



Original Article

The efficacy and safety of oral paracetamol versus oral ibuprofen for patent ductus arteriosus closure in preterm neonates – A systematic review and meta-analysis

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ABSTRACT

Objective: This systematic review and meta-analysis aimed to synthesize the latest evidence on the efficacy and safety of oral acetaminophen compared to oral ibuprofen for patent ductus arteriosus (PDA) in preterm infants.

Methods: We performed a systematic literature search on topics that assesses the use of oral paracetamol compared to oral ibuprofen in preterm neonates diagnosed with PDA from PubMed, EuropePMC, Cochrane Central Database, ScienceDirect, ProQuest, ClinicalTrials.gov, and hand-sampling from potential articles.

Results: There were 1547 subjects from 10 selected studies. Primary closure rate was similar in both groups. Subgroup analysis on studies enrolling neonates with ≤ 30 weeks gestational age showed that ibuprofen was superior (OR 0.52 [0.31, 0.90], I^2 : 0%). On the other hand, paracetamol was superior neonates with ≤ 34 weeks gestational age (OR 1.73 [1.01, 2.94], I^2 : 30%). Reopening rate, surgical closure rate, mortality, intraventricular hemorrhage, and necrotizing enterocolitis were similar in both groups. Rate of renal dysfunction (OR 0.27 [0.10, 0.77], I^2 : 0%) and gastrointestinal bleeding (OR 0.31 [0.11, 0.88], I^2 : 0%) were lower in paracetamol group. Subgroup analysis of randomized controlled studies (RCTs) showed similar results. Meta-regression analysis showed that the primary closure rate was not influenced by gestational age, birth weight, and gender. GRADE demonstrates a low level of certainty for primary closure and mortality. Renal dysfunction and gastrointestinal bleeding have a moderate level of certainty.

Conclusion: There was no significant difference between the efficacy of oral paracetamol and oral ibuprofen. However, the rate of renal dysfunction and gastrointestinal bleeding were higher in oral ibuprofen.

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1. Introduction

Pharmacological intervention in patent ductus arteriosus (PDA) relies on several agents, currently, indomethacin and ibuprofen are the only agents that are approved “on-label” use to promote PDA constriction in infants.¹ Oral ibuprofen has been shown to have comparable or superior in terms of efficacy to intravenous ibuprofen^{2–5} and indomethacin,^{6,7} with a better safety profile.

However, the use of these drugs is not without side-effects, as their mechanism of action relies through their effect on the cyclooxygenase cycle, effectively altering the number of vasoconstrictive substances produced by this cycle. With the strong net vasoconstrictor effect, several side effects might arise including acute or chronic renal failure, proteinuria, impairment of cerebral perfusion and necrotizing enterocolitis.⁸

As a significant portion of PDA occurs in preterm infants who are commonly treated in the ICU, the use of NSAIDs for treating PDA may potentially complicate the course of the treatment due to the fact that these agents interfere with blood coagulation, thus posing the risk of intraventricular hemorrhage in preterm infants or

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causing a protracted course of recovery.¹ Acetaminophen rose as a possibly safer agent to be used in treating PDA as it does not interfere directly with the cyclooxygenase cycle. There are several conflicting studies that showed oral paracetamol or oral ibuprofen is superior compared to one another. This systematic review and meta-analysis aimed to synthesize the latest evidence on the efficacy and safety of oral acetaminophen compared to oral ibuprofen for treating PDA in preterm infants.

2. Methods

2.1. Search strategy

A systematic literature search was performed on topics that evaluate the use of oral paracetamol compared to oral ibuprofen in preterm neonates diagnosed with PDA using the keywords ["paracetamol", "ibuprofen", "patent ductus arteriosus"] and its synonym from inception up until December 2019 through PubMed, EuropePMC, Cochrane Central Database, ScienceDirect, ProQuest, ClinicalTrials.gov, and hand-sampling from potential articles cited by the other studies. The records were then systematically evaluated using inclusion and exclusion criteria. We also perform hand-sampling from references of the included studies. Two researchers (E.Y and R.P) independently performed an initial search, discrepancies were resolved by discussion. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the literature search strategy of studies was presented in Fig. 1.

2.2. Selection criteria

The inclusion criteria for this study are all studies that assess the use of oral paracetamol compared to oral ibuprofen in preterm neonates diagnosed with PDA. We include all related clinical researches/original articles and exclude animal studies, case reports, review articles, and non-English language articles.

2.3. Data extraction

Data extraction and quality assessment were done by two independent authors (R.P and R.V) using standardized extraction form which includes authors, year of publication, study design, inclusion criteria, paracetamol dosing protocol, ibuprofen dosing protocol, sample size, mean gestational age, mean birthweight, proportion of male, postnatal age on diagnosis/treatment, primary closure rate, reopening rate, need for surgical closure, mortality, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), renal dysfunction, hepatic dysfunction, and gastrointestinal bleeding.

The primary outcome was the primary closure rate defined as closure of PDA after the first course of treatment. The secondary outcomes were reopening rate (defined as reopening of PDA after previous closure with administration of paracetamol/ibuprofen), need for surgical closure, mortality, IVH, NEC, renal dysfunction, hepatic dysfunction, and gastrointestinal bleeding.

2.4. Statistical analysis

We used RevMan version 5.3 software (Cochrane Collaboration) and STATA 16.0 (StataCorp LLC, Texas, US) to perform the meta-analysis. We used the Mantel-Haenszel method to calculate the odds ratio (OR) and its 95% confidence interval for a pooled measure of dichotomous data. We primarily used a fixed-effect model for the meta-analysis, and a random-effect model was used in case of heterogeneity. To evaluate heterogeneity across the studies, we used the inconsistency index (I^2) test, which ranges from 0 to 100%.

A value above 50% or $p < 0.10$ indicates statistically significant heterogeneity. Sensitivity analysis was performed if there is a difference in drug protocol. Funnel plot analysis will be performed to assess the risk of publication bias. Small study effect was assessed using a regression-based test (Harbord test) for binary outcomes. All p values were two-tailed with a statistical significance set at 0.05 or below. Meta-regression for the primary closure rate was performed with gestational age, birthweight, and male gender as covariates, one at a time. Cochrane Risk of Bias Assessment tool (Cochrane Collaboration) will be used to assess the risk of bias for RCTs. The certainty of the evidence for RCTs was assessed by using Guideline Development Tool by GRADE pro GDT (McMaster University and Evidence Prime Inc.)

3. Results

3.1. Study selection and characteristics

We found a total of 572 results, and 375 records remained after the removal of duplicates. 349 records were excluded after screening the title/abstracts. After assessing 26 full-text for eligibility, we excluded 16 studies because of the following reasons: 1) single-arm studies ($n = 3$), 2) intravenous route ($n = 8$), 3) comparator was not ibuprofen/paracetamol ($n = 1$), 4) combination treatments ($n = 2$), 5) protocol for clinical trial ($n = 1$), and 6) outcome was on neurodevelopmental only ($n = 1$). We included 10 studies in qualitative synthesis and 10 in meta-analysis [Fig. 1]. 8 studies were randomized controlled trials, and 2 studies were retrospective cohorts. There were a total of 1547 subjects from 10 studies.^{9–18} The studies enrolled neonates ≤ 28 weeks (1 study), ≤ 30 weeks (2 studies), ≤ 32 weeks (2 studies), ≤ 34 weeks (2 studies), and ≤ 37 weeks (3 studies) of gestational age. Birthweights varied across studies. PDA was diagnosed using echocardiography in all studies. The protocol for paracetamol administration was 15 mg/kg every 6 h for 3 days in all but one study, in which 10 mg/kg every 6 h was administered for 3 days. The protocol for ibuprofen administration was 15 mg/kg every 6 h for 3 days except in Bagheri et al who provided 20 mg/kg followed by 10 mg/kg after 24 and 48 h [Table 1].

3.2. Primary closure

Meta-analysis showed that the primary closure rate was similar in both paracetamol and ibuprofen group (OR 1.02 [0.77, 1.35], $p = 0.89$; I^2 :38%, $p = 0.11$) [Fig. 2A] [Table 2]. The primary closure rate was similar in studies enrolling neonates with ≤ 28 weeks, ≤ 32 weeks, and ≤ 37 weeks of gestational age. However, a subgroup analysis on studies enrolling neonates with ≤ 30 weeks of gestational age showed that ibuprofen was superior compared to paracetamol (OR 0.52 [0.31, 0.90], $p = 0.02$; I^2 : 0%, $p = 0.39$). On the other hand, subgroup analysis on ≤ 34 weeks of gestational age demonstrated that paracetamol was superior to ibuprofen (OR 1.73 [1.01, 2.94], $p = 0.04$; I^2 : 30%, $p = 0.23$). Ghaderian et al (≤ 32 weeks) has a similar mean gestational age as Dang et al and El-farrash et al (≤ 34 weeks) study, albeit a lower birthweight when included in the meta-analysis of ≤ 34 weeks subgroup, showed paracetamol is slightly superior to ibuprofen in terms of primary closure rate (OR 1.65 [1.01, 2.71], $p = 0.05$; I^2 : 0%, $p = 0.44$). Subgroup analysis of all studies that enroll patients with ≤ 32 weeks (including ≤ 28 weeks, ≤ 30 weeks, and ≤ 32 weeks) of gestational age showed no significant differences between oral paracetamol and oral ibuprofen (OR 0.67 [0.43, 1.05], $p = 0.08$; I^2 : 0%, $p = 0.42$). On sensitivity analysis by removing Bagheri et al study, which administers a higher dose of ibuprofen, the primary closure rate remains statistically not significant (OR 0.95 [0.71, 1.28], $p = 0.75$; I^2 : 37, $p = 0.12$).

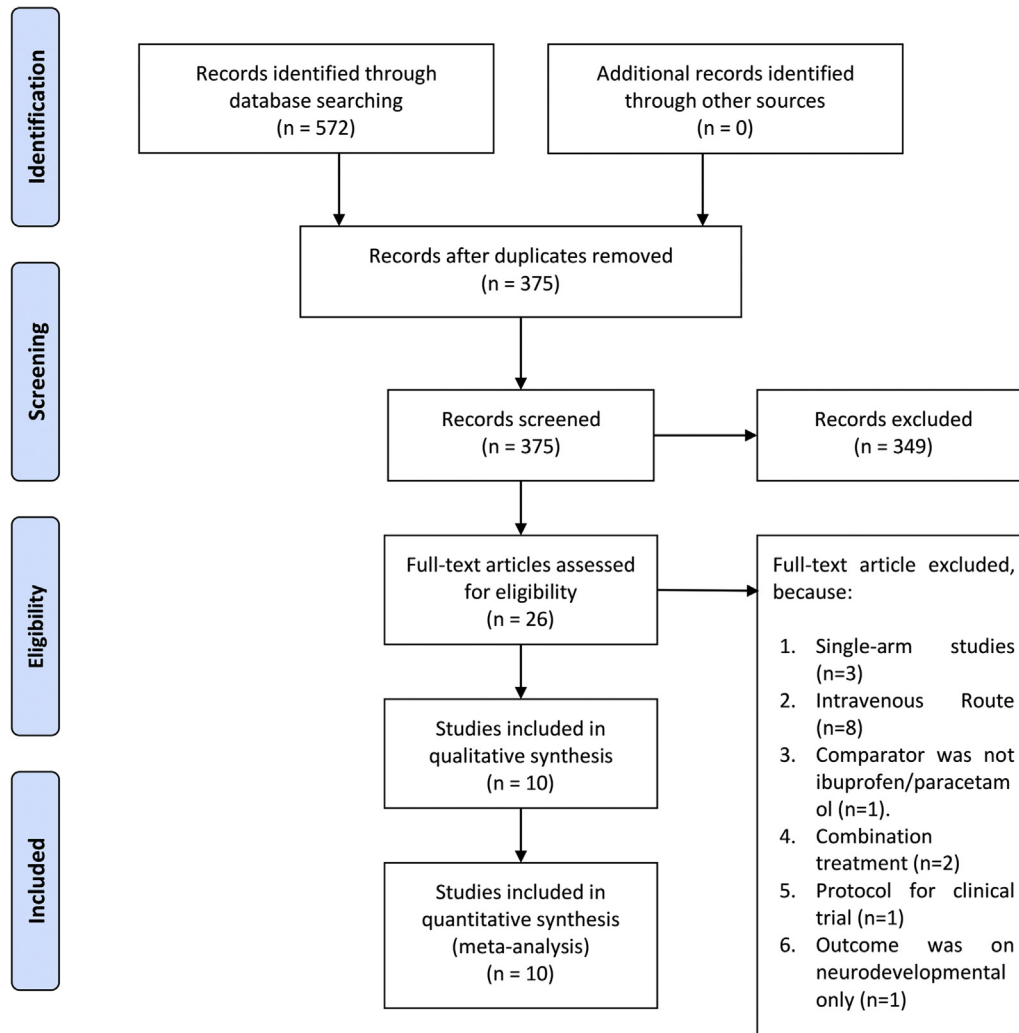


Fig. 1. Study flow diagram.

3.3. Reopening rate and surgical closure rate

The reopening rate was shown to be similar in paracetamol and ibuprofen group (OR 1.16 [0.59, 2.30], $p = 0.67$; $I^2: 0\%$, $p = 0.87$). The need for surgical closure was also similar in both groups (OR 0.42 [0.10, 1.84], $p = 0.25$; $I^2: 0\%$, $p = 0.80$).

3.4. Morbidity and mortality

The rate of mortality was similar in paracetamol and ibuprofen group (OR 1.00 [0.61, 1.63], $p = 1$; $I^2: 0\%$, $p = 0.92$) [Fig. 2B]. The rate of IVH (OR 1.11 [0.65, 1.92], $p = 0.70$; $I^2: 0\%$, $p = 0.80$) and NEC (OR 1.18 [0.62, 2.24], $p = 0.62$; $I^2: 0\%$, $p = 0.90$) were similar in both groups. There were four studies that report the outcome for renal dysfunction, albeit unclear definition, and 2 of them have zero incidences in both groups. The rate of acute renal dysfunction was lower in paracetamol group (OR 0.27 [0.10, 0.77], $p = 0.01$; $I^2: 0\%$, $p = 0.90$) based on 2 assessable studies. Nevertheless, there are 4 studies that reported no significant difference in blood urea nitrogen/creatinine change between paracetamol or ibuprofen group. 4 studies reported no significant difference between aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin between the two groups. However, one study by Dang et al reported a higher incidence of hyperbilirubinemia in the ibuprofen

group. Meta-analysis showed that the rate of gastrointestinal bleeding was lower in paracetamol group (OR 0.31 [0.11, 0.88], $p = 0.03$; $I^2: 0\%$, $p = 0.95$) [Fig. 2C].

3.5. Randomized controlled trials subgroup

The primary closure rate was similar in paracetamol and ibuprofen groups (OR 1.24 [0.89, 1.73], $p = 0.21$; $I^2: 0\%$, $p = 0.48$) [Fig. 2D]. The reopening rate (OR 1.11 [0.52, 2.34], $p = 0.79$; $I^2: 0\%$, $p = 0.73$), mortality (OR 0.93 [0.54, 1.61], $p = 0.79$; $I^2: 0\%$, $p = 0.89$), intraventricular hemorrhage (OR 1.11 [0.61, 2.00], $p = 0.73$; $I^2: 0\%$, $p = 0.67$), and NEC (OR 1.18 [0.62, 2.24], $p = 0.62$; $I^2: 0\%$, $p = 0.90$) were similar in both groups. The rate of acute renal dysfunction (OR 0.27 [0.10, 0.77], $p = 0.01$; $I^2: 0\%$, $p = 0.90$) and gastrointestinal bleeding (OR 0.31 [0.11, 0.88], $p = 0.03$; $I^2: 0\%$, $p = 0.95$) was lower in paracetamol group. On sensitivity analysis by removing Bagheri et al study which administer a higher dose of ibuprofen, the primary closure rate remains statistically not significant (OR 1.16 [0.81, 1.67], $p = 0.41$; $I^2: 0\%$, $p = 0.45$).

3.6. Random-effect meta-regression analysis

A restricted maximum-likelihood random-effect meta-regression analysis was performed for the primary closure rate.

Table 1
Characteristics of studies included in the systematic review.

Authors	Study Design	Inclusion Criteria	Paracetamol Protocol	Ibuprofen Protocol	Sample Size	Gestational Age (weeks)	Birth Weight (grams)	Male (%)	Postnatal Age for dx or tx (days)
Karabulut 2019	Retrospective Cohort	GA \leq 28 weeks with echocardiographically diagnosed PDA	15 mg/kg every 6 h for 3 days	10 mg/kg followed by 5 mg/kg after 24 and 48 h	87 (36/51)	26.78 \pm 1.03 vs 26.37 \pm 1.34	917 \pm 226 vs 934 \pm 255	41.6 vs 43.1	2.02 \pm 0.68 vs 1.87 \pm 0.44
Lu 2019	Retrospective Cohort	GA $<$ 30 weeks, birthweight $<$ 1500 g, and an echocardiographically diagnosed PDA	15 mg/kg every 6 h for 3 days	10 mg/kg followed by 5 mg/kg after 24 and 48 h	170 (83/87)	28.1 \pm 3.6 vs 28.1 \pm 4.1	1160 \pm 253 vs 1195 \pm 183	43.7 vs 49.4	5.0 \pm 1.2 vs 4.9 \pm 2.0
Oncel 2014	RCT	GA \leq 30 weeks, birthweight \leq 1250 g, and postnatal age 48–96 h with echocardiographically diagnosed PDA	15 mg/kg every 6 h for 3 days	10 mg/kg followed by 5 mg/kg after 24 and 48 h	80 (40/40)	27.3 \pm 1.7 vs 27.3 \pm 2.1	931 \pm 217 vs 973 \pm 224	57.5 vs 47.5	N/A
Al-lawama 2018	RCT	GA \leq 32 weeks, birthweight \leq 1500 g, with echocardiographically diagnosed PDA	10 mg/kg every 6 h for 3 days	10 mg/kg followed by 5 mg/kg after 24 and 48 h	22 (13/9)	28 (23–32) vs 28 (25–35)	1059 \pm 386 vs 1192 \pm 269	84.6 vs 66.7	N/A
Ghaderian 2019	RCT	GA \leq 32 weeks, birthweight $<$ 1500 g, postnatal age $<$ 14 days and an echocardiographically diagnosed PDA	15 mg/kg every 6 h for 3 days	10 mg/kg followed by 5 mg/kg after 24 and 48 h	40 (20/20)	30.35 \pm 2.13 vs 30.80 \pm 1.99	1125.78 \pm 200.06 vs 1230.53 \pm 182.1	38 vs 45	N/A
Dang 2013	RCT	GA \leq 34 weeks, birthweight \leq 2500 g, postnatal age \leq 14 days and an echocardiographically diagnosed PDA	15 mg/kg every 6 h for 3 days	10 mg/kg followed by 5 mg/kg after 24 and 48 h	160 (80/80)	31.2 \pm 1.8 vs 30.9 \pm 2.2	1591.96 \pm 348.6 vs 1531.06 \pm 453.5	51.2 vs 52.5	N/A
El-farrash 2018	RCT	GA \leq 34 weeks, postnatal age 2–7 days and an echocardiographically diagnosed PDA	15 mg/kg every 6 h for 3 days	10 mg/kg followed by 5 mg/kg after 24 and 48 h	60 (30/30)	30.53 \pm 1.55 vs 31.73 \pm 1.98	1.53 \pm 0.56 vs 1.74 \pm 0.47	46.7 vs 46.7	6.05 \pm 5.26 vs 7.85 \pm 5.96
Bagheri 2016	RCT	GA $<$ 37 weeks, postnatal age \leq 14 days and an echocardiographically diagnosed PDA	15 mg/kg every 6 h for 3 days	20 mg/kg followed by 10 mg/kg after 24 and 48 h	129 (67/62)	31.53 \pm 2.31 vs 31.7 \pm 2.24	1646.26 \pm 59.14 vs 1642.62 \pm 58.46	53.7 vs 53.2	2.85 \pm 1.28 vs 3.42 \pm 2.12
Balachander 2018	RCT	GA \leq 37 weeks, birthweight \leq 2500 g, postnatal age 1–28 days and an echocardiographically diagnosed PDA	15 mg/kg every 6 h for 3 days	10 mg/kg followed by 5 mg/kg after 24 and 48 h	110 (55/55)	31.58 \pm 2.9 vs 31.54 \pm 2.9	1534.8 \pm 408.2 vs 1513.4 \pm 414.9	43.6 vs 43.6	N/A
Yang 2016	RCT	GA $<$ 37 weeks, postnatal age \leq 10 days and an echocardiographically diagnosed PDA	15 mg/kg every 6 h for 3 days	10 mg/kg followed by 5 mg/kg after 24 and 48 h	87 (44/43)	33.6 \pm 2.1 vs 33.4 \pm 2.1	2219 \pm 606 vs 2091 \pm 657	61.4 vs 58.1	6.4 \pm 1.8 vs 5.8 \pm 2.0

Dx: Diagnosis; GA: Gestational Age; N/A: Not Available/Applicable; PDA: Patent Ductus Arteriosus; RCT: Randomized Controlled Trials; tx: Treatment.

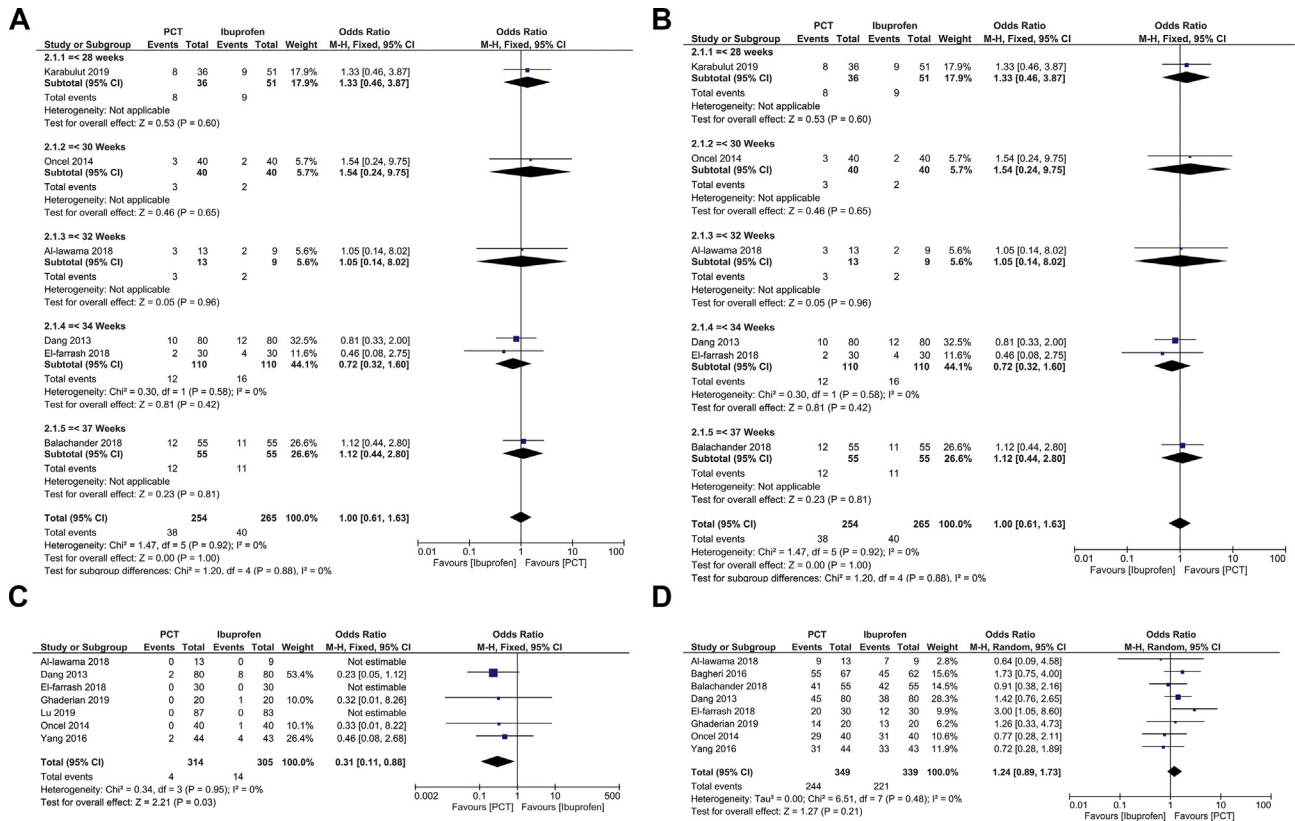


Fig. 2. Primary Closure and Mortality. Meta-analysis showed that there is no difference in primary closure rate between oral PCT and oral ibuprofen, however, subgroup ≤ 30 weeks favours ibuprofen and ≤ 34 weeks favours PCT [Fig. 2A]. Mortality rate was similar in both groups [Fig. 2B]. Gastrointestinal bleeding was more frequent in ibuprofen group [Fig. 2C]. Subgroup analysis on RCTs studies showed no significant difference in terms of primary closure rate between oral PCT and oral ibuprofen [Fig. 2D]. PCT: Paracetamol, RCTs: Randomized Controlled Trials.

Our analyses show that the primary closure rate did not vary significantly with gestational age in weeks ($p = 0.255$; Fig. 3A), birthweight in grams ($p = 0.541$; Fig. 3B), and male gender in percentage ($p = 0.951$; Fig. 3C).

3.7. Publication bias

Cochrane Risk of bias assessment indicates a high risk of performance bias due to different daily dosage, which prohibits adequate blinding for the personnel. There are studies with unclear risk of bias. One study did not blind the outcome assessor and one study did not report mortality but is able to report other complications [Fig. 4A]. Funnel plot analysis was relatively asymmetrical, indicating a risk for publication bias [Fig. 4B]. Regression-based Harbord's test showed that there were no statistically significant small-study effects for primary closure ($p = 0.594$; Fig. 4C), reopening rate ($p = 0.744$), surgical closure ($p = 0.184$), mortality ($p = 0.914$), IVH ($p = 0.420$), and NEC ($p = 0.693$).

3.8. Grading of recommendations assessment, development, and evaluation approach

Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was performed for the RCTs subgroup, and it showed a low level of certainty for the primary closure outcome, its ≤ 34 Weeks Subgroup, and mortality which was due to the risk of bias, the absence of large study effect, and wide confidence interval. Evidence for renal dysfunction and gastrointestinal bleeding has a moderate level of certainty due to the small number of events (Table 3).

4. Discussion

This meta-analysis showed that there was no significant difference in primary closure rate, reopening rate, need for surgical closure, mortality, IVH, and NEC between oral paracetamol and oral ibuprofen. The rate of renal dysfunction and gastrointestinal bleeding seemed to be higher in the ibuprofen group.

The result of this meta-analysis supports the notion of a previously published meta-analysis that paracetamol was as effective as ibuprofen with lower adverse events.¹⁹ The previously published meta-analysis pooled five studies that compare paracetamol and ibuprofen in both oral and intravenous forms.¹⁹ The current meta-analysis only includes the comparison between the oral form of paracetamol and ibuprofen. The current study also performed meta-regression analysis which showed that the primary closure rate did not vary significantly with gestational age in weeks, birth weight in grams, and male gender in percentage; this analysis was not performed in the previous meta-analysis. Furthermore, the current meta-analysis also provides subgroup analysis based on gestational age for oral forms of paracetamol and ibuprofen; which showed different effectiveness of either drug based on gestational age.

A subgroup analysis on ≤ 30 weeks showed that oral ibuprofen was superior compared to paracetamol in terms of primary closure, in contrast to subgroup analysis on ≤ 34 weeks, which demonstrated the superiority of oral paracetamol. The mean gestational age for the ≤ 30 weeks and ≤ 34 weeks was 27.84 ± 3.37 and 31.07 ± 1.96 , respectively. Both of these subgroup analysis was based on two studies and may be insufficient to draw a definite conclusion. In order to boost the number of studies, we observed

Table 2
Summary of meta-analysis.

	Odds Ratio (95% Confidence Interval), <i>p</i> -value	Heterogeneity (<i>I</i> ²), <i>p</i> -value	Regression-Based Harbord's Test	Number of Studies
Primary Closure	1.02 [0.77, 1.35], 0.89	38%, 0.11	0.594	10
Reopening Rate	1.16 [0.59, 2.30], 0.67	0%, 0.87	0.744	5
Surgical Closure	0.42 [0.10, 1.84], 0.25	0%, 0.80	0.184	3
Mortality	1.00 [0.61, 1.63], 1	0%, 0.92	0.914	6
Intraventricular Hemorrhage	1.11 [0.65, 1.92], 0.70	0%, 0.80	0.420	6 (1 with 0 incidence)
NEC	1.16 [0.64, 2.11], 0.63	0%, 0.97	0.693	7 (2 with 0 incidence)
Renal Dysfunction	0.27 [0.10, 0.77], 0.01	0%, 0.90	–	4 (2 with 0 incidence)
Gastrointestinal Bleeding	0.31 [0.11, 0.88], 0.03	0%, 0.95	0.374	7 (3 with 0 incidence)
RCT Subgroup				
Primary Closure	1.24 [0.89, 1.73], 0.21	0%, 0.48	0.502	8
Reopening Rate	1.11 [0.52, 2.34], 0.79	0%, 0.73	0.973	3
Mortality	0.93 [0.54, 1.61], 0.79	0%, 0.89	0.980	5
Intraventricular Hemorrhage	1.11 [0.61, 2.00], 0.73	0%, 0.67	0.494	6 (1 with 0 incidence)
NEC	1.18 [0.62, 2.24], 0.62	0%, 0.90	0.711	5 (1 with 0 incidence)
Renal Dysfunction	0.27 [0.10, 0.77], 0.01	0%, 0.90	–	4 (2 with 0 incidence)
Gastrointestinal Bleeding	0.31 [0.11, 0.88], 0.03	0%, 0.95	0.374	6 (2 with 0 incidence)

NEC: Necrotizing Enterocolitis; RCT: Randomized Controlled Trials.

that Ghaderian et al (≤ 32 weeks) have a similar mean gestational age 30.57 ± 2.05 to ≤ 34 weeks subgroup and when the study is included in the meta-analysis, the result shows that paracetamol was only slightly superior. The analysis for ≤ 30 weeks was weaker because the study design for Lu et al study (≤ 30 weeks) was not RCT. Nevertheless, the finding that either drug was superior might be incidental. Meta-regression also showed that the primary closure was not significantly influenced by gestational age or birthweight, however, it should be noted that meta-regression typically has low power to detect relationships.²⁰

NSAIDs mediates PDA closure by decreasing the number of prostaglandins produced from the cyclooxygenase cycle, and this is achieved by inhibiting the enzyme cyclooxygenase. As the level of prostaglandin decreases, the muscular wall of arteries will constrict, including the one at the ductus arteriosus. Unfortunately, this mechanism is not specific, and the decrease of prostaglandin occurs at a systemic level, which creates potent vasoconstriction across the body, this strong vasoconstriction can cause gastrointestinal bleeding, especially on the stomach lining, and renal failure from the intense afferent vasoconstriction.⁸ It is

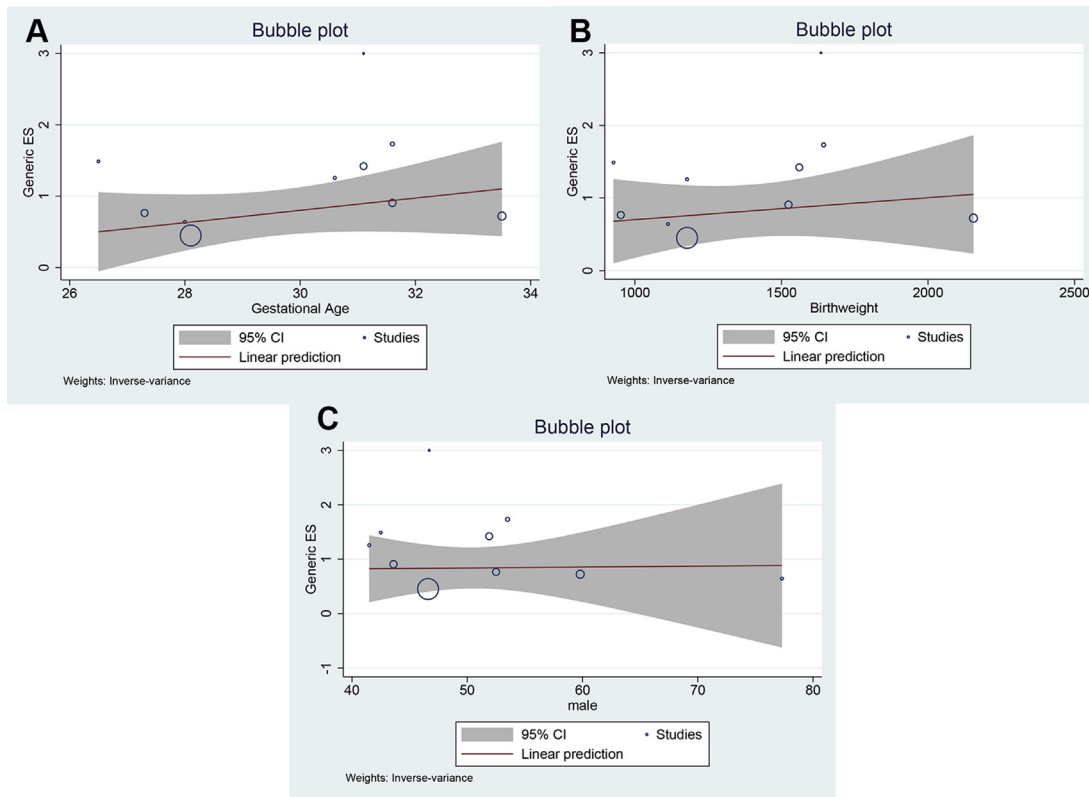


Fig. 3. Meta-regression for Primary Closure. A Restricted maximum-likelihood random-effect meta-regression analysis showed that the primary closure rate did not varies significantly with gestational age in weeks [Fig. 3A], birthweight in grams [Fig. 3B], and male gender in percentage [Fig. 3C]. PCT: Paracetamol.

Table 3
GRADE approach for randomized controlled trials.

Certainty assessment							N ^o of patients		Effect		Certainty	Note
N ^o of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol	Ibuprofen	Relative (95% CI)	Absolute (95% CI)		
Primary Closure												
8	randomised trials	serious ^a	not serious	not serious	serious ^d	None	244/349 (69.9%)	221/339 (65.2%)	OR 1.24 (0.89–1.73)	47 more per 1000 (from 27 fewer to 112 more)	⊕⊕○○ LOW	Funnel-plot for RCT was relatively symmetrical ^e
Mortality												
5	randomised trials	serious ^a	not serious	not serious	serious ^{b, c, d}	None	30/218 (13.8%)	31/214 (14.5%)	OR 0.93 (0.54–1.61)	9 fewer per 1000 (from 61 fewer to 69 more)	⊕⊕○○ LOW	
Primary Closure (≤ 34 Weeks)												
2	randomised trials	serious ^a	not serious	not serious	serious ^{b, c, d}	None	65/110 (59.1%)	50/110 (45.5%)	OR 1.73 (1.01–2.94)	136 more per 1000 (from 2 more to 256 more)	⊕⊕○○ LOW	≤34 Weeks subgroup
Renal Dysfunction												
3	randomised trials	serious ^a	not serious	not serious	serious ^b	strong association	5/165 (3.0%)	16/165 (9.7%)	OR 0.27 (0.10–0.77)	69 fewer per 1000 (from 86 fewer to 21 fewer)	⊕⊕⊕○ MODERATE	
Gastrointestinal Bleeding												
6	randomised trials	serious ^a	not serious	not serious	serious ^b	strong association	4/227 (1.8%)	14/222 (6.3%)	OR 0.31 (0.11–0.88)	43 fewer per 1000 (from 56 fewer to 7 fewer)	⊕⊕⊕○ MODERATE	

CI: Confidence interval; OR: Odds ratio; RCT: Randomized Controlled Trial.

Explanations

^a Blinding of the medical personnel administering drug was not possible due to different dosage and administration. There are studies with unclear risk of bias. One study did not blind the outcome assessor and one study did not report mortality but is able to report other complications.

^b Small number of events

^c Null effect and lower CI of Effect Estimate <0.75.

^d Null effect and upper CI of Effect Estimate >1.25.

^e Funnel plot analysis was asymmetrical.

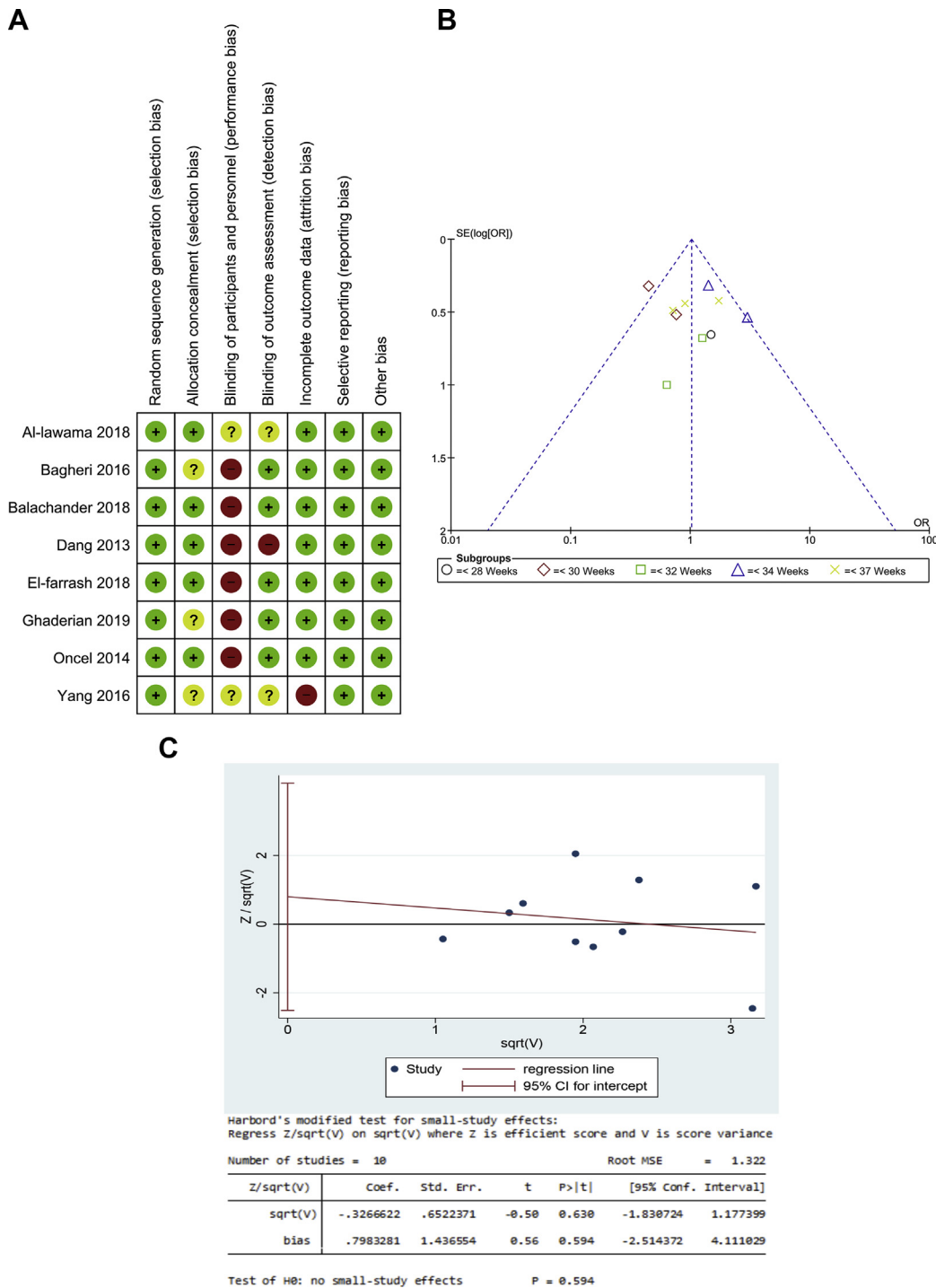


Fig. 4. Publication Bias. The risk of bias assessment was displayed in [Fig. 4A]. Funnel-plot analysis was asymmetrical [Fig. 4B]. Regression-based Harbord's test showed that there were no statistically significant small-study effects for primary closure [Fig. 4C].

important to notice that Ibuprofen, due to a more selective effect on COX-1 compared to indomethacin, poses a reduced risk of side effects, and a less protracted course. Even in the event of renal failure, the use of ibuprofen results in a less severe renal impairment and disruption of microcirculation compared to indomethacin use.⁸ A study by Dani et al showed that paracetamol and ibuprofen treatment of PDA in very preterm infants did not affect cerebral oxygenation, however, resistance index was decreased in ibuprofen group.²¹

There were studies that reported the use of high dose ibuprofen. Lu et al also investigates high dose oral ibuprofen (10 mg/kg/day oral ibuprofen for 3 days), the high dose ibuprofen was shown to have a higher rate of ductal closure compared to standard dose ibuprofen and paracetamol.¹³ High dose ibuprofen was shown to be associated with an increase in bilirubin, however, it was reported to have little clinical significance. Bagheri et al study¹⁷ also reported the use of high dose ibuprofen (an initial dose of 20 mg/kg, followed by 10 mg/kg at 24 and 48 h), the study used a higher initial dose

compared to Lu et al study. The rate of primary closure was similar in ibuprofen and paracetamol group in the aforementioned study, the author of the study recommended paracetamol over ibuprofen due to minimal complications associated with paracetamol. A study by Guimarães et al showed that low dose oral acetaminophen (25 mg/kg initial dose followed by 30 mg/kg/day, for 3–7 days) is an effective replacement if indomethacin or ibuprofen failed or contraindicated.²²

4.1. Clinical implications

This study demonstrated that there was no significant difference in efficacy outcomes of oral paracetamol and oral ibuprofen. The incidence of renal dysfunction and gastrointestinal bleeding was higher in the oral ibuprofen group with a moderate certainty of evidence. The rate of IVH, NEC, and mortality were similar in both groups. Hence, oral paracetamol 15 mg/kg every 6 h for 3 days administered through orogastric tube seemed to be superior in terms of safety close PDA of preterm neonates medically. However, it should be noted that for the safety outcome, the incidence was low and the studies might be underpowered to detect the difference between them.

4.2. Limitations

The limitation of this systematic review and meta-analysis is the possibility of publication bias, as indicated by the asymmetrical funnel plot. The statistical power for subgroup analysis was also limited due to the small study size. The incidence of safety outcomes such as acute renal failure might be insufficient to detect any significant difference between the paracetamol and ibuprofen groups at given sample size. Outcomes such as primary closure and mortality have a null effect and wide confidence interval. For a definite conclusion, further studies with a larger sample size are required. The efficacy and adverse events of different dosages of the paracetamol and ibuprofen also require further study.

5. Conclusion

There was no significant difference between the efficacy of oral paracetamol and oral ibuprofen. However, the rate of renal dysfunction and gastrointestinal bleeding was higher in oral ibuprofen. Large multicenter randomized controlled trials are needed to establish the safety outcome of oral paracetamol versus oral ibuprofen. Furthermore, these studies should perform a subgroup analysis based on the gestational age. This meta-analysis showed that from the current studies, oral paracetamol/ibuprofen might be affected by the gestational age, as evidenced by the abovementioned subgroup analysis. Larger trial needs to confirm or deny these findings.

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Competing interests statement

All authors have none to declare.

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