JAMA | Original Investigation

Association of Placebo, Indomethacin, Ibuprofen, and Acetaminophen With Closure of Hemodynamically Significant Patent Ductus Arteriosus in Preterm Infants

A Systematic Review and Meta-analysis

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IMPORTANCE Despite increasing emphasis on conservative management of patent ductus arteriosus (PDA) in preterm infants, different pharmacotherapeutic interventions are used to treat those developing a hemodynamically significant PDA.

OBJECTIVES To estimate the relative likelihood of hemodynamically significant PDA closure with common pharmacotherapeutic interventions and to compare adverse event rates.

DATA SOURCES AND STUDY SELECTION The databases of MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched from inception until August 15, 2015, and updated on December 31, 2017, along with conference proceedings up to December 2017. Randomized clinical trials that enrolled preterm infants with a gestational age younger than 37 weeks treated with intravenous or oral indomethacin, ibuprofen, or acetaminophen vs each other, placebo, or no treatment for a clinically or echocardiographically diagnosed hemodynamically significant PDA.

DATA EXTRACTION AND SYNTHESIS Data were independently extracted in pairs by 6 reviewers and synthesized with Bayesian random-effects network meta-analyses.

MAIN OUTCOMES AND MEASURES Primary outcome: hemodynamically significant PDA closure; secondary: included surgical closure, mortality, necrotizing enterocolitis, and intraventricular hemorrhage.

RESULTS In 68 randomized clinical trials of 4802 infants, 14 different variations of indomethacin, ibuprofen, or acetaminophen were used as treatment modalities. The overall PDA closure rate was 67.4% (2867 of 4256 infants). A high dose of oral ibuprofen was associated with a significantly higher odds of PDA closure vs a standard dose of intravenous ibuprofen (odds ratio [OR], 3.59; 95% credible interval [CrI], 1.64-8.17; absolute risk difference, 199 [95% CrI, 95-258] more per 1000 infants) and a standard dose of intravenous indomethacin (OR, 2.35 [95% CrI, 1.08-5.31]; absolute risk difference, 124 [95% CrI, 14-188] more per 1000 infants). Based on the ranking statistics, a high dose of oral ibuprofen ranked as the best pharmacotherapeutic option for PDA closure (mean surface under the cumulative ranking [SUCRA] curve, 0.89 [SD, 0.12]) and to prevent surgical PDA ligation (mean SUCRA, 0.98 [SD, 0.08]). There was no significant difference in the odds of mortality, necrotizing enterocolitis, or intraventricular hemorrhage with use of placebo or no treatment compared with any of the other treatment modalities.

CONCLUSIONS AND RELEVANCE A high dose of oral ibuprofen was associated with a higher likelihood of hemodynamically significant PDA closure vs standard doses of intravenous ibuprofen or intravenous indomethacin; placebo or no treatment did not significantly change the likelihood of mortality, necrotizing enterocolitis, or intraventricular hemorrhage.

TRIAL REGISTRATION PROSPERO Identifier: CRD42015015797

JAMA. 2018;319(12):1221-1238. doi:10.1001/jama.2018.1896

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A common early cardiovascular problem of prematurely born infants is hemodynamically significant patent ductus arteriosus (PDA). The utility of active management and the timing and modality of PDA treatment have been debated.[1] Persistent ductal shunting may lead to pulmonary overcirculation, increasing the risk of bronchopulmonary dysplasia; conversely, shunting may induce systemic hypoperfusion, increasing the risk of necrotizing enterocolitis, intraventricular hemorrhage, renal failure, and death.[2-4] Nonsteroidal anti-inflammatory drugs along with other pharmacotherapeutic agents have been used to close PDAs to prevent such complications. However, conservative management of PDA without the use of pharmacotherapeutic agents has recently increased.[5,6] The hypothesis is that a large proportion of the PDAs that occur in preterm infants would spontaneously close within the first few days, thereby having minimal effect on clinical outcomes.[5,7] As a result, emphasis has been placed on targeted pharmacotherapeutic treatment of PDAs when deemed hemodynamically significant by the clinician based on clinical and echocardiographic parameters.[7] However, lack of pharmacokinetic and pharmacodynamic data on nonsteroidal anti-inflammatory drug use in preterm infants has led to the use of different drugs in varying doses and routes of administration.[8] The 2 most commonly used treatment options are standard doses of intravenous ibuprofen and intravenous indomethacin.[8,9]

The availability of different management options poses a challenge for neonatologists when making evidence-based management decisions after diagnosing hemodynamically significant PDAs. The dilemma is whether to use pharmacotherapy at all, and if a decision is made to treat the PDA medically, what should be the ideal choice of pharmacotherapy.[1,7] Therefore, a comprehensive systematic review and Bayesian network meta-analysis was conducted to summarize the evidence from randomized clinical trials comparing placebo, indomethacin, ibuprofen, and acetaminophen for the treatment of hemodynamically significant PDAs in preterm infants.[10]

Key Points

Question What pharmacological treatments are associated with the highest likelihood of hemodynamically significant patent ductus arteriosus (PDA) closure in premature infants?

Findings In this network meta-analysis that included 68 randomized trials with 4802 infants, a high dose of oral ibuprofen was associated with a statistically significantly higher likelihood of hemodynamically significant PDA closure vs standard doses of intravenous ibuprofen (odds ratio, 3.59) or intravenous indomethacin (odds ratio, 2.35). Placebo or no treatment was not associated with an increased likelihood of mortality, necrotizing enterocolitis, or intraventricular hemorrhage.

Meaning A high dose of oral ibuprofen may offer the highest likelihood of hemodynamically significant PDA closure in preterm infants. Conservative management of hemodynamically significant PDA is not likely to increase morbidity and mortality.

Methods

The network meta-analysis protocol is available in Supplement 1 and has been published.[11,12] This study complies with the recommendations of the International Society for Pharmacoeconomics and Outcomes Research guidance on network meta-analysis and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension statement for reporting of systematic reviews incorporating network meta-analysis of health care interventions.[13,14] The differences between the protocol and the final article are summarized in Supplement 2.

Eligibility Criteria

Studies were included if they were randomized clinical trials that enrolled preterm infants with a gestational age younger than 37 weeks at birth or low-birth-weight infants (<2500 g) who were treated with either intravenous or oral formulations of indomethacin, ibuprofen, or acetaminophen compared with another medication, placebo, or no treatment for hemodynamically significant PDA diagnosed clinically or echocardiographically during the neonatal period (defined as <28 days of life; a full glossary of abbreviations and acronyms, including medication doses and routes, appears in eTable 1 in Supplement 3). Studies were excluded in which a medication was used prophylactically (ie, within the first 24 hours of life without documented clinical or echocardiographic evidence of hemodynamically significant PDA) or surgery was a primary treatment modality.

Primary and Secondary Outcomes

Fourteen outcomes were defined a priori, which included 3 effectiveness outcomes and 11 adverse events (**Table**). The primary outcome was hemodynamically significant PDA closure within 1 week of administration of the first dose of the intervention and defined echocardiographically (as physical closure of PDA or change from hemodynamically significant to nonsignificant status based on a priori-defined parameters) or clinically (disappearance of cardiac murmur). The other 2 effectiveness outcomes were need for repeat pharmacotherapy and surgical ligation.

The adverse events were death at postmenstrual age of 36 weeks or before hospital discharge, necrotizing enterocolitis (≥stage 2 based on the Bell criteria), bronchopulmonary dysplasia (defined as oxygen use at postmenstrual age of 36 weeks), intraventricular hemorrhage (any grade based on the Papile criteria), and oliguria (defined as urine output <1 mL/kg/h).[15-17] The 6 outcomes that were not included in the quantitative synthesis due to lack of sufficient data were severe intraventricular hemorrhage, periventricular leukomalacia, neurodevelopmental disability, intestinal perforation, gastrointestinal bleeding, and time to full enteral feedings (Table).

Information Sources and Trial Search

MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched electronically from inception

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until August 15, 2015, and updated on December 31, 2017, prior to the final data analysis (eTable 2 in Supplement 3). Registered details of selected trials in the US National Institutes of Health resource (http://www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (http://www.who.int/ictrp/en/) search portal were sought.

Additional related trials were sought from personal communication with experts in the field, reviewing the reference lists of relevant articles, abstracts, and conference proceedings (European Society for Pediatric Research and US pediatric academic societies from 1990-2017). There were no language restrictions.

Study Selection and Risk of Bias

The retrieved titles, abstracts, and full text were screened by 2 independent reviewers in duplicate (S.M., I.D.F., M.E.T., A.M.Z., Y.Z., B.S.) to assess their eligibility. The risk of bias for the eligible studies was assessed according to a modified and validated version of the Cochrane Collaboration risk of bias tool by 2 independent reviewers[18,19] (eFigure 1 and eText 1 in Supplement 3).

Data extraction was performed by 6 reviewers (S.M., I.D.F., M.E.T., A.M.Z., Y.Z., B.S.) using a prespecified standardized data extraction form and working independently in pairs and in duplicate. Discrepancies were resolved through discussion or in consultation with a third reviewer (S.M. or I.D.F.).

Data Synthesis and Analysis

For each outcome, an initial pairwise meta-analysis was conducted using a random-effects model for every direct pairwise comparison, followed by a Bayesian random-effects network meta-analysis to compare all interventions simultaneously using the Markov-chain Monte Carlo method[20,21] conducted under the assumption of transitivity.[22,23]

Transitivity was defined as the assumption that the studies were sufficiently similar in their distribution of effect modifiers so that indirect comparisons could be used as a valid method to compare 2 treatment options.[22,23] Transitivity was assessed by subjectively comparing the distribution of the population, the intervention, and the methodological characteristics of the studies. The consistency assumption among the combined sources of evidence in the network was first evaluated globally for the entire network using the design × treatment interaction model, and then locally for each treatment comparison using the node-splitting model.[24-26]

The mean surface under the cumulative ranking (SUCRA) curve for each intervention was calculated. Based on the mean SUCRA values, heat maps were generated to efficiently recognize what were most likely the best and worst interventions for each outcome.[27] For both the meta-analysis and the network meta-analysis, Bayesian hierarchical models with noninformative priors assigned to all model parameters were used.

For each meta-analysis, the I^2 statistic was used to assess the heterogeneity of the trials.[18] In the network meta-analysis, a common within-network heterogeneity was assumed because the treatments were of similar nature. A series of 100 000 simulations was used to allow convergence, and after thinning of 10 and discarding the first 20 000 simulations, the outputs were produced. The model convergence was assessed on the basis of Gelman and Rubin diagnostic tests.[28]

Odds ratios (ORs) and 95% credible intervals (95% CrIs) were estimated from the medians and the 2.5th and 97.5th percentiles of the posterior distributions in the simulations. A network absolute risk difference was calculated from the network OR estimates using an assumed control risk that was derived by dividing the total event number by the total infant number in the control groups in the network.[18,29]

Table. A Priori–Defined Outcome Measures

Outcome Measure	Definition
Primary Outcome	
Effectiveness outcome	
PDA closure[a]	Closure within 1 wk of administration of the first dose (PDA diagnosed either clinically or by echocardiographic criteria)
Secondary Outcomes	
Effectiveness outcomes	
Need for repeat pharmacotherapy[a]	No. of neonates who require a repeat course following initial treatment of persistent hemodynamically significant PDA
Need for surgical closure of the PDA[a]	No. of neonates who require closure following failure of pharmacological PDA closure
Adverse Events	
Neonatal mortality[a]	Death at postmenstrual age of 36 wks or before hospital discharge
Gastrointestinal events	
Necrotizing enterocolitis[a]	No. of neonates with ≥stage 2 based on the Bell criteria
Intestinal perforation	No. of neonates with event
Gastrointestinal bleeding	No. of neonates with event
Time to full enteral feedings	Postnatal age at stopping parenteral nutrition and achievement of full enteral feedings
Bronchopulmonary dysplasia[a]	No. of neonates who require oxygen at postmenstrual age of 36 weeks
Neurological events	
Intraventricular hemorrhage[a]	No. of neonates with any grade based on the Papile criteria
Severe intraventricular hemorrhage	No. of neonates with grades 3-4 based on the Papile criteria
Periventricular leukomalacia	No. of neonates with any grade documented on cranial ultrasound
Neurodevelopmental disability	No. of children with any reported disability at 1-2 y of age (ie, motor, cognitive, sensory impairments)
Oliguria[a]	No. of neonates with reduced urine output defined as <1 mL/kg/h

Abbreviation: PDA, patent ductus arteriosus.

[a] Indicates an outcome included in the network meta-analysis

Network Sensitivity and Meta-Regression Analyses

The following potential sources of heterogeneity were identified a priori: gestational age, birth weight, different doses of the interventions, age at the time of administration of the first dose of the intervention, echocardiographic findings, and risk of bias. The overall risk of bias for each study was assessed by taking the average of the 3 most important risk of bias items

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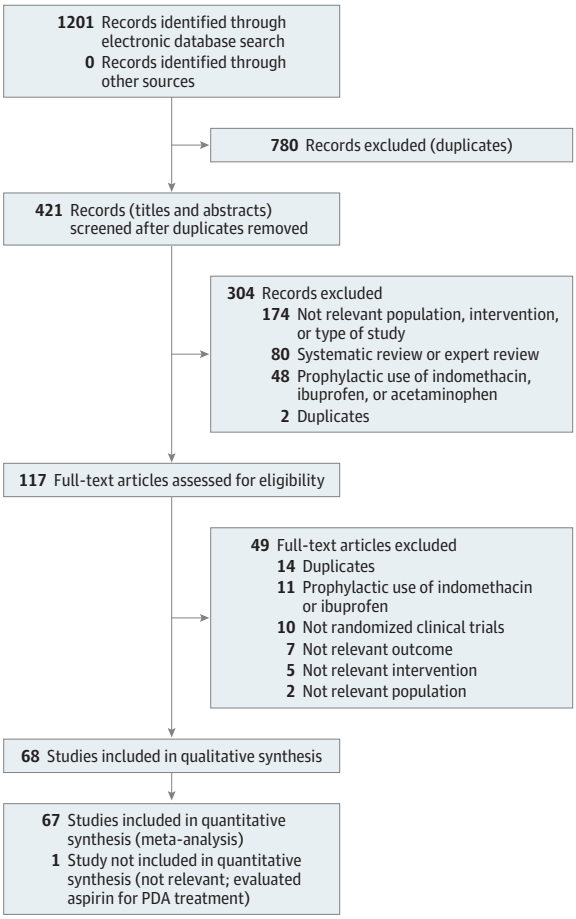
Figure 1. Literature Search and Study Selection Flow Diagram



PDA indicates patent ductus arteriosus.

identified by expert consensus (ie, sequence generation, allocation concealment, and blinding).[30]

Sensitivity analyses were conducted for all outcomes including only the high-quality studies (those with low risk and probably low risk of bias). When at least 10 studies were available, network meta-regression was conducted assuming a common fixed coefficient across comparisons to explore the effect of gestational age, birth weight, age of treatment initiation, and year of publication on the most important clinical outcomes (ie, PDA closure, need for repeat pharmacotherapy, mortality, and necrotizing enterocolitis).

All analyses were performed using WinBUGS version 1.4.3 and OpenBUGS version 3.2.3 revision 1012 (MRC Biostatistics Unit), NetMetaXL, GeMTC GUI, and RStudio packages.[31-33] The design × treatment model was performed in Stata version 15 (StataCorp) using the network command.[34]

Assessment of the Quality of the Evidence

The quality of the evidence for each direct, indirect, and network effects estimate was evaluated for the primary and main secondary outcomes according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method for network meta-analysis.[35,36] The quality of the evidence for the direct estimates started as high and was decreased to moderate, low, or very low based on risk of bias, imprecision, heterogeneity, indirectness, and publication bias.[35]

Publication bias was assessed by visual inspection of asymmetry in the funnel plots. The quality of the evidence for estimates of the indirect and network effects were computed from the direct estimates by evaluating each indirect comparison from the network geometry, qualitative assessment of intransitivity, and quantitative assessment of incoherence based on the inconsistency test.[36]

Results

Among 1201 records retrieved, 68 randomized clinical trials met inclusion criteria and included 4802 preterm infants. Details regarding the study selection appear in the flow diagram (**Figure 1**). Forty-nine studies were excluded after full-text screening (eTable 3 in Supplement 3). The clinical and methodological characteristics of the included studies appear in eTable 4 in Supplement 3.[37-104] The studies were published between 1980 and 2017. Sixty-one of the 68 studies were published in English. The remaining were published in Polish, Turkish, Persian, Spanish, Korean, Chinese, and French.[37,38,54,57,68,70,72]

Fourteen different variations of indomethacin, ibuprofen, or acetaminophen were used as treatment modalities across the studies. The variations included differences in route of administration (intravenous or oral), dose of medication (standard dose, high dose, prolonged course), method of administration (bolus dose, continuous infusion), and cointerventions (concomitant use of furosemide, dopamine, or echocardiographically guided indomethacin infusion). The dosage for intravenous indomethacin was defined as 0.1 to 0.3 mg/kg administered intravenously every 12 to 24 hours for a total of 3 doses. A standard dose of ibuprofen was defined as 10 mg/kg followed by 5 mg/kg administered every 12 to 24 hours for a total of 3 doses (both intravenous and oral administrations). A high dose of ibuprofen was defined as 15 to 20 mg/kg followed by 7.5 to 10 mg/kg administered every 12 to 24 hours for a total of 3 doses (both intravenous and oral administrations). The detailed definitions of the different doses and methods of administration of the medications appear in eTable 1 in Supplement 3.

One study used aspirin for the treatment of PDA.[95] This study was excluded from the analysis due to lack of relevance in the current context. Intravenous indomethacin was the most commonly used intervention (in 38 studies), followed by standard doses of intravenous ibuprofen (used in 23 studies) and oral ibuprofen (used in 21 studies). Oral acetaminophen was used in 5 studies and higher doses of intravenous and oral ibuprofen were used in 1 and 3 studies, respectively (eTable 4 in Supplement 3).

The criteria for hemodynamically significant PDA varied across studies and appear in eTable 4 in Supplement 3. A PDA diameter of more than 1.5 mm and a ratio of 1.4 or greater for left atrium to aortic root were the 2 most commonly used

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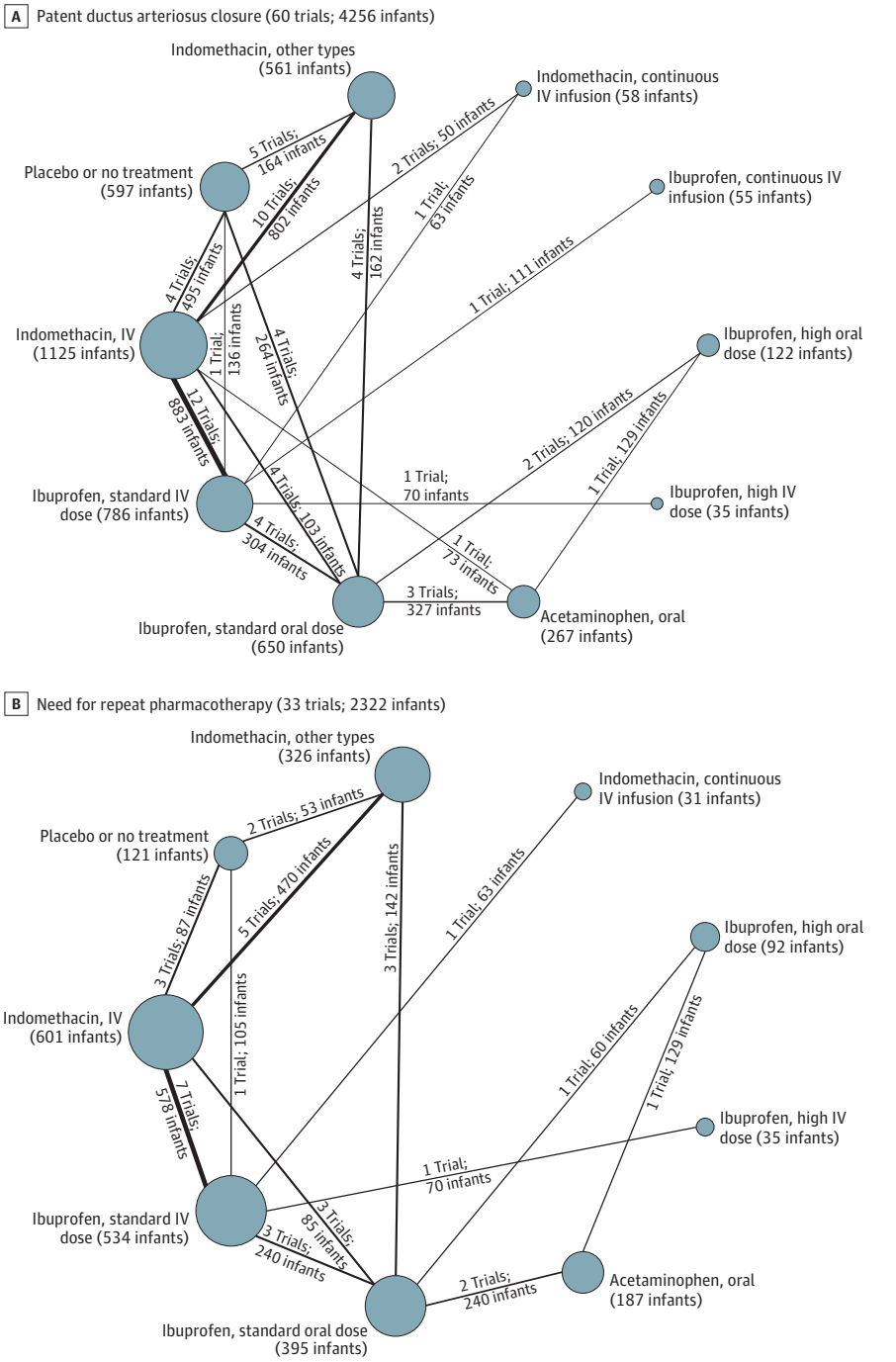
Figure 2. Network Plots for Patent Ductus Arteriosus Closure and Need for Repeat Pharmacotherapy



These 2 outcome measures for treatment of hemodynamically significant patent ductus arteriosus were evaluated in the Bayesian network meta-analysis. Each node indicates a treatment modality and is sized proportionally to the number of infants who received the treatment modality. Each line connecting 2 nodes indicates a direct comparison between 2 modalities, and the thickness of each is proportional to the number of trials directly comparing the 2 modalities. Seldom-used variations of indomethacin were condensed into a single node termed *indomethacin, other types*. A standard dose of ibuprofen is 10 mg/kg followed by 5 mg/kg every 12 to 24 hours for a total of 3 doses. A high dose of ibuprofen is 15 to 20 mg/kg followed by 7.5 to 10 mg/kg every 12 to 24 hours for a total of 3 doses. IV indicates intravenous.

echocardiographic criteria for defining hemodynamically significant PDA (eTable 4 in Supplement 3). Sixteen studies were found to have a low risk of bias (eFigure 2 in Supplement 3). Twenty-eight studies had a risk of bias that was considered probably low, whereas 21 studies had a risk of bias that was considered probably high. Three studies did not report any of sequence generation, allocation concealment, or blinding and were therefore judged to have a high risk of bias (eFigures 2 and 3 in Supplement 3).

The Network Plots

Head-to-head comparisons between the different therapeutic options were depicted as network plots for each outcome (**Figures 2, 3, 4,** and **5**). In the figures, (1) each node indicates a treatment modality and is sized proportionally to the number of infants who received the treatment modality and (2) each line connecting 2 nodes indicates a direct comparison between 2 modalities. The thickness of each line is proportional to the number of trials directly comparing the 2 modalities.

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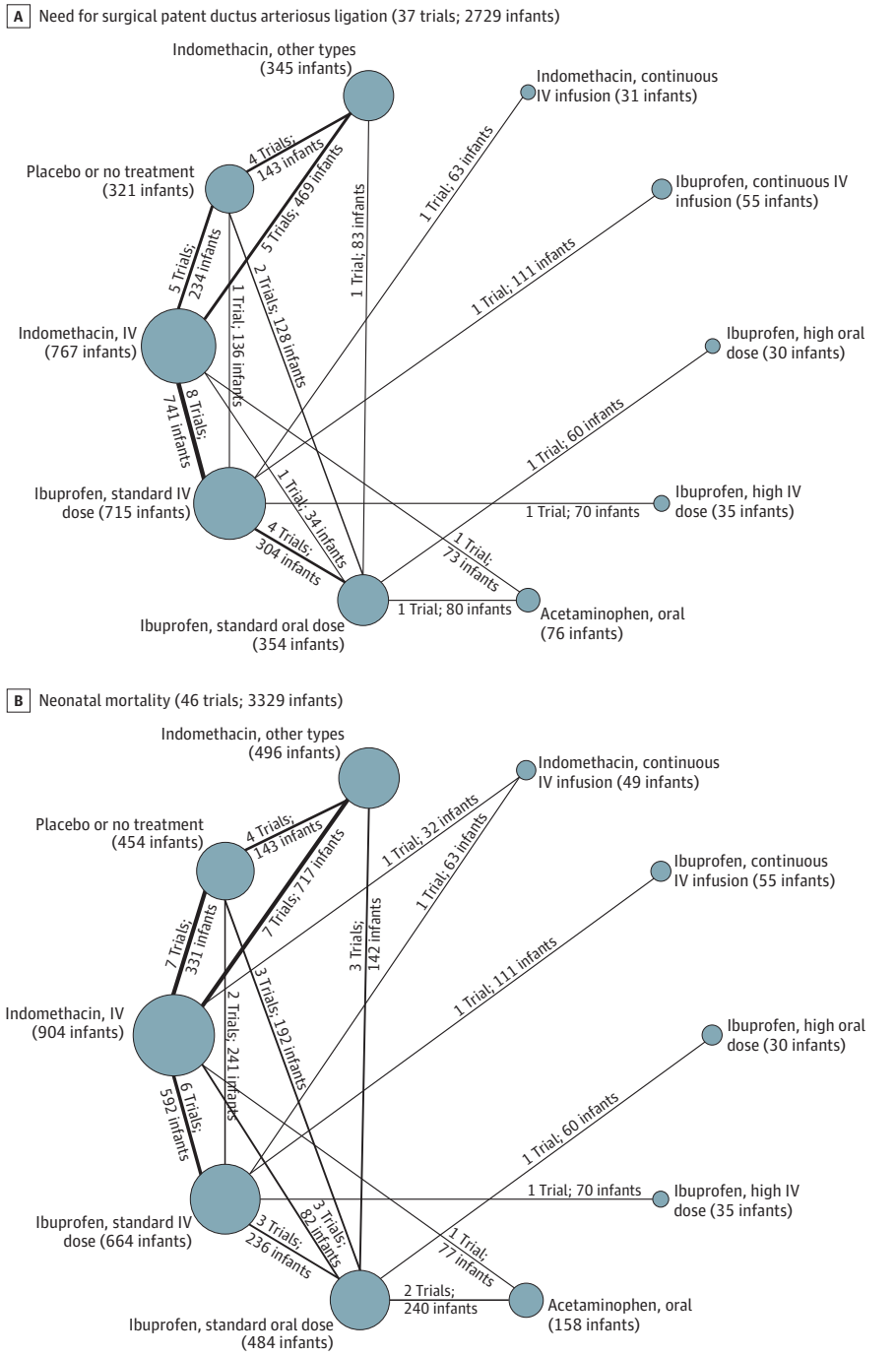
Figure 3. Network Plots for Surgical Patent Ductus Arteriosus Ligation and Neonatal Mortality



These 2 outcome measures for treatment of hemodynamically significant patent ductus arteriosus were evaluated in the Bayesian network meta-analysis. Each node indicates a treatment modality and is sized proportionally to the number of infants who received the treatment modality. Each line connecting 2 nodes indicates a direct comparison between 2 modalities, and the thickness of each is proportional to the number of trials directly comparing the 2 modalities. Seldom-used variations of indomethacin were condensed into a single node termed *indomethacin, other types*. A standard dose of ibuprofen is 10 mg/kg followed by 5 mg/kg every 12 to 24 hours for a total of 3 doses. A high dose of ibuprofen is 15 to 20 mg/kg followed by 7.5 to 10 mg/kg every 12 to 24 hours for a total of 3 doses. IV indicates intravenous.

Seldom-used variations of indomethacin were condensed into a single node named other types of indomethacin to make the results more relevant in the current clinical context (eTable 1 in Supplement 3). Similarly, placebo or no treatment were combined into a single node. Therefore, the final network meta-analysis was conducted with 10 nodes, each depicting a treatment modality (Figures 2, 3, 4, and 5).

PDA Closure, Need for Repeat Pharmacotherapy, and Surgical Ligation

A total of 60 studies including 4256 infants reported the primary outcome. The overall PDA closure rate was 67.4% (2867 of 4256 infants) in all studies combined and 38% in the placebo or no treatment group. A high dose of oral ibuprofen was associated with a significantly higher odds of PDA closure

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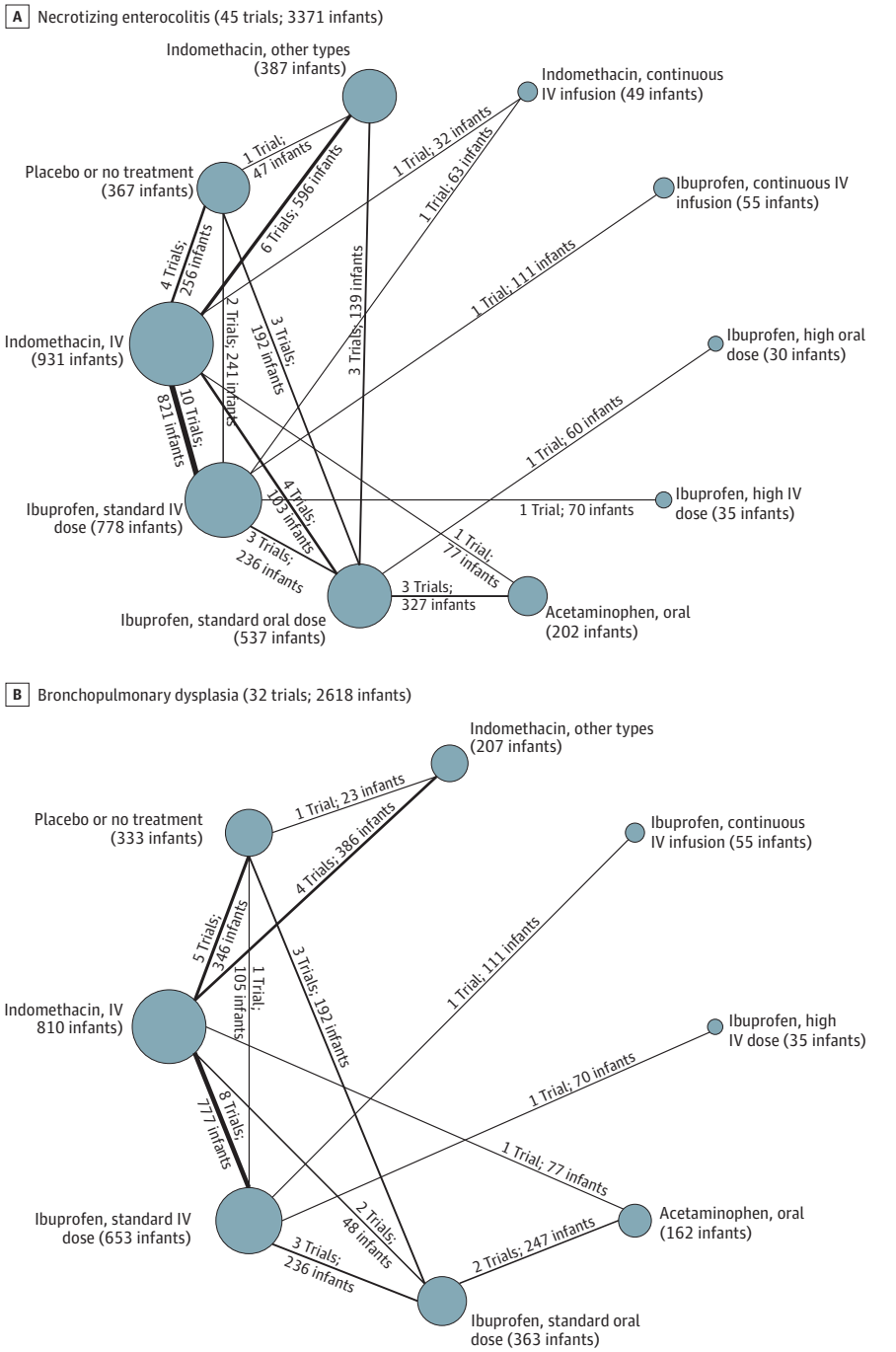
Figure 4. Network Plots for Necrotizing Enterocolitis and Bronchopulmonary Dysplasia



These 2 outcome measures for treatment of hemodynamically significant patent ductus arteriosus were evaluated in the Bayesian network meta-analysis. Each node indicates a treatment modality and is sized proportionally to the number of infants who received the treatment modality. Each line connecting 2 nodes indicates a direct comparison between 2 modalities, and the thickness of each is proportional to the number of trials directly comparing the 2 modalities. Seldom-used variations of indomethacin were condensed into a single node termed *indomethacin, other types*. A standard dose of ibuprofen is 10 mg/kg followed by 5 mg/kg every 12 to 24 hours for a total of 3 doses. A high dose of ibuprofen is 15 to 20 mg/kg followed by 7.5 to 10 mg/kg every 12 to 24 hours for a total of 3 doses. IV indicates intravenous.

vs a standard dose of intravenous ibuprofen (OR, 3.59; 95% CrI, 1.64-8.17; absolute risk difference, 199 [95% CrI, 95-258] more per 1000 infants) and a standard dose of intravenous indomethacin (OR, 2.35 [95% CrI, 1.08-5.31]; absolute risk difference, 124 [95% CrI, 14-188] more per 1000 infants) (**Figure 6**A; eTables 5-6, eFigures 4-5, and eText 2 in Supplement 3).

Compared with a standard dose of intravenous ibuprofen, the following were associated with a significantly higher odds of PDA closure: a high dose of intravenous ibuprofen (OR, 3.68 [95% CrI, 1.09-14.59]; absolute risk difference, 201 [95% CrI, 18-281] more per 1000 infants), oral acetaminophen (OR, 2.93 [95% CrI, 1.53-5.62]; absolute risk difference, 177 [95% CrI, 83-236] more per 1000 infants), and a standard dose of oral ibuprofen (OR, 2.22 [95% CrI, 1.44-3.40]; absolute risk difference, 142 [95% CrI, 72-194] more per 1000 infants) (Figure 6A).

The network OR for each possible comparison for all 8 outcomes along with their mean SUCRA values and median

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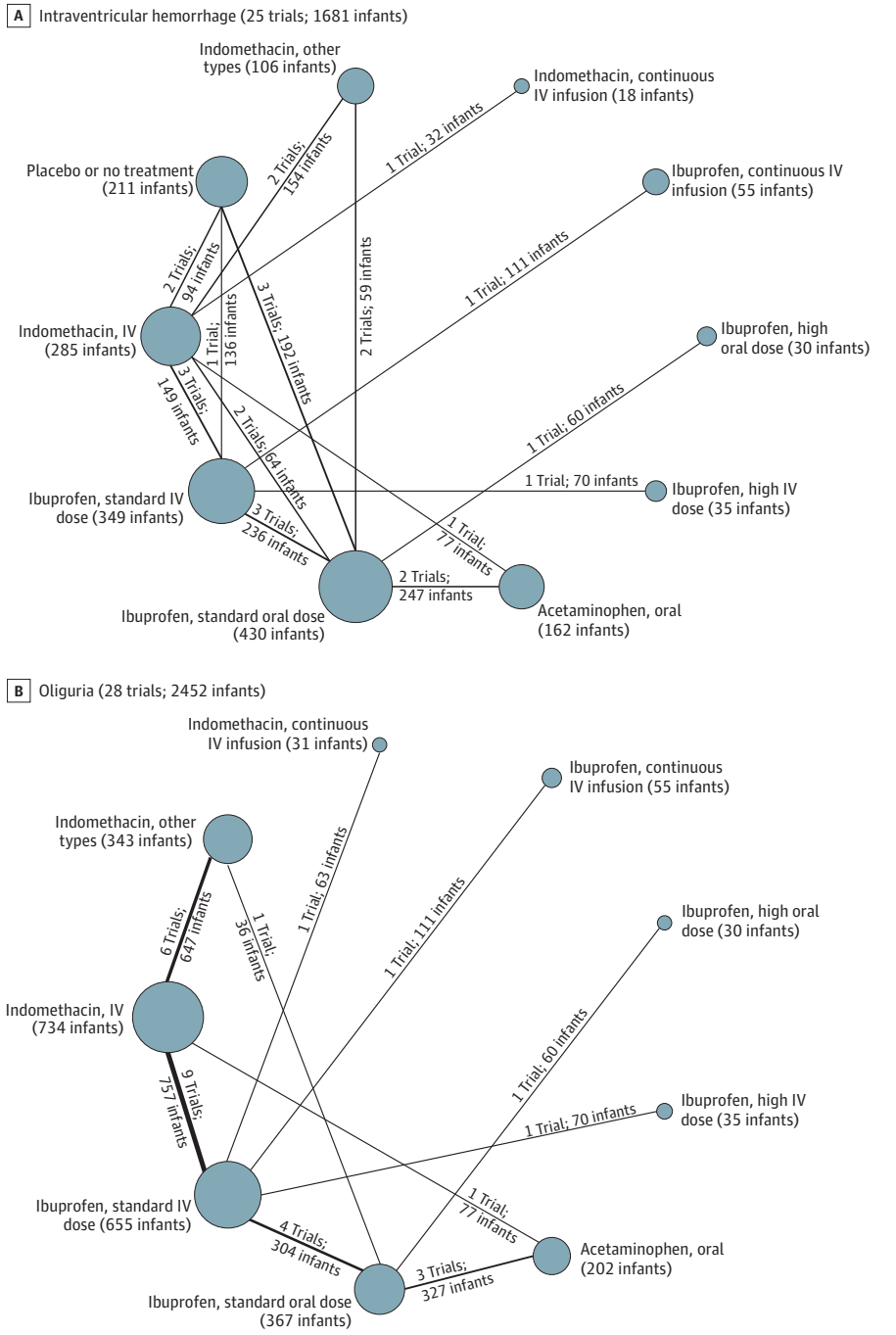
Figure 5. Network Plots for Intraventricular Hemorrhage and Oliguria



These 2 outcome measures for treatment of hemodynamically significant patent ductus arteriosus were evaluated in the Bayesian network meta-analysis. Each node indicates a treatment modality and is sized proportionally to the number of infants who received the treatment modality. Each line connecting 2 nodes indicates a direct comparison between 2 modalities, and the thickness of each is proportional to the number of trials directly comparing the 2 modalities. Seldom-used variations of indomethacin were condensed into a single node termed *indomethacin, other types*. A standard dose of ibuprofen is 10 mg/kg followed by 5 mg/kg every 12 to 24 hours for a total of 3 doses. A high dose of ibuprofen is 15 to 20 mg/kg followed by 7.5 to 10 mg/kg every 12 to 24 hours for a total of 3 doses. IV indicates intravenous.

ranks appear in Figures 6, **7**, **8**, and **9**. Based on mean SUCRA values, a high dose of oral ibuprofen was ranked as the best treatment option for PDA closure (mean SUCRA, 0.89 [SD, 0.12]) and for reducing surgical PDA ligation (mean SUCRA, 0.98 [SD, 0.08]). In terms of reducing the need for repeat pharmacotherapy, a high dose of intravenous ibuprofen (mean SUCRA, 0.83 [SD, 0.24]) and oral acetaminophen (mean SUCRA, 0.82 [SD, 0.15]) were ranked as the best (Figure 6B; eTables 5-10 and eFigures 4-9 in Supplement 3).

Adverse Events

Neonatal mortality was reported in 46 studies (3329 infants). The incidence of death was 11.9% in all studies and 17.4% in the placebo or no treatment group. Although a standard dose of oral ibuprofen ranked best in terms of preventing mortality (mean SUCRA, 0.71 [SD, 0.20]), there was no statistically significant difference between any of the treatment modalities in the network in relation to neonatal mortality (Figure 7B; eTables 11-12 and eFigures 10-11 in Supplement 3).

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Figure 6. Network Effect Estimates and Ranking Statistics for Patent Ductus Arteriosus Closure and the Need for Repeat Pharmacotherapy

The unlabeled data in the boxes are odds ratios (ORs) and 95% credible intervals (CrIs). An OR >1 suggests that the upper left treatment is associated with a higher odds of having the outcome of interest vs the corresponding lower right treatment and the opposite is true for an OR <1. SUCRA, surface under the cumulative ranking curve.

[a] $P < .05$ indicates statistically significant inconsistency between the direct and indirect estimates in the network as assessed by the design × treatment interaction model.

[b] No studies using a continuous IV infusion of ibuprofen reported on the need for repeat pharmacotherapy; therefore, this intervention was excluded from the respective outcome network.

A Patent ductus arteriosus closure, $P = .07$ for network inconsistency[a]

	Ibuprofen, high oral dose	Ibuprofen, high IV dose	Acetaminophen, oral	Ibuprofen, standard oral dose	Indomethacin, IV	Indomethacin, other types	Indomethacin, continuous IV infusion	Ibuprofen, standard IV dose	Ibuprofen, continuous IV infusion	Placebo or no treatment
	Mean SUCRA, 0.89 (SD, 0.12); median rank, 2 (95% CrI, 1-5)									
	0.98 (0.20-4.24)	Mean SUCRA, 0.84 (SD, 0.20); median rank, 2 (95% CrI, 1-7)								
	1.23 (0.62-2.48)	1.25 (0.31-5.77)	Mean SUCRA, 0.82 (SD, 0.12); median rank, 3 (95% CrI, 1-5)							
	1.63 (0.84-3.24)	1.66 (0.45-7.07)	1.33 (0.81-2.17)	Mean SUCRA, 0.68 (SD, 0.10); median rank, 4 (95% CrI, 2-6)						
	2.35 (1.08-5.31)	2.41 (0.68-9.86)	1.92 (1.00-3.68)	1.45 (0.94-2.24)	Mean SUCRA, 0.48 (SD, 0.1); median rank, 6 (95% CrI, 4-7)					
	2.36 (1.04-5.46)	2.42 (0.64-10.35)	1.93 (0.95-3.84)	1.46 (0.87-2.37)	1.01 (0.64-1.52)	Mean SUCRA, 0.47 (SD, 0.13); median rank, 6 (95% CrI, 3-8)				
	2.84 (0.85-9.59)	2.91 (0.62-15.44)	2.31 (0.76-7.05)	1.74 (0.64-4.77)	1.20 (0.47-3.10)	1.19 (0.44-3.40)	Mean SUCRA, 0.40 (SD, 0.21); median rank, 7 (95% CrI, 2-9)			
	3.59 (1.64-8.17)	3.68 (1.09-14.59)	2.93 (1.53-5.62)	2.22 (1.44-3.40)	1.53 (1.13-2.09)	1.51 (0.95-2.56)	1.27 (0.50-3.19)	Mean SUCRA, 0.24 (SD, 0.07); median rank, 8 (95% CrI, 7-9)		
	5.01 (1.56-17.00)	5.19 (1.13-26.09)	4.08 (1.35-12.47)	3.08 (1.16-8.35)	2.14 (0.84-5.50)	2.12 (0.79-5.99)	1.79 (0.49-6.24)	1.39 (0.58-3.41)	Mean SUCRA, 0.17 (SD, 0.13); median rank, 9 (95% CrI, 5-9)	
	16.12 (7.25-37.34)	16.53 (4.50-70.42)	13.16 (6.75-26.26)	9.93 (6.23-16.08)	6.88 (4.62-10.28)	6.82 (4.21-11.41)	5.71 (2.07-15.60)	4.49 (2.90-6.95)	3.23 (1.20-8.58)	Mean SUCRA, 0.001 (SD, 0.012); median rank, 10 (95% CrI, 10-10)

B Need for repeat pharmacotherapy,[b] $P = .39$ for network inconsistency[a]

	Ibuprofen, high oral dose	Ibuprofen, high IV dose	Acetaminophen, oral	Ibuprofen, standard oral dose	Indomethacin, IV	Indomethacin, other types	Indomethacin, continuous IV infusion	Ibuprofen, standard IV dose	Placebo or no treatment
	Mean SUCRA, 0.72 (SD, 0.22); median rank, 3 (95% CrI, 1-7)								
	1.39 (0.29-7.69)	Mean SUCRA, 0.83 (SD, 0.24); median rank, 1 (95% CrI, 1-7)							
	1.16 (0.53-2.78)	0.82 (0.18-3.64)	Mean SUCRA, 0.82 (SD, 0.15); median rank, 2 (95% CrI, 1-5)						
	0.89 (0.40-2.18)	0.62 (0.15-2.60)	0.77 (0.40-1.39)	Mean SUCRA, 0.67 (SD, 0.14); median rank, 4 (95% CrI, 2-6)					
	0.49 (0.21-1.42)	0.35 (0.10-1.42)	0.43 (0.18-0.96)	0.56 (0.32-1.00)	Mean SUCRA, 0.33 (SD, 0.11); median rank, 6 (95% CrI, 4-8)				
	0.75 (0.30-2.18)	0.53 (0.14-2.26)	0.65 (0.28-1.55)	0.75 (0.30-2.18)	1.49 (0.94-2.63)	Mean SUCRA, 0.58 (SD, 0.16); median rank, 5 (95% CrI, 2-6)			
	0.51 (0.11-2.39)	0.36 (0.06-2.18)	0.44 (0.10-1.72)	0.56 (0.14-2.09)	1.01 (0.32-3.58)	0.65 (0.17-2.39)	Mean SUCRA, 0.38 (SD, 0.24); median rank, 6 (95% CrI, 1-8)		
	0.35 (0.14-0.95)	0.25 (0.07-0.91)	0.30 (0.12-0.67)	0.39 (0.21-0.72)	0.70 (0.46-1.08)	0.47 (0.25-0.79)	0.71 (0.21-2.43)	Mean SUCRA, 0.17 (SD, 0.07); median rank, 8 (95% CrI, 6-8)	
	0.07 (0.02-0.24)	0.05 (0.01-0.21)	0.06 (0.02-0.17)	0.08 (0.03-0.19)	0.15 (0.06-0.27)	0.10 (0.04-0.21)	0.14 (0.03-0.56)	0.21 (0.10-0.40)	Mean SUCRA, 0.0003 (SD, 0.0056); median rank, 9 (95% CrI, 9-9)

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Figure 7. Network Effect Estimates and Ranking Statistics for Need for Surgical Patent Ductus Arteriosus Ligation and Neonatal Mortality

The unlabeled data in the boxes are odds ratios and 95% credible intervals (CrIs). SUCRA, surface under the cumulative ranking curve.

[a] $P < .05$ indicates statistically significant inconsistency between the direct and indirect estimates in the network as assessed by the design × treatment interaction model.

A Need for surgical patent ductus arteriosus ligation, $P = .37$ for network inconsistency[a]

	Ibuprofen, high oral dose	Ibuprofen, high IV dose	Acetaminophen, oral	Ibuprofen, standard oral dose	Indomethacin, IV	Indomethacin, other types	Indomethacin, continuous IV infusion	Ibuprofen, standard IV dose	Ibuprofen, continuous IV infusion	Placebo or no treatment
Ibuprofen, high oral dose	Mean SUCRA, 0.98 (SD, 0.08); median rank, 1 (95% CrI, 1-3)									
Ibuprofen, high IV dose	0.01 (0-0.67)	Mean SUCRA, 0.33 (SD, 0.30); median rank, 8 (95% CrI, 2-10)								
Acetaminophen, oral	0.04 (0-2.81)	4.0 (0.10-100.00)	Mean SUCRA, 0.65 (SD, 0.28); median rank, 3 (95% CrI, 1-10)							
Ibuprofen, standard oral dose	0.02 (0-0.51)	2.22 (0.14-50.00)	0.59 (0.03-7.45)	Mean SUCRA, 0.59 (SD, 0.17); median rank, 4 (95% CrI, 2-8)						
Indomethacin, IV	0.01 (0-0.39)	1.41 (0.10-25.00)	0.37 (0.02-5.08)	0.63 (0.21-1.76)	Mean SUCRA, 0.41 (SD, 0.41); median rank, 6 (95% CrI, 4-9)					
Indomethacin, other types	0.02 (0-0.44)	1.59 (0.11-25.00)	0.41 (0.02-6.11)	0.71 (0.23-2.02)	1.12 (0.55-2.33)	Mean SUCRA, 0.47 (SD, 0.17); median rank, 6 (95% CrI, 3-9)				
Indomethacin, continuous IV infusion	0.02 (0-1.45)	2.33 (0.08-100.00)	0.62 (0.01-21.65)	1.02 (0.08-15.35)	1.64 (0.14-20.00)	1.43 (0.12-20.00)	Mean SUCRA, 0.55 (SD, 0.29); median rank, 4 (95% CrI, 2-10)			
Ibuprofen, standard IV dose	0.01 (0-0.26)	0.97 (0.07-14.23)	0.26 (0.01-3.52)	0.44 (0.14-1.18)	0.70 (0.33-1.26)	0.62 (0.24-1.41)	0.43 (0.03-4.09)	Mean SUCRA, 0.24 (SD, 0.12); median rank, 8 (95% CrI, 5-9)		
Ibuprofen, continuous IV infusion	0.05 (0-2.19)	4.78 (0.19-127.84)	1.23 (0.03-31.98)	2.08 (0.21-19.89)	3.37 (0.41-26.70)	2.89 (0.34-25.56)	2.04 (0.08-43.79)	4.69 (0.71-37.43)	Mean SUCRA, 0.73 (SD, 0.21); median rank, 3 (95% CrI, 1-9)	
Placebo or no treatment	0 (0-0.11)	0.40 (0.03-7.18)	0.10 (0.01-1.57)	0.18 (0.05-0.54)	0.29 (0.12-0.65)	0.25 (0.11-0.57)	0.18 (0.01-2.12)	0.41 (0.17-1.11)	0.09 (0.01-0.76)	Mean SUCRA, 0.05 (SD, 0.08); median rank, 10 (95% CrI, 8-10)

B Neonatal mortality, $P = .37$ for network inconsistency[a]

	Ibuprofen, high oral dose	Ibuprofen, high IV dose	Acetaminophen, oral	Ibuprofen, standard oral dose	Indomethacin, IV	Indomethacin, other types	Indomethacin, continuous IV infusion	Ibuprofen, standard IV dose	Ibuprofen, continuous IV infusion	Placebo or no treatment
Ibuprofen, high oral dose	Mean SUCRA, 0.32 (SD, 0.38); median rank, 9 (95% CrI, 1-10)									
Ibuprofen, high IV dose	2.03 (0.09-92.38)	Mean SUCRA, 0.52 (SD, 0.34); median rank, 6 (95% CrI, 1-10)								
Acetaminophen, oral	2.47 (0.15-80.63)	1.24 (0.25-6.83)	Mean SUCRA, 0.66 (SD, 0.26); median rank, 4 (95% CrI, 1-9)							
Ibuprofen, standard oral dose	2.61 (0.19-76.13)	2.22 (0.14-50)	1.03 (0.49-2.34)	Mean SUCRA, 0.71 (SD, 0.20); median rank, 3 (95% CrI, 1-8)						
Indomethacin, IV	2.19 (0.15-72.38)	1.07 (0.27-4.81)	0.87 (0.35-2.10)	0.84 (0.45-1.53)	Mean SUCRA, 0.58 (SD, 0.17); median rank, 5 (95% CrI, 2-8)					
Indomethacin, other types	1.91 (0.12-61.77)	0.94 (0.23-4.53)	0.75 (0.32-1.95)	0.72 (0.37-1.45)	0.87 (0.59-1.32)	Mean SUCRA, 0.45 (SD, 0.20); median rank, 6 (95% CrI, 2-9)				
Indomethacin, continuous IV infusion	1.22 (0.04-53.71)	0.60 (0.06-4.01)	0.45 (0.06-2.59)	0.44 (0.06-2.08)	0.53 (0.08-2.36)	0.60 (0.09-2.75)	Mean SUCRA, 0.29 (SD, 0.31); median rank, 9 (95% CrI, 1-10)			
Ibuprofen, standard IV dose	2.39 (0.15-88.03)	1.20 (0.32-5.06)	0.95 (0.38-2.52)	0.91 (0.52-1.83)	1.10 (0.69-1.78)	1.27 (0.70-2.25)	2.09 (0.49-14.65)	Mean SUCRA, 0.66 (SD, 0.19); median rank, 4 (95% CrI, 1-7)		
Ibuprofen, continuous IV infusion	2.51 (0.02-293.17)	1.21 (0.03-41.79)	0.91 (0.02-26.32)	0.95 (0.02-24.84)	1.11 (0.03-29.26)	1.27 (0.03-36.40)	2.26 (0.03-87.92)	1.02 (0.03-25.35)	Mean SUCRA, 0.56 (SD, 0.43); median rank, 4 (95% CrI, 1-10)	
Placebo or no treatment	1.41 (0.09-50.18)	0.71 (0.18-3.38)	0.57 (0.24-1.40)	0.55 (0.30-1.03)	0.65 (0.42-1.09)	0.75 (0.46-1.29)	1.27 (0.27-8.39)	0.60 (0.34-1.05)	0.61 (0.02-22.92)	Mean SUCRA, 0.26 (SD, 0.15); median rank, 8 (95% CrI, 4-10)

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Figure 8. Network Effect Estimates and Ranking Statistics for Necrotizing Enterocolitis and Bronchopulmonary Dysplasia

The unlabeled data in the boxes are odds ratios and 95% credible intervals (CrIs). SUCRA, surface under the cumulative ranking curve.

[a] $P < .05$ indicates statistically significant inconsistency between the direct and indirect estimates in the network as assessed by the design × treatment interaction model.

[b] No studies using a high oral dose of ibuprofen and continuous IV infusion of indomethacin reported on bronchopulmonary dysplasia; therefore, these interventions were excluded from the respective outcome network.

A Necrotizing enterocolitis, $P = .99$ for network inconsistency[a]

	Ibuprofen, high oral dose	Ibuprofen, high IV dose	Acetaminophen, oral	Ibuprofen, standard oral dose	Indomethacin, IV	Indomethacin, other types	Indomethacin, continuous IV infusion	Ibuprofen, standard IV dose	Ibuprofen, continuous IV infusion	Placebo or no treatment
Ibuprofen, high oral dose	Mean SUCRA, 0.74 (SD, 0.29); median rank, 2 (95% CrI, 1-10)									
Ibuprofen, high IV dose	0.31 (0.02-3.63)	Mean SUCRA, 0.30 (SD, 0.31); median rank, 8 (95% CrI, 1-10)								
Acetaminophen, oral	0.66 (0.10-4.24)	2.16 (0.29-18.21)	Mean SUCRA, 0.62 (SD, 0.24); median rank, 4 (95% CrI, 1-9)							
Ibuprofen, standard oral dose	0.75 (0.15-3.72)	2.39 (0.38-16.16)	1.12 (0.42-2.88)	Mean SUCRA, 0.70 (SD, 0.15); median rank, 4 (95% CrI, 1-7)						
Indomethacin, IV	0.30 (0.05-1.72)	0.97 (0.17-6.29)	0.46 (0.16-1.29)	0.41 (0.21-0.75)	Mean SUCRA, 0.21 (SD, 0.11)); median rank, 8 (95% CrI, 6-9)					
Indomethacin, other types	0.20 (0.03-1.18)	0.63 (0.10-4.36)	0.30 (0.10-0.91)	0.27 (0.12-0.57)	0.65 (0.38-1.13)	Mean SUCRA, 0.06 (SD, 0.09); median rank, 10 (95% CrI, 7-10)				
Indomethacin, continuous IV infusion	0.73 (0.08-5.80)	2.33 (0.28-20.42)	1.08 (0.20-5.80)	0.98 (0.23-4.01)	2.40 (0.61-9.37)	3.68 (0.84-15.96)	Mean SUCRA, 0.65 (SD, 0.27); median rank, 4 (95% CrI, 1-10)			
Ibuprofen, standard IV dose	0.45 (0.08-2.65)	1.46 (0.27-8.94)	0.68 (0.23-2.04)	0.61 (0.30-1.16)	1.48 (0.88-2.51)	2.30 (1.10-4.81)	0.63 (0.17-2.22)	Mean SUCRA, 0.42 (SD, 0.14); median rank, 6 (95% CrI, 4-8)		
Ibuprofen, continuous IV infusion	1.21 (0.12-14.21)	3.90 (0.40-52.83)	1.78 (0.30-13.66)	1.62 (0.32-10.70)	3.96 (0.83-25.32)	6.18 (1.15-42.37)	1.67 (0.23-16.00)	2.68 (0.60-15.69)	Mean SUCRA, 0.81 (SD, 0.24); median rank, 2 (95% CrI, 1-9)	
Placebo or no treatment	0.52 (0.08-3.15)	1.63 (0.27-11.94)	0.76 (0.24-2.45)	0.69 (0.30-1.52)	1.67 (0.82-3.50)	2.58 (1.06-6.65)	0.70 (0.17-3.02)	1.14 (0.55-2.36)	0.42 (0.06-2.13)	Mean SUCRA, 0.50 (SD, 0.19); median rank, 6 (95% CrI, 2-9)

B Bronchopulmonary dysplasia,[b] $P = .59$ for network inconsistency[a]

	Ibuprofen, high IV dose	Acetaminophen, oral	Ibuprofen, standard oral dose	Indomethacin, IV	Indomethacin, other types	Ibuprofen, standard IV dose	Ibuprofen, continuous IV infusion	Placebo or no treatment
Ibuprofen, high IV dose	Mean SUCRA, 0.12 (SD, 0.22); median rank, 8 (95% CrI, 2-8)							
Acetaminophen, oral	3.73 (0.90-15.61)	Mean SUCRA, 0.86 (SD, 0.21); median rank, 1 (95% CrI, 1-6)						
Ibuprofen, standard oral dose	3.49 (0.99-12.43)	0.91 (0.38-2.15)	Mean SUCRA, 0.87 (SD, 0.13); median rank, 2 (95% CrI, 1-4)					
Indomethacin, IV	2.37 (0.73-8.02)	0.63 (0.25-1.53)	0.68 (0.40-1.14)	Mean SUCRA, 0.61 (SD, 0.16); median rank, 4 (95% CrI, 2-6)				
Indomethacin, other types	1.75 (0.47-6.33)	0.46 (0.17-1.27)	0.50 (0.24-1.02)	0.74 (0.43-1.27)	Mean SUCRA, 0.32 (SD, 0.22); median rank, 6 (95% CrI, 2-8)			
Ibuprofen, standard IV dose	2.14 (0.71-6.86)	0.57 (0.22-1.38)	0.62 (0.36-1.03)	0.91 (0.65-1.28)	1.23 (0.65-2.35)	Mean SUCRA, 0.50 (SD, 0.16); median rank, 4 (95% CrI, 2-7)		
Ibuprofen, continuous IV infusion	1.87 (0.41-9.17)	0.50 (0.13-2.11)	0.55 (0.17-1.83)	0.80 (0.27-2.47)	1.10 (0.31-3.93)	0.88 (0.31-2.55)	Mean SUCRA, 0.43 (SD, 0.33); median rank, 5 (95% CrI, 1-8)	
Placebo or no treatment	1.72 (0.49-6.01)	0.46 (0.17-1.12)	0.50 (0.28-0.84)	0.73 (0.45-1.12)	0.98 (0.50-1.92)	0.80 (0.48-1.32)	0.90 (0.28-2.88)	Mean SUCRA, 0.29 (SD, 0.18); median rank, 6 (95% CrI, 3-8)

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Figure 9. Network Effect Estimates and Ranking Statistics for Intraventricular Hemorrhage and Oliguria

The unlabeled data in the boxes are odds ratios and 95% credible intervals (CrIs). SUCRA, surface under the cumulative ranking curve.

[a] $P < .05$ indicates statistically significant inconsistency between the direct and indirect estimates in the network as assessed by the design × treatment interaction model.

[b] No studies using placebo or no treatment reported on oliguria; therefore, this intervention was excluded from the respective outcome network.

A Intraventricular hemorrhage, $P = .62$ for network inconsistency[a]

	Ibuprofen, high oral dose	Ibuprofen, high IV dose	Acetaminophen, oral	Ibuprofen, standard oral dose	Indomethacin, IV	Indomethacin, other types	Indomethacin, continuous IV infusion	Ibuprofen, standard IV dose	Ibuprofen, continuous IV infusion	Placebo or no treatment
Ibuprofen, high oral dose	Mean SUCRA, 0.65 (SD, 0.31); median rank, 3 (95% CrI, 1-10)									
Ibuprofen, high IV dose	1.29 (0.19-8.48)	Mean SUCRA, 0.73 (SD, 0.31); median rank, 2 (95% CrI, 1-10)								
Acetaminophen, oral	0.67 (0.17-2.48)	0.52 (0.10-2.69)	Mean SUCRA, 0.42 (SD, 0.27); median rank, 7 (95% CrI, 2-10)							
Ibuprofen, standard oral dose	0.73 (0.23-2.18)	0.57 (0.12-2.64)	1.09 (0.54-2.22)	Mean SUCRA, 0.49 (SD, 0.20); median rank, 6 (95% CrI, 2-9)						
Indomethacin, IV	0.68 (0.19-2.34)	0.53 (0.11-2.50)	1.02 (0.46-2.23)	0.93 (0.51-1.66)	Mean SUCRA, 0.43 (SD, 0.22); median rank, 6 (95% CrI, 2-9)					
Indomethacin, other types	0.49 (0.12-1.85)	0.38 (0.07-2.01)	0.74 (0.27-1.95)	0.68 (0.30-1.47)	0.72 (0.36-1.41)	Mean SUCRA, 0.21 (SD, 0.22); median rank, 9 (95% CrI, 3-10)				
Indomethacin, continuous IV infusion	0.56 (0-148.43)	0.44 (0-124.55)	0.85 (0-221.80)	0.78 (0-199.52)	0.83 (0-207.80)	1.15 (0-288.80)	Mean SUCRA, 0.45 (SD, 0.46); median rank, 8 (95% CrI, 1-10)			
Ibuprofen, standard IV dose	0.76 (0.21-2.57)	0.59 (0.14-2.45)	1.14 (0.50-2.59)	1.04 (0.62-1.77)	1.12 (0.61-2.04)	1.54 (0.66-3.64)	1.34 (0.01-1413.00)	Mean SUCRA, 0.52 (SD, 0.21); median rank, 5 (95% CrI, 2-9)		
Ibuprofen, continuous IV infusion	1.10 (0.18-6.66)	0.85 (0.13-5.98)	1.63 (0.36-8.16)	1.50 (0.39-6.38)	1.62 (0.40-7.01)	2.24 (0.48-11.08)	1.99 (0.01-2354.00)	1.44 (0.42-5.47)	Mean SUCRA, 0.68 (SD, 0.31); median rank, 3 (95% CrI, 1-10)	
Placebo or no treatment	0.67 (0.19-2.32)	0.53 (0.11-2.49)	1.02 (0.44-2.32)	0.93 (0.56-1.56)	1.00 (0.54-1.85)	1.37 (0.59-3.25)	1.19 (0-1314.75)	0.89 (0.52-1.53)	0.62 (0.14-2.43)	Mean SUCRA, 0.42 (SD, 0.23); median rank, 6 (95% CrI, 2-10)

B Oliguria,[b] $P = .03$ for network inconsistency[a]

	Ibuprofen, high oral dose	Ibuprofen, high IV dose	Acetaminophen, oral	Ibuprofen, standard oral dose	Indomethacin, IV	Indomethacin, other types	Indomethacin, continuous IV infusion	Ibuprofen, standard IV dose	Ibuprofen, continuous IV infusion
Ibuprofen, high oral dose	Mean SUCRA, 0.02 (SD, 0.10); median rank, 9 (95% CrI, 8-9)								
Ibuprofen, high IV dose	2.43e+10 (1.40-7.54e+17)	Mean SUCRA, 0.40 (SD, 0.23); median rank, 6 (95% CrI, 2-8)							
Acetaminophen, oral	1.12e+11 (6.51-4.06e+18)	4.71 (0.30-71.49)	Mean SUCRA, 0.79 (SD, 0.16); median rank, 2 (95% CrI, 1-6)						
Ibuprofen, standard oral dose	5.71e+10 (3.48-2.2e+18)	2.45 (0.19-33.70)	0.55 (0.22-1.27)	Mean SUCRA, 0.60 (SD, 0.19); median rank, 4 (95% CrI, 2-7)					
Indomethacin, IV	1.15e+10 (0.62-4.34e+17)	0.47 (0.06-3.88)	0.10 (0.02-0.58)	0.20 (0.04-0.92)	Mean SUCRA, 0.20 (SD, 0.09); median rank, 8 (95% CrI, 6-8)				
Indomethacin, other types	5.07e+10 (2.20-1.99e+18)	2.16 (0.29-17.87)	0.48 (0.08-2.93)	0.89 (0.16-4.66)	4.56 (2.63-8.10)	Mean SUCRA, 0.61 (SD, 0.17); median rank, 4 (95% CrI, 2-7)			
Indomethacin, continuous IV infusion	8.83e+10 (2.69-1.98e+18)	1.21 (0-718.30)	0.29 (0-91.66)	0.53 (0-166.25)	2.69 (0.01-1009.00)	0.59 (0-248.40)	Mean SUCRA, 0.50 (SD, 0.35); median rank, 6 (95% CrI, 1-8)		
Ibuprofen, standard IV dose	4.53e+10 (1.99-1.37e+18)	1.64 (0.24-11.85)	0.35 (0.07-1.98)	0.68 (0.15-2.99)	3.42 (2.16-5.68)	0.76 (0.37-1.55)	1.28 (0-226.60)	Mean SUCRA, 0.49 (SD, 0.14); median rank, 5 (95% CrI, 3-7)	
Ibuprofen, continuous IV infusion	4.84e+11 (66.5 -2.88e+20)	26.5 (0.52-4923.00)	5.55 (0.10 -976.50)	10.40 (0.20-1519.00)	48.00 (1.93-7496.00)	11.13 (0.40-1693.00)	17.44 (0.02-36 280.00)	14.15 (0.54-1916.00)	Mean SUCRA, 0.90 (SD, 0.18); median rank, 1 (95% CrI, 1-6)

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Incidence of necrotizing enterocolitis was reported in 45 studies (3371 infants). The overall incidence of necrotizing enterocolitis was 8.7% and it was 6.5% in the placebo or no treatment group. Continuous infusion of intravenous ibuprofen (mean SUCRA, 0.81 [SD, 0.24]) was associated with the lowest incidence of necrotizing enterocolitis (Figure 8A; eTables 13-14 and eFigures 12-13 in Supplement 3). A standard dose of intravenous ibuprofen (mean SUCRA, 0.42 [SD, 0.14]) and a high dose of intravenous ibuprofen (mean SUCRA, 0.30 [SD, 0.31]) and a standard dose of intravenous indomethacin (mean SUCRA, 0.21 [SD, 0.11]) ranked worse than placebo or no treatment (mean SUCRA, 0.50 [SD, 0.19]) in terms of necrotizing enterocolitis incidence; however, the differences in their effect estimates failed to reach statistical significance (Figure 8A).

A standard dose of oral ibuprofen was associated with the lowest incidence of bronchopulmonary dysplasia (mean SUCRA, 0.87 [SD, 0.13]; Figure 8B). A high dose of intravenous ibuprofen was associated with the lowest incidence of intraventricular hemorrhage (mean SUCRA, 0.73 [SD, 0.31]; Figure 9A). A continuous infusion of intravenous ibuprofen was associated with the lowest incidence of oliguria (mean SUCRA, 0.90 [SD, 0.18]; Figure 9B) (eTables 15-20 and eFigures 14-19 in Supplement 3). Heat maps depicting the hierarchy of the 10 treatment modalities according to mean SUCRA values across all 8 outcomes appear in **Figure 10**. Due to the paucity of data, quantitative synthesis was not performed on the remaining a priori-defined outcomes (Table).

Assessment of the Quality of the Evidence

For the primary outcome of PDA closure, there were 17 direct comparisons and 45 possible comparisons in the network. Using the GRADE assessment methods, the quality of evidence for 6 comparisons was judged to be of high quality, 14 of moderate quality, 20 of low quality, and 5 of very low quality (eTable 5 in Supplement 3). The quality of the evidence for a number of secondary outcome comparisons (especially adverse events) was rated as low or very low due to the imprecise effect estimates as evidenced by the wide 95% CrIs (eTables 7, 9, 11, 13, 15, 17, 19 in Supplement 3). For the global assessment of network inconsistency using the design × treatment interaction model, only the oliguria network effect estimate showed significant inconsistency (P = .03; Figure 9B).

Sensitivity Analyses

The sensitivity analyses for the outcomes were only conducted for the high-quality studies (Figure 10; eTables 21-36 and eFigures 20-27 in Supplement 3). A high dose of oral ibuprofen still ranked as the best treatment option for PDA closure (mean SUCRA, 0.88 [SD, 0.15]) and reducing surgical ligation (mean SUCRA, 0.97 [SD, 0.09]) (eTables 22 and 26 in Supplement 3). It also emerged as the best-ranked treatment for preventing necrotizing enterocolitis (mean SUCRA, 0.97 [SD, 0.09]) vs a continuous intravenous infusion of ibuprofen (mean SUCRA, 0.74 [SD, 0.19]) (eTable 30 in Supplement 3).

Meta-Regression Analysis

In the meta-regression analysis exploring the effects of potential sources of heterogeneity, such as gestational age, birth weight, and year of publication, a high dose of oral ibuprofen remained the best-ranked treatment for PDA closure (eTables 37-44 and eText 3 in Supplement 3). Even after controlling for potential effect modifiers, a high dose of oral ibuprofen still had a significantly higher odds of PDA closure compared with standard doses of intravenous ibuprofen and intravenous indomethacin (eTable 37 in Supplement 3).

Discussion

In this network meta-analysis, a high dose of oral ibuprofen was found to be associated with the best odds of hemodynamically significant PDA closure among all available pharmacotherapeutic options. The quality of evidence was high or moderate for 20 of the 45 comparisons for the primary outcome, whereas it was uniformly lower for most of the secondary outcomes in light of the imprecision resulting from wide 95% CrIs on the network meta-analysis.

Management of PDA has evolved during the last 4 decades from requiring prophylactic closure using pharmacotherapy or surgical intervention to one that is amenable to more conservative management strategies.[1,7] Conservative management strategies have ranged from targeted pharmacotherapy (based on echocardiographic or clinical criteria for hemodynamic significance) to no PDA treatment combined with cointerventions such as fluid restriction and ventilator adjustments.[7] Despite ranking worst in terms of PDA closure, placebo or no treatment was not associated with a higher odds of death, necrotizing enterocolitis, or intraventricular hemorrhage compared with any other treatment modality. This raises the question whether active pharmacological closure of hemodynamically significant PDA necessarily improves clinical outcomes. With increasing emphasis on conservative management of PDA, these results may encourage researchers to revisit placebo-controlled trials against newer pharmacotherapeutic options.[1,5]

Targeted PDA treatment has become the preferred approach; therefore, the question of choice of pharmacotherapy has become more important.[7,9] A number of Cochrane systematic reviews of randomized clinical trials have provided head-to-head comparisons of the various management options. They concluded that ibuprofen was as effective as indomethacin for PDA closure, whereas the former reduced the risk of necrotizing enterocolitis and transient renal insufficiency.[105] There was insufficient evidence to suggest benefit of any of the variations in treatment with a standard dose of indomethacin.[106] Oral acetaminophen was found to be as effective as oral ibuprofen for PDA closure based on only 2 unblinded randomized clinical trials.[107]

However, none of the reviews conducted an in-depth comparison of the different doses and modes of administration for the different medications. In regard to the multiple treatment comparisons, only 1 network meta-analysis[108] compared intravenous indomethacin, intravenous ibuprofen, and placebo for hemodynamically significant PDA but did not include evidence for acetaminophen. Oral acetaminophen has recently emerged as a new treatment option as well as higher

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Figure 10. Heat Maps of 10 Treatment Modalities Studied in Preterm Infants With Hemodynamically Significant PDA for 8 Outcomes

A Network meta-analysis with all studies included

Treatment modality

Outcome	Ibuprofen, high oral dose	Ibuprofen, high IV dose	Acetaminophen, oral	Ibuprofen, standard oral dose	Indomethacin, IV	Indomethacin, other types	Indomethacin, continuous IV infusion	Ibuprofen, standard IV dose	Ibuprofen, continuous IV infusion	Placebo or no treatment
PDA closure (n = 60)	0.89 (0.12)	0.84 (0.20)	0.82 (0.12)	0.68 (0.10)	0.48 (0.10)	0.47 (0.13)	0.40 (0.21)	0.24 (0.07)	0.17 (0.13)	0 (0.01)
Need for repeat pharmacotherapy (n = 33)	0.72 (0.22)	0.83 (0.24)	0.82 (0.15)	0.67 (0.14)	0.33 (0.11)	0.58 (0.16)	0.38 (0.24)	0.17 (0.07)	NA	0 (0.01)
Need for surgical PDA ligation (n = 37)	0.98 (0.08)	0.33 (0.30)	0.65 (0.28)	0.59 (0.17)	0.41 (0.14)	0.47 (0.17)	0.55 (0.29)	0.24 (0.12)	0.73 (0.21)	0.05 (0.08)
Neonatal mortality (n = 46)	0.32 (0.38)	0.52 (0.34)	0.66 (0.26)	0.71 (0.20)	0.58 (0.17)	0.45 (0.20)	0.29 (0.31)	0.66 (0.19)	0.56 (0.43)	0.26 (0.15)
Necrotizing enterocolitis (n = 45)	0.74 (0.29)	0.30 (0.31)	0.62 (0.24)	0.70 (0.15)	0.21 (0.11)	0.06 (0.09)	0.65 (0.27)	0.42 (0.14)	0.81 (0.24)	0.50 (0.19)
Bronchopulmonary dysplasia (n = 32)	NA	0.12 (0.22)	0.86 (0.21)	0.87 (0.13)	0.61 (0.16)	0.32 (0.22)	NA	0.50 (0.16)	0.43 (0.33)	0.29 (0.18)
Intraventricular hemorrhage (n = 25)	0.65 (0.31)	0.73 (0.31)	0.42 (0.27)	0.49 (0.20)	0.43 (0.22)	0.21 (0.22)	0.45 (0.46)	0.52 (0.21)	0.68 (0.31)	0.42 (0.23)
Oliguria (n = 28)	0.02 (0.10)	0.40 (0.23)	0.79 (0.16)	0.60 (0.19)	0.20 (0.09)	0.61 (0.17)	0.50 (0.35)	0.49 (0.14)	0.90 (0.18)	NA

Mean SUCRA 1.0 0.5 0

B Subgroup analysis of high-quality studies[a]

Treatment modality

Outcome	Ibuprofen, high oral dose	Ibuprofen, high IV dose	Acetaminophen, oral	Ibuprofen, standard oral dose	Indomethacin, IV	Indomethacin, other types	Indomethacin, continuous IV infusion	Ibuprofen, standard IV dose	Ibuprofen, continuous IV infusion	Placebo or no treatment
PDA closure (n = 39)	0.88 (0.15)	0.78 (0.25)	0.83 (0.15)	0.64 (0.13)	0.51 (0.13)	0.56 (0.16)	0.38 (0.22)	0.23 (0.08)	0.19 (0.16)	0.01 (0.03)
Need for repeat pharmacotherapy (n = 21)	0.71 (0.21)	0.80 (0.23)	0.83 (0.16)	0.69 (0.15)	0.46 (0.14)	0.08 (0.06)	0.62 (0.17)	0.26 (0.05)	NA	0.05 (0.09)
Need for surgical PDA ligation (n = 28)	0.97 (0.09)	0.30 (0.30)	0.62 (0.29)	0.48 (0.18)	0.39 (0.14)	0.64 (0.14)	0.55 (0.29)	0.24 (0.12)	0.74 (0.19)	0.08 (0.11)
Neonatal mortality (n = 31)	0.37 (0.39)	0.47 (0.33)	0.67 (0.25)	0.71 (0.20)	0.55 (0.19)	0.59 (0.25)	0.25 (0.28)	0.62 (0.18)	0.55 (0.42)	0.24 (0.14)
Necrotizing enterocolitis (n = 28)	0.97 (0.09)	0.30 (0.30)	0.62 (0.29)	0.48 (0.18)	0.39 (0.14)	0.64 (0.14)	0.55 (0.29)	0.24 (0.12)	0.74 (0.19)	0.08 (0.11)
Bronchopulmonary dysplasia (n = 22)	NA	0.15 (0.24)	0.81 (0.25)	0.89 (0.13)	0.55 (0.18)	0.26 (0.26)	NA	0.54 (0.17)	0.45 (0.32)	0.37 (0.20)
Intraventricular hemorrhage (n = 17)	0.61 (0.33)	0.69 (0.32)	0.42 (0.29)	0.47 (0.22)	0.36 (0.25)	NA	0.46 (0.46)	0.46 (0.21)	0.65 (0.32)	0.38 (0.23)
Oliguria (n = 19)	0.01 (0.05)	0.37 (0.23)	0.70 (0.20)	0.66 (0.19)	0.21 (0.09)	0.65 (0.18)	0.54 (0.34)	0.48 (0.14)	0.89 (0.19)	NA

Mean SUCRA 1.0 0.5 0

Each column represents a treatment modality and each row represents an outcome. For each outcome (column 1), the No. of studies included in the analysis is presented in parentheses. IV indicates intravenous; PDA, patent ductus arteriosus; SUCRA, surface under the cumulative ranking curve. Each box is colored according to the mean SUCRA value of the corresponding treatment and outcome. The color scale consists of values that represent mean SUCRA which range from 0 (red, indicating a treatment is always last) to 1 (green, indicating a treatment is always first). Uncolored boxes labeled NA (data not available) show that the underlying treatment was not included for that particular outcome. The values in each box represent the mean (SD) SUCRA value of the corresponding treatment and outcome. A standard dose of ibuprofen is 10 mg/kg followed by 5 mg/kg every 12 to 24 hours for a total of 3 doses. A high dose of ibuprofen is 15 to 20 mg/kg followed by 7.5 to 10 mg/kg every 12 to 24 hours for a total of 3 doses.

[a] High-quality studies indicates there is a low or probably low risk of bias.

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doses of oral ibuprofen.[107,109] Use of a network meta-analysis framework has enabled comparisons among currently used PDA treatment modalities, which has increased the statistical power by taking advantage of direct and indirect treatment comparisons.

In this network meta-analysis, a high dose of oral ibuprofen (15-20 mg/kg followed by 7.5-10.0 mg/kg every 12-24 hours for a total of 3 doses) was found to be associated with a significantly higher likelihood of PDA closure than 2 of the most widely used forms of pharmacotherapy (ie, standard doses of intravenous ibuprofen and intravenous indomethacin). The ibuprofen dose that is traditionally used (10 mg/kg, 5 mg/kg, and 5 mg/kg, each given at 24-hour intervals) is based on old pharmacokinetic data obtained from the experiences of preterm infants.[110] More recent pharmacokinetic studies have shown benefit from using higher doses.[111] In a double-blind dose-finding study, Desfrere et al[112] showed that among infants with a gestational age of younger than 27 weeks, the estimated minimum effective dose regimen of 20 mg/kg, 10 mg/kg, and 10 mg/kg had a higher estimated probability of success (54.8%; 95% CrI, 22%-84%) compared with the conventional dose regimen (30.6%; 95% CrI, 13%-56%). The results of this network meta-analysis are consistent with the above pharmacokinetic data.

Apart from the high dose of oral ibuprofen, oral acetaminophen also consistently ranked high across all effectiveness outcomes, suggesting that it could be an alternative to intravenous ibuprofen and intravenous indomethacin for hemodynamically significant PDA closure. In contrast, the standard dose of intravenous ibuprofen generally ranked just above placebo across all effectiveness outcomes, suggesting that the standard intravenous doses may be ineffective in achieving PDA closure beyond the first few days of life. In the 2015 Cochrane review,[105] intravenous ibuprofen was significantly less efficacious than oral ibuprofen (relative risk, 0.37; 95% confidence interval, 0.23-0.61) in achieving PDA closure. Similar findings were observed in this network meta-analysis in which the intravenous formulation ranked below the oral formulation across most outcomes. Although this finding may appear counterintuitive, available pharmacokinetic data support this observation.[113] Pacifici[114] postulated that a slower absorption rate along with a longer half-life prolong the time of contact with the PDA, leading to higher responsiveness of oral ibuprofen compared with the intravenous formulation.

Despite supporting pharmacokinetic evidence, clinicians have often been reluctant to use oral ibuprofen formulations due to concerns about necrotizing enterocolitis.[115] In this network meta-analysis, a high dose of oral ibuprofen was not associated with an increased incidence of necrotizing enterocolitis (Figure 8A). In the sensitivity analysis of the high-quality studies (Figure 10B), high-dose oral ibuprofen was associated with the best cumulative probability for preventing necrotizing enterocolitis, suggesting that hemodynamically significant PDA in itself is probably a significant risk factor for necrotizing enterocolitis and closing it successfully when hemodynamically significant could in turn reduce the risk of necrotizing enterocolitis.[2]

Despite ranking lower than a high dose of oral ibuprofen across the effectiveness outcomes, a standard dose of oral ibuprofen ranked as the best treatment for preventing death (Figure 10). This apparent paradox in the network meta-analysis results was likely artifactual due to substantial imprecision in the effect estimates for the secondary outcomes as evidenced by the wide 95% CrIs of the ranking statistics (Figure 7B). No statistically significant difference in mortality rates was observed with any of the interventions based on the available evidence, which suggests that active pharmacological closure of a hemodynamically significant PDA may not be associated with lower mortality in preterm infants.

The overall high-ranking probabilities across outcomes suggest that high and standard doses of oral ibuprofen and oral acetaminophen could be effective alternatives to the standard regimens of intravenous ibuprofen and intravenous indomethacin currently used to close a hemodynamically significant PDA (Figure 10). Well-designed randomized clinical trials with optimal sample sizes to detect clinically important differences in effectiveness and safety using such medications are needed to confirm or refute the validity of the network meta-analysis results.

Limitations

This study has several limitations. First, this network meta-analysis was based on the assumption of transitivity, which in turn was based on the assumption that population and intervention characteristics were largely similar across the studies. This transitivity assumption could have been violated due to variation in gestational age, birth weight, timing of treatment, or associated cointerventions, which have changed during the last 4 decades. This was accounted for in the meta-regression analysis conducted for the most important outcomes and controlling for the effect modifiers.

Second, the ranking order of interventions was based on mean SUCRA values, which does not necessarily imply that a higher-ranked intervention was statistically significantly better than a lower-ranked intervention. In addition to the absolute ranks, the dispersion around the ranking statistics and the absolute risk differences between interventions should be taken into account when choosing a pharmacotherapeutic option for hemodynamically significant PDA treatment.

Third, limited sample size resulted in substantial imprecision in the effect estimates for a number of the secondary outcomes in the primary analyses as well as many of the analyses restricted to the higher-quality studies, precluding derivation of meaningful inferences. Clinical outcomes (such as necrotizing enterocolitis, bronchopulmonary dysplasia, intraventricular hemorrhage, and mortality) beyond immediate PDA closure should be explored in future studies.

Conclusions

A high dose of oral ibuprofen was associated with a higher likelihood of hemodynamically significant PDA closure vs standard doses of intravenous ibuprofen or intravenous indomethacin; placebo or no treatment did not significantly change the likelihood of mortality, necrotizing enterocolitis, or intraventricular hemorrhage.

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Accepted for Publication: February 12, 2018.

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Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

Additional Contributions: We thank Jack Young, MLIS (McMaster University Health Sciences Library), for his assistance in the design of the search strategy and Timothy Disher, RN, BScN (Dalhousie University), for his assistance with some of the graphical outputs of the network meta-analysis results. Neither received any compensation for his contribution to the study.

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