E2 levels, with E2 being more important due to its ductal vasodilatory potency (400 to 1000 times greater than E1), which is produced in the placenta.[5,6] However, in some newborns, especially premature babies, the ductus arteriosus does not close properly, which is known as patent ductus arteriosus (PDA).[7] This creates a left-to-right shunt, which can lead to complications such as pulmonary edema and left heart failure. In addition, compensatory mechanisms may be activated, such as activation of the sympathetic system and the RAAS, which contribute to myocardial hypertrophy and fluid retention, aggravating volume overload.[8]

Therefore, patent ductus arteriosus represents a significant clinical problem due to its hemodynamic implications, especially in premature newborns, which has led to multiple studies on its management. Currently, drug treatment plays a fundamental role in PA closure, and although there is no consensus on its pharmacological management, it consists mainly of the use of nonsteroidal anti-inflammatory drugs (NSAIDs), which are non-selective inhibitors of the cyclooxygenase (COX) enzyme, responsible for the synthesis of prostaglandins.[9]

Given the above, and considering that in many cases spontaneous closure of the DA does not occur, pharmacological management becomes highly relevant. This highlights the importance of identifying which of these drugs is most effective and safest for promoting PDA closure in this population.

PDA in premature newborns is one of the most common congenital heart anomalies, with an estimated prevalence of 10 % of all congenital heart malformations, ranking third in frequency after ASD and VSD until 2017.[10] Although drug therapy is the mainstay of management of this condition, with NSAIDs being a determining factor,[11] there is no clear consensus on which drugs are most effective and safe in this particular population.

Therefore, this study raises the question: what is the most effective treatment for PDA closure in preterm newborns? To this end, aims to find the drug with the highest PDA closure efficacy rates and the fewest adverse effects.

## METHOD

To develop the following study, a systematic descriptive review of the literature was carried out, following the guidelines established in the PRISMA statement, which has been designed primarily for systematic reviews,[12] ensuring the necessary quality in the systematization of information.

Several search engines were used for the research, using the following databases: SCOPUS, PUBMED, SCIELO, COCHRANE, and LILACS, as they are easily accessible and reliable. In addition, the following search terms were used: “pharmacological treatment,” “drug therapy,” “pharmacotherapy,” “patent ductus arteriosus,” “ductus arteriosus,” “PDA,” “adverse effects,” “side effects,” “complications,” “preterm infants,” “premature infants,” “preterm neonates,” and “premature neonates” were used as search terms, which were formulated by combining the Boolean terms AND and OR.

Search formula: ("pharmacological treatment" OR "drug therapy" OR "pharmacotherapy") AND ("patent ductus arteriosus" OR "ductus arteriosus" OR "PDA") AND ("adverse effects" OR "side effects" OR "complications") AND ("preterm infants" OR "premature infants" OR "preterm neonates" OR "premature neonates").

The following inclusion criteria were established:

1. Study period: 2020–2024.
2. Document type: systematic review, cohort studies, and case-control studies.
3. Language: english, spanish, portuguese.
4. Access: free and/or open.

On the other hand, articles that did not address the study topic and did not meet the aforementioned inclusion criteria were excluded.

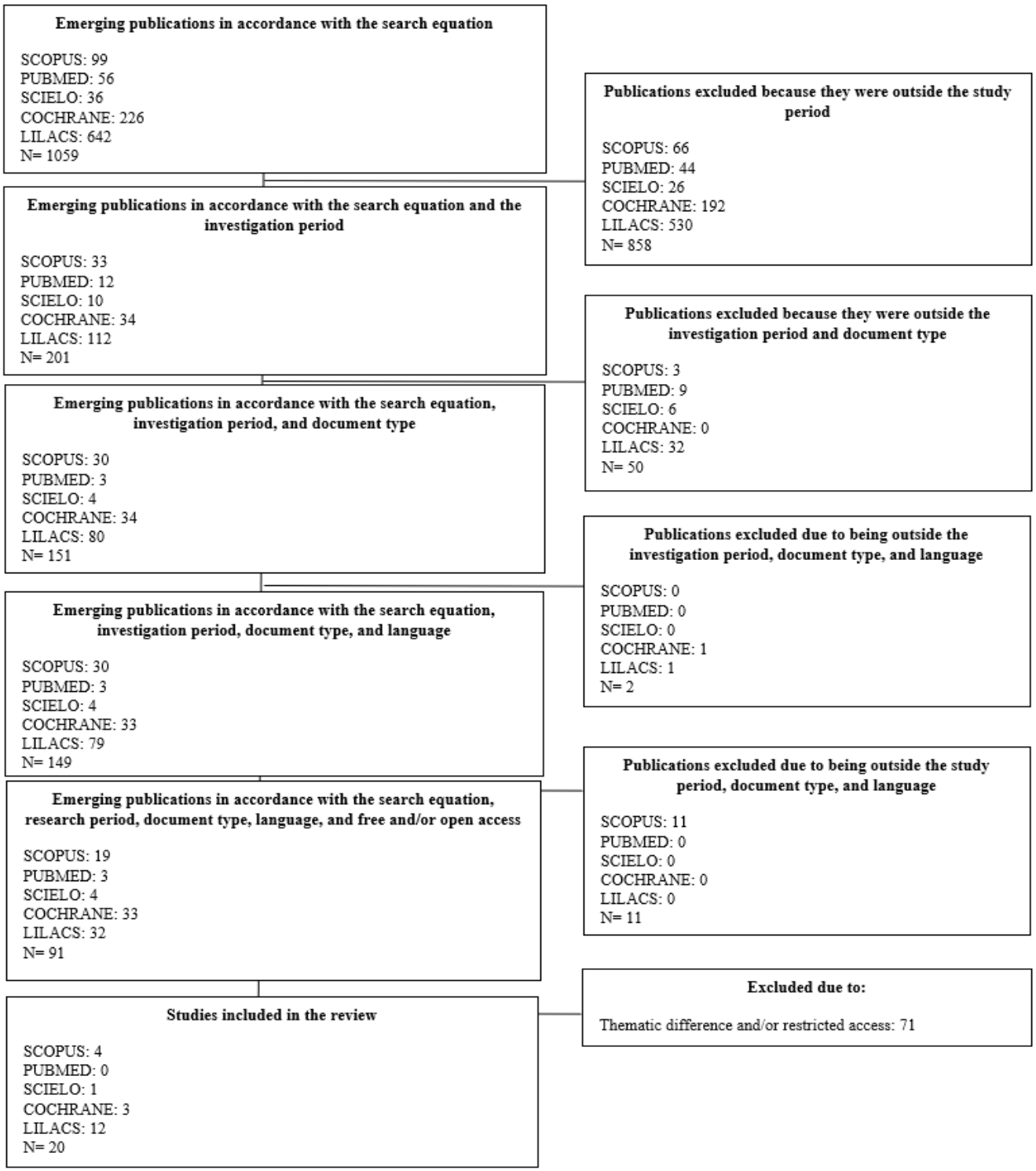


**Figure 1**. PRISMA flow chart of the systematization process

Figure 1 details the search process, initially excluding research outside the study period, then according to document type, language, and finally those with restricted access.

Subsequently, the bibliography was systematically reviewed and selected, detailing: date of publication and author, title of the research, country of origin, and results or findings of these studies.

**Table 1.** Matrix of selected articles

| No. | Author | Title | DOI | Country | Result/finding |
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| 1 | Silva et al.[13] | Therapeutic efficacy and safety of acetaminophen vs. ibuprofen in patent ductus arteriosus in newborns: a systematic review | https://doi.org/10.36660/abc.20240058i | Brazil | In this study, no statistically significant difference was found in terms of PDA closure (p > 0,05) for both drug therapies (paracetamol: 40 % to 81,2 % vs. ibuprofen: 31,8 % to 90,34 %) at standard oral or intravenous doses. However, among the adverse effects, ibuprofen had a higher incidence of ARF, gastrointestinal bleeding, and hyperbilirubinemia compared to paracetamol. |
| 2 | Remy et al.[14] | Late postnatal steroid therapy with oral betamethasone may help close the ductus arteriosus in extremely premature infants who cannot be weaned from ventilation. | https://doi.org/10.1007/s00431-024-05840-9 | France | In this retrospective study, a sample of 51 neonates with a mean GA of 26 weeks dependent on ventilatory support after 3 weeks of life was used. Eighty-eight percent received ibuprofen and/or paracetamol as initial treatment and subsequently received betamethasone treatment. At the end of betamethasone treatment, 98 % of infants had a closed or non-hemodynamically significant ductus arteriosus, which was significantly higher in infants with a GA < 26 weeks at birth compared to those who were ≥ 26 weeks (p = 0,015). However, among the adverse effects, 69 % of neonates treated with betamethasone had transient hypertension and 15 % had hyperglycemia. |
| 3 | Matsumura et al.[15] | Is ibuprofen superior to indomethacin for the treatment of patent ductus arteriosus in Japanese premature infants? | https://doi.org/10.1111/ped.14566 | Japan | This study included 30 patients treated with indomethacin and 30 treated with ibuprofen (26<GA<30), in which no significant difference was found in PDA closure rates in the first treatment cycle (IND vs. IBU: 46,7 % vs. 50,0 %, P = 0,796). On the other hand, there were no significant differences in adverse effects; both groups showed oliguria, elevated serum creatinine levels after treatment, jaundice, and hypoglycemia. However, this elevation in serum creatinine of >0,3 mg/dl, a criterion for acute kidney injury, was less frequent in the ibuprofen group (35,7 %) compared to the indomethacin group (84,2 %), P = 0,004). |

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| 4 | Kimani et al.[16] | Use of combination therapy with acetaminophen and ibuprofen for closure of patent ductus arteriosus in preterm neonates | https://doi.org/10.1093/pch/pxaa057 | Canada | In this cohort study, 140 neonates were analyzed, of whom 17 received combination therapy (ibuprofen and acetaminophen) and 123 received monotherapy (ibuprofen, indomethacin, or acetaminophen). The study found that the rate of ductal closure was not different between combination therapy and monotherapy (P = 0,100). However, it should be noted that indomethacin had the highest rate of PDA closure at 41,7 % and ibuprofen had the lowest at 31,8 %. In addition, combination therapy did not show any increase in adverse h y effects (nephrotoxicity, hepatotoxicity, severe t h r o m b o c y t o p e n i a , spontaneous intestinal perforation, or necrotizing enterocolitis) that are commonly seen with monotherapy. |
| 5 | Mitra et al.[17] | Early treatment versus expectant management of hemodynamically significant patent ductus arteriosus in premature infants. | h t t p s : / / d o i . org/10.1002/14651858.CD013278.pub2 | Canada and United Kingdom | In this systematic review study, early treatment (at seven days of age) and very early treatment (at 72 hours) for patent ductus arteriosus (PDA) were compared with expectant management. Although the study does not directly state the PDA closure rate, it mentions that no significant differences in overall mortality were reported, nor were any relevant adverse effects observed. However, the use of IV indomethacin and IV ibuprofen showed a statistically significant difference between the early treatment and expectant management groups in oliguria in favor of the expectant management group (intravenous indomethacin: typical RR 4,59; 95 % CI 1,39 to 15,2; intravenous ibuprofen: typical RR 39,00; 95 % CI 2,40 to 633,01). |
| 6 | Su BH et al.[18] | Therapeutic strategy for patent ductus arteriosus in extreme preterm infants. | h t t p s : / / d o i . o r g / 1 0 . 1 0 1 6 / j . pedneo.2019.10.002 | Taiwan | This review found that indomethacin and ibuprofen have very similar closure rates (83 % in infants weighing 1000 to 1750 g and 54 % in infants weighing <1000 g). Paracetamol is considered a promising alternative, but there is insufficient evidence for its standard use in PDA closure. On the other hand, although treatment with three cycles of indomethacin shows |

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| | | | | | a closure rate of 90 %, its use is associated with an increased risk of intraventricular hemorrhage, hyponatremia, and transient renal impairment. Ibuprofen can cause pulmonary hypertension and increased levels of free bilirubin. Similarly, paracetamol raises concerns about possible adverse effects on the liver and the possible development of autism or autism spectrum disorders in childhood and language delay. |
| 7 | Al-Shaibi et al.[19] | Cost-effectiveness analysis of ibuprofen versus indomethacin or paracetamol for the treatment of patent ductus arteriosus in preterm infants. | https://doi.org/10.1016/j.cpcardiol.2023.101751 | Qatar | This study evaluated the efficacy of different treatments for patent ductus arteriosus. Oral ibuprofen showed an efficacy of 90,34 %, surpassing intravenous indomethacin, which had an efficacy of 75,46 %. In a direct comparison, ibuprofen had an efficacy rate of 72,56 % compared to intravenous indomethacin. Compared to oral paracetamol, the latter showed an efficacy of 63,27 %, slightly higher than oral ibuprofen (62,58 %). In addition, oral paracetamol was more effective than intravenous ibuprofen (47,06 %). In terms of adverse effects, all three drugs can cause periventricular leukomalacia (PVL), retinopathy of prematurity (ROP), and bronchopulmonary dysplasia (BPD), with no statistically significant differences between them. |
| 8 | Dias Maia et al.[20] | Neonatal acute kidney injury during indomethacin treatment: does it predict ductal closure? | https://doi.org/10.1007/s40620-023-01634-8 | USA | This retrospective cohort study included 150 premature infants; indomethacin achieved 73 % efficacy. Acute kidney injury occurred in 8 % (KDIGO stage 1). The patent ductus arteriosus closed in 52,9 % of the non-acute kidney injury group and in 66,7 % of the acute kidney injury group (p = 0,55). We found no association between acute kidney injury during indomethacin treatment and closure of the patent ductus arteriosus. |
| 9 | Shen X et al.[21] | Oral ibuprofen promotes cholestatic liver disease in very low birth weight infants with patent ductus arteriosus | https://doi.org/10.1016/j.clinre.2020.06.019 | Japan | In this retrospective cohort study, infants with hsPDA treated with ibuprofen (n=64) were compared with untreated infants with PDA (n=58). Although ibuprofen treatment in infants with patent ductus arteriosus showed remarkable efficacy, specific PDA closure |

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| | | | | | rates were not provided. However, they found that ibuprofen treatment was associated with a significant increase in the duration of parenteral nutrition (7 days, P = 0,008) and chronic liver disease (CLD, P = 0,024). It was also associated with early thrombocytopenia (P = 0,004) and late sepsis (P = 0,011). CHD was also influenced by treatment duration (P = 0,030), platelet count (P = 0,013), and antibiotic duration (P = 0,046). |
| 10 | Waldvogel et al.[22] | High-dose indomethacin for closure of patent ductus arteriosus increases neonatal morbidity. | https://doi.org/10.1055/s-0039-3400996 | Switzerland | This retrospective study analyzed 248 premature infants, of whom 196 received standard-dose indomethacin (SDI) and 52 received high-dose indomethacin (HDI). The rate of closure of the patent ductus arteriosus (PDA) was almost identical between the two groups, at 65,3 % for SDI and 65,4 % for HDI. However, when considering the entire population, the PDA closure rate increased from 65,3 % with SDI to 79,0 % with HDI (p < 0,001). In terms of adverse effects, the group receiving HDI showed a higher incidence of gastrointestinal bleeding (32,7 % vs. 11,7 %, p < 0,001), bronchopulmonary dysplasia (78,8 % vs. 55,1 %, p < 0,003), and retinopathy of prematurity (13,5 % vs. 2,6 %, p = 0,004) compared to the SDI group. However, oliguria was less frequent in the HDI group (17,3 % vs. 35,2 %, p = 0,04), and creatinine levels were significantly lower after HDI administration compared with SDI (p < 0,001). |
| 11 | de Klerk et al.[23] | Treatment with ibuprofen after the first days of life in premature neonates with patent ductus arteriosus | https://doi.org/10.1080/14767058.2019.1667323 | Netherlands | In this review, a population of 273 neonates was studied, divided into two groups: group A (207) with a standard dose and group B (66) with a dose proposed based on the neonate's hours of life. Treatment with ibuprofen was 33,2 % and 44,7 % (p = 0,17) in groups A and B, respectively. Adverse effects were reported in 32,9 % of patients in group A and 33,3 % in group B ( ). The most common side effects included gastrointestinal dysfunction (20 % in group A; 27 % in group B), necrotizing enterocolitis (NCE) (7,8 % in group A; 18 % in group B), and |

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| | | | | | onset or worsening of intraventricular hemorrhage (IVH) (4,4 % in group A; 32 % in group B). There were significantly more reversible side effects with postnatal age-adjusted ibuprofen doses (p = 0,04). |
| 12 | Ohlsson A et al.[24] | Ibuprofen for treatment of patent ductus arteriosus in premature or low birth weight infants (or both) | https://doi.org/10.1002/14651858.CD003481.pub8 | Canada and United Kingdom | In this review, intravenous (IV) ibuprofen was found to significantly reduce failure to close the patent ductus arteriosus (PDA) compared to placebo (RR 0,62). No significant differences were observed between ibuprofen (IV or oral) and indomethacin (RR 1,07). However, ibuprofen showed benefits in reducing necrotizing enterocolitis (NEC) (RR 0,68) and oliguria (RR 0,28). Compared with indomethacin, oral ibuprofen also reduced the risk of NEC (RR 0,41) and showed a lower risk of PDA closure failure compared with IV ibuprofen (RR 0,38). In addition, high doses of IV ibuprofen were more effective than standard doses (RR 0,37). |
| 13 | Ohlsson A et al.[25] | Paracetamol (acetaminophen) for patent ductus arteriosus in premature or low birth weight infants | https://doi.org/10.1002/14651858.CD010061.pub4 | Canada | In this review, there was no significant difference in the rate of duct closure between paracetamol and ibuprofen, with a relative risk (RR) of 0,95. Compared with indomethacin, there was also no significant difference in the rate of PDA closure failure (RR 0,96). In addition, prophylactic administration of paracetamol showed a lower rate of ductal closure failure compared to placebo (RR 0,49, P = 0,05). In terms of adverse effects, paracetamol was associated with a lower risk of gastrointestinal bleeding compared to ibuprofen (RR 0,28) and lower serum creatinine and bilirubin levels. Prophylactic treatment with paracetamol showed no significant differences in long-term neurological outcomes (18-24 months). |
| 14 | Nishizaki et al.[26] | Influence of ibuprofen treatment on renal function of patent ductus arteriosus in extremely low birth weight infants. | https://doi.org/10.1111/ped.14057 | Japan | In this case-control study, they found that the primary closure rate was 80 % in the indomethacin group and 67 % in the ibuprofen group (P = 0,49). Regarding adverse effects and/or complications, the incidence of intraventricular hemorrhage (IVH) was 10 % in |

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| | | | | | the indomethacin group and 17 % in the ibuprofen group (P = 0,63), and there were no gastrointestinal complications or hospital mortality in either group. It was observed that uL-FABP levels at 7 days of life were lower in the ibuprofen group compared to the indomethacin group (P = 0,009). |
| 15 | Chen X et al.[27] | Neonatal ibuprofen exposure and bronchopulmonary dysplasia in extremely preterm infants | https://dx.doi.org/10.1038/s41372-019-0444-4 | China | This study analyzed 203 extremely preterm infants and found that 42,8 % received ibuprofen to treat patent ductus arteriosus, achieving a closure rate of 35,6 % (31/87) within 48 hours. On the other hand, the PDA rate was significantly higher in infants with early exposure to ibuprofen (42,5 %) compared to infants without exposure (P = 0,001). In addition, 23 % (20/87) of these infants experienced adverse effects, including food intolerance and gastric complications, within 72 hours of drug administration (p = 0,016). |
| 16 | Luo H et al.[28] | The impact of route of administration on the efficacy and safety of pharmacologic therapy for patent ductus arteriosus in premature infants: a systematic review and meta-analysis | https://dx.doi.org/10.7717/peerj.16591 | China | In this review, 630 premature infants were observed, of whom 480 received ibuprofen (oral vs. intravenous), 78 received paracetamol (oral vs. intravenous), and 72 received ibuprofen (rectal vs. oral). The rate of patent ductus arteriosus (PDA) closure after the first cycle of ibuprofen was 84 % for the group receiving oral ibuprofen (156/186) and 66 % for the group treated intravenously (128/195), showing a significant difference (RR = 1,27; P < 0,0001). However, after the total course of therapy, closure rates were 90 % for oral ibuprofen (200/220) and 79 % for intravenous ibuprofen, with no statistically significant differences. For paracetamol, closure rates were 63 % for the oral group (17/27) and 40 % for the intravenous group (12/30), with no significant differences (RR = 1). When comparing the efficacy of rectal versus oral ibuprofen, closure rates were 86 % for rectal (31/36) and 83 % for oral (30/36; RR = 1,03; P = 0,74). In terms of adverse effects, no significant differences were found in the incidence of serious adverse events (chronic lung disease, retinopathy of prematurity, intraventricular hemorrhage, perforated bowel syndrome, |

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| | | | | | sepsis, gastrointestinal hemorrhage), suggesting that neither ibuprofen nor paracetamol is associated with a significant increase in the frequency of these events. |
| 17 | Zhong B et al.[29] | Early neurodevelopmental outcomes in extremely preterm infants exposed to acetaminophen: a retrospective cohort study. | https://dx.doi.org/10.1038/s41390-023-02649-4 | Australia | In a study involving 242 infants, 123 of whom received paracetamol, exposure to paracetamol was found to show no significant associations with early cerebral palsy (p > 0,05) or abnormal or absent GMA (p > 0,05). No statistically significant relationship was observed for the HINE score (p > 0,05). |
| 18 | Katsaras et al.[30] | Comparative safety and efficacy of acetaminophen vs. nonsteroidal anti-inflammatory agents in neonates with patent ductus arteriosus: a systematic review and meta-analysis of randomized controlled trials | https://doi.org/10.1111/bcp.15291 | Greece | In this review, they show a similar overall PDA closure rate for paracetamol and ibuprofen in most of the studies included, but indomethacin is slightly superior to ibuprofen but not statistically significant (p>0,05). However, in neonates weighing <1000 g, paracetamol showed greater efficacy in the closure rate (RR: 3,50, p = 0,032). In terms of adverse effects, paracetamol was associated with a lower incidence of oliguria (RR: 0,51, p = 0,041) and less renal impairment (RR: 0,27, p = 0,019) than ibuprofen. Indomethacin also presented a higher risk of adverse effects, including renal failure (5,5 % vs. 0,8 % for paracetamol; p=0,019) and gastrointestinal bleeding (8 % vs. 2 % for ibuprofen; p=0,041). |
| 19 | Shah et al.[31] | Efficacy of two-drug therapy (oral acetaminophen and oral ibuprofen) for the treatment of patent ductus arteriosus in extremely premature infants: a feasibility trial | https://doi.org/10.1055/s-0040-1722329 | USA | In this prospective case-control cohort study, of 31 eligible patients, 20 received dual medication therapy with ibuprofen plus paracetamol (DMT), while 11 received standard single intravenous medication therapy with ibuprofen (SMT) with IBU. Fifty-five percent (11/20) of infants in the DMT group were successfully treated for CAP after the first therapy, compared with 36 % (4/11) in the SMT group (p = 0,46). Likewise, a significant reduction in CAP size was observed in the DMT group (adjusted p = 0,0002), but not in the SMT group (adjusted p = 0,414). No significant changes were found in AST (p = 0,821), ALT (p = 0,995), total bilirubin (p = 0,858), or creatinine (p = 0,194) levels between the two groups during treatment. DMT |

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| | | | | | achieved a greater degree of PCA closure than SMT and did not produce abnormalities in the hepatic and renal profile. |
| 20 | Evans et al.[32] | Indomethacin for symptomatic patent ductus arteriosus in preterm neonates | https://doi.org/10.1002/14651858.CD013133.pub2 | USA | In this review, IND showed an average PDA closure rate of 80 %, with rates ranging from 58 % to 100 % in different studies. In terms of adverse effects, the incidence of HIV was 8 % in the IND group versus 10 % in the control group (p = 0,45), and late-onset bacterial sepsis occurred in 6 % of the IND-treated group compared to 7 % in the control group (p = 0,67). On the other hand, no significant differences were observed in neonatal mortality before discharge (RR = 0,78; p = 0,33). |

**Note:** PDA: patent ductus arteriosus, IND: indomethacin, IBU: ibuprofen, AC: acetaminophen, IVH: intraventricular hemorrhage, NEC: necrotizing enterocolitis, ARF: acute renal failure

## DISCUSSION

This systematic review provides a comprehensive framework for evaluating the different treatment options and their clinical implications or adverse effects for the pharmacological treatment of PDA closure in preterm infants. It is necessary to consider the efficacy and safety of the drugs used, which are generally indomethacin, ibuprofen, and paracetamol.

### Molecular mechanisms for PDGVA permeability in fetal life

The PA requires various vasodilator and/or vasoconstriction inhibitor mechanisms to remain permeable during fetal life. Among these mechanisms, prostaglandins stand out, especially prostaglandin E2, which is produced by the placenta and activates prostaglandin E2 receptor four (EP4), which induces membrane hyperpolarization through K efflux, reducing calcium influx and, in turn, its intracellular concentration, resulting in the inhibition of myosin light chain (MLC) phosphorylation and thus the inhibition of vasoconstriction.[6,33]

Another important mechanism is the release of nitric oxide by the endothelium, which binds to guanylate cyclase, leading to the production of cyclic guanosine monophosphate (cGMP) from guanosine triphosphate. cGMP activates cGMP-dependent protein kinase (PKG), which ultimately induces vasodilation.[2,6,34]

Additionally, carbon monoxide (CO) dilates the duct by inhibiting cytochrome P450 3A13, which detects O2, thereby interrupting endothelin-1 signaling and preventing vasoconstriction.[2,35]

### Molecular mechanisms of DA closure

A few hours (12–24) after birth, the functional phase of DA closure begins. Initially, DA vasoconstriction occurs due to a decrease in prostaglandins caused by the absence of placental production and increased PGE2 catabolism in the lungs.[6] Likewise, the increase in O2 saturation shortly after birth is the main trigger of DA vasoconstriction, as it promotes the role of retinoic acid in DA contraction and also stimulates the interaction between endothelial CYP450 and endothelin-1, thereby increasing vasoconstriction.[36]

Finally, there is the anatomical phase, which includes the formation of an intimal cushion, characterized by the disarticulation of the internal elastic lamina, a decrease in elastic fibers in the medial layer, and the proliferation and migration of smooth muscle cells and platelet interaction. This is accompanied by vasoconstriction that occludes the vasa vasorum, decreasing the supply of oxygen and nutrients to the muscular layer, which leads to hypoxia and cell death. After the first 2 to 3 weeks, although sometimes it can last up to 3 months, the DA transforms into the arterial ligament through fibrosis.[4,37]

### Mechanism of action of nonsteroidal anti-inflammatory drugs (NSAIDs)

The main mechanism of NSAIDs is the inhibition of the enzyme cyclooxygenase (COX), which is responsible for the synthesis of prostaglandins from arachidonic acid and other precursor fatty acids.[38]

In the case of ibuprofen (a propionic acid derivative), the dose generally used in the studies reviewed consists of a standard initial dose of 10 mg/kg, followed by two additional doses of 5 mg/kg each, administered at 24-hour intervals, either orally or intravenously (10-5-5 mg/kg regimen).[19,26,27,28,30] However, there were

studies that modified this dose to oral ibuprofen at a dose of 10 mg/kg once a day for 3 consecutive days.[21] Another study considered administering high doses of oral or intravenous ibuprofen (20-10-10 mg/kg/day).[24] Finally, one study used and proposed modified doses according to postnatal age (PNA), following the following 3-dose schedule at 24-hour intervals: PNA<70 hours, 10–5–5 mg/kg; PA 70–108 hours, 14–7–7 mg/kg; and PA 108–180 hours, 20–10–10 mg/kg.[23]

On the other hand, for treatment with indomethacin (derived from acetic acid), a first dose of 0,2 to 0,3 mg/kg intravenously was generally used, followed by two doses of 0,2 to 0,25 mg/kg on successive days.[17,18,20,32] However, the interval between each dose may vary. One study used IV indomethacin at 0,2 mg/kg administered at 12-hour intervals for three doses.[19] Similarly, another study used one or two cycles of intravenous indomethacin, consisting of three doses of indomethacin every 12 hours as a 30-minute infusion, with a first dose of 0,2 mg/kg and the second and third doses of 0,2 mg/kg within the first 7 days of life, or 0,25 mg/kg after the seventh day of life, respectively.[22]

**Mechanism of action of paracetamol**

Unlike the two drugs mentioned above, paracetamol does not directly inhibit cyclooxygenase (COX), but acts by inhibiting the enzyme COX peroxidase (POX). Prostaglandins are synthesized from arachidonic acid through the action of COX, but the intermediate products of this reaction can be unstable and susceptible to oxidation. Peroxidase helps stabilize these intermediates and facilitate their conversion into prostaglandins. Therefore, when inhibited, it will decrease the production of prostaglandins and thus facilitate the closure of the ductus arteriosus.[39]

Within the doses that have been used in treatment with paracetamol, in general, all the studies reviewed used a cycle of intravenous, oral, or rectal acetaminophen at 15 mg/kg at six-hour intervals for three to seven days.[18,19,25,28,29,30]

**Mechanism of action of steroids**

Unlike NSAIDs, glucocorticoids act by inhibiting the release of arachidonic acid from phospholipids through the inhibition of the phospholipase enzyme. This process is reinforced by increased synthesis of lipomodulin (macrocortin), a protein that further inhibits phospholipase, thereby reducing the production of arachidonic acid, a precursor of prostaglandins and leukotrienes. As a result, the synthesis of prostaglandins decreases, including PGE2, which is essential for keeping the ductus arteriosus open; as its levels decrease, the closure of the persistent ductus arteriosus is favored.[40]

In our review, we found a retrospective study that used betamethasone (BTM) at around 21 days of life in extremely premature infants who had previously received a course of ibuprofen or paracetamol. The dose consisted of 6 days of oral administration: 0,3 mg/kg/day for 3 days, 0,15 mg/kg/day for the following 2 days, and 0,05 mg/kg/day on the last day.[14]

**Indomethacin vs Ibuprofen Treatment**

The studies reviewed indicate that indomethacin and ibuprofen have similar PDA closure rates.[16,24] However, some studies mention that indomethacin has a higher closure rate, but without statistical significance.[18,30] In general, indomethacin closure rates vary widely, with studies reporting rates from 41,7 % to 100 %. Some factors that contribute to its effectiveness are: dose, treatment cycles, route of administration, and the weight and gestational age of the newborn.[16,18,19,20,22,32] Similarly, closure rates for ibuprofen vary between 31,8 % and 90 %, depending on the dose, treatment cycles, and route of administration.[16,19,23,26,32]

In terms of adverse effects, the use of indomethacin is associated with an increased risk of intraventricular hemorrhage, hyponatremia, and transient renal impairment.[18] Similarly, another study adds that indomethacin had a higher risk of gastrointestinal bleeding (8 % vs. 2 % for ibuprofen).[30] On the other hand, among the adverse effects of ibuprofen, it was reported that it can cause pulmonary hypertension, increased levels of free bilirubin, and chronic liver disease.[18,21] In addition, treatment with intravenous ibuprofen was associated with a lower incidence of necrotizing enterocolitis (NEC) and oliguria compared to indomethacin.[24] Furthermore, another study showed that elevated serum creatinine (a criterion for acute kidney injury) was less frequent in the ibuprofen group (35,7 %) than in the indomethacin group (84,2 %), p=0,004.[15]

**Treatment with paracetamol vs. indomethacin**

In general, several reviews and studies found no significant differences in PDA closure rates between paracetamol and indomethacin.[16,19,23,32] The efficacy of paracetamol for PDA closure varies from 37,9 % to 81 %.[13,16,19,30,31] In addition, it should be mentioned that, in neonates weighing less than 1000 grams, one study indicates that paracetamol showed greater efficacy in the closure rate compared to indomethacin, and the closure rate increased from 65 % to 79 % when the route of administration was changed from oral to intravenous.[30] These results are similar to those found by a group of researchers in Chile, who mention in their

findings that the ductal closure rate with the first cycle of treatment was 69,4 %, and with the second cycle it increased to 87,1 % in newborns with very low birth weight.[41]

Despite the similarity in efficacy between these two drugs, indomethacin presents greater risks of adverse effects, such as intraventricular hemorrhage, hyponatremia, and transient renal impairment, as mentioned above. However, paracetamol was associated with a lower incidence of oliguria and less renal impairment compared to indomethacin.[32] These findings are questionable when compared to another study that mentions an increase in the incidence of retinopathy of prematurity and acute renal injury after administration of paracetamol therapy.[41] On the other hand, there are concerns about possible hepatotoxicity and the use of paracetamol and the possible development of autism or autism spectrum disorders in childhood and language delay, but the data were inconclusive.[16,18] On the other hand, another study concluded that there were no significant associations between paracetamol exposure and early cerebral palsy or high risk of cerebral palsy diagnosis, abnormal or absent GMA, or HINE score.[29]

**Treatment with paracetamol vs. ibuprofen**

Most studies, as with the previous drugs, found no statistically significant differences in PDD closure rates between paracetamol and ibuprofen, either at standard oral or intravenous doses.[13,25,30] Likewise, this study contrasts with another conducted in Ukraine, reporting that there was no statistically significant difference when comparing the efficacy of these two drugs.[42]

In terms of adverse effects, paracetamol had a lower risk of gastrointestinal bleeding compared to ibuprofen (RR 0,28) and lower serum creatinine and bilirubin levels.[25] It was also associated with a lower incidence of oliguria (RR: 0,51, p=0,041) and less renal impairment (RR: 0,27, p=0,019) than ibuprofen.[30]

**Routes of administration and their efficacy**

Oral ibuprofen appears to be more effective than intravenous ibuprofen in the first cycle of treatment (84 % vs. 66 %). However, after the entire cycle of therapy, the differences are not as significant (90 % vs. 79 %). On the other hand, oral paracetamol also proves to be more effective than intravenous paracetamol in the first cycle of treatment (63 % vs. 40 %). As for rectal and oral ibuprofen, no significant differences were found in terms of the effectiveness of PDA closure.[24,28]

**Combination therapies**

In general, combination therapy with ibuprofen and acetaminophen has not been shown to be significantly superior to monotherapy in terms of CAP closure rate. One study found that closure rates were 41,2 % with combination therapy, compared to 41,7 % with indomethacin, 37,9 % with acetaminophen, and 31,8 % with ibuprofen.[16] In terms of the safety of combination therapy, it does not appear to increase adverse effects compared to monotherapy.[4,16,19,31]

These findings contradict a study conducted by a group of researchers in Canada, who present combination therapy as a novel strategy supported by evidence of safety and feasibility.[43]

**Other treatments**

A retrospective study in France,[14] which included 51 neonates with an average gestational age of 26 weeks, investigated the use of betamethasone in infants who were still dependent on ventilatory support after 3 weeks of life. Eighty-eight percent of these infants had received ibuprofen and/or paracetamol as initial treatment without effective results, so betamethasone was used as an alternative treatment. After this therapy, 98 % of the infants had a closed or non-hemodynamically significant ductus arteriosus. However, we must clarify that the percentage of efficacy was significantly higher in infants with a gestational age of less than 26 weeks at birth, compared to those who were 26 weeks or older (p = 0,015).

On the other hand, this alternative treatment was not without adverse effects, as 69 % of neonates treated with betamethasone had transient hypertension and 15 % had hyperglycemia

## CONCLUSIONS

- Although evidence was shown regarding the efficacy and adverse effects of the drugs studied, the choice of drug should be based on an individualized assessment of the newborn, considering their weight, gestational age, clinical status, and risks associated with each drug.
- Both ibuprofen and indomethacin, non-selective cyclooxygenase (COX) inhibitors, have comparable rates of PDA closure. The variability in success rates (indomethacin: 41,7 %-100 %; ibuprofen: 31,8 %-90 %) suggests that factors such as dose, treatment cycles, route of administration, and gestational age of the newborn influence the results. Paracetamol, a COX peroxidase (POX) inhibitor, shows similar efficacy to NSAIDs in PDH closure, with closure rates ranging from 37,9 % to 81 %. In neonates weighing less than 1000 grams, paracetamol appears to be more effective in PDH closure.

- Indomethacin is associated with an increased risk of adverse effects such as intraventricular hemorrhage (IVH), hyponatremia, transient renal impairment, and gastrointestinal bleeding. The studies reviewed have reported adverse effects such as pulmonary hypertension, increased free bilirubin, and chronic liver disease. However, intravenous ibuprofen appears to reduce the risk of necrotizing enterocolitis (NEC) and oliguria compared to indomethacin. Paracetamol stands out for its favorable safety profile compared to NSAIDs (ibuprofen and indomethacin), presenting a lower risk of adverse effects such as gastrointestinal bleeding, kidney problems, and oliguria.
- Further randomized controlled clinical trials are needed to determine with greater certainty the most effective and safest treatment, as well as to optimize the doses, duration, and routes of administration of the drugs.

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