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Early Prophylactic Paracetamol for Patent Ductus Arteriosus in Preterm Infants: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Patent ductus arteriosus (PDA) remains common in very preterm infants. Paracetamol has emerged as a potential alternative to non-steroidal anti-inflammatory drugs for ductal closure, but the efficacy, safety, and clinical value of prophylactic administration remain uncertain. PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials were searched from database inception through September 2026 for prospective randomized controlled trials comparing early prophylactic acetaminophen/paracetamol with placebo, saline, or no prophylactic therapy in preterm or low-birth-weight infants. The primary outcome was persistent PDA after the initial prophylactic course. Random-effects meta-analysis was used to pool risk ratios (RRs) for dichotomous outcomes and mean differences (MDs) for continuous outcomes, and risk of bias was assessed using Cochrane Risk of Bias 2 (RoB-2). Certainty of evidence was assessed using GRADE (Grading of Recommendations Assessment, Development and Evaluation). Six randomized controlled trials encompassing 1,163 preterm infants were included. Prophylactic paracetamol reduced persistent PDA (RR = 0.43; 95% confidence interval (CI) 0.28 to 0.64; P < 0.0001; I^2 = 65.9%). Rescue PDA treatment did not differ significantly (RR = 0.67; 95% CI 0.45 to 1.00; P = 0.0503; I^2 = 37.7%). Ductal diameter (MD = -0.30 mm; 95% CI -0.50 to -0.11) and left atrial-to-aortic root ratio (MD = -0.07; 95% CI -0.08 to -0.06) were also reduced. No statistically significant differences were observed in surgical PDA closure, mortality, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, retinopathy of prematurity, sepsis, culture-positive sepsis, duration of mechanical ventilation, or length of hospital stay. The primary effect remained directionally and statistically robust in leave-one-out analyses and in the analysis restricted to intravenous/parenteral regimens. Early prophylactic paracetamol accelerates anatomical ductal closure without a demonstrated reduction in subsequent rescue treatment, but the available randomized evidence does not demonstrate improvement in major patient-centered neonatal outcomes. These findings do not support routine universal prophylaxis; adequately powered trials of targeted treatment strategies with long-term safety and neurodevelopmental follow-up are needed.

Categories: Pharmacology, Cardiology, Pediatrics
Keywords: acetaminophen, meta-analysis, paracetamol, patent ductus arteriosus, preterm infants, prophylaxis, randomized controlled trials

Introduction And Background

Patent ductus arteriosus (PDA) remains a frequent and significant cardiovascular complication among very preterm infants [1]. In the setting of substantial left-to-right transductal shunting, prolonged ductal patency has been associated with increased risks of neonatal morbidity and mortality, including bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and severe intraventricular hemorrhage (IVH) [1,2]. Traditional pharmacological approaches have relied predominantly on non-steroidal anti-inflammatory drugs (NSAIDs), such as indomethacin and ibuprofen, which facilitate ductal closure by non-selectively inhibiting cyclooxygenase (COX) enzymes [3]. However, these therapies are frequently complicated by peripheral vasoconstriction, renal impairment, and gastrointestinal adverse events, while prospective trials have shown that prophylactic NSAID administration fails to improve survival without long-term neurosensory impairment [4,5].

Consequently, paracetamol (acetaminophen) has emerged as an alternative therapeutic candidate [6]. Paracetamol acts primarily at the peroxidase catalytic site of prostaglandin endoperoxide H_2 synthase, attenuating prostaglandin synthesis without compromising platelet aggregation or precipitating systemic vasoconstriction [7]. Although paracetamol demonstrates therapeutic efficacy comparable to ibuprofen for

symptomatic PDA [8], evidence supporting early prophylactic administration remains controversial. Recent randomized trials suggest that prophylactic paracetamol accelerates anatomical ductal closure without improving survival free of severe neonatal morbidities, while potentially increasing risks of adverse events such as cholestasis [9]. Accordingly, this systematic review and meta-analysis was conducted to evaluate the efficacy and safety of prophylactic paracetamol in preterm neonates.

Review

Study design and reporting

This systematic review and meta-analysis was reported in accordance with the PRISMA 2020 statement [10]. No verifiable prospective protocol registration number was available. The review was designed to evaluate the efficacy and safety of early prophylactic acetaminophen (paracetamol) for prevention or early closure of PDA in preterm infants, and eligibility was restricted to prospective randomized controlled trials.

Literature search and data collection

A comprehensive literature search was performed in PubMed/MEDLINE, Scopus, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) from database inception through September 2026. The search strategy combined controlled vocabulary and free-text terms related to acetaminophen or paracetamol, PDA, prematurity, and randomized trials. The core search terms included combinations of "acetaminophen," "paracetamol," “patent ductus arteriosus," “ductus arteriosus," "PDA," "preterm," "premature," "neonate," "infant," "newborn," "randomized," "trial," "placebo," and “controlled trial." The complete database-specific search strategies and the number of records retrieved from each electronic database are reported in Supplemental material 1.

All retrieved records were imported into EndNote software (Clarivate, Philadelphia, PA, USA) for deduplication and subsequently uploaded to the Rayyan platform for screening [11]. ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) were searched for completed, ongoing, or unpublished trials, and the reference lists of potentially eligible studies and relevant systematic reviews were screened manually to identify additional eligible trials. No language restriction was applied at the search stage.

Study selection and eligibility criteria

Four reviewers independently screened the titles and abstracts of all retrieved records, followed by full-text assessment of potentially eligible articles. Disagreements were resolved by discussion and consensus, with consultation of an additional reviewer when required.

Studies were eligible if they met the following criteria: (1) prospective randomized controlled trial; (2) preterm infants (<37 weeks’ gestation) and/or low-birth-weight infants; (3) the experimental group received early prophylactic acetaminophen/paracetamol, administered orally or intravenously, before development of clinically treatment-requiring or hemodynamically significant PDA; (4) the comparator group received placebo, saline, or no prophylactic acetaminophen; and (5) at least one prespecified PDA-related efficacy, neonatal morbidity, mortality, respiratory, hospitalization, or safety outcome was reported. Trials in which ductal patency was confirmed by screening echocardiography remained eligible when no ductal-size or hemodynamic-significance threshold was required and treatment was initiated with prophylactic intent.

The exclusion criteria comprised non-randomized or quasi-randomized studies, retrospective studies, single-arm studies, case reports or series, review articles, guidelines, editorials, conference abstracts without adequate extractable data, animal or laboratory studies, and pharmacokinetic-only or non-comparative dose-finding studies. Trials in which acetaminophen was initiated only after established symptomatic or hemodynamically significant PDA were excluded from the primary prophylaxis synthesis, as were head-to-head treatment trials of acetaminophen versus ibuprofen or indomethacin for established PDA unless a separately extractable prophylactic comparison was available. Duplicate or overlapping reports were linked to the same underlying trial and were not double counted.

Data extraction

Data from the original articles and available supplementary materials were extracted to a standardized Google Spreadsheet (Google LLC, Mountain View, CA, USA) by four independent reviewers. Extracted study-level information included first author, publication year, country and clinical setting, study design, randomized and analyzed sample sizes, eligibility criteria, comparator type, treatment duration, follow-up or assessment schedule, and reported study outcomes.

Baseline neonatal characteristics included gestational age, birth weight, sex, five-minute Apgar score, cesarean delivery, premature rupture of membranes, antenatal corticosteroid exposure, preeclampsia, multiple birth or twin status, and surfactant administration when reported. Intervention characteristics included route of acetaminophen administration, loading and maintenance doses, dosing frequency, treatment duration, and postnatal age at treatment initiation. Comparator characteristics and relevant

cointerventions were also extracted.

Dichotomous outcomes were extracted as the number of events and total number of participants in each treatment arm, whereas continuous outcomes were extracted as mean, standard deviation, and total number of participants. Study-specific outcome definitions and assessment time points were recorded, and outcomes were pooled only when the definitions and timing were considered clinically and methodologically comparable.

Outcome measures

The primary efficacy outcome was persistent PDA, corresponding to failure of ductal closure after the initial prophylactic acetaminophen course according to the echocardiographic definition and assessment schedule used in each trial. Secondary PDA-related efficacy outcomes included rescue PDA treatment, surgical PDA closure, ductal diameter, and the left atrial-to-aortic root (LA/Ao) ratio. Ductal diameter and LA/Ao ratio were analyzed as continuous outcomes on their reported scales.

Secondary neonatal and safety outcomes included all-cause mortality, BPD, IVH, NEC, retinopathy of prematurity (ROP), sepsis, culture-positive sepsis, duration of mechanical ventilation, and length of hospital stay. Outcomes were analyzed according to the definitions reported by the individual trials and were kept separate when clinically distinct.

Risk of bias assessment

The risk of bias of the included randomized controlled trials was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool [12], which evaluates five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Studies were categorized as having "low risk of bias," "some concerns," or "high risk of bias" according to domain-level judgments and the overall RoB 2 algorithm.

Statistical analysis

Statistical analyses were conducted using R (version 4.4.2; R Foundation for Statistical Computing, Vienna, Austria). Dichotomous outcomes were summarized using risk ratios (RRs) with corresponding 95% confidence intervals (CIs), whereas continuous outcomes measured on the same scale were summarized using mean differences (MDs) with 95% CIs.

A random-effects model was adopted as the primary method of quantitative synthesis to account for expected clinical and methodological heterogeneity across trials. Mantel-Haenszel random-effects methods were used for binary outcomes, and inverse-variance random-effects methods were used for continuous outcomes. Meta-analysis was undertaken when at least two clinically and methodologically comparable randomized trials reported the same outcome. For trials with zero events in one treatment arm, a continuity correction of 0.5 was applied when required for estimation of the RR; studies with zero events in both groups did not contribute to conventional RR estimates.

Statistical heterogeneity was evaluated using Cochran's Q test, the between-study variance (tau-squared), and the Higgins and Thompson I-squared statistic. A P-value < 0.10 for Cochran's Q was considered evidence of heterogeneity, and an I-squared value > 50% was considered to indicate substantial heterogeneity.

Leave-one-out sensitivity analysis was conducted for the primary outcome by sequentially excluding each study and recalculating the pooled RR, 95% CI, P-value, tau-squared, and I-squared. An additional sensitivity analysis restricted the primary synthesis to trials using intravenous or parenteral acetaminophen.

Prespecified subgroup analyses for the primary outcome were conducted according to treatment duration (⩽3 days vs. ⩾4 days) and comparator type (placebo vs. no-treatment control). Subgroup differences were assessed using the corresponding test for interaction. Meta-regression was not undertaken because the number of studies contributing to the pooled outcomes was insufficient for reliable study-level moderator analysis.

Small-study effects were considered in relation to the number of studies contributing to each outcome. Because fewer than 10 studies were available for all pooled outcomes, conventional funnel-plot asymmetry tests and Egger's regression were not performed. For the primary outcome, asymmetry was explored using a Doi plot and the Luis Furuya-Kanamori (LFK) index as an exploratory assessment. A two-sided P-value < 0.05 was considered statistically significant for pooled treatment-effect estimates and subgroup-specific effects, except for tests of heterogeneity, for which P < 0.10 was considered indicative of heterogeneity.

Certainty of evidence (GRADE)

Certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and

Evaluation (GRADE) framework. Randomized evidence was initially considered high certainty and evaluated across five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias.

Results

Literature Search

The initial comprehensive search yielded 1,641 records: 328 from PubMed, 756 from Scopus, 369 from Web of Science, and 188 from the Cochrane Library. After removal of 576 duplicate records, 1,065 records remained for title and abstract screening. Of these, 1,035 records were excluded, leaving 30 full-text reports for detailed eligibility assessment. All 30 reports were successfully retrieved. Following full-text assessment, 24 reports were excluded because of wrong population or PDA strategy (n = 6), ineligible intervention or comparator (n = 4), non-randomized or otherwise ineligible study design (n = 7), treatment of established symptomatic or hemodynamically significant PDA (n = 5), or duplicate/overlapping reports (n = 2). Ultimately, six randomized controlled trials fulfilled the predefined eligibility criteria and were included in the systematic review and quantitative synthesis. The study-selection process is summarized in the PRISMA 2020 flow diagram (Figure *1*).

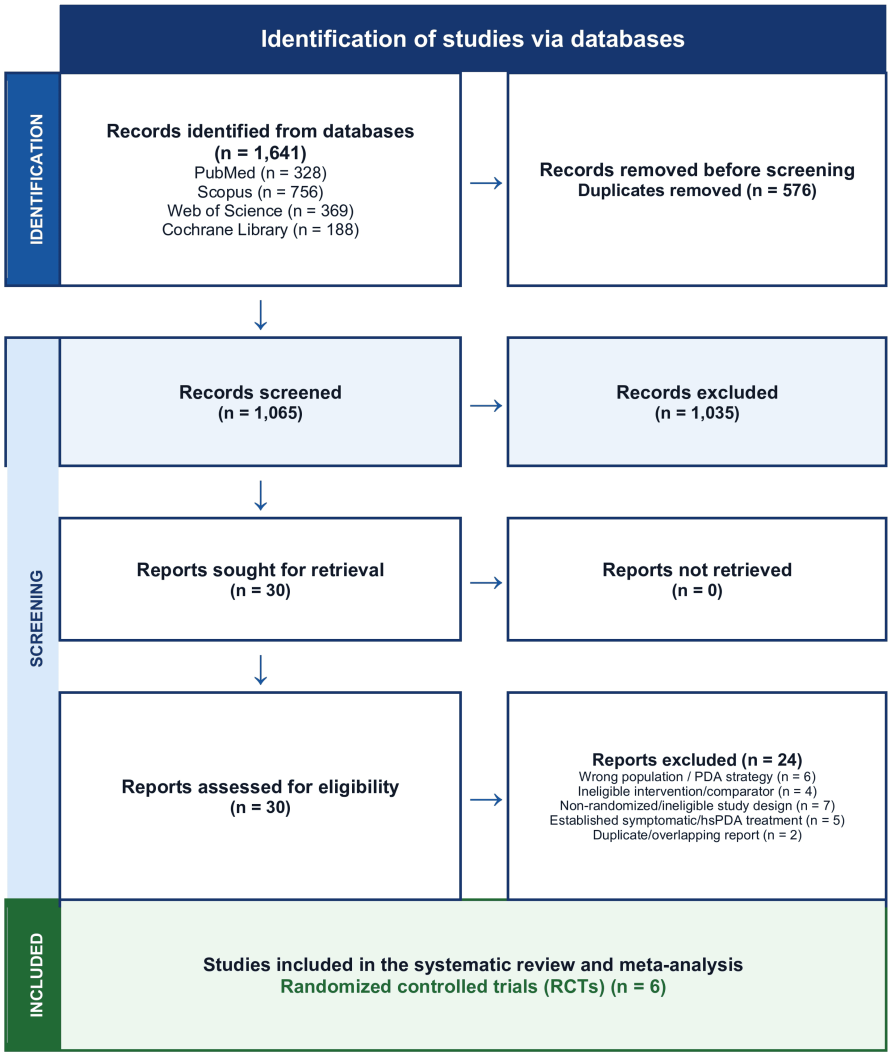


FIGURE 1: PRISMA 2020 flow diagram of the study selection process

PDA: patent ductus arteriosus; hsPDA: hemodynamically significant patent ductus arteriosus

Source: [10]

Characteristics and Risk of Bias Assessment of the Included Studies

The six included randomized controlled trials [9,13-17] were published between 2016 and 2026 and

collectively randomized 1,163 preterm infants. Individual trial sample sizes ranged from 40 to 791 participants. Three trials were conducted in Iran, two were single-center trials conducted in Finland, and the TREOCAPA trial was a multicenter study conducted across 43 neonatal intensive care units in 14 European countries. The enrolled populations consisted of preterm or extremely preterm neonates, although eligibility thresholds varied across trials with respect to gestational age, birth weight, and ductal status at enrollment.

Acetaminophen regimens varied with respect to route, dose, and duration. One trial administered oral acetaminophen, whereas the remaining five trials used intravenous or parenteral acetaminophen. Treatment duration ranged from three to nine days. Three trials used no prophylactic pharmacological treatment as the comparator, whereas three used saline placebo. Detailed study and baseline characteristics are summarized in Tables *1*, *2*.

Study ID	Study design	Country/setting	Population	Total randomized	Intervention (dose, route, & timing)	Comparator	Primary outcome(s)	Follow-up/assessment	Key result	Conclusion
Asadpour et al., 2021	Randomized clinical trial; double-blind; computerized randomization; single-center	Iran; Hajar Hospital, Shahrekord	Preterm infants < 31 wk; symptomatic PDA requiring ibuprofen and major congenital/cardiopulmonary conditions excluded	64	Oral acetaminophen 10 mg/kg every 6 h for 5 d	No prophylactic treatment	PDA closure; ALT/AST safety	Echo and liver enzymes at day 10; persistent PDA reassessed at 1 mo after rescue ibuprofen	Closure 84.4% vs. 50.0% (P = 0.007); persistent PDA 15.6% vs. 50.0%; no clinically significant liver toxicity	Improved early PDA closure without evident hepatic toxicity
Bagheri et al., 2018	Randomized double-masked clinical trial; balanced block randomization; single-center	Iran; Afzalipour Tertiary Medical Center/NICU, Kerman	Preterm neonates ≤ 34 wk; major cardiac anomalies, PPHN, severe asphyxia, and hepatic failure excluded	160	Parenteral paracetamol: 20 mg/kg loading, then 7.5 mg/kg every 6 h for first 3 postnatal d	No prophylactic drug	PDA incidence by echocardiography at day 4	Echo at day 4; daily liver function tests during first 3 d	PDA 15.0% vs. 71.25% (P < 0.001); no significant difference in ventilator days, mortality, or shortening fraction; no hepatic complications	Prophylactic parenteral paracetamol reduced PDA incidence without observed hepatic toxicity
Farhat et al., 2023	Randomized clinical trial; single-blind; sealed-envelope allocation; single-center	Iran; Imam Reza Hospital NICU, Mashhad	Preterm neonates < 30 wk and birth weight < 1,500 g	60	Parenteral acetaminophen 10 mg/kg every 6 h for 3 d, starting 12 h after birth	No placebo; no preventive medication unless symptomatic PDA developed	Ductal closure and echocardiographic ductal parameters	Daily clinical exams; echocardiography after prophylaxis and on day 14	Closure: 33.3% vs. 26.7% at early assessment and 63.0% vs. 41.4% at day 14 (both P = 0.106); no significant differences in secondary outcomes	Numerically greater PDA closure with acetaminophen, without a statistically significant overall difference
Härkin et al., 2016 (PreParaS)	Randomized, double-blind, placebo-controlled phase I-II trial; single-center	Finland; Oulu University Hospital NICU	Very low gestational age infants < 32 wk requiring intensive care within 24 h of birth	48	IV paracetamol: 20 mg/kg loading within 24 h, then 7.5 mg/kg every 6 h for 4 d	0.45% NaCl placebo	Ductal caliber decrease and closure without adverse effects	Daily echo through 1 d after treatment, then 1-2 times weekly until discharge; safety monitoring	Earlier closure with paracetamol (HR 0.49, 95% CI 0.25-0.97; P = 0.016); mean closure age 177 vs. 338 h; no detectable drug-related adverse effects	Prophylactic IV paracetamol accelerated ductal closure without detectable adverse effects
Rozé et al., 2026 (TREOCAPA)	Multicenter, double-blind, randomized, placebo-controlled phase 3 superiority trial	14 European countries; 43 NICUs	Preterm infants 23 + 0 to 28 + 6 wk, enrolled within 12 h after birth	791	IV acetaminophen for 5 d starting <12 h: 20 mg/kg loading + 7.5 mg/kg every 6 h (27-28 wk) or 25 mg/kg + 10 mg/kg every 6 h (23-26 wk)	0.9% isotonic sodium chloride placebo	Survival without severe neonatal morbidity at 36 wk PMA	Primary outcome at 36 wk PMA; day-7 echo; safety monitoring to 40 wk PMA	Survival without severe morbidity 66.2% vs. 63.6% (RR 1.04, 95% CI 0.94-1.16); day-7 closure 71.2% vs. 52.2% (RR 1.36, 95% CI 1.21-1.53); cholestasis 6.4% vs. 2.6%	Accelerated ductal closure but did not improve survival without severe morbidity and increased cholestasis
Ukkonen et	Randomized, double-blind, placebo-	Finland; Oulu	ELGA infants < 28 wk and/or birth weight < 1,000 g; ductal patency confirmed by pre-		IV paracetamol: 20 mg/kg loading, then 7.5 mg/kg every 6 h	0.45% saline	Time to ductal	Daily cardiac ultrasound until 1 d after ductal closure or final	Median closure time 3 (IQR 10) vs. 14 (20) d (P = 0.031);	Prolonged low-dose IV paracetamol accelerated

al., 2026	controlled phase II pilot trial; single-center	University Hospital NICU	randomization cardiac ultrasound; no ductal size or hemodynamic-significance criterion	40	for 9 d; treatment started before 96 h (median ~22 h)	placebo	closure	study dose; neonatal outcomes through hospital discharge	closure during study 75% vs. 37% (P = 0.016); HR 2.69 (95% CI 1.09-6.68)	ductal closure without a significant increase in adverse events

TABLE 1: Characteristics of the included randomized controlled trials

ALT: alanine aminotransferase; AST: aspartate aminotransferase; HR: hazard ratio; IV: intravenous; NICU: neonatal intensive care unit; PDA: patent ductus arteriosus; PMA: postmenstrual age; PPHN: persistent pulmonary hypertension of the newborn; RR: risk ratio; CI: confidence interval; ELGA: extremely low gestational age; IQR: interquartile range

Source studies: Asadpour et al. [13], Bagheri et al. [14], Farhat et al. [15], Härkin et al. [16], Rozé et al. [9], and Ukkonen et al. [17]

Study information			**Neonatal characteristics**				**Maternal/obstetric characteristics**					**Early respiratory characteristics**
Study ID	Arm	Sample size	Gestational age (weeks), mean (SD)	Birth weight (g), mean (SD)	Male, n (%)	Apgar score at 5 min, mean (SD)	Cesarean delivery, n (%)	Premature rupture of membranes, n (%)	Antenatal corticosteroids, n (%)	Preeclampsia, n (%)	Multiple birth/twins, n (%)	Surfactant administration, n (%)
Asadpour et al., 2021	Oral acetaminophen	32	29.41 (1.24)	NA	NA	NA	NA	NA	NA	NA	NA	NA
	Control	32	29.41 (1.24)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Bagheri et al., 2018	IV paracetamol	80	30.36 (1.19)	1,400.31 (217.77)	NA	NA	NA	NA	NA	NA	NA	NA
	Control	80	30.38 (1.44)	1,355.25 (245.92)	NA	NA	NA	NA	NA	NA	NA	NA
Farhat et al., 2023	IV acetaminophen	30	28.3 (0.987)	1,167.5 (181.2)	18 (60)	7.96 (0.927)	24 (80)	8 (26.7)	NA	5 (16.7)	NA	NA
	Control	30	28.26 (1)	1,086.66 (213.9)	19 (63.3)	7.40 (1.19)	25 (83.3)	7 (23.3)	NA	4 (13.3)	NA	NA
Härkin et al., 2016 (PreParaS)	IV paracetamol	23	28.4 (2.36)	1,220 (430)	13 (57)	7.00 (1.11)	15 (65)	10 (43)	20 (87)	NA	7 (30)	16 (70)
	Placebo	25	28.3 (2.06)	1,120 (340)	14 (56)	6.25 (1.30)	10 (40)	6 (24)	25 (100)	NA	10 (40)	22 (88)
Rozé et al., 2026 (TREOCAPA)	IV acetaminophen	391	26.3 (1.4)	855.83 (242.59)	209 (53.5)	7.67 (2.22)	261 (66.8)	122 (32.3)	366 (93.6)	77 (19.9)	95 (24.3)	160 (41.3)
	Placebo	387	26.2 (1.4)	851.83 (231.48)	194 (50.1)	8.00 (1.48)	249 (64.3)	131 (34.5)	365 (94.8)	70 (18.1)	98 (25.3)	166 (43.3)
Ukkonen et al., 2026	IV paracetamol	20	25.9 (1.7)	786 (209)	11 (55)	6 (4)	16 (80)	2 (10)	19 (95)	NA	1 (5)	NA
	Placebo	20	25.8 (1.9)	764 (197)	12 (60)	6 (2)	16 (80)	1 (5)	20 (100)	NA	2 (10)	NA

TABLE 2: Baseline characteristics of included randomized trials

Values are presented as mean (SD) or n (%), as applicable.

NA: not reported; IV: intravenous; SD: standard deviation

Source studies: Asadpour et al. [13], Bagheri et al. [14], Farhat et al. [15], Härkin et al. [16], Rozé et al. [9], and Ukkonen et al. [17]

The Cochrane RoB 2 assessment classified five trials as having some concerns overall (Asadpour et al., Bagheri et al., Farhat et al., Härkin et al., and Ukkonen et al.) and the Rozé et al. (TREOCAPA) trial as low risk overall. Some concerns arose in the randomization-process domain for Asadpour et al., Bagheri et al., Farhat et al., and Ukkonen et al., and in selection of the reported result for Härkin et al.; all other displayed domain judgments were low risk. No trial was judged high risk overall (Figure 2).

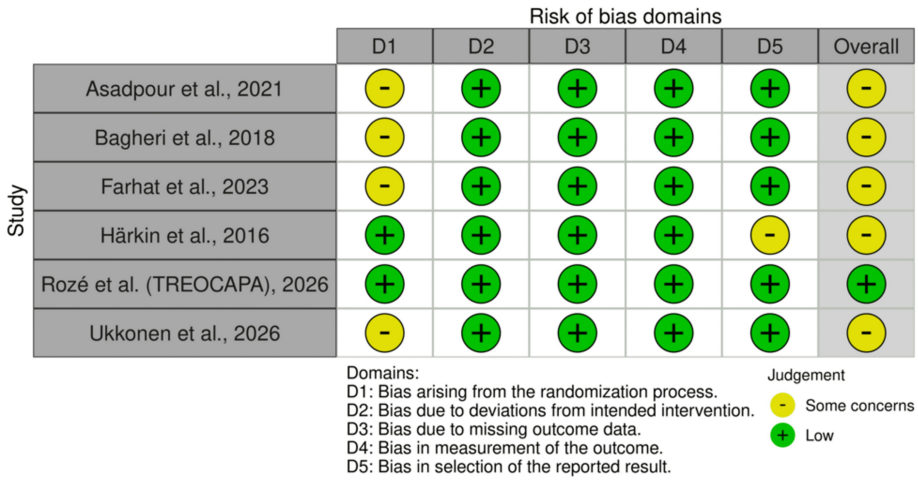


FIGURE 2: Risk-of-bias assessment of the six included randomized controlled trials using the Cochrane Risk of Bias 2 (RoB 2) tool

Source: [9,13-17]

Primary Effectiveness: Persistent PDA

Six studies contributed to the primary analysis of persistent PDA. The pooled random-effects estimate demonstrated a significantly lower risk of persistent PDA with acetaminophen compared with control (RR = 0.43; 95% CI (0.28 to 0.64); P < 0.0001; I^2 = 65.9%) (Figure 3).

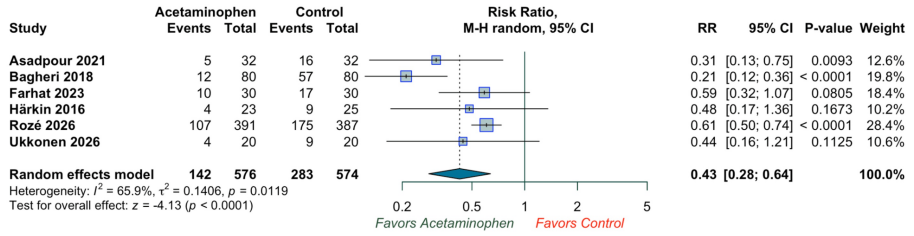


FIGURE 3: Forest plot comparing prophylactic acetaminophen with control for persistent patent ductus arteriosus. Pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated using a random-effects meta-analysis

Source: [9,13-17]

For this binary endpoint, the plotted events/denominators (paracetamol versus control) were Asadpour et al. 5/32 versus 16/32, Bagheri et al. 12/80 versus 57/80, Farhat et al. 10/30 versus 17/30, Härkin et al. 4/23 versus 9/25, Rozé et al. 107/391 versus 175/387, and Ukkonen et al. 4/20 versus 9/20. The pooled endpoint represents a patent duct on each trial's reported post-treatment or early echocardiographic assessment, not a common fixed-day outcome or a pooled time-to-closure hazard ratio. Assessments differed: day 4 in Bagheri et al., day 7 in TREOCAPA, day 10 in Asadpour et al., after the three-day course in Farhat et al., and serial echocardiography during treatment in Härkin et al. and Ukkonen et al. The binary counts from the latter two trials reflect persistence at the assessment used in the forest plot; their time-to-closure analyses were not pooled as RRs. Because the clinical definitions and schedules are not identical, the combined estimate should be interpreted as an exploratory synthesis of early anatomical patency. The six trials

randomized 1,163 infants, but the plotted outcome denominators sum to 1,150 (576 and 574); the 13-person difference arises from the TREOCAPA outcome denominators of 391 and 387 versus its 791 randomized infants.

Leave-one-out sensitivity analysis demonstrated that the direction and statistical significance of the pooled effect were maintained after sequential exclusion of each study. Pooled RRs ranged from 0.37 to 0.58, with all corresponding CIs remaining below the null value. Heterogeneity ranged from $I^2 = 0\%$ after exclusion of Bagheri et al. to $I^2 = 72.7\%$ after exclusion of Härkin et al. (Supplemental material 2). A sensitivity analysis restricted to trials using intravenous or parenteral acetaminophen yielded a similar result, with acetaminophen remaining associated with a significantly lower risk of persistent PDA (RR = 0.44; 95% CI (0.28 to 0.70); P = 0.0004; $I^2 = 69.8\%$) (Supplemental material 3).

Subgroup analysis according to treatment duration showed no statistically significant difference between subgroups (P for subgroup differences = 0.4206) (Supplemental material 4). Among trials using acetaminophen for ⩽3 days, acetaminophen was associated with a lower risk of persistent PDA (RR = 0.35; 95% CI (0.13 to 0.96); P = 0.041; $I^2 = 84.1\%$). A significant reduction was also observed among trials using treatment for ⩾4 days (RR = 0.54; 95% CI (0.40 to 0.73); P < 0.001; $I^2 = 0\%$).

Subgroup analysis according to comparator type likewise showed no statistically significant subgroup difference (P for subgroup differences = 0.0998) (Supplemental material 5). In trials using a no-treatment control, acetaminophen was associated with a significantly reduced risk of persistent PDA (RR = 0.34; 95% CI (0.18 to 0.64); P < 0.001; $I^2 = 68.3\%$). The pooled effect also favored acetaminophen in placebo-controlled trials (RR = 0.59; 95% CI (0.49 to 0.72); P < 0.001; $I^2 = 0\%$).

The Doi plot for persistent PDA yielded an LFK index of −4.0, indicating major asymmetry (Supplemental material 6). This exploratory signal cannot establish publication bias with only six trials; chance, between-study heterogeneity, and differences in design or outcome timing could also produce asymmetry.

Secondary Effectiveness Outcomes

Five randomized trials contributed to the rescue PDA treatment analysis, excluding Bagheri et al. The pooled results showed no statistically significant difference between the paracetamol and control groups (RR = 0.67; 95% CI 0.45-1.00; P = 0.0503; $I^2 = 37.7\%$) (Figure *4*). Similarly, no significant difference was observed in surgical PDA closure (RR = 1.12; 95% CI 0.44-2.88; P = 0.8097; $I^2 = 16.8\%$) (Supplemental material 7A).

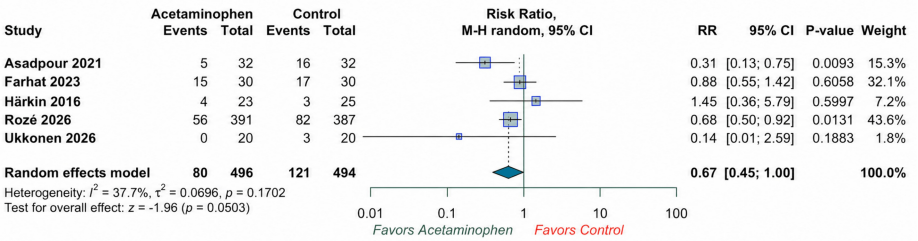


FIGURE 4: Forest plot comparing prophylactic acetaminophen with control for rescue PDA treatment. Pooled RRs and 95% CIs were calculated using a random-effects meta-analysis

PDA: patent ductus arteriosus; RR: risk ratio; CI: confidence interval

Source: [9,13,15-17]

Acetaminophen was associated with a significantly smaller ductal diameter (MD = −0.30 mm; 95% CI (−0.50 to −0.11); P = 0.022; $I^2 = 0\%$) (Figure *5*) and a significantly lower LA/Ao ratio (MD = −0.07; 95% CI (−0.08 to −0.06); P < 0.001; $I^2 = 0\%$) (Figure *6*).

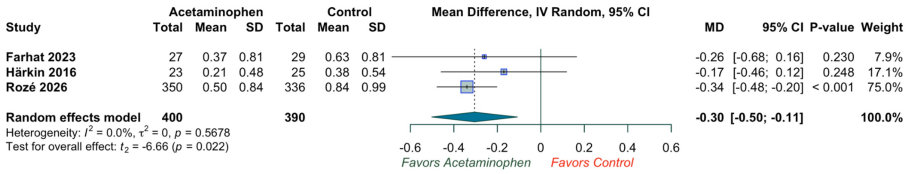


FIGURE 5: Forest plot comparing ductal diameter between the acetaminophen and control groups. Pooled mean differences (MDs) and 95% CIs were calculated using a random-effects meta-analysis

CI: confidence interval; SD: standard deviation

Source: [9,15,16]

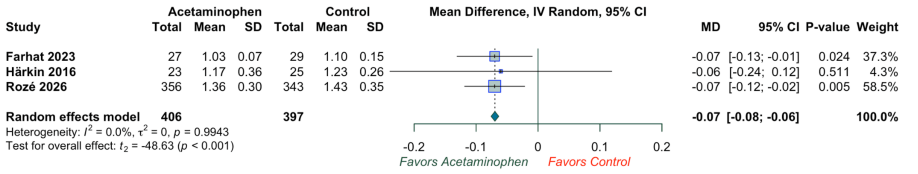


FIGURE 6: Forest plot comparing the left atrial-to-aortic root (LA/Ao) ratio between the acetaminophen and control groups. The pooled mean difference (MD) and 95% confidence interval (CI) are presented

SD: standard deviation

Source: [9,15,16]

Safety and Neonatal Morbidity Outcomes

Mortality did not differ significantly between the acetaminophen and control groups (RR = 0.80; 95% CI (0.58 to 1.09); P = 0.1513; I^2 = 0%) (Supplemental material 7B). Similarly, no significant differences were observed in BPD (RR = 1.00; 95% CI (0.82 to 1.21); P = 0.9611; I^2 = 1.9%) (Supplemental material 8A), IVH (RR = 0.97; 95% CI (0.82 to 1.14); P = 0.6735; I^2 = 0%) (Supplemental material 8B), NEC (RR = 0.80; 95% CI (0.54 to 1.18); P = 0.2640; I^2 = 0%) (Supplemental material 9A), or ROP (RR = 0.96; 95% CI (0.81 to 1.15); P = 0.6784; I^2 = 0%) (Supplemental material 9B).

There were also no significant differences in sepsis (RR = 0.72; 95% CI (0.47 to 1.09); P = 0.1211; I^2 = 0%) (Supplemental material 10A) or culture-positive sepsis (RR = 0.95; 95% CI (0.42 to 2.15); P = 0.9086; I^2 = 20.0%) (Supplemental material 10B). No significant between-group differences were observed in duration of mechanical ventilation (MD = −0.67 days; 95% CI (−4.00 to 2.65); P = 0.236; I^2 = 0%) (Supplemental material 11A) or length of hospital stay (MD = −2.39 days; 95% CI (−13.63 to 8.85); P = 0.226; I^2 = 0%) (Supplemental material 11B).

Certainty of evidence (GRADE)

The GRADE assessment rated the certainty of evidence as low for persistent PDA in the primary six-trial analysis, reflecting risk-of-bias concerns and inconsistency (I^2 = 65.9%). Certainty was very low for rescue PDA treatment because of risk of bias, variation in rescue-treatment definitions, and imprecision. Evidence for all-cause mortality, BPD, IVH, NEC, and ROP was rated moderate certainty; evidence for surgical PDA closure, sepsis, and duration of mechanical ventilation was rated low, and evidence for culture-positive sepsis and length of hospital stay was rated very low. The TREOCAPA outcomes of survival without severe neonatal morbidity and cholestasis were rated moderate certainty. Detailed assessments are provided in Supplemental material 12.

For persistent PDA, we downgraded one level for risk of bias because five of six trials had overall “some concerns” (four in randomization and one in selective reporting), and one level for inconsistency because I^2 was 65.9% and the direction and size of effects varied across populations, regimens, and assessment schedules. We did not downgrade this outcome for indirectness or imprecision; the CI excluded no effect, although its clinical meaning is limited to anatomical patency. With only six studies, the Doi/LFK finding

was treated as exploratory and was not used as a definitive publication-bias judgment. These two downgrades yield low certainty from a high-certainty randomized starting point. The 1,163 figure is the total randomized across trials; 1,150 is the sum of the six study-specific denominators with primary-outcome data, as displayed in Figure *3*.

Discussion

In this systematic review and meta-analysis of six randomized controlled trials encompassing 1,163 preterm infants, early prophylactic paracetamol was associated with a statistically significant reduction in persistent PDA (RR = 0.43; 95% CI (0.28 to 0.64); P < 0.0001; I^2 = 65.9%), but not rescue PDA treatment (RR = 0.67; 95% CI (0.45 to 1.00); P = 0.0503; I^2 = 37.7%). Continuous echocardiographic metrics demonstrated statistically significant reductions in ductal diameter (MD = -0.30 mm; 95% CI (-0.50 to -0.11); P = 0.022; I^2 = 0%) and LA/Ao ratio (MD = -0.07; 95% CI (-0.08 to -0.06); P < 0.001; I^2 = 0%). Conversely, prophylactic paracetamol was not associated with statistically significant reductions in surgical ligation (RR = 1.12; 95% CI (0.44 to 2.88); P = 0.8097) or all-cause mortality (RR = 0.80; 95% CI (0.58 to 1.09); P = 0.1513). Group differences were likewise not statistically significant for BPD (RR = 1.00; 95% CI (0.82 to 1.21); P = 0.9611), IVH (RR = 0.97; 95% CI (0.82 to 1.14); P = 0.6735), NEC (RR = 0.80; 95% CI (0.54 to 1.18); P = 0.2640), ROP (RR = 0.96; 95% CI (0.81 to 1.15); P = 0.6784), overall sepsis (RR = 0.72; 95% CI (0.47 to 1.09); P = 0.1211), or culture-positive sepsis (RR = 0.95; 95% CI (0.42 to 2.15); P = 0.9086). Mechanical ventilation duration (MD = -0.67 days; 95% CI (-4.00 to 2.65); P = 0.236) and hospital stay (MD = -2.39 days; 95% CI (-13.63 to 8.85); P = 0.226) were not statistically significant, with wide CIs indicating marked imprecision.

The observed reduction in persistent ductal patency appears consistent with several randomized trials evaluating prophylactic paracetamol in preterm neonates. Bagheri et al. [14] reported a lower frequency of echocardiographic PDA following parenteral prophylaxis (15.0% vs. 71.25%), while Asadpour et al. [13] observed higher closure rates with oral administration (84.4% vs. 50.0%). In exploratory pilot trials, Härkin et al. [16] and Ukkonen et al. [17] observed that intravenous paracetamol accelerated ductal constriction. However, the broader literature exhibits notable discrepancies. Farhat et al. [15] observed that ductal closure was numerically higher with paracetamol by day 14 (63.0% vs. 41.4%), though this difference was not statistically significant. Similarly, Akbari Asbagh et al. [18] identified no statistically significant difference in closure following a two-day oral regimen (75.0% vs. 50.0%). These divergent findings may indicate that variations in dosing protocols, administration routes, treatment durations, and echocardiographic timing substantially influence closure estimates across cohorts.

The pharmacological mechanisms underlying paracetamol-induced ductal constriction distinguish this agent from traditional COX inhibitors. As characterized by Rudolph [19] and synthesized by Graham and Scott [20] and Hallman et al. [7], prostaglandin endoperoxide H2 synthase contains two distinct catalytic regions: a COX active site and a peroxidase catalytic site. While non-steroidal anti-inflammatory agents competitively inhibit the COX domain, paracetamol acts as a selective reducing cosubstrate at the peroxidase site, suppressing prostaglandin synthesis under low cellular peroxide concentrations, as described by Anderson [21]. Because tissue peroxide tone varies across organ beds, paracetamol selectively reduces ductal prostaglandin E2 synthesis while avoiding the generalized vasoconstriction typical of COX inhibitors, as discussed by Al-Kuraishy et al. [22]. In addition, anatomical lumen closure involves platelet activation and aggregate formation [23]. Because paracetamol does not inhibit neonatal platelet aggregation, it has been hypothesized to facilitate anatomical remodeling without aggravating hemorrhagic risks, although this hypothesis requires clinical confirmation.

Despite these theoretical pharmacological advantages, the disconnect between accelerated ductal closure and substantive clinical outcomes reflects a recognized paradox in neonatal medicine. Landmark trials of prophylactic indomethacin by Schmidt et al. [4] demonstrated anatomical ductal closure and reductions in severe IVH, yet survival without neurosensory impairment remained unchanged. Subsequent trials evaluating ibuprofen by Gournay et al. [3], Hundscheid et al. [5], and Gupta et al. [24] similarly demonstrated that pharmacologically driven closure did not reduce BPD or mortality. Systematic overviews by Jasani et al. [8] and Buvaneswarran et al. [25] confirmed that active pharmacological closure does not demonstrate clinical superiority over expectant management. In the TREOCAPA trial by Rozé et al. [9], closing the ductus did not alter ventilatory support, inotropic therapy, or nutritional tolerance during the first postnatal week. This recurring pattern suggests that major preterm morbidities are largely driven by fundamental pulmonary and vascular immaturity, ventilator trauma, and systemic inflammation rather than ductal shunting in isolation.

From a clinical perspective, these pooled findings indicate that routine prophylactic paracetamol should not be adopted into clinical practice. Although paracetamol administration was associated with a statistically significant reduction in persistent PDA, these endpoints represent surrogate anatomical and process-of-care measures. Critical patient-centered outcomes-including all-cause mortality, BPD, and IVH-showed no statistically significant benefit, with CIs spanning the null. Favorable point estimates for mortality or sepsis should not be interpreted as evidence of clinical benefit, as the available evidence remains inconclusive. Furthermore, potential safety concerns require caution; Rozé et al. [9] reported a statistically significant increase in neonatal cholestasis among infants allocated to prophylactic paracetamol (6.4% vs. 2.6%; absolute risk difference = 3.8 percentage points), with nearly one-third remaining unresolved at discharge.

In the absence of demonstrated improvements in survival or chronic neonatal morbidities, universal prophylaxis exposes infants to unnecessary drug exposure, suggesting that expectant management or selective symptomatic rescue remains preferable.

This systematic review and meta-analysis exhibits several genuine methodological strengths. Eligibility was strictly restricted to prospective randomized controlled trials, with five trials judged as having some concerns and one at low overall risk of bias under the Cochrane RoB 2 tool. The integration of the multicenter trial by Rozé et al. [9] enlarged the pooled cohort to 1,163 infants, providing enhanced statistical power for evaluating secondary clinical morbidities and safety endpoints that were underpowered in earlier pilot trials. Continuous echocardiographic outcomes exhibited zero statistical heterogeneity ($I^2 = 0\%$), demonstrating consistent effect estimates across contributing trials. Furthermore, leave-one-out sensitivity analyses and restriction to intravenous administration regimens confirmed that the direction and statistical significance of the primary anatomical endpoint remained robust across analytical models. Nevertheless, these methodological strengths cannot overcome the intrinsic clinical limitations and residual uncertainties present within the available evidence base.

Several important limitations must be considered when interpreting these findings. Substantial heterogeneity was observed for persistent PDA ($I^2 = 65.9\%$), whereas heterogeneity for rescue PDA treatment was lower ($I^2 = 37.7\%$). Subgroup analyses suggested that comparator design contributed to this variation, as open-label trials with no-treatment controls yielded larger effect estimates than double-blind placebo-controlled trials. Furthermore, intervention protocols varied considerably across studies, ranging from oral drops in Asadpour et al. [13] to intravenous regimens spanning three days in Bagheri et al. [14] to nine days in Ukkonen et al. [17]. Potential publication bias or small-study effects cannot be excluded, as indicated by an LFK index of -4.0 demonstrating major asymmetry on the Doi plot. Finally, secondary clinical outcomes including surgical ligation, culture-positive sepsis, mechanical ventilation, and hospital stay exhibited small event counts, yielding wide CIs and statistical imprecision that preclude definitive conclusions regarding potential subtle benefits or harms.

Interpretation of the primary heterogeneity remains uncertain. Gestational age and birth-weight eligibility, baseline ductal status, oral versus intravenous administration, duration of treatment, placebo versus no-treatment controls, and the timing and definition of echocardiographic patency all differed. The duration and comparator subgroup analyses involved very few trials, had no significant interaction, and cannot identify the source of $I^2 = 65.9\%$ or establish that any one factor explains it. Likewise, the LFK index of −4.0 describes asymmetry in an exploratory six-study Doi plot; it does not establish publication bias, and chance or clinical and methodological heterogeneity remain plausible explanations.

Future clinical research should move away from universal prophylaxis and focus on developing targeted predictive strategies to identify neonates who may genuinely benefit from ductal closure. As emphasized by McNamara and Sehgal [26] and Clyman [27], defining early echocardiographic and hemodynamic biomarkers is essential to differentiate benign, spontaneously closing ducts from hemodynamically significant shunts associated with organ hypoperfusion. In extremely preterm infants born below 26 weeks of gestation, further pharmacokinetic and pharmacodynamic investigations are required to determine optimal dosing and evaluate hepatic and biliary tolerance, as discussed by Bouazza et al. [28]. Prospective trials must also incorporate long-term neurodevelopmental follow-up to address safety concerns regarding early analgesic exposure raised by Baker et al. [29] and Alemany et al. [30].

Conclusions

In conclusion, the available evidence suggests that early prophylactic paracetamol accelerates anatomical ductal closure in preterm infants, without a statistically significant reduction in subsequent rescue medical treatment. However, because this anatomical response does not translate into statistically significant improvements in survival, BPD, or other major neonatal morbidities, the findings do not justify routine changes in clinical practice. Adequately powered, high-quality randomized trials evaluating targeted strategies are required before practice-changing recommendations can be made.

Appendices

Supplemental material 1

Database	Search term	Filter	Results
PubMed	(acetaminophen OR paracetamol OR APAP) AND ("patent ductus arteriosus" OR "patent arterial duct" OR "ductus arteriosus" OR "ductal closure" OR "ductal patency" OR PDA) AND (preterm OR premature OR neonatal OR newborn OR infant OR "low birth weight" OR "very low birth weight" OR "extremely low birth weight" OR VLBW OR ELBW OR ELGA)	All fields	328
Scopus	(acetaminophen OR paracetamol OR APAP) AND ("patent ductus arteriosus" OR "patent arterial duct" OR "ductus arteriosus" OR "ductal closure" OR "ductal patency" OR PDA) AND (preterm OR premature OR neonatal OR newborn OR infant OR "low birth weight" OR "very low birth weight" OR "extremely low birth weight" OR VLBW OR ELBW OR ELGA)	Article title, abstract, and keywords	756
Web of Science	(acetaminophen OR paracetamol OR APAP) AND ("patent ductus arteriosus" OR "patent arterial duct" OR "ductus arteriosus" OR "ductal closure" OR "ductal patency" OR PDA) AND (preterm OR premature OR neonatal OR newborn OR infant OR "low birth weight" OR "very low birth weight" OR "extremely low birth weight" OR VLBW OR ELBW OR ELGA)	All fields	369
Cochrane Library	(acetaminophen OR paracetamol OR APAP) AND ("patent ductus arteriosus" OR "patent arterial duct" OR "ductus arteriosus" OR "ductal closure" OR "ductal patency" OR PDA) AND (preterm OR premature OR neonatal OR newborn OR infant OR "low birth weight" OR "very low birth weight" OR "extremely low birth weight" OR VLBW OR ELBW OR ELGA)	All fields	188

TABLE 3: Database-specific electronic search strategies and search results

Supplemental material 2

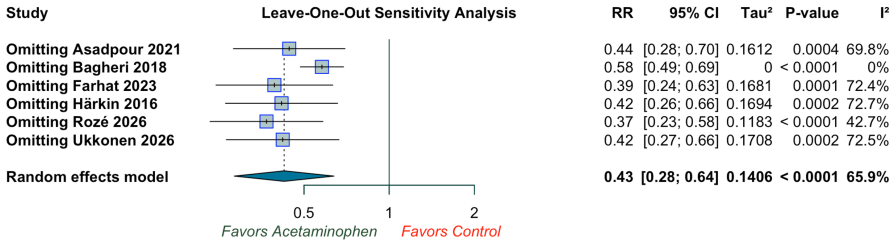


FIGURE 7: Leave-one-out sensitivity analysis of persistent patent ductus arteriosus based on six randomized controlled trials. Each study was sequentially excluded to evaluate its influence on the pooled risk ratio (RR) and heterogeneity

CI: confidence interval

Source: [9,13-17]

Supplemental material 3

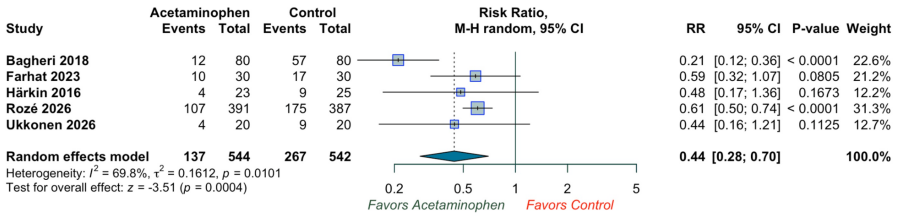


FIGURE 8: Sensitivity analysis of persistent patent ductus arteriosus restricted to five randomized controlled trials using intravenous or parenteral acetaminophen. The pooled risk ratio (RR) and 95% confidence interval (CI) are presented

Source: [9,14-17]

Supplemental material 4

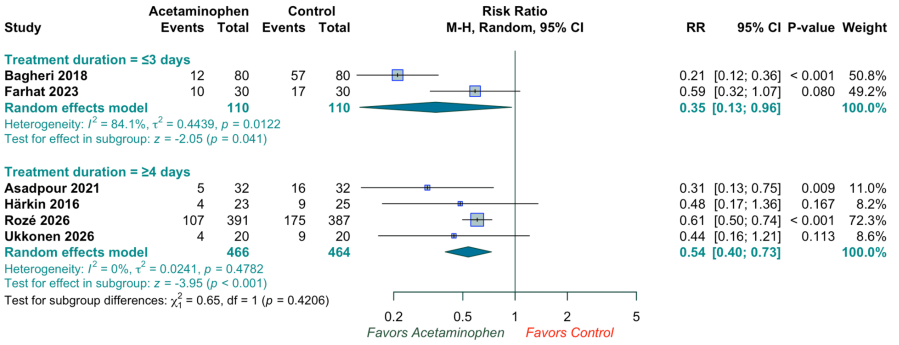


FIGURE 9: Subgroup analysis of persistent patent ductus arteriosus according to acetaminophen treatment duration (≤3 days versus ≥4 days) based on six randomized controlled trials. Subgroup-specific pooled risk ratios (RRs) and the test for subgroup differences are presented

CI: confidence interval

Source: [9,13-17]

Supplemental material 5

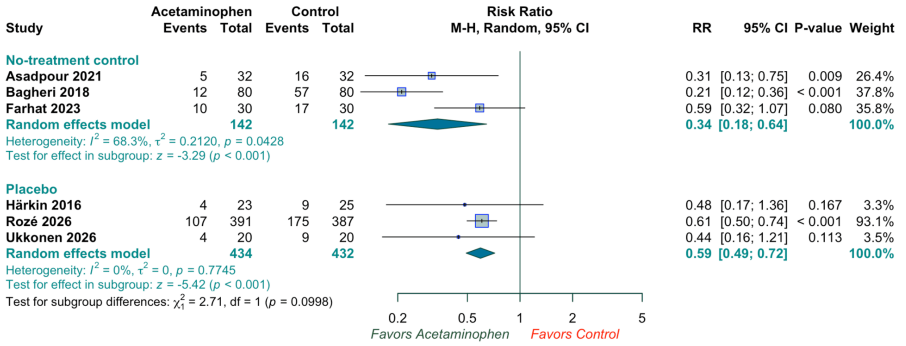


FIGURE 10: Subgroup analysis of persistent patent ductus arteriosus according to comparator type (no-treatment control versus placebo) based on six randomized controlled trials. Forest plot comparing the effects of prophylactic paracetamol in trials using no-treatment controls versus placebo controls. Subgroup-specific pooled risk ratios (RRs) and confidence intervals (95% CIs) and the test for subgroup differences are presented

Source: [9,13-17]

Supplemental material 6

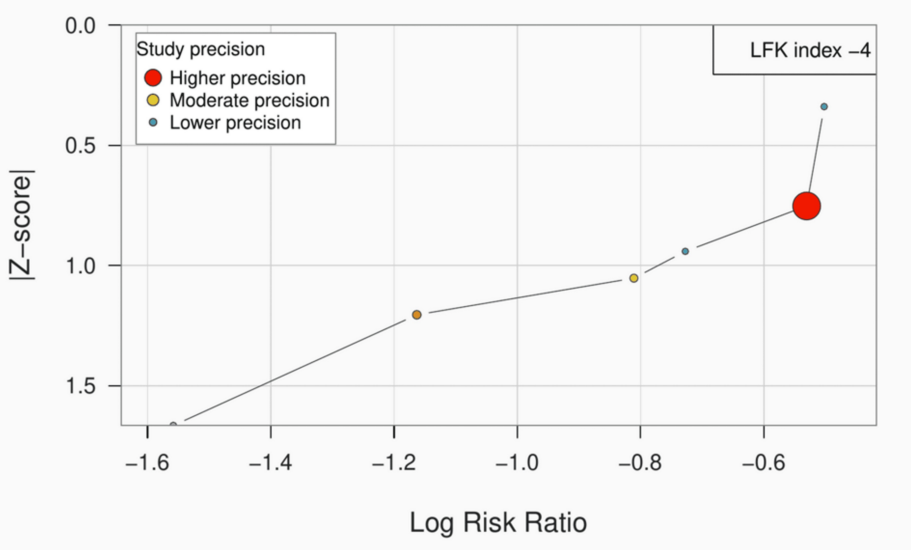


FIGURE 11: Doi plot exploring potential small-study effects and asymmetry for persistent patent ductus arteriosus based on six randomized controlled trials. The Luis Furuya-Kanamori (LFK) index is presented as an exploratory measure of asymmetry

Source: [9,13-17]

Supplemental material 7

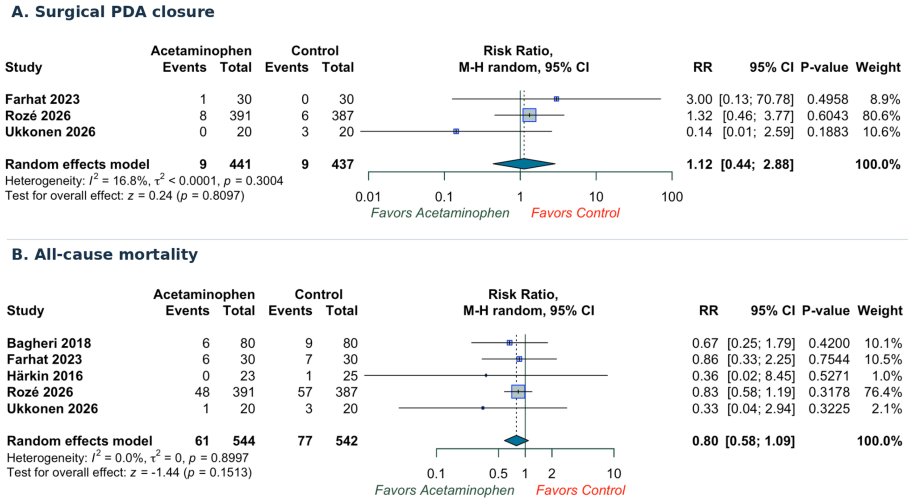


FIGURE 12: Forest plots comparing acetaminophen with control for (A) surgical patent ductus arteriosus (PDA) closure based on three randomized controlled trials and (B) all-cause mortality based on five randomized controlled trials. The pooled risk ratios (RRs) and 95% confidence intervals (CIs) are presented

Source: [9,14-17]

Supplemental material 8

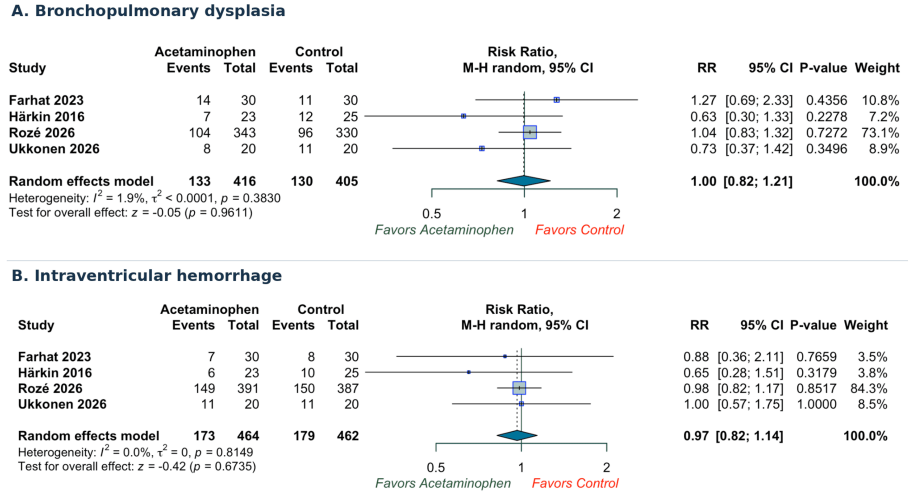


FIGURE 13: Forest plots comparing acetaminophen with control for neonatal morbidity outcomes: (A) bronchopulmonary dysplasia and (B) intraventricular hemorrhage. Both analyses included four randomized controlled trials, with pooled risk ratios (RRs) and 95% confidence intervals (CIs) presented

Source: [9,15-17]

Supplemental material 9

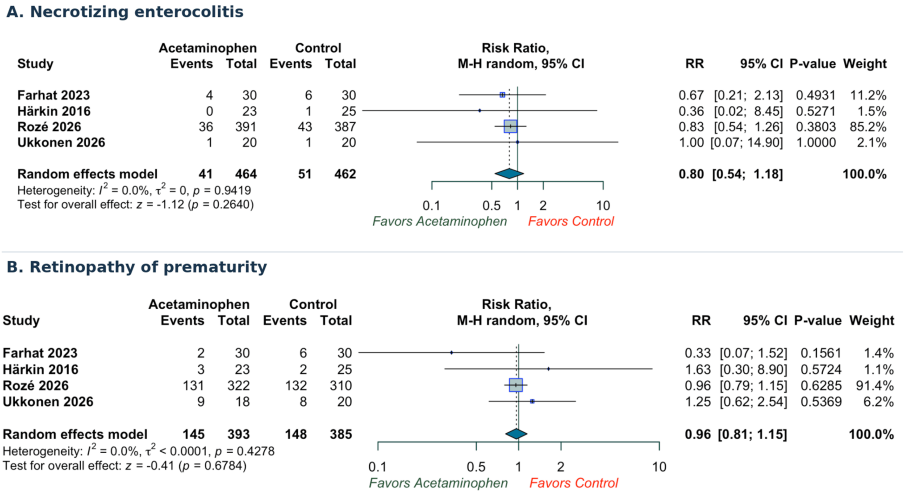


FIGURE 14: Forest plots comparing acetaminophen with control for neonatal morbidity outcomes: (A) necrotizing enterocolitis and (B) retinopathy of prematurity. Both analyses included four randomized controlled trials, with pooled risk ratios (RRs) and 95% confidence intervals (CIs) presented

Source: [9,15-17]

Supplemental material 10

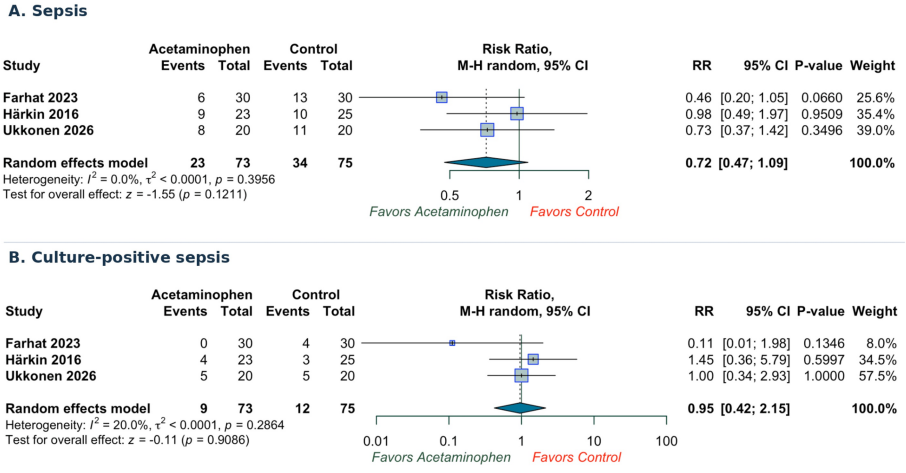


FIGURE 15: Forest plots comparing acetaminophen with control for infectious outcomes: (A) sepsis and (B) culture-positive sepsis. Both analyses included three randomized controlled trials, with pooled risk ratios (RRs) and 95% confidence intervals (CIs) presented

Source: [15-17]

Supplemental material 11

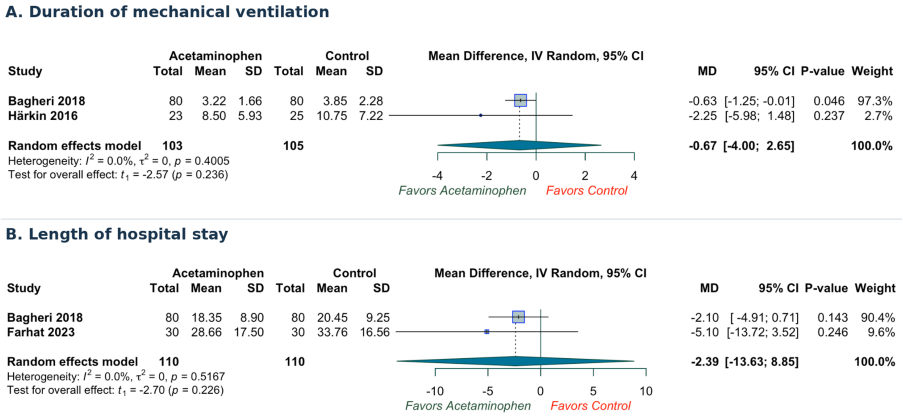


FIGURE 16: Forest plots comparing acetaminophen with control for (A) duration of mechanical ventilation based on two randomized controlled trials and (B) length of hospital stay based on two randomized controlled trials. The pooled mean differences (MDs) and 95% confidence intervals (CIs) are presented

SD: standard deviation

Source: [14-16]

Supplemental material 12

Certainty assessment							Summary of findings				
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients		Effect		Certainty
							Paracetamol	Control	Relative/MD (95% CI)	Absolute (95% CI)	
(a) Persistent PDA - all six randomized trials (primary analysis)											
6	RCTs	Serious	Serious	Not serious	Not serious	Comparator type assessed in subgroup; exploratory Doi asymmetry	576	574	RR 0.43 (0.28 to 0.64)	281 fewer per 1,000 (355 fewer to 177 fewer)	⊕⊕◯◯ Low
(b) Rescue PDA treatment - five-trial analysis (Bagheri et al. excluded)											
5	RCTs	Serious	Not serious	Serious	Serious	Rescue definitions vary; publication bias not assessable	496	494	RR 0.67 (0.45 to 1.00)	80 fewer per 1,000 (135 fewer to <1 more)	⊕◯◯◯ Very low
(c) Surgical PDA closure											
3	RCTs	Not serious	Not serious	Not serious	Very serious	Very sparse events; publication bias not assessable	441	437	RR 1.12 (0.44 to 2.88)	2 more per 1,000 (12 fewer to 39 more)	⊕⊕◯◯ Low
All-cause mortality (d)											
5	RCTs	Not serious	Not serious	Not serious	Serious	Publication bias not reliably assessable	544	542	RR 0.80 (0.58 to 1.09)	28 fewer per 1,000 (60 fewer to 13 more)	⊕⊕⊕◯ Moderate
(e) Bronchopulmonary dysplasia											
4	RCTs	Not serious	Not serious	Not serious	Serious	Publication bias not reliably assessable	416	405	RR 1.00 (0.82 to 1.21)	No difference per 1,000 (58 fewer to 67 more)	⊕⊕⊕◯ Moderate
(f) Intraventricular hemorrhage (IVH)											

4	RCTs	Not serious	Not serious	Not serious	Serious	Publication bias not reliably assessable	464	462	RR 0.97 (0.82 to 1.14)	12 fewer per 1,000 (70 fewer to 54 more)	⊕⊕⊕◯ Moderate
(g) Necrotizing enterocolitis (NEC)											
4	RCTs	Not serious	Not serious	Not serious	Serious	Publication bias not reliably assessable	464	462	RR 0.80 (0.54 to 1.18)	22 fewer per 1,000 (51 fewer to 20 more)	⊕⊕⊕◯ Moderate
(h) Retinopathy of prematurity (ROP)											
4	RCTs	Not serious	Not serious	Not serious	Serious	Publication bias not reliably assessable	393	385	RR 0.96 (0.81 to 1.15)	15 fewer per 1,000 (73 fewer to 58 more)	⊕⊕⊕◯ Moderate
(i) Sepsis											
3	RCTs	Serious	Not serious	Not serious	Serious	Few small trials; publication bias not assessable	73	75	RR 0.72 (0.47 to 1.09)	127 fewer per 1,000 (240 fewer to 41 more)	⊕⊕◯◯ Low
(j) Culture-positive sepsis											
3	RCTs	Serious	Not serious	Not serious	Very serious	Sparse events; publication bias not assessable	73	75	RR 0.95 (0.42 to 2.15)	8 fewer per 1,000 (93 fewer to 184 more)	⊕◯◯◯ Very low
(k) Duration of mechanical ventilation (days)											
2	RCTs	Serious	Not serious	Not serious	Serious	Only two trials; no formal small-study effect test	103	105	MD -0.67 (-4.00 to 2.65)	0.67 days shorter (4.00 shorter to 2.65 longer)	⊕⊕◯◯ Low
(l) Length of hospital stay (days)											
2	RCTs	Serious	Not serious	Not serious	Very serious	Only two trials; no formal small-study effect test	110	110	MD -2.39 (-13.63 to 8.85)	2.39 days shorter (13.63 shorter to 8.85 longer)	⊕◯◯◯ Very low
(m) Survival without severe neonatal morbidity - TREOCAPA											
1	RCTs	Not serious	Not serious	Not serious	Serious	Single large randomized trial	391	387	RR 1.04 (0.94 to 1.16)	25 more per 1,000 (38 fewer to 102 more)	⊕⊕⊕◯ Moderate
(n) Cholestasis - TREOCAPA safety population											
1	RCTs	Not serious	Not serious	Not serious	Serious	Single trial; safety outcome; 35 total events	392	386	RR 2.46 (1.20 to 5.06)	38 more per 1,000 (5 more to 105 more)	⊕⊕⊕◯ Moderate

TABLE 4: Summary of findings and quality of evidence based on the GRADE system

MD: mean difference; CI: confidence interval; PDA: patent ductus arteriosus; RCT: randomized controlled trial; RR: risk ratio; GRADE: Grading of Recommendations Assessment, Development and Evaluation

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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