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Original Article

Pharmacological treatment strategies for neonates with patent ductus arteriosus: a systematic review

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Abstract

Background A hospital-based cancer registry can be used as Background Patent ductus arteriosus (PDA) has a variety of treatment options, ranging from pharmacologic, with nonsteroidal anti-inflammatory drugs (NSAIDs) as first line therapy, to surgical ligation. However, treatment with NSAIDs is associated with severe side effects as well as many contraindications. Paracetamol is a non-classic NSAID with the prospect of fewer side effects compared to other NSAID counterparts.

Objectives To compare the efficacy and safety of paracetamol to ibuprofen or indomethacin for neonates with PDA by systematic review of the literature.

Methods Our literature search was conducted on four databases: PubMed, Scopus, Ovid, and The Cochrane Library, to find studies that compared paracetamol to ibuprofen or indomethacin in neonates with PDA. Articles were selected based on pre-set eligibility criteria. Outcomes extracted from each study included PDA closure rates as well as adverse events rates.

Results Seven randomized controlled trials (RCTs) were included in this study. Five compared paracetamol to ibuprofen and one used indomethacin as a control. The studies were of good quality, with several variations in methodology. All trials reported similar closure rates of paracetamol compared to ibuprofen or indomethacin. Three studies reported similar rates of adverse events, whereas another three reported safety profiles that favoured paracetamol over ibuprofen.

Conclusion Paracetamol has similar efficacy to ibuprofen and indomethacin with regards to rate of PDA closure following a course of treatment. Paracetamol is also reportedly relatively safe in terms of adverse events rates experienced by patients. **[Paediatr Indones. 2019;59:229-36 ; doi: http://dx.doi.org/10.14238/pi59.5.2019.229-36**].

Keywords: *patent ductus arteriosus; congenital heart disease; NSAID; paracetamol; ibuprofen; indomethacin; systematic review*

Patent ductus arteriosus (PDA) is one of the most common congenital heart diseases and refers to the failure of the ductus arteriosus (DA) to close within 72 hours of birth.[1] During gestation, low fetal blood oxygen, with circulating prostaglandins from the metabolism of arachidonic acid by cyclooxygenase (COX), maintains the patency of the DA.[1] Upon birth, the decreased sensitivity of the DA to prostaglandins causes it to constrict, leading to hypoxia, subsequent remodelling of the duct, and eventually permanent closure.[1] For full term infants, PDA closure is typically achieved within the first 72 hours of life.[2] If delayed, the PDA will close in over 95% of healthy infants by 6 months of age.[3]

An open DA causes a left-to-right shunt of blood from the aorta to the pulmonary artery, adding to the load of the pulmonary circulation. This can eventually lead to pulmonary congestion, edema, and respiratory failure.[2] This shunting also steals blood away from the systemic circulation, compromising

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perfusion to organ systems.[2] Consequentially, PDA is associated with numerous adverse events, including prolongation of assisted ventilation, necrotizing enterocolitis, impaired renal function, cerebral palsy, and death.[4] Determinants of PDA closure include sensitivity to oxygen tension, which promotes closure, and prostaglandin E2, which relaxes smooth muscle and maintains patency.[5] Many conditions can modify these determinants, such as low gestational age, which has been associated with decreased sensitivity to oxygen and increased sensitivity to prostaglandin E2. Concurrent infections have also been shown to produce prostaglandins which contribute to late closure.[1,3]

A number of treatment options that have been implemented for PDA involve inhibition of the COX enzyme that produces prostaglandins. These treatments include indomethacin, ibuprofen, and paracetamol.[3,6] Indomethacin is an NSAID that was first introduced to treat PDA due to its potent vasoconstrictor properties. It is also recommended for prophylaxis, but is associated with side effects due to excessive vasoconstriction, such as impaired renal function, white matter damage, and intestinal perforation.[6] Ibuprofen is another NSAID that has milder side effects compared to indomethacin due to its weaker vasoconstrictor capacity. However, both NSAIDs have been implicated in nephrotoxicity due to prostaglandin suppression, which is requisite for neonatal renal adaptation and development.6 In addition, various contraindications for NSAID use, such as hematuria, blood in stool, sepsis, pulmonary hemorrhage, and renal dysfunction, limit the use of these NSAIDs for PDA, leaving physicians with surgical ligation as a last resort.[6]

Recently, paracetamol, a non-classic NSAID, was shown to be safer and associated with fewer side effects compared to the former two medications. One study reported that paracetamol administration was associated with lower urinary PGE2 reduction and incidence of oliguria, indicating less nephrotoxicity.[7] This greater safety profile compared to classical NSAIDs may be attributed to paracetamol's different mechanism of action, which is in the perioxidase region of the COX enzyme.[8] Using an evidence-based case review, we aimed to compare the efficacy and safety of paracetamol to that of ibuprofen and indomethacin in treating PDA.

Methods

In accordance with the aim of this review, we made the following clinical question, "Which drug, among paracetamol, ibuprofen, and indomethacin, is the most effective and safe to induce PDA closure in preterm neonates?" **Table 1** shows the patient, intervention, comparison, and outcome (PICO) framework used in our review.

This systematic review was written according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) guidelines.[9] The literature search was performed on the February 15, 2018, using PubMed, The Cochrane Library, Scopus, and Ovid. The keywords used were "patent ductus arteriosus," "PDA," "neonates," "infants," "children," "paracetamol," "ibuprofen," "indomethacin," and "echocardiography." From PubMed, The Cochrane Library, Scopus, and Ovid, we found 219, 13, 45, and 13 articles, respectively (**Table 2**).

Inclusion criteria included studies that compared the effects of paracetamol in one group of PDA patients, to ibuprofen or indomethacin in another group of PDA patients, by quantifying closure after a course of treatment. Studies that combined treatments, performed studies on adult populations or were in any language than other English or Indonesian were excluded. All study types that fit the inclusion criteria were included.

The selected studies were critically analyzed, by consensus of all authors, using the Critical Appraisal for Randomized Controlled Trials checklist from www.

Table 1. PICO

Patient	Intervention	Comparison	Outcome
Neonate with PDA	Paracetamol	Ibuprofen and/or Indomethacin	Primary: percent of PDA closure after courses of treatment as evaluated by echocardiography Secondary: rate of adverse events
Study type: therapy			

Table 2. Literature search strategy

Database (date)	Applied search keywords	Hits
Pubmed (15/02/2019)	((((((((((patent ductus arteriosus[Title/Abstract]) OR pda[Title/Abstract])) AND (neonates[Title/Abstract]) OR neonate[Title/Abstract]) OR infant[Title/Abstract]) OR infants) OR children))) AND ((((Paracetamol[Title/Abstract]) OR Acetaminophen[Title/Abstract]) AND (Ibuprofen[Title/Abstract]) OR Indomethacin[Title/Abstract]))) AND (echocardio*[Title/Abstract])	219
Cochrane (15/02/2019)	patent ductus arteriosus OR PDA in Title Abstract Keyword AND Echocardiography OR echocardiogram in Title Abstract Keyword AND neonate OR neonates OR infant OR infants OR children in Title Abstract Keyword AND Paracetamol OR Acetaminophen in Title Abstract Keyword AND Ibuprofen OR Indomethacin	13
Scopus (15/02/2019)	patent AND ductus AND arteriosus OR PDA) AND TITLE-ABS-KEY (neonate OR neonates OR infants OR children) AND TITLE-ABS-KEY (paracetamol OR acetaminophen) AND TITLE-ABS-KEY (ibuprofen OR indomethacin) AND TITLE-ABS-KEY (echocardiogram OR echocardiography)	45
Ovid (15/02/2019)	patent AND ductus AND arteriosus OR pda) AND TITLE-ABS-KEY (neonate OR neonates OR infants OR children) AND TITLE-ABS-KEY (paracetamol OR acetaminophen) AND TITLE-ABS-KEY (ibuprofen OR indomethacin) AND TITLE-ABS-KEY (echocardiogram OR echocardiography) patent AND ductus AND arteriosus OR pda) AND TITLE-ABS-KEY (neonate OR neonates OR infants OR children) AND TITLE-ABS-KEY (paracetamol OR acetaminophen) AND TITLE-ABS-KEY (ibuprofen OR indomethacin) AND TITLE-ABS-KEY (echocardiogram OR echocardiography)	13

cebm.net which was developed by Oxford University.[10] The data extracted from each paper included study design, patient characteristics (population criteria, disease, and treatment received), PDA closure after first and second courses of treatment as the primary outcome and adverse events between groups as the secondary outcome. We aimed to compare the rate of PDA closure as a function of treatment course from the evaluated treatments, as well as to review the adverse effects of each treatment, in this systematic review.

Results

A total of 290 articles were found from the four databases. After title and abstract screening, 13 papers were selected for full text review. Subsequently, five duplicates were removed. Full text review yielded 8 viable articles, including 1 article describing a trial that had not been completed, hence, it was excluded. A remaining 7 articles were included in this study (**Figure 1**).

Five studies compared oral paracetamol to oral ibuprofen; one study compared enteral paracetamol to intravenous indomethacin; and one study compared intravenous administrations of paracetamol, ibuprofen, and indomethacin. The studies included were all done in preterm neonates with varying criteria for gestational ages and PDA confirmation. All studies reported the percentage of closed ducts following the first or second course of treatment by a second echocardiogram, as a primary outcome. Associations with adverse events were secondary outcomes. A summary of the studies' designs are compiled in **Table 3**.[8,11-16]

Outcomes from all studies were similar in that paracetamol was equally effective in closing PDA as compared to ibuprofen or indomethacin. Adverse effects observed varied from study to study. The trials by Bagheri *et al.*,[8] Balachander *et al.*,[11] Dang *et al.*,[12] and El-Mashad *et al.*[16] associated paracetamol with less adverse reactions compared to ibuprofen and indomethacin, including hyperbilirubinemia, acute kidney injury, renal dysfunction, thrombocytopenia and gastrointestinal bleeding The other studies demonstrated similar rates of adverse reactions between paracetamol and ibuprofen or indomethacin (**Table 3**).[13-15]

To assess the quality of the selected studies, a critical appraisal tool from Oxford CEBM was used.[10] Overall, the studies appeared to have good quality, with slight variations in attempts at blinding and intention-to-treat analyses. Studies were also relatively recent and had similar designs (**Table 4**).

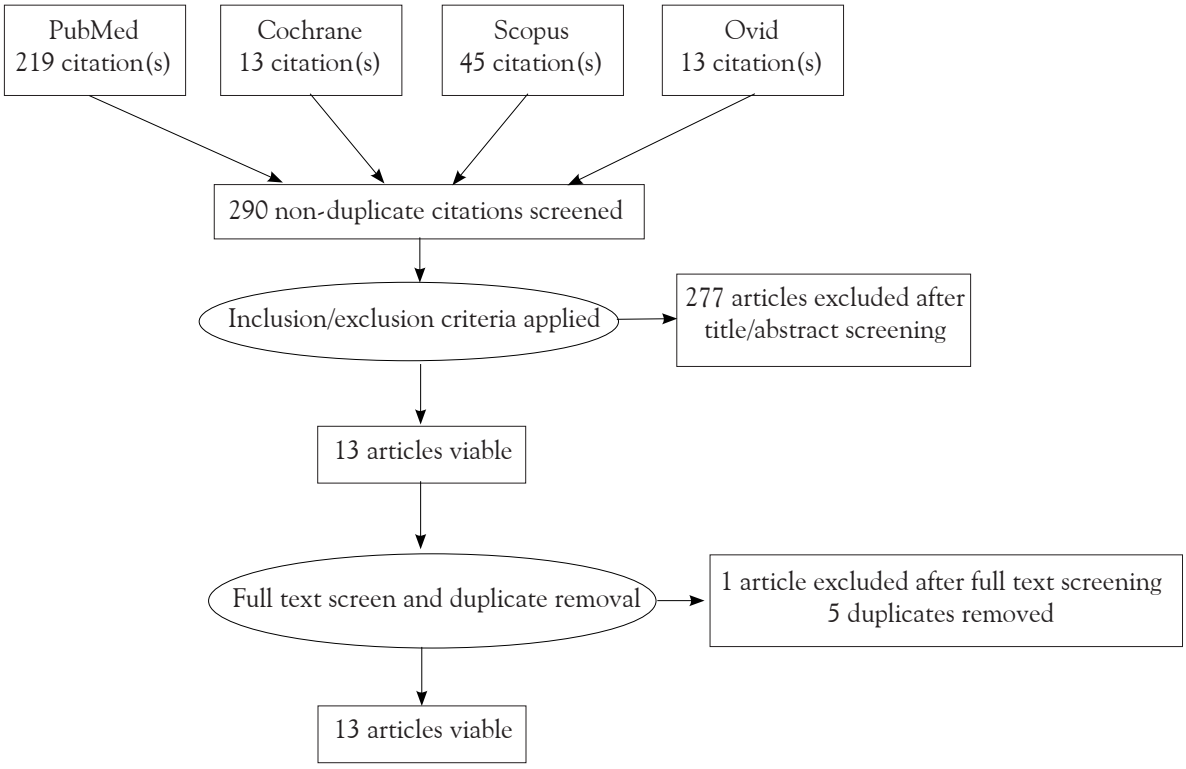

Figure 1. Flowchart of search strategy

Discussion

Congenital heart disease represent one of the most complicated congenital defects in newborns, the most frequent of which is PDA. This congenital heart disease was once associated with poor prognoses, but now has many treatment options ranging from pharmacological therapy with NSAIDs, to surgical ligation. However, the classic NSAIDs used for PDA closure, indomethacin and ibuprofen, are potentially accompanied by detrimental side effects and are also contraindicated in many conditions. Paracetamol, a non-classic NSAID, may serve as an alternative for PDA treatment. In this systematic review, we aimed to compile all relevant evidence to date that directly compared paracetamol efficacy and safety to that of ibuprofen or indomethacin, in achieving PDA closure.

The baseline characteristics of infants in the included studies were preterm infants of gestational age less than 37 weeks, birth weight less than 1,500 g or less than 28 days of life, with ductal-independent PDA, no congenital anomalies, or other clinically concerning conditions. The studies included in this systematic review were all RCTs with a good level of evidence, and published relatively recently (within the past 10 years). Most studies adhered to similar treatment protocols and dosages for drugs used, except for the study by Dash *et al.*[15] which compared intravenous indomethacin with oral paracetamol and El-Mashad *et al.*[16] that compared the three drugs delivered intravenously. A methodological limitation of the studies was the lack of blinding due to the varying dose of one or more drugs. Also, Bagheri *et al.*,[8] did not implement an intention-to-treat analysis, but still retained a drop-out rate of under 20% (14%).

Results from all studies consistently showed that paracetamol was as effective as ibuprofen or indomethacin in closing PDA in preterm infants, with no statistically significant differences between treatment and control groups. This finding held true for the first, second, or even rescue courses of treatment.

Incidence of DA reopening was reported only in studies by Balachander *et al.*,[11] Dang *et al.*[12] and

Table 3. Characteristics of included studies

Author	Patient population	Treatment (intervention and placebo)	Result (% PDA closure)	Conclusion
Bagheri *et al.*[8] (2016)	Preterm neonates (<37 week gestation) with significant PDA	Control: oral ibuprofen 20mg/kg initially, then 10mg/kg after 24 and 48 hours (N=62) Intervention: oral acetaminophen 15mg/kg every 6 hours for 3 days (N=67)	First course: (P= 0.381) • Acetaminophen: 82.1% • Ibuprofen: 75.8% Second course: (P= 0.212) • Acetaminophen: 50% • Ibuprofen: 73.3%	Conclusion: Paracetamol and ibuprofen demonstrated equal efficacy for PDA closure in preterm neonates. Ibuprofen was associated with more adverse effects
Balachander *et al.*[11] (2018)	Preterm neonates with PDA size >1.5mm, with LR shunt after 24 hours of life up to day 28 Control: oral ibuprofen 10mg/kg on day 1 and 5mg/kg 24 hours later (N=55) Intervention: oral paracetamol 15mg/kg every 6 hours for 2 days (N=55) Rescue: an additional course of ibuprofen if the duct failed to close after the first course Stratification: neonates <34 weeks and 34-37 weeks of age		First course: (P=1.00) • Paracetamol: 71.5% • Ibuprofen: 76.4% Rescue course: (P=0.64) • Paracetamol: 18.2% • Ibuprofen: 23.6%	Conclusion: Paracetamol and ibuprofen demonstrated equal efficacy for PDA closure in preterm neonates. Paracetamol was safer and associated with lower risk for acute kidney injury.
Dang *et al.*[12] (2013)	Preterm infants (<34 week gestation), <14 days of age with echocardiographically-confirmed PDA	Control: oral ibuprofen 10mg/kg initially, then 5mg/kg after 24 and 48 hours (N = 80) Intervention: oral paracetamol 15mg/kg every 6 hours for 3 days (N=80)	First course: (P= 0.268) • Paracetamol: 56.3% • Ibuprofen: 47.5% Second course: (P=0.379) • Paracetamol: 25% • Ibuprofen: 31.3%	Conclusion: Paracetamol and ibuprofen demonstrated equal efficacy for PDA closure in preterm neonates. Paracetamol was safer and associated with significantly less hyperbilirubinemia or gastrointestinal bleeding.

Table 3. Characteristics of included studies (continued)

Author	Patient population	Treatment (intervention and placebo)	Result (% PDA closure)	Conclusion
Oncel *et al.*[13] (2014)	Preterm infants (<32 weeks gestation), birthweight <1250g, 48-96 hours of age with echocardiographically- confirmed PDA size >1.5mm		Control: oral ibuprofen 10mg/kg initially, then 5mg/kg after 24 and 48 hours (N=40) Intervention: oral paracetamol 15mg/kg every 6 hours for 3 days (N=40) First course: (P= 0.6) • Paracetamol: 72.5% • Ibuprofen: 77.5% Second course: (P=0.43) • Paracetamol: 27.5% • Ibuprofen: 32.5%	Conclusion: Paracetamol and ibuprofen demonstrated equal efficacy for PDA closure in preterm neonates. Rates of adverse reactions were similar in both groups.
Al-Lawama *et al.*[14] (2017)	Preterm infants (<32 weeks gestation), or birthweight <1500g, with echocardiographically- confirmed, hemodynamically significant PDA	Control: oral ibuprofen 10mg/kg daily for 3 days (N = 9) Intervention: oral paracetamol 10mg/kg every 6 hours for 3 days (N=13)	First course: (P= 0.658) • Paracetamol: 69.2% • Ibuprofen: 77.8% Rescue Course: (P=N/A) • Paracetamol: 23% • Ibuprofen: 11.1%	Conclusion: Paracetamol and ibuprofen demonstrated equal efficacy for PDA closure in preterm neonates. Rates of adverse reactions were similar in both groups
Dash *et al.*[15] (2014)	Preterm infants (<32 weeks gestation), birthweight <1500g, 48-96 hours of age with echocardiographically- confirmed PDA size >1.5mm	Control: intravenous indomethacin 0.2mg/kg daily for 3 days (N = 36) Intervention: enteral paracetamol 15mg/kg every 6 hours for 7 days (N=37)	After treatment: (P= 0.13) • Paracetamol: 100% • Indomethacin: 94.6%	Conclusion: Paracetamol and indomethacin demonstrated equal efficacy for PDA closure in preterm neonates. Neither drug exhibited significantly more adverse reactions, particularly hepatotoxicity.
El-Mashad *et al.*[16] (2016)	Preterm infants (<28 weeks gestation), birthweight <1500g, echocardiographically confirmed PDA	Group 1: paracetamol 15mg/kg IV for 30 mins, followed by 15mg/kg/6hours IV infusion for 3 days (N=100) Group 2: ibuprofen 10mg/kg IV, followed by 5mg/kg/day for 2 days (N=100) Group 3: indomethacin IV 0.2mg/kg for 30 mins for 3 doses at 12-hour intervals (N=100)	First course: (P=0.868) • Paracetamol: 80% • Ibuprofen: 77% • Indomethacin: 81% Second course: (P=0.868) • Paracetamol: 8% • Ibuprofen: 6% • Indomethacin: 6%	Conclusion: Paracetamol, ibuprofen, and indomethacin demonstrated equal efficacy for PDA closure in preterm neonates. Paracetamol was significantly safer with regards to the incidence of gastrointestinal tract bleeding, thrombocytopenia, and renal dysfunction (serum creatinine levels)

N/A: Not available in full text

Table 4. Critical analysis of all studies

Articles	Relevance				Validity							Applicability		
	Domain	Determinant	Outcome	Levels of evidence*	Study design	Number of patients	Randomization	Similarity at baseline	Blinding	Equality outside treatment	Accountability	Applicability to patient	Clinically important outcomes	Benefits > cost?
Bagheri *et al.*[8] (2013)	+	+	+	2	RCT	129	+	+	-	+	-	+	+	+
Balachander *et al.*[13] (2014)	+	+	+	2	RCT	124	+	+	+/-	+	+	+	+	+
Dang *et al.*[12] (2013)	+	+	+	2	RCT	160	+	+	-	+	+	+	+	+
Oncel *et al.*[15] (2014)	+	+	+	2	RCT	80	+	+	+/-	+	+	+	+	+
Al-Lawama *et al.*[14] (2013)	+	+	+	2	RCT	22	+	+	-	+	+	+	+	+
Kumar *et al.*[12] (2014)	+	+	+	2	RCT	73	+	+	-	+	+	+	+	+
El-Mashad *et al.*[16] (2016)	+	+	+	2	P-cohort	300	+	+	+/-	+	+	+	+	+

RCT: Randomized controlled trial; + Clearly stated in the article; - Not done in the article; ? Not clearly stated; * Levels of evidence based on *The Oxford Centre of Evidence Based Medicine 2011*[10] +/- blinding, and no blinding, were done in echocardiography, and drug administration, respectively.

Oncel *et al.*[13] These reopening rates varied between 7-24%, and were similar in both the paracetamol and ibuprofen groups. Of the reopened ducts, a reclosure rate of >60% was observed in all groups that continued treatment, as reported by Dang *et al.*[12] and Oncel *et al.*[13] indicating the possible benefits of extending treatment duration. Dash *et al.*[15] performed the second echocardiographic imaging a full 7 days after administering paracetamol, unlike the other studies, indicating a possibility that spontaneous PDA closure could have taken place prior to that, or may have been due to the additional paracetamol administration. This study was noteworthy in that it was the only study that achieved a 100% closure rate, further supporting the notion that a longer-term paracetamol regimen may be more beneficial for preterm neonates with PDA.

In the studies by Oncel *et al.*,[13] Al-Lawama *et al.*,[14] and Dash *et al.*,[15] paracetamol was associated with a similar rate of adverse reactions as ibuprofen and indomethacin. In contrast, Bagheri *et al.*,[8] Balachander *et al.*,[11] Dang *et al.*,[12] and El-Mashad *et al.*[16] reported the relative safety of paracetamol, in that it was associated with significantly lower rates of various adverse events such as acute kidney injury, thrombocytopenia, hyperbilirubinemia, gastrointestinal bleeding, liver or renal dysfunction, intraventricular haemorrhage, and retinopathy of prematurity. These findings were consistent with previous studies that supported the relative safety of paracetamol as compared to its NSAID counterparts, making paracetamol an even more attractive pharmacologic option to treat neonates with PDA.[10]

In conclusion, given the consistent findings among all seven studies that demonstrated similar efficacy along with the three studies that reported the relative safety of paracetamol compared to ibuprofen and indomethacin, it is safe to conclude that paracetamol is a viable, first-line treatment option for preterm neonates with PDA.

Recommendations

Future studies with similar designs should aim to implement blinding with the use of an opaque covering for syringes, to blind the clinicians involved in caregiving, but that are pre-prepared by unblinded clinicians.[17] Studies should also aim to implement intention-to-treat analyses so as to maintain similar baseline characteristics of the study population. In accordance with the findings of Dash *et al.*,[15] we recommend that the treatment regimen with paracetamol be extended. This extension may potentially reduce the incidence of re-openings or

even preempt them, should they occur during the extended course of treatment.

Conflicts of interest

None declared.

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