# TREATMENT OF PATENT DUCTUS ARTERIOSUS IN PRETERM INFANT

# THE EFFECTIVENESS AND SAFETY OF TREATMENTS USED FOR THE MANAGEMENT OF PATENT DUCTUS ARTERIOSUS (PDA) IN PRETERM INFANTS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS

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TITLE: The effectiveness and safety of treatments used for the management of patent ductus arteriosus (PDA) in preterm infants: a systematic review and network meta-analysis

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## LAY ABSTRACT

The following thesis explores the effectiveness and safety of commonly used drugs for the treatment of a heart condition in premature infants called the patent ductus arteriosus (PDA). Article 1 outlines the protocol for the systematic review and network meta-analysis designed to evaluate the effectiveness and safety of indomethacin, ibuprofen and acetaminophen for the treatment of PDA in preterm infants. Article 2 provides in detail the results of the network meta-analysis that examined all eligible randomized controlled trials that compared intravenous or oral formulations of indomethacin, ibuprofen or acetaminophen compared against to other or placebo for the treatment of a PDA that may be harmful for a premature infant based on certain clinical and echocardiographic criteria set by the clinicians and researchers. Overall, this body of work suggests that a higher dose of oral ibuprofen is the best treatment for PDA in premature infants.

## ABSTRACT

OBJECTIVES: The objective of this thesis is to explore the effectiveness and safety of common pharmacotherapeutic options used for the management of patent ductus arteriosus (PDA) in preterm infants.

METHODS: Following the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidance, article 1 develops the protocol to conduct the systematic review and network meta-analysis to answer the research question. Article 2 details the actual methods implemented to conduct the network meta-analysis and presents the results in the form of network plots, league tables, rank heat maps, rankograms and forest plots.

RESULTS: Article 1 suggests the need to conduct a Bayesian random-effects network meta-analysis of randomized controlled trials (RCTs) as the analysis would involve multiple treatments with potentially both direct and indirect comparisons. Article 1 also *a priori* defines potential effect modifiers and statistical strategies to control for the same. In article 2, the results of the meta-analysis show that in 68 RCTs that included 4802 infants, 14 different variations of indomethacin, ibuprofen or acetaminophen were used. Oral high-dose ibuprofen was associated with a significantly higher odds of PDA closure compared with standard-dose intravenous ibuprofen (Odds Ratio [OR], 3.59; 95% Credible Interval [CrI],1.64-8.17) and intravenous indomethacin (OR, 2.35; 95% CrI,1.08-5.31). Oral high-dose ibuprofen ranked the best option for PDA closure (SUCRA [surface under the cumulative ranking curve],0.89 [SD, 0.12]) and to prevent surgical PDA ligation (SUCRA,0.98 [SD, 0.08]). There was no significant difference in the odds of mortality, necrotizing enterocolitis or intra-ventricular hemorrhage with use of placebo or no treatment compared with any of the other treatment modalities.

CONCLUSION: This thesis suggests that oral high-dose ibuprofen could be the best treatment option for closure of a hemodynamically significant PDA. Placebo or no treatment for a hemodynamically significant PDA may not increase morbidity and mortality.

Keywords: preterm; patent ductus arteriosus; indomethacin; ibuprofen; acetaminophen; network meta-analysis

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## LIST OF ABBREVIATIONS & SYMBOLS

- PDA: Patent ductus arteriosus
- Hs-PDA: hemodynamically-significant PDA
- CENTRAL: Cochrane Central Register of Controlled Trials
- NEC: Necrotizing enterocolitis
- BPD: bronchopulmonary dysplasia
- IVH: Intraventricular hemorrhage
- RCT: Randomized Controlled Trial
- OR: Odds ratio
- CrI: Credible interval
- SUCRA: Surface under the cumulative ranking
- PROSPERO: International prospective register of systematic reviews
- DA: ductus arteriosus
- NMA: Network meta-analysis
- ISPOR: International Society For Pharmacoeconomics and Outcomes Research
- PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- ECHO: echocardiography
- RoB: Risk of Bias
- RE: Random effects
- DBT: Design by treatment
- GRADE: Grading of Recommendations Assessment, Development and Evaluation
- RR: Relative Risk
- CI: Confidence intervals
- AUC: Area under the curve
- BW: Birth weight
- GA: Gestational age

## DECLARATION OF ACADEMC ACHIEVEMENT

This "sandwich" thesis consists of two papers conceived of and written by the student as the first author. He developed their background, objectives, hypotheses, conducted majority of the data analyses, and prepared the chapters in keeping with suggestions of his supervisory committee and co-authors. All of this work was completed between September 2014 and June 2018. As such, the work herein adequately meets the requirements for inclusion in the main text of this thesis. As per the requirements of a "sandwich" thesis, the following highlights the contributions made to each study by my co-authors.

Article 1, published in *BMJ Open,* outlined the protocol for a Bayesian random-effects network meta-analysis of randomized controlled trials (RCTs) of different treatment options for a hemodynamically significant PDA. It was co-authored by my thesis supervisor, Dr. Lehana Thabane, my thesis co-supervisor Dr Lawrence Mbuagbaw, along with Drs Ivan D Florez, Maria E Tamayo, Dagfinn Aune and Areti-Angeliki Veroniki. All co-authors critically reviewed the manuscript and made suggestions to improve it prior to submission for publication. My thesis co-supervisor Dr Gordon Guyatt also provided helpful inputs during the manuscript preparation.

Article 2, published in JAMA, details the results of the network meta-analysis that examined all eligible RCTs that compared intravenous or oral formulations of indomethacin, ibuprofen or acetaminophen compared against each other or placebo for the treatment of a hemodynamically significant PDA. This study was co-authored by my thesis supervisor, Dr. Lehana Thabane, my thesis co-supervisor Dr Lawrence Mbuagbaw, along with Drs Ivan D Florez, Maria E Tamayo, Areti-Angeliki Veroniki, Adriana M. Zea, Yuan Zhang, Behnam Sadeghirad and Ms Thuva Vanniyasingham. Dr Veroniki assisted with the meta-regression analysis. All authors provided critical review of the manuscript prior to submission for publication.

# CHAPTER ONE

## BACKGROUND

### *The physiology of the ductus arteriosus*

Ductus arteriosus (DA) is a blood vessel that is present in fetal life and connects the two major arteries coming out of the heart, i.e., the aorta from the left ventricle and the pulmonary artery from the right ventricle (1). In the fetal life as the fluid-filled lungs do not partake in gas exchange, the pulmonary blood vessels remain collapsed and therefore the pressure in the pulmonary bed remains normally elevated (2). Hence, the DA plays an important role in maintaining fetal circulation as it helps to shunt majority of the right ventricular output into the systemic circulation and prevents build-up of pressure on the right ventricle (2). If the DA closes before birth then the fetus may develop right ventricular failure and may die in utero. The relatively hypoxic environment in fetal life together with optimal concentrations of the E series of prostaglandins (PGE2 mainly as well as PGE1) produced by the DA and the placenta help to keep the DA open in the fetal life (3). As the fluid in the fetal lungs are cleared when an infant is born, the lung alveoli expand and are filled with oxygen (4). This leads to dilatation of the pulmonary arteries and reduction in pulmonary pressures. At the same time, with the clamping of the umbilical cord, the resistance in the systemic circulation increases as it is no longer connected to the low resistance placental circulation. This leads to a reversal of the direction of blood flow through the DA with more oxygenated blood being shunted from the aorta to the pulmonary artery (4). This leads to activation of a constrictor mechanism by the natural rise in blood oxygen tension (5). At the same time, following birth of the infant, there is downregulation of the prostaglandin E(2)-based DA relaxation sustaining prenatal patency (5). A combination of

these two mechanisms lead to functional closure of the DA around 24-72 hours after birth followed by structural closure in the next few days to weeks (6).

*The closure ductus arteriosus in preterm infants*

In premature infants the closure is delayed due to a number of factors including immaturity of the ductal musculature, hypoxia, acidosis, pro-inflammatory state secondary to maternal chorioamnionitis (7). In healthy preterm neonates >30 weeks gestation, PDA closes by day 4 in 90% and by day 7 in 98% of infants (8). In extremely premature infants born <24 weeks of gestation, the spontaneous PDA closure rates are only about 8% and 13% by day 4 and day 7, respectively (8). Among infants less than 1500 g who still have a PDA at the time of hospital discharge, spontaneous closure occurs by the end of the first year in 86% of the infants (9). It has also been found that among infants <27 weeks of gestation, with a PDA at the time of hospital discharge, 75% of the infants spontaneously close the DA by the end of the first year, whereas an interventional closure is required in the remaining 25% of infants (10). A number of other factors have been implicated in modulating the time of ductal closure in preterm neonates. These include excessive fluid intake, development of late onset sepsis, use of aminoglycoside antibiotics and use of phototherapy (7,11).

*Problems with persistent ductus arteriosus in preterm infants*

When the DA persists beyond the first few day of life, blood starts flowing left-to-right from the aorta into the pulmonary arteries (6). As pulmonary vascular resistance declines over the first several days after birth, the proportion of aortic blood flow that is diverted into the pulmonary circulation correspondingly increases (6). This “ductal steal” results in excessive blood flow through the lungs, predisposing to development of pulmonary congestion, pulmonary edema, and worsening respiratory failure (6). At the same time, diversion of blood flow from the systemic

circulation leads to systemic hypoperfusion, resulting in compromised perfusion to the bowel, kidney, and brain. Prolonged patency is associated with numerous adverse outcomes, including prolongation of assisted ventilation and higher rates of death, bronchopulmonary dysplasia (BPD), pulmonary hemorrhage, necrotizing enterocolitis (NEC), impaired renal function, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and cerebral palsy (6,11).

*Management of the patent ductus arteriosus in preterm infants*

Due to the above mentioned potential life-threatening complications, non-steroidal anti-inflammatory drugs (NSAIDs) such as indomethacin and ibuprofen are used to close the PDA when deemed hemodynamically significant (11). A PDA is defined as hemodynamically significant when it is considered to cause significant hemodynamic disturbances in the infant based on clinical and/or echocardiographic criteria (11). NSAIDs act by inhibition of the cyclo-oxygenase (COX) enzyme thereby leading to downregulation of PGE2, a potent relaxant of the PDA (11). In recent times, acetaminophen has also emerged as a potential pharmacotherapeutic option for PDA closure. Acetaminophen is postulated to exert its action through inhibition of the peroxidase enzyme thereby leading to downregulation of PGE2 production (12). If pharmacotherapy fails to close the PDA and it is still deemed hemodynamically significant, then surgical PDA ligation is contemplated.

*Controversy around management of PDA in preterm infants*

Controversy exists on whether the PDA should be actively treated in preterm infants. This is because the extent to which adverse outcomes such as BPD, NEC, IVH are attributable to the hemodynamic consequences of ductal patency, if at all, has not been established (6). On the other hand, there is some evidence that use of NSAIDs in preterm infants may lead to adverse

consequences such as oliguria, renal failure and cerebral ischemia (11). Consequently, there are two schools of thoughts on whether to actively close the PDA. According to the first, a persistent hemodynamically significant PDA may induce systemic hypoperfusion thereby leading to increased risk of NEC and renal failure. At the same time it would also cause pulmonary overcirculation thereby increasing the risk of BPD (Figure 1). Therefore, the PDA should be closed using the most effective NSAID available, knowing that NSAIDs do carry their own risks in preterm infants, especially on the gut and kidneys.

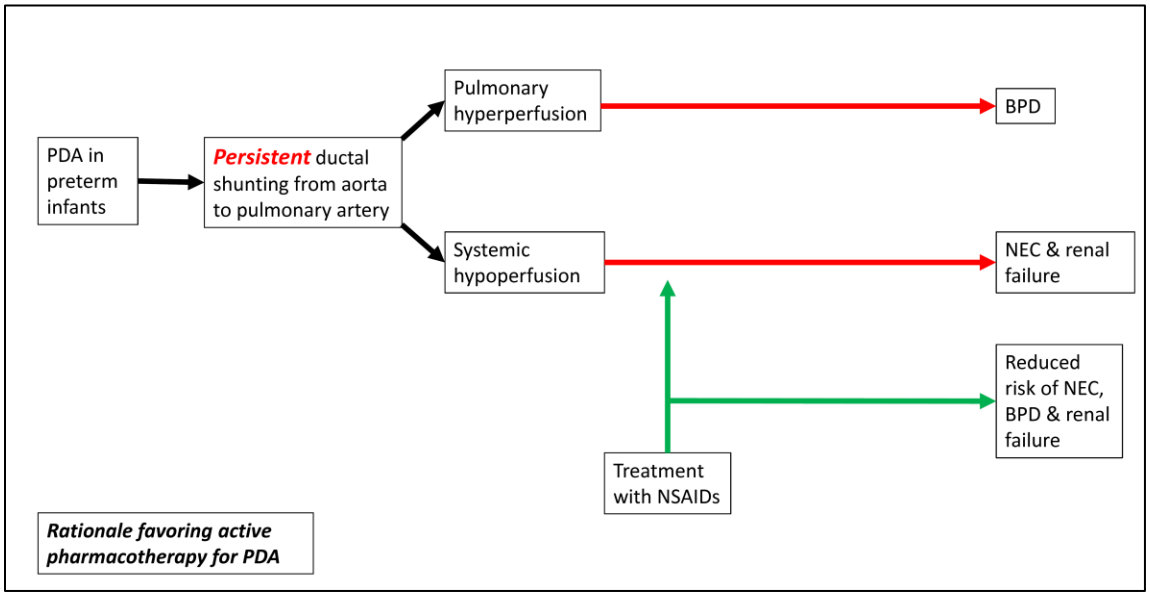


***Figure 1. Rationale favoring active treatment for PDA***

On the other hand, according to the second hypothesis, there is little evidence to support that successfully closing the PDA actually changes clinical outcomes in preterm infants, as many of the PDAs will spontaneously close over time without negatively impacting end-organ perfusion (Figure 2). In that case, by exposing a number of babies to NSAIDs which are known to negatively impact the gut and kidneys, we may be unnecessarily increasing the risk of NEC and renal failure in these infants.

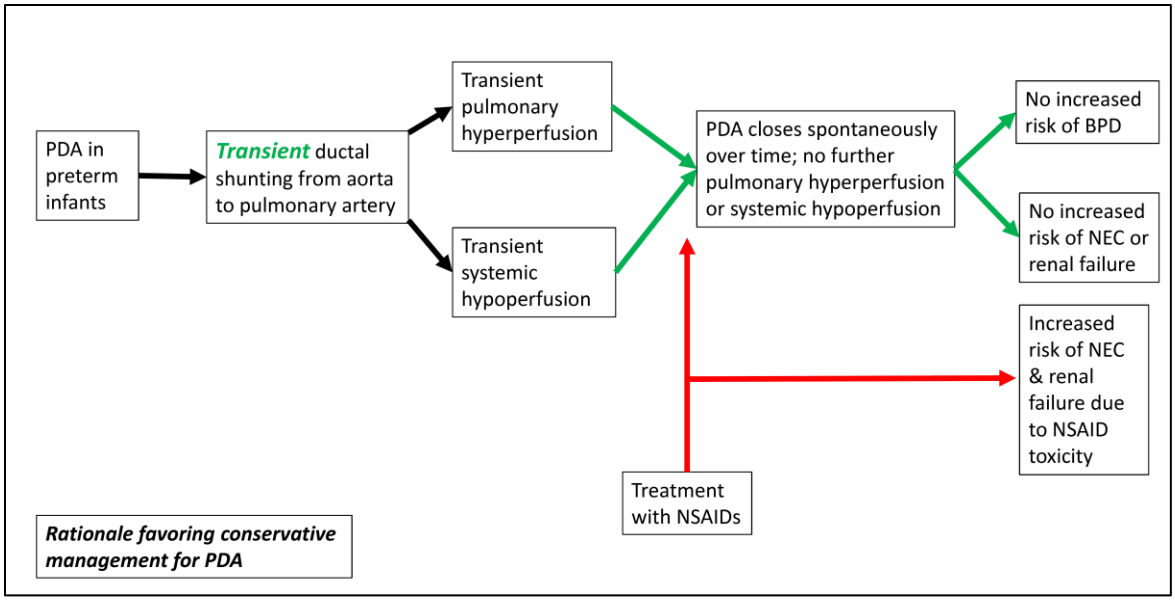


***Figure 2. Rationale favoring conservative management of the PDA***

Furthermore, there is very little knowledge on the pharmacokinetic and pharmacodynamics properties of NSAIDs when used in preterm infants. This has led to the use of different NSAIDs in different doses and routes for PDA closure. As a result, randomized controlled trials have been conducted comparing different doses, routes and timings of different medications versus each other or versus placebo/no-treatment for closure of a hemodynamically significant PDA.

*Thesis Overview*

The controversy around management options for a hemodynamically significant PDA as discussed above has led to confusion among clinicians when it comes to ideal choice of therapy. To date 15 Cochrane reviews have been published that have provided head-to-head comparisons of the various management options (13–27). However, the Cochrane systematic reviews have only provided head-to-head to comparisons of two treatment options at a time. This provides a narrow perspective to the problem especially when a number of different treatment options are involved. To the best of our knowledge there is one previous network meta-analysis conducted by Jones et al in 2011 comparing intravenous (IV) indomethacin, IV ibuprofen and placebo for

hs-PDA using a frequentist approach that did not include the evidence for acetaminophen (28). In recent times, oral acetaminophen has emerged as a preferred treatment option and so has oral ibuprofen. Similarly emergence of different dosing regimens of the said drugs have also contributed to the dilemma among clinicians with regards to choice of pharmacotherapy that has necessitated our systematic review and network meta-analysis.

In study one, we developed the protocol for the systematic review designed to evaluate the effectiveness and safety of indomethacin, ibuprofen and acetaminophen for the treatment of PDA in preterm infants using Bayesian network meta-analysis. This paper was published in BMJ Open (29).

The second study provides in detail the results of the network meta-analysis that examined all eligible randomized controlled trials that compared intravenous or oral formulations of indomethacin, ibuprofen or acetaminophen compared against each other or placebo for the treatment of a hemodynamically significant PDA. We compared ten different treatment modalities for each of eight outcomes that included three effectiveness outcomes (PDA closure, need for repeat pharmacotherapy, surgical PDA ligation) and five safety outcomes (mortality, NEC, BPD, IVH and oliguria). For each outcome, initial pairwise meta-analysis was conducted using a random-effects (RE) model for every direct pairwise comparison. This was followed by a Bayesian RE network meta-analysis (NMA) to compare all interventions simultaneously. We then conducted a network meta-regression analysis to explore the effect of gestational age, birth weight, age of treatment initiation and year of publication on the clinically most important effectiveness and safety outcomes, i.e., PDA closure, need for repeat therapy, mortality and NEC. The quality of evidence of each direct, indirect, and network effects estimate was

evaluated for all eight outcomes according to the GRADE method for network meta-analysis (30).

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# CHAPTER TWO

## STUDY 1

**TITLE**: Effectiveness and safety of treatments used for the management of patent ductus arteriosus (PDA) in preterm infants: a protocol for a systematic review and network meta-analysis

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**CONTEXT AND IMPLICATIONS OF THIS STUDY**: The first paper of the "sandwich" thesis outlines the protocol for a Bayesian random-effects network meta-analysis of randomized controlled trials (RCTs) of different treatment options for a hemodynamically significant PDA. This paper also a priori defines potential effect modifiers and statistical strategies to control for the same.

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**CONFLICTS OF INTEREST**: None declared.

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**ABSTRACT**

**Introduction:** Management of patent ductus arteriosus (PDA) in preterm infants is one of the most controversial topics in neonatal medicine. The availability of different pharmacotherapeutic options often poses a practical challenge to the practicing neonatologist as to which one to choose as a therapeutic option. Our objectives are to determine the relative merits of the available pharmacotheurapeutic options for the management of PDA.

**Methods and Analysis**: We will conduct a systematic review of all randomized controlled trials (RCT) evaluating the use of intravenous or oral: indomethacin, ibuprofen and acetaminophen for the treatment of PDA in preterm infants. The primary outcome is failure of closure of the PDA. Secondary outcomes are neonatal mortality, need for surgical closure, duration of ventilator support, chronic lung disease, intraventricular haemorrhage, periventricular leukomalacia, necrotizing enterocolitis, gastrointestinal bleeding, time to full enteral feeds and oliguria. We will search Medline, Embase and CENTRAL as well grey literature resources. Two reviewers will independently screen titles and abstracts, review full texts, extract information, assess the risk of bias (ROB) and the confidence in the estimate (with GRADE approach). Subgroup analysis according to gestational age, birth weight, different doses of interventions, time of administration of the first dose of the intervention, echocardiographic definition of hemodynamically significant PDA and ROB are planned. We will perform a Bayesian network meta-analysis to combine the pooled direct and indirect treatment effect estimates for each outcome, if adequate data is available.

**Ethics and Dissemination:** The results will help to reduce the uncertainty about the safety and effectiveness of the interventions, will identify knowledge gaps or will encourage further research for other therapeutic options. Therefore, its results will be disseminated through peer-

reviewed publications and conference presentations. Based on the nature of its design, no ethics approval is necessary for this study. Protocol registration number: PROSPERO CRD42015015797

**Strengths and Limitations**

- This systematic review and network meta-analysis will assess the effectiveness and safety of the interventions used to treat hemodynamically significant PDA in preterm infants. It will be the first NMA to assess the comparative effectiveness of ibuprofen, paracetamol and indomethacin.
- Among additional strengths this review will be based on a comprehensive search strategy, broad inclusion criteria and will use the GRADE Approach to assess the certainty on the evidence.

## INTRODUCTION

One of the most common cardiovascular problems that prematurely born infants experience early in life is patent ductus arteriosus (PDA). The ductus arteriosus is a blood vessel that connects the two major arteries, namely the aorta and the pulmonary artery, and is essential in maintaining circulation in fetal life.(1) After the baby is born and the fetal circulation changes to adult circulation, the ductus arteriosus functionally closes between 18-24 h of life(1). However, in babies born prematurely, the ductus arteriosus often fails to close spontaneously and leads to a number of morbidities. It has been shown that in infants born less than 1,000 g birth weight, the ductus arteriosus remains open in 66% of infants beyond the first week of life. In the extreme premature population born at 24 weeks of gestation, only 13% of infants are found to have their ductus closed by the end of the first week (2). This makes PDA an important issue from the clinical management perspective in the first few days of life in preterm infants. Management of PDA in preterm infants is one of the most controversial topics in neonatal medicine. It is associated with a number of co-morbidities like necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD) and intraventricular hemorrhage (IVH)(3-5). The management controversy has mainly focused on when to treat and with what to treat. To increase the complexity of matters, these two aspects of PDA management are not mutually exclusive, with the modality of treatment often being dictated by the timing of treatment. There have been a large number of published studies, meta-analyses and editorials focusing on different aspects of management (6-8). Regarding the timing of treatment, prophylactic therapy has gradually fallen out of favour and neonatal units have shifted towards a more conservative approach by treating only the clinically and echocardiographically significant PDA(6). However, the big dilemma that still persists among neonatologists is what to use as the primary modality of treatment.

Indomethacin, which is a prostaglandin inhibitor, has been traditionally used as the first line treatment for PDA. However, because of its potent vasoconstrictive effect, it has been found to be associated with brain white matter injury, necrotizing enterocolitis, intestinal perforation, renal impairment and platelet dysfunction (7-11).Hence, ibuprofen was later introduced as a treatment modality, which promised to have a lesser vasoconstrictive effect on end organ microcirculation(12).Nevertheless, it has also been associated with some renal effects along with pulmonary hypertension and hyperbilirubinemia(13-15). More recently acetaminophen has been used as an additional effective treatment for PDA without any significant adverse effects reported (16, 17).

Randomized controlled trials (RCTs) comparing indomethacin with placebo as well as oral and intravenous (IV) ibuprofen with placebo, have been conducted. The most recent Cochrane review on the use of ibuprofen for PDA has combined the above mentioned studies into a comprehensive meta-analysis which showed that ibuprofen was much safer compared to indomethacin in terms of incidence of NEC and oliguria, without any difference in efficacy(12). Meanwhile, acetaminophen has been compared with oral ibuprofen in two RCTs, evidence that has been summarized in a recent Cochrane systematic review (18), which again showed no difference in efficacy between the two drugs.

The availability of different pharmacotherapeutic options often poses a practical challenge to the practicing neonatologist as to which one to choose as a therapeutic option. As the number of available treatment options increase, the required number of pairwise systematic reviews would increase exponentially. Pairwise meta-analysis of multiple treatments is laborious and time-consuming. In addition, the newer pharmacotherapeutic agents like acetaminophen have not been compared with placebo. This may lead to a dilemma in choosing the safest and the most effective therapeutic option. Newer agents compared head to head in recent RCTs show no

statistically significant difference in effectiveness(19). This lack of difference may be attributed to the fact that either the studies may have had insufficient number of subjects or there were methodological flaws in the trials.

The use of network meta-analysis allows the comparison of the efficacy and important safety profiles of the different pharmacotherapeutic options for PDA closure that are available. The Cochrane handbook considers network meta-analysis (NMA) as a highly valuable tool to evaluate and rank treatment options according to their safety and effectiveness(20). Bayesian NMA have been proposed as an effective method for evaluating the effectiveness of multiple treatment comparisons (21, 22).To the best of our knowledge there is one previous NMA conducted by Jones et al in 2011 comparing indomethacin, ibuprofen and placebo using a frequentist approach (23). However, more evidence regarding ibuprofen and indomethacin have been generated since then, and also the advent of evidence about acetaminophen showing that it could be a promising alternative(18). Therefore, we decided to conduct a systematic review and NMA using a Bayesian approach comparing all the pharmacological treatments for PDA in preterm infants to determine their relative effectiveness and safety in relation to one another.

## OBJECTIVE

We aim to determine the comparative effectiveness and safety of the available pharmacological treatments for PDA in preterm infants. For this purpose we will use a Bayesian network meta-analysis.

## METHODS & DESIGN

This systematic review and NMA protocol has been registered on PROSPERO International prospective register of systematic reviews (CRD42015015797).This protocol was

developed following the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) guidance(24). The final report will comply with the recommendations of the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions(25).

**Search Strategy**

We will search from their conception to August 2015, the following databases: Medline and Embase through the Ovid platform, Cochrane Central Register of Controlled Trials (CENTRAL). We will use a combination of controlled terms (Medical Subject Heading, MeSH, and Emtree), and free-text terms with various synonyms for PDA, indomethacin, ibuprofen and acetaminophen. We will use the validated RCTs filters created by McMaster University Health Information Research Unit for Medline and Embase through the Ovid platform(26). Search alerts will be set up for monthly notification and the search will be repeated before the final manuscript submission to identify any new relevant trials. Search strategies have been developed with liaison with an experienced librarian at McMaster University Library. No language, publication status or date limit will be used. An example for the search strategy for Medline through Ovid is detailed in the *appendix A.*

We will seek registered details of selected trials in the U.S. National Institutes of Health resource (www.*clinicaltrials.gov*) and the WHO International Clinical Trials Registry Platform Search Portal. We intend to obtain additional grey literature from personal communication from experts in the field, reviewing the reference lists of relevant articles, abstracts and conference proceedings (Society for Pediatric Research, European Society for Pediatric Research) and

seeking results of unpublished trials. We intend to contact authors of unpublished work and authors of published trials in order to clarify information when necessary.

**Eligibility criteria**

We will include RCTs and quasi-RCTs that evaluate the effectiveness or safety of treatments for the PDA. Studies will have to have the following characteristics: 1) Participants: Preterm infants <37 weeks gestational age or low birth weight infants (<2500 g) with a PDA diagnosed clinically or echocardiographically (ECHO) in the neonatal period (<28 days of life); 2) Interventions: Indomethacin, ibuprofen, acetaminophen, or other cyclo-oxygenase inhibitors. We will include studies that used any of the interventions regardless of the dose and method of administration (intravenously or orally); and 3) Outcomes: Our primary outcome will be the failure of permanent PDA closure within a week of administration of the first dose of the intervention. The secondary outcomes are other measures of effectiveness, such as mortality, need for additional courses or doses of the intervention, surgical treatment and reopening of the ductus, as well as safety outcomes. All the outcomes, its definitions and measures are detailed in Table 1.

**Table 1: Characteristics of the outcomes' measures**

| **Outcome** | **Measurement of Variable (units)** | **Statistical Estimates and Measurement of Association** |
|---|---|---|
| **Primary**<br>Failure of permanent PDA closure | Failure to closure of the PDA. We will emphasize in closure definition within a week of administration of the first dose of the intervention (PDA diagnosed either clinically or by ECHO criteria), but we will use the time defined by authors to analyse the outcome accordingly. | OR (95%CI) |

| | | |
|---|---|---|
| **Secondary**<br>**General outcomes**<br>Neonatal mortality<br>Reopening of the ductus arteriosus.<br><br>Need for surgical closure of the PDA<br>Chronic lung disease (CLD) | <br><br>Death during the first 28 days of life<br>Number of neonates with echocardiographically determination of reopening of the ductus<br>Number of neonates that required surgical treatment of the PDA<br>Total number of neonates with oxygen requirement at 28 days postnatal age in addition to compatible clinical and roentgenographic findings. | OR (95%CI) |
| **Neurological Effects**<br>• Intraventricular haemorrhage (IVH)<br>• Severe IVH<br>• Periventricular leukomalacia (PVL).<br>• Neurodevelopmental disability | Number of neonates with IVH (I-IV).<br>Number of neonates with Severe IVH<br>Number of neonates with PVL<br>Number of children with any reported disability at 1-2 years of age (e.g., motor, cognitive, sensory impairments) | OR (95%CI) |
| **Gastrointestinal and Nutritional Effects**<br>• Intestinal perforation.<br>• Gastrointestinal bleed (GB)<br>• Necrotising enterocolitis (NEC) Time to full enteral feeds | • Number of neonates with Intestinal perforation<br>• Number of neonates with GB<br>• Postnatal age at time of achieving full enteral feeds.<br>• Number of neonates with NEC (any stage). | • OR (95%CI)<br>• OR (95%CI)<br>• OR (95%CI)<br>• MD(95%CI) |
| **Renal Effects**<br>• Decreased urine output | Number of neonates with urine output, defined as < 1 cc/kg/hr | • OR (95%CI) |

We will exclude studies of infants with congenital structural heart disease or other congenital anomalies. In case the trial have included some infants with heart disease, and the authors report the results separately in infants with and without heart disease, we will use the latter for the analysis. In case they do not report results separately, we will include the study if

we have information about the proportion of infants with these diseases, and this is less than 30% of the total population. We will exclude studies in which the intervention was surgical treatment.

**Study selection**

The titles and abstracts retrieved will be screened by two independent reviewers to assess its eligibility (SM, IDF, MET, DA). As a second step, the full text articles of the potentially eligible studies will be screened to assess their eligibility. We will include the full text of all studies for which both reviewers agree about their inclusion. Any disagreements between the reviewers will be resolved by discussion and if no agreement can be reached, a third member of the team (IDF, SM) will decide whether the study shall be included or not. We will refer to inclusion and exclusion criteria during the screening process. Records of ineligible full text articles along with the reason for ineligibility will be saved for future reference. We will present the PRISMA flow diagram(27) demonstrating the search and screening process. We will contact authors of primary studies, during screening, to provide any missing information that may influence eligibility.

A pre-tested and standardized Microsoft Excel data extraction form will be used to extract the data from the eligible studies. Data items to be extracted include: (a) publication year, (b) mean gestational age, (c) mean birth weight (d) number of infants randomized, (e) number of losses to follow-up (d), mode and doses of treatment, (g) any co-interventions during treatment and (h) continuous and dichotomous outcome measures, (i) adverse effects (neurological, renal, hematologic, hepatic and gastrointestinal effects). The data extraction form will be pilot tested independently by all reviewers before its use, to standardize the process. Four reviewers (SM, IDF, MET, DA) will carry out the extraction, working independently in pairs. In case of disagreement in assessing the methodological quality of the study we will try to resolve it by

consensus. If consensus cannot be reached a third designated reviewer (IDF or SM) will be invited to arbitrate.

**Assessment of Risk of Bias**

The risk of bias (ROB) of eligible studies will be assessed according to a modified version of the Cochrane Collaboration's ROB tool(20). The criteria to be assessed are sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of follow up, selective outcome reporting, and presence of other biases. Each domain will be assigned a score 'definitely low risk', or 'definitely high risk' or 'unclear risk'. We will further categorize the 'unclear risk' to ' probably low risk', or 'probably high risk'(28). Two independent reviewers (SM, IDF, MET, DA) will assess the ROB. We will try to reach consensus when disagreements between two reviewers when assessing the methodological quality of the studies. Nevertheless, if consensus cannot be reached, a third reviewer (IDF or SM) will resolve it.

**Direct Comparisons and Assessment of Heterogeneity**

We will first describe the results narratively and, where possible, the direct evidence will be pooled. Given that we expect clinical and methodological heterogeneity among the studies (see below in Rating the Confidence in Estimates section), which in turn will create statistical heterogeneity, we will pool direct evidence for each treatment comparison using a random-effects (RE) model. In comparison to the fixed-effect model (FE), the RE model is conservative in the sense that it accounts for both within- and between-study variability. The RE model assumes that the observed treatment effect for a study is a combination of a treatment effect common to all studies plus a component specific to that study alone (29, 30).

We will pool the outcome data using a Bayesian RE model (31). Effect estimates along with 95% credible intervals (CrIs) will be estimated using odds ratio (OR) for binary outcomes, and mean difference (MD) for continuous outcomes, if they are reported using the same scale, or standardized mean difference (SMD) otherwise (see table 1).For studies with binary outcomes, we will add 0.5 to each cell if one arm is zero, whereas we will exclude studies from the analyses with zero events in both arms. We will use non-informative priors for all model parameters apart from the heterogeneity variance parameter, for which we will use the informative prior suggested by Turner et al(32) and Rhodes et al(33). All Bayesian analyses will be performed using the Markov Chain Monte Carlo method.

We will assess heterogeneity by estimating the magnitude of the between-study variance using the empirical distribution as estimated by Turner et al(32) and Rhodes et al (33), and by using the $I^2$ statistic to quantify the percentage of variability that is due to true differences between studies rather than sampling error(34, 35). We will interpret the $I^2$ statistic using the thresholds set forth by the Cochrane Collaboration(20). In case there is important heterogeneity, we will use meta-regression to explain it, if we have enough data to do so. Otherwise we will perform subgroup analyses.

We propose, *a priori*, the following potential sources of heterogeneity, which could be possible effect modifiers: gestational age (<28; 28-32;>32 weeks of gestational age), birth weight (<1,000g; 1000-1500g; >1500g), different doses of the interventions, time of administration of the first dose of the intervention(<3 days, 3-7 days, >7 days)., echocardiographic findings (PDA size & left Atrium:Aortic root ratio), time of PDA assessment post pharmacotherapy (<24 hours, 24 hours to 3 days, and > 7 days) and previous medical PDA medical therapy. We hypothesize that lower gestational age, lower birth weight, lower doses, more time from diagnosis to

administration of the intervention, the echocardiographic findings of increased PDA size and increased left Atrium:Aortic root ratio, and previous medical therapy will be related to a lower treatment effect. We will perform meta-regression or subgroup analysis as appropriate using these hypotheses as the study level covariates and we will perform a sensitivity analysis based on the studies with high ROB and based on studies based on patients that had clinical diagnosis of the PDA.

**Assessment of reporting bias**

We will construct a funnel plot for each treatment comparison and outcome to assess the potential publication bias and small-study effects (36), if we retrieve at least 10 studies(20). Visual inspection to determine the funnel asymmetry will be used for this purpose, as well as Begg's rank correlation (37)and Egger's regression tests(38).

**The Network Meta-Analysis**

Given that many of the treatment combinations available to treat PDA have not been compared in head-to-head studies, we expect that some of the possible comparisons between the interventions will not have direct evidence. Hence, we will perform a RE network meta-analysis (NMA), if the assumptions of between-study homogeneity, transitivity and coherence across treatment comparisons are judged to be justifiable. In the absence of direct evidence for a given comparison an indirect comparison will provide an estimate of the treatment effect. In the presence of direct evidence, the NMA will provide a combined estimate (i.e., direct and indirect evidence)(39). For instance, in a triangular network ABC composed of studies that directly compare A vs. B and A vs. C treatments, we can indirectly estimate the effect of B vs. C

treatments. In case direct evidence of B vs. C treatment comparison is also available, then a combined estimate of direct and indirect evidence of B vs. C can be calculated using a NMA.

Evidence from a NMA may be inconsistent if the direct and indirect evidence are incompatible (loop inconsistency) or the studies involving one of the treatments is fundamentally different from the studies involving another treatment (design inconsistency). In order to evaluate both design and loop inconsistency, we will apply the design-by-treatment interaction model, and if this suggests inconsistency then we will apply the loop-specific method to assess local inconsistency (40-42). We will perform a network meta-regression or subgroup analysis using the same potential treatment effect modifiers described in section 'Direct comparisons and assessment of heterogeneity' to explore important heterogeneity or inconsistency. We will also perform sensitivity analyses for different heterogeneity priors to assess the robustness of results(32, 33, 43).

For each outcome, we will present the network diagram and a forest plot with the network estimates. Effect estimates will be presented along with their corresponding 95% credible interval (CrI), as well as their 95% predictive interval (PrI) representing the interval within which we would expect the treatment effect of a future study to lie (44, 45). We will rank the probabilities with its 95%CrIs as well as the Surface Under the Cumulative RAnking curve (SUCRA) values and cumulative probability rankograms(46). SUCRA values range from 0% to 100% and it is expected that the best treatments will have high SUCRA values.

We will fit a Bayesian hierarchical model with non-informative priors adjusting for correlation of multi-arm trials, and assuming a common-within network heterogeneity variance. Series of 100,000 simulations will be used to allow convergence and after thinning of 10and discarding the first 20,000 simulations we will produce the outputs. We will assess model

convergence on the basis of Gelman and Rubin diagnostic test(47). The analysis will be performed in OpenBUGs (version 3.2.3)(48).

**Rating the confidence in estimates of the effect**

We will assess the confidence in the estimates for each outcome using the GRADE approach (49). For this purpose, two authors will independently do the assessment (SM, IDF, MET, DA). The confidence in the estimates will be based on four levels: high, moderate, low and very low. For the direct comparisons we will assess and rate each outcome based on the categories: ROB, imprecision, inconsistency and publication bias (50-54).

We will assess and rate the confidence in all the indirect comparisons –if available- obtained from first order loops following the GRADE categories used for assessing the direct comparisons in addition to the transitivity assessment. Transitivity, also called similarity(55), is the assumption that an indirect comparison is a valid method to compare two treatments that have not been compared in a head-to-head trial, because the studies are sufficiently similar in important clinical and methodological characteristics, or in other words, that they are similar in their distributions of effect modifiers(56, 57). Then, we will rate the confidence in each NMA effect estimate using the higher rating when both direct and indirect evidence are present.

We will assess and rate the confidence in estimates of effect from the direct comparisons in our pairwise meta-analyses described previously. In order to rate the confidence in the indirect comparisons, we will focus our assessments on first-order loops (FOLs), i.e., loops connected to the interventions of interest through only one other intervention. For instance, if for A, B and C interventions, there are direct comparisons of A vs. B (AB) and B vs. C (BC), we will be able to indirectly estimate the effects of A vs. C (AC). The AC indirect estimation will be a FOLs. We

will choose the FOLs with the lowest variances, and thus contribute the most to the estimates of effect, for rating the confidence.

Within FOLs, the indirect comparison confidence will be the lowest of the confidence ratings we have assigned to the contributing direct comparisons. For example, if we find that AB has moderate confidence and BC has high confidence, we will judge the associated indirect comparison, AC, as moderate confidence. We may rate down confidence in the indirect comparisons further if we have a strong suspicion that the transitivity assumption has been violated.

Our overall judgment of confidence in the NMA estimate for any pairwise comparison will be the higher of the confidence rating amongst the contributing direct and indirect comparisons. However, we may rate down confidence in the network estimate if we find that the direct and indirect estimates have inconsistency. For this purpose the GRADE approach recommends to assess the incoherence (or inconsistency as described in the 'The Network Meta-Analysis' section) criteria, which is defined as the differences between direct and indirect estimates of effect(58).

**Discussion**

The present systematic review will provide evidence of comparative effectiveness and safety of the medical treatments for the closure of PDA in preterm babies. To the best of our best knowledge this will be the first review that will include the three available medical drugs. Its results will be of interest to a broad audience: practice guideline developers, pediatricians, neonatologists, policy makers and researchers, because it could be used to give clinical

recommendations for infants with PDA, and will also identify gaps in knowledge that could be subject of future research.

Our review will have several methodological strengths. First, we will implement a wide comprehensive search will include published work in the most comprehensive databases, as well as unpublished work. Second, we will use the novel method for rating the confidence in the estimates recommended by the GRADE working group. Third, our review will take into account the birth weight and gestational age and other potential sources of heterogeneity. Finally, we will pool the results using a Bayesian framework, which will provide probability distributions that will summarize the likely values for the treatment effect of each intervention relative to each other(59).

On the other hand, some challenges for this review exists. We anticipate some degree of clinical heterogeneity with regard to the possible sources that we described. Finally, if the extent of included studies is small, the ability to explore heterogeneity maybe limited.

We hope that this review will provide evidence to reduce the uncertainty about the ranking of the interventions in terms of effectiveness and safety, improve neonatal care, and will encourage further research for other therapeutic options for the treatment of PDA in preterm infants.

**Ethics and Dissemination**

No ethical approval is required; this review is a study based on the analysis of the published evidence. No personal data of patients was required. The results of the review will be submitted to a peer-reviewed journal focusing on pediatrics or neonatology fields, for publication. We also plan to present results in future conferences.

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**Author's disclosure**

Authors declare that there is no conflict of interest related to the topic of this review.

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**List of abbreviations**

PDA: Patent Ductus arteriosus; GRADE: Grading of Recommendations Assessment, Development and Evaluation; RCT: randomized controlled trials; NMA: network meta-analysis;

**Glossary of terms**

Direct Estimates: Estimated provided by a head-to-head comparison; Indirect estimate: Estimated provided by 2 or more head-to-head comparisons that share a common comparator (e.g., Direct comparisons: AB and BC, Indirect estimation: AC); NMA (Network Meta-analysis): Combination of direct (when available) and indirect estimates of a comparison; Loops: Two or more head-to-head comparisons that contribute to an indirect estimate. First order loops (FOL) are those loops that involve only a single additional intervention; Heterogeneity: Differences in estimates of effect across studies that assessed the same comparison; Inconsistency**(60)**: The GRADE approach criterion for rating the degree of consistency among the results in the meta-

analysis (heterogeneity); Incoherence(60): The GRADE approach term used as criterion for rating the inconsistency, specifically in NMA. It refers to the differences between direct and indirect estimates of effect; Intransitivity(60): Differences in study characteristics that may modify treatment effect in the direct comparisons, and could bias the indirect estimate.

**Author contributions:**

Conceptualized and designed the study: SM, IDF, and LT

Manuscript Drafting: SM, IDF, and AAV

Critically reviewed the protocol & manuscript as submitted: SM, IDF, MET, DA, LM, AAV and LT

Note: All authors read and approved the final manuscript

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**Appendix A. Medline Search Strategy**

**Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) From 1946 to Present**

1. Infant, Premature/
2. Premature Birth/
3. Infant, Newborn/
4. Infant, Premature, Diseases/
5. preterm.mp.
6. low birth weight.mp.
7. Infant, Low Birth Weight/
8. very low birth weight.mp.
9. Infant, Extremely Low Birth Weight/
10. lbw.mp.
11. vlbw.mp.
12. or/1-11
13. Ductus Arteriosus, Patent/
14. patent ductus arteriosus.mp.
15. ductus arteriosus.mp.
16. Ductus Arteriosus/
17. ductus.mp.
18. PDA.mp.
19. persistent ductus arteriosus.mp.
20. or/13-19
21. indomethacin.mp.
22. Indomethacin/
23. indometacin.mp.
24. indocid.mp.
25. ibuprofen.mp.
26. Ibuprofen/
27. brufen.mp.
28. paracetamol.mp.
29. Acetaminophen/
30. tylenol.mp.
31. acetaminophen.mp.
32. Anti-Inflammatory Agents, Non-Steroidal/
33. Cyclooxygenase Inhibitors/
34. prostaglandin synthetase inhibitor.mp.
35. NSAID?.mp.
36. or/21-35
37. 12 and 20 and 36
38. randomized controlled trial.pt.
39. randomized.mp.
40. placebo.mp.
41. or/38-40
42. 37 and 41

# CHAPTER THREE

## STUDY 2

**TITLE**: 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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**CONTEXT AND IMPLICATIONS OF THIS STUDY**: Study 2 of the 'sandwich thesis' details the results of the network meta-analysis that examined all eligible randomized controlled trials that compared intravenous or oral formulations of indomethacin, ibuprofen or acetaminophen compared against each other or placebo for the treatment of a hemodynamically significant PDA. This study puts available evidence into perspective with respect to all the important effectiveness and safety outcomes related to PDA in preterm infants. This study also assesses the strength of evidence using the GRADE guidelines that will help clinicians make evidence-based decisions when it comes to management of the PDA in preterm infants. This will further help to identify important gaps in knowledge that will drive future research on this topic. .

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network meta-analysis results. Neither received any compensation for his contribution to the study.

**CONFLICTS OF INTEREST**: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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**ABSTRACT**

Importance: There is increasing emphasis on conservative management of patent ductus arteriosus (PDA) in preterm infants. Nonetheless, different pharmacotherapeutic interventions are commonly used to treat preterm infants developing a hemodynamically significant (hs) PDA.

Objectives: To estimate the relative likelihood of closure of an hs-PDA with common pharmacotherapeutic interventions and to compare adverse event rates.

Data Sources: Medline, Embase, CENTRAL and conference proceedings up to December 2017

Study Selection: Randomized clinical trials (RCTs) that enrolled preterm infants <37 weeks' gestational age who were treated with intravenous or oral indomethacin, ibuprofen or acetaminophen compared against each other or placebo or no treatment for a clinically or echocardiographically diagnosed hs-PDA. Studies using prophylactic pharmacotherapy and surgical intervention were excluded.

Data Extraction & Synthesis: Data were independently extracted in pairs by 6 reviewers and synthesized with Bayesian random-effects network meta-analyses.

Main Outcomes: The primary outcome was hs-PDA closure. Secondary outcomes included need for repeat pharmacotherapy, surgical closure, mortality, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH) and oliguria.

Results: In 68 RCTs that included 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). Oral high-dose ibuprofen was associated with a significantly higher odds of PDA closure compared with standard-dose intravenous ibuprofen (Odds Ratio

[OR], 3.59; 95% Credible Interval [CrI],1.64-8.17; absolute risk difference [RD],199 more [from 95 to 258 more] per 1000 infants) and intravenous indomethacin (OR, 2.35; 95% CrI,1.08-5.31; absolute RD, 124 more [from 14 to 188 more] per 1000 infants). Based on the ranking statistics, oral high-dose ibuprofen ranked the best pharmacotherapeutic option for PDA closure (SUCRA [surface under the cumulative ranking curve],0.89) and to prevent surgical PDA ligation (SUCRA,0.98). There was no significant difference in the odds of mortality, NEC or IVH with use of placebo or no treatment compared with any of the other treatment modalities. The quality of evidence was high or moderate for 20 out of 45 comparisons for the primary outcome.

Conclusions and Relevance: In this network meta-analysis, oral high-dose ibuprofen was associated with a higher likelihood of hs-PDA closure compared with standard doses of intravenous ibuprofen or intravenous indomethacin. Placebo or no treatment for hs-PDA did not significantly change the likelihood of mortality, NEC or IVH.

Protocol registration: The review was registered on PROSPERO international registry of systematic reviews (CRD42015015797).

## KEY POINTS

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

**Findings:** In this network meta-analysis that included 68 randomized trials with 4802 participants, oral high-dose ibuprofen was associated with a statistically significantly higher likelihood of hs-PDA closure compared with 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:** Oral high-dose ibuprofen may offer the highest likelihood of closure of a hs-PDA in preterm infants. Conservative management of hs-PDA is not likely to increase morbidity and mortality.

## INTRODUCTION

A common early cardiovascular problem of prematurely born infants is a hemodynamically significant (hs) patent ductus arteriosus (PDA). The utility of active management of PDA, 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 (BPD); conversely, shunting may induce systemic hypoperfusion, increasing the risk of necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), renal failure and death (2–4). Pharmacotherapy using non-steroidal anti-inflammatory drugs has been used to close a PDA to prevent such complications. However, recently conservative management of PDA without the use of pharmacotherapeutic agents has increased (5,6). The hypothesis is that a large proportion of PDAs in preterm infants would spontaneously close in 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 the PDA when deemed hemodynamically significant by the clinician based on clinical and echocardiographic parameters(7). However, lack of pharmacokinetic and pharmacodynamic data on non-steroidal 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 intravenous (IV) indomethacin and standard-dose IV ibuprofen (8,9).

The availability of different management options poses a challenge for neonatologists when making an evidence-based management decision after diagnosing an hs-PDA. The dilemma is first whether to use pharmacotherapy at all, and second, 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 (NMA) was conducted to

summarize the evidence from randomized clinical trials (RCTs) comparing placebo, indomethacin, ibuprofen and acetaminophen for treatment of hs-PDA in preterm infants (10).

## METHODS

The NMA 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 NMA and the PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating NMAs of Health Care Interventions (13,14). The differences between the protocol and the final article are summarized in Supplement 1.

### Eligibility Criteria

Studies were included if they were RCTs that enrolled preterm infants <37 weeks gestational age at birth or low birth weight infants (<2500 g) who were treated with either IV or oral formulations of indomethacin, ibuprofen or acetaminophen compared with another medication or placebo or no treatment for an hs-PDA diagnosed clinically or echocardiographically in the neonatal period (<28 days of life) (Glossary of abbreviations and acronyms including medication doses and routes available in eTable 1). Studies in which a medication was used prophylactically (within the first 24 h of life without documented clinical or echocardiographic evidence of an hs-PDA) or surgery was a primary treatment modality were excluded.

### Primary and Secondary Outcomes

Fourteen outcomes were defined *a priori* that included 3 effectiveness outcomes and 11 adverse events (Table 1).

**Table 1. *A priori* defined outcome measures**

| Outcome Measure | Definition |
|---|---|
| ***Primary Outcome*** | |
| PDA closure[a] | Closure of the PDA within a week of administration of the first dose of the intervention (PDA diagnosed either clinically or by echocardiographic criteria) |
| ***Secondary outcomes*** | |
| ***Effectiveness outcomes*** | |
| Need for repeat pharmacotherapy[a] | Number of neonates who require a repeat course of pharmacotherapy following an initial course for treatment of a persistent hemodynamically significant PDA |
| Need for surgical closure of the PDA[a] | Number of neonates who require surgical closure of the PDA following failure of pharmacological PDA closure |
| ***Adverse events*** | |
| **General** | |
| Neonatal Mortality[a] | Death at 36 weeks' postmenstrual age or before discharge |
| **Gastrointestinal effects** | |
| Necrotizing enterocolitis (NEC)[a] | Number of neonates with NEC (stage II or higher based on Bell criteria) |
| Intestinal perforation | Number of neonates with intestinal perforation |
| Gastrointestinal bleed | Number of neonates with gastrointestinal bleed |
| Time to full enteral feeds | Postnatal age at stopping parenteral nutrition and achievement of full enteral feeds |
| **Respiratory effects** | |
| Bronchopulmonary dysplasia (BPD)[a] | Number of neonates who require oxygen at 36 weeks' postmenstrual age |
| **Neurological effects** | |
| Intraventricular haemorrhage (IVH)[a] | Number of neonates with IVH any grade (based on Papile criteria) |
| Severe IVH | Number of neonates with Severe IVH (grades III-IV) (based on Papile criteria) |
| Periventricular leucomalacia (PVL) | Number of neonates with PVL (of any grade documented on cranial ultrasound) |
| Neurodevelopmental disability | Number of children with any reported disability at 1–2 years of age (ie, motor, cognitive, sensory impairments). |
| **Renal Effects** | |

| | |
|---|---|
| Oliguria[a] | Number of neonates with reduced urine output, defined as < 1 ml/kg/hour |

Table 1. A priori defined outcome measures and their definitions

a Outcomes included in the network meta-analysis

The primary outcome was PDA closure within a week of administration of the first dose of the intervention, defined echocardiographically (as physical closure of PDA or change from a hemodynamically significant to non-significant status based on *a priori* defined parameters) or clinically (disappearance of cardiac murmur). Additional effectiveness outcomes included need for repeat pharmacotherapy and need for surgical ligation. Adverse events were death at 36 weeks' postmenstrual age or before discharge, NEC (stage 2 or higher based on the Bell criteria), BPD (defined as oxygen use at 36 weeks' postmenstrual age), IVH (any grade, based on the Papile criteria), oliguria (defined as urine output < 1ml/kg/h)(15–17). The 6 outcomes that were not included in the quantitative synthesis due to lack of sufficient data were severe IVH, periventricular leukomalacia, neurodevelopmental disability, intestinal perforation, gastrointestinal bleeding and time to full enteral feeding (Table 1).

**Information Sources and Search**

Medline, Embase, and Cochrane Central Register of Controlled Trials were searched electronically from inception until August 15, 2015 and updated on December 31, 2017 prior to final data analysis (eTable 2). Registered details of selected trials in the US National Institutes of Health resource (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform 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, Pediatric American Societies 1990 to 2017). There were no language restrictions.

**Study Selection and Risk of Bias**

The retrieved titles and abstracts followed by the full texts were screened by 2 independent reviewers in duplicate (SM, IDF, MET, AMZ, BS, YZ) to assess their eligibility. The risk of bias (RoB) of eligible studies was assessed according to a modified and validated version of the Cochrane Collaboration's RoB tool by 2 independent reviewers (18,19)(eText 1,eFigure 1). Data extraction was done using a pre-specified standardized data extraction form by 6 reviewers (SM, IDF, MET, AMZ, BS, YZ) working independently in pairs and in duplicate. Discrepancies were resolved through discussion or in consultation with a third reviewer (SM or IDF).

**Data Synthesis and Analysis**

For each outcome, initial pairwise meta-analysis was conducted using a random-effects model for every direct pairwise comparison, followed by a Bayesian random-effects NMA 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 two treatment options (22,23). Transitivity was assessed by subjectively comparing the distribution of population, intervention and methodological characteristics of the studies. The consistency assumption between the combined sources of evidence in the network was first evaluated globally for the entire network using the design-by-treatment interaction model, and then locally for each treatment comparison using the node-splitting model (24–26). The surface under the cumulative ranking (SUCRA) curve for each intervention was calculated, and based on the SUCRA values, heat maps were generated to efficiently recognize what were most likely the best and worst interventions for each outcome (27). For both meta-analysis and NMA, Bayesian hierarchical models with non-

informative priors assigned to all model parameters were used. For each meta-analysis, the $I^2$ statistic was used to assess heterogeneity of trials (18). In the NMA, a common-within network heterogeneity was assumed, since 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 2.5th and 97.5th percentile of the posterior distributions in the simulations, respectively. A network absolute risk difference (RD) 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).

**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 of administration of the first dose of the intervention, echocardiographic findings and RoB. The overall RoB for each study was assessed by taking the average of the 3 most important RoB items 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 and probably low RoB). 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 NEC. All analyses were performed using WinBUGS (version 1.4.3), OpenBUGS (version 3.2.3 rev 1012),

NetmetaXL, GeMTC GUI and R studio packages (31–33). The design-by-treatment model was performed in Stata using the network command (34).

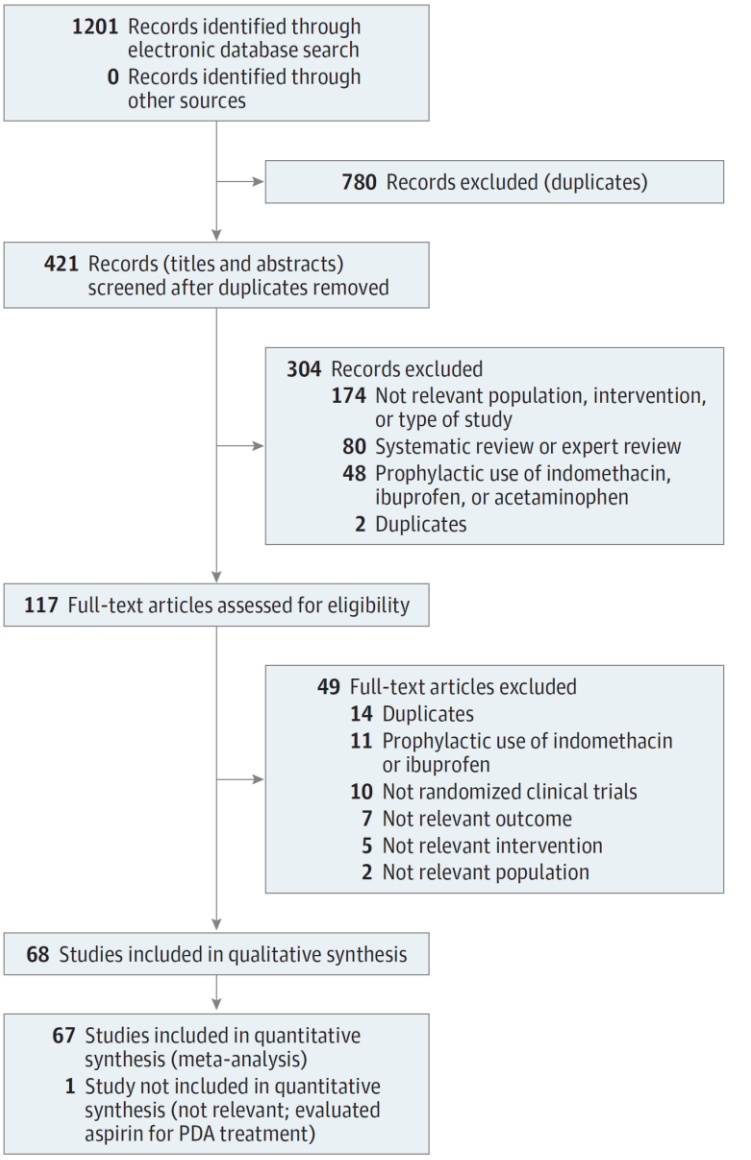
**Assessment of Quality of Evidence**

The quality of evidence of each direct, indirect, and network effects estimate was evaluated for the primary and main secondary outcomes according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) method for NMA (35,36). The quality of evidence of direct estimates started as high and was decreased to moderate, low, or very low based on RoB, imprecision, heterogeneity, indirectness, and publication bias (35). Publication bias was assessed by visual inspection of asymmetry in the funnel plots. The quality of evidence of indirect and network effects estimates 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 tests (36).

## RESULTS

Among 1201 records retrieved, 68 RCTs met inclusion criteria and included 4802 preterm infants. The study selection is presented in the flow diagram (Figure 1).

Figure 1. Literature Search and Study Selection Flow Diagram




PDA indicates patent ductus arteriosus.

Forty-nine studies were excluded after full-text screening (eTable 3). The clinical and methodological characteristics of the included studies are presented in eTable 4 (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).

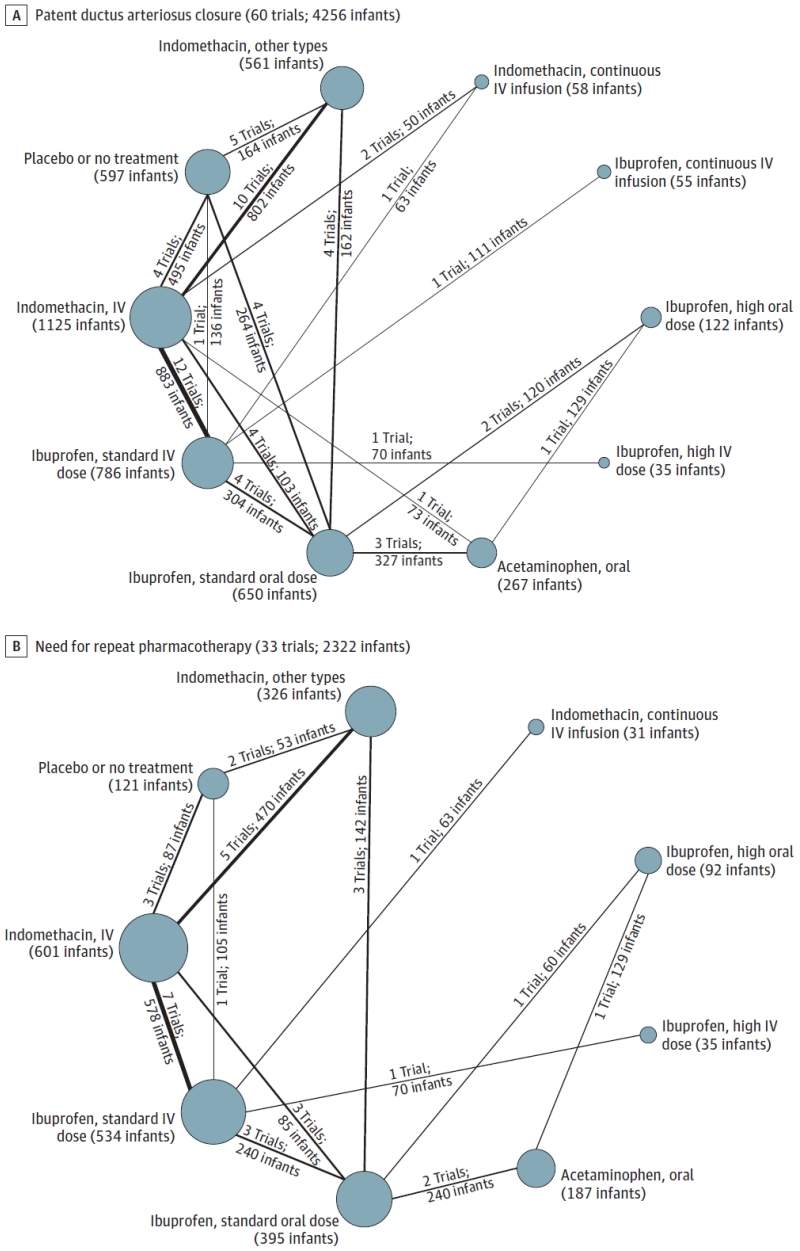
Fourteen different variations of indomethacin, ibuprofen or acetaminophen were used as treatment modalities across the studies. The variations included differences in route of administration (IV or oral), dose of medication (standard dose; high dose; prolonged course), method of administration (bolus dose; continuous infusion) and co-interventions (concomitant use of furosemide, dopamine or echocardiography-guided indomethacin infusion). Dosage for IV indomethacin was defined as 0.1-0.3 mg/kg IV every 12-24h for a total of 3 doses, standard dose ibuprofen was defined as 10 mg/kg followed by 5mg/kg every 12-24 h for a total of 3 doses (both IV and oral) and high-dose ibuprofen was defined as 15-20 mg/kg followed by 7.5-10 mg/kg every 12-24 h for a total of 3 doses (both IV and oral) (detailed definitions of the different doses and methods of administration of the medications are listed in eTable 1). One study used aspirin for treatment of PDA (95). The study was excluded from the analysis due to lack of relevance in the current context. IV indomethacin, used in 38 studies, was the most commonly used intervention, followed by standard doses of IV ibuprofen and oral ibuprofen, used in 23 and 21 studies, respectively. Oral acetaminophen was used in 5 studies while higher doses of IV ibuprofen and oral ibuprofen were used in 1 and 3 studies, respectively (eTable 4). PDA diameter more than 1.5mm and left atrium to aortic root ratio of 1.4 or more were the two most commonly used echocardiographic criteria for defining hs-PDA (eTable 4). Sixteen studies were found to have a low RoB (eFigure 2). Twenty-eight studies had a “probably low” RoB while 21

studies had a “probably high” RoB. Three studies did not report any of sequence generation, allocation concealment or blinding and were therefore judged to have a high RoB (eFigures 2 and 3).

**The Network Plots**

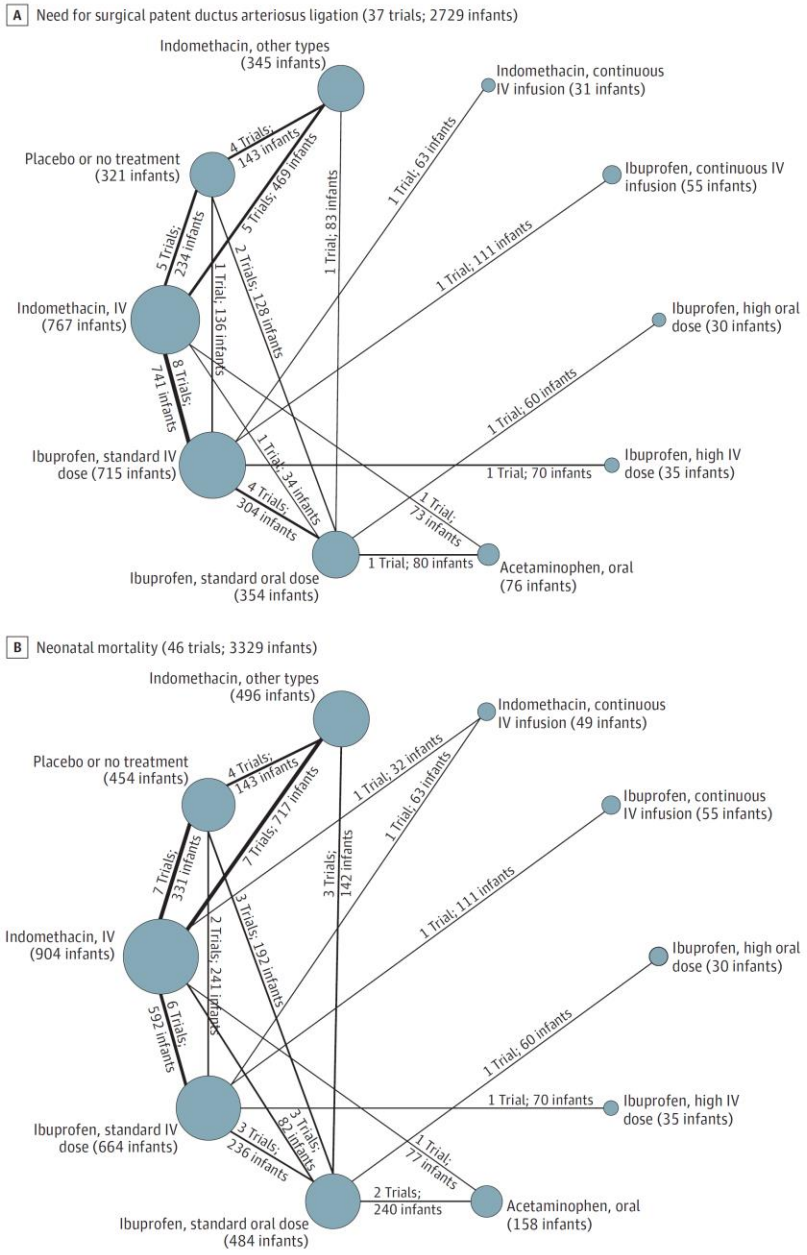
Head-to-head comparisons between the different therapeutic options were depicted as network plots for each outcome (Figure 2-5 A&B). Seldom used variations of indomethacin were condensed into a single node named ‘indomethacin-others’ to make the results more relevant in the current clinical context (eTable 1). Similarly, for ease of analysis, placebo and no treatment were combined into a single node named ‘placebo/no treatment’. Hence the final NMA was conducted with 10 nodes, each depicting a treatment modality.

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



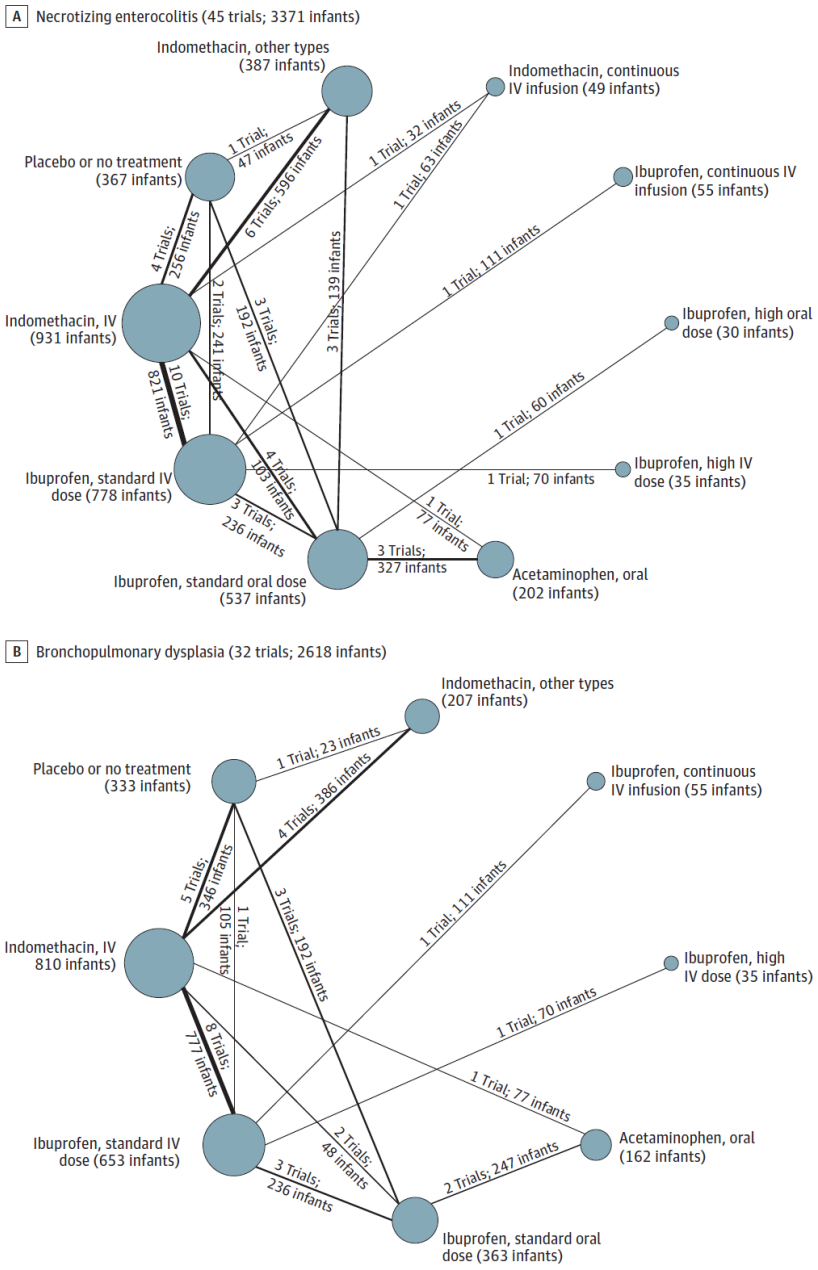

These 2 outcome measures for treatment of hemodynamically significant patent ductus arteriosus were evaluated in the Bayesian network meta-analysis. Each node indicates a treatment modality and is sized proportionally to the number of infants who received the treatment modality. Each line connecting 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.

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



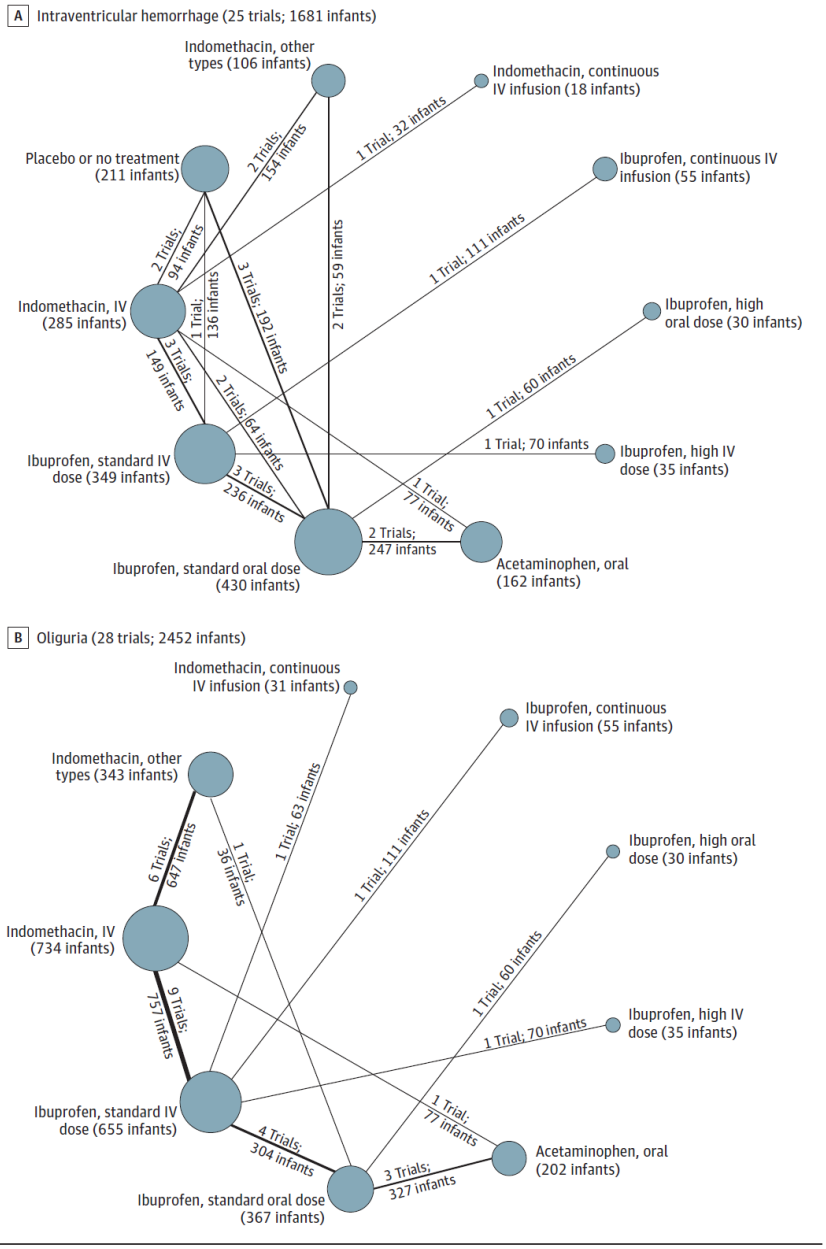

These 2 outcome measures for treatment of hemodynamically significant patent ductus arteriosus were evaluated in the Bayesian network meta-analysis. Each node indicates a treatment modality and is sized proportionally to the number of infants who received the treatment modality. Each line connecting 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.

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.

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.

**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% all studies combined and 38% in the placebo/no treatment group. Oral high-dose ibuprofen was associated with a significantly higher odds of PDA closure compared with standard-dose intravenous ibuprofen (OR,3.59; 95% CrI,1.64-8.17; absolute RD,199 more [from 95 to 258 more] per 1000 infants) and intravenous indomethacin (OR,2.35; 95% CrI,1.08-5.31; absolute RD, 124 more [from 14 to 188 more] per 1000 infants) (Figure 6A,eText 2;eFigures 4-5;eTables 5-6). High-dose IV ibuprofen (OR,3.68; 95% CrI,1.09-14.59; absolute RD, 201 more [from 18 to 281 more] per 1000 infants), oral acetaminophen (OR,2.93; 95% CrI,1.53-5.62; absolute RD, 177 more [from 83 to 236 more] per 1000 infants) and standard-dose oral ibuprofen (OR,2.22; 95% CrI,1.44-3.40; absolute RD, 142 more [from 72 to 194 more] per 1000 infants) were also associated with a significantly higher odds of PDA closure compared with standard-dose IV ibuprofen (Figure 6A). Figures 6-9 depicts the network OR for each possible comparison for all 8 outcomes along with their SUCRA values and median ranks. Based on mean SUCRA values, high-dose oral ibuprofen ranked the best treatment option for PDA closure (SUCRA, 0.89) and for reducing surgical PDA ligation (SUCRA, 0.98) while high-dose IV ibuprofen and oral acetaminophen (SUCRAs, 0.83 and 0.82, respectively) ranked best in terms of reducing the need for repeat pharmacotherapy (Figure 6B;eFigures 4-9;eTables 5-10).

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

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) | Mean SUCRA, 0.84 (SD, 0.20); median rank, 2 (95% CrI, 1-7) | Mean SUCRA, 0.82 (SD, 0.12); median rank, 3 (95% CrI, 1-5) | Mean SUCRA, 0.68 (SD, 0.10); median rank, 4 (95% CrI, 2-6) | Mean SUCRA, 0.48 (SD, 0.1); median rank, 6 (95% CrI, 4-7) | Mean SUCRA, 0.47 (SD, 0.13); median rank, 6 (95% CrI, 3-8) | Mean SUCRA, 0.40 (SD, 0.21); median rank, 7 (95% CrI, 2-9) | Mean SUCRA, 0.24 (SD, 0.07); median rank, 8 (95% CrI, 7-9) | Mean SUCRA, 0.17 (SD, 0.13); median rank, 9 (95% CrI, 5-9) | Mean SUCRA, 0.001 (SD, 0.012); median rank, 10 (95% CrI, 10-10) |
| 0.98 (0.20-4.24) | | | | | | | | | |
| 1.23 (0.62-2.48) | 1.25 (0.31-5.77) | | | | | | | | |
| 1.63 (0.84-3.24) | 1.66 (0.45-7.07) | 1.33 (0.81-2.17) | | | | | | | |
| 2.35 (1.08-5.31) | 2.41 (0.68-9.86) | 1.92 (1.00-3.68) | 1.45 (0.94-2.24) | | | | | | |
| 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) | | | | | |
| 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) | | | | |
| 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) | | | |
| 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) | | |
| 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) | |

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) | Mean SUCRA, 0.83 (SD, 0.24); median rank, 1 (95% CrI, 1-7) | Mean SUCRA, 0.82 (SD, 0.15); median rank, 2 (95% CrI, 1-5) | Mean SUCRA, 0.67 (SD, 0.14); median rank, 4 (95% CrI, 2-6) | Mean SUCRA, 0.33 (SD, 0.11); median rank, 6 (95% CrI, 4-8) | Mean SUCRA, 0.58 (SD, 0.16); median rank, 5 (95% CrI, 2-6) | Mean SUCRA, 0.38 (SD, 0.24); median rank, 6 (95% CrI, 1-8) | Mean SUCRA, 0.17 (SD, 0.07); median rank, 8 (95% CrI, 6-8) | Mean SUCRA, 0.0003 (SD, 0.0056); median rank, 9 (95% CrI, 9-9) |
| 1.39 (0.29-7.69) | | | | | | | | |
| 1.16 (0.53-2.78) | 0.82 (0.18-3.64) | | | | | | | |
| 0.89 (0.40-2.18) | 0.62 (0.15-2.60) | 0.77 (0.40-1.39) | | | | | | |
| 0.49 (0.21-1.42) | 0.35 (0.10-1.42) | 0.43 (0.18-0.96) | 0.56 (0.32-1.00) | | | | | |
| 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) | | | | |
| 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) | | | |
| 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) | | |
| 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) | |

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.

**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 |
|---|---|---|---|---|---|---|---|---|---|
| Mean SUCRA, 0.98 (SD, 0.08); median rank, 1 (95% CrI, 1-3) | Mean SUCRA, 0.33 (SD, 0.30); median rank, 8 (95% CrI, 2-10) | Mean SUCRA, 0.65 (SD, 0.28); median rank, 3 (95% CrI, 1-10) | Mean SUCRA, 0.59 (SD, 0.17); median rank, 4 (95% CrI, 2-8) | Mean SUCRA, 0.41 (SD, 0.41); median rank, 6 (95% CrI, 4-9) | Mean SUCRA, 0.47 (SD, 0.17); median rank, 6 (95% CrI, 3-9) | Mean SUCRA, 0.55 (SD, 0.29); median rank, 4 (95% CrI, 2-10) | Mean SUCRA, 0.24 (SD, 0.12); median rank, 8 (95% CrI, 5-9) | Mean SUCRA, 0.73 (SD, 0.21); median rank, 3 (95% CrI, 1-9) | Mean SUCRA, 0.05 (SD, 0.08); median rank, 10 (95% CrI, 8-10) |
| 0.01 (0-0.67) | | | | | | | | | |
| 0.04 (0-2.81) | 4.0 (0.10-100.00) | | | | | | | | |
| 0.02 (0-0.51) | 2.22 (0.14-50.00) | 0.59 (0.03-7.45) | | | | | | | |
| 0.01 (0-0.39) | 1.41 (0.10-25.00) | 0.37 (0.02-5.08) | 0.63 (0.21-1.76) | | | | | | |
| 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) | | | | | |
| 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) | | | | |
| 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) | | | |
| 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) | | |
| 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) | |

**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 |
|---|---|---|---|---|---|---|---|---|---|
| Mean SUCRA, 0.32 (SD, 0.38); median rank, 9 (95% CrI, 1-10) | Mean SUCRA, 0.52 (SD, 0.34); median rank, 6 (95% CrI, 1-10) | Mean SUCRA, 0.66 (SD, 0.26); median rank, 4 (95% CrI, 1-9) | Mean SUCRA, 0.71 (SD, 0.20); median rank, 3 (95% CrI, 1-8) | Mean SUCRA, 0.58 (SD, 0.17); median rank, 5 (95% CrI, 2-8) | Mean SUCRA, 0.45 (SD, 0.20); median rank, 6 (95% CrI, 2-9) | Mean SUCRA, 0.29 (SD, 0.31); median rank, 9 (95% CrI, 1-10) | Mean SUCRA, 0.66 (SD, 0.19); median rank, 4 (95% CrI, 1-7) | Mean SUCRA, 0.56 (SD, 0.43); median rank, 4 (95% CrI, 1-10) | Mean SUCRA, 0.26 (SD, 0.15); median rank, 8 (95% CrI, 4-10) |
| 2.03 (0.09-92.38) | | | | | | | | | |
| 2.47 (0.15-80.63) | 1.24 (0.25-6.83) | | | | | | | | |
| 2.61 (0.19-76.13) | 2.22 (0.14-50) | 1.03 (0.49-2.34) | | | | | | | |
| 2.19 (0.15-72.38) | 1.07 (0.27-4.81) | 0.87 (0.35-2.10) | 0.84 (0.45-1.53) | | | | | | |
| 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) | | | | | |
| 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) | | | | |
| 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) | | | |
| 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) | | |
| 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) | |

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

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 |
|---|---|---|---|---|---|---|---|---|---|
| Mean SUCRA, 0.74 (SD, 0.29); median rank, 2 (95% CrI, 1-10) | Mean SUCRA, 0.30 (SD, 0.31); median rank, 8 (95% CrI, 1-10) | Mean SUCRA, 0.62 (SD, 0.24); median rank, 4 (95% CrI, 1-9) | Mean SUCRA, 0.70 (SD, 0.15); median rank, 4 (95% CrI, 1-7) | Mean SUCRA, 0.21 (SD, 0.11)); median rank, 8 (95% CrI, 6-9) | Mean SUCRA, 0.06 (SD, 0.09); median rank, 10 (95% CrI, 7-10) | Mean SUCRA, 0.65 (SD, 0.27); median rank, 4 (95% CrI, 1-10) | Mean SUCRA, 0.42 (SD, 0.14); median rank, 6 (95% CrI, 4-8) | Mean SUCRA, 0.81 (SD, 0.24); median rank, 2 (95% CrI, 1-9) | Mean SUCRA, 0.50 (SD, 0.19); median rank, 6 (95% CrI, 2-9) |
| 0.31 (0.02-3.63) | 2.16 (0.29-18.21) | 0.66 (0.10-4.24) | 2.39 (0.38-16.16) | 1.12 (0.42-2.88) | 0.97 (0.17-6.29) | 0.46 (0.16-1.29) | 0.41 (0.21-0.75) | 0.30 (0.03-1.18) | 0.63 (0.10-4.36) |
| 0.30 (0.05-1.72) | 0.63 (0.10-4.36) | 0.30 (0.10-0.91) | 0.27 (0.12-0.57) | 0.65 (0.38-1.13) | 2.40 (0.61-9.37) | 3.68 (0.84-15.96) | 2.33 (0.28-20.42) | 1.08 (0.20-5.80) | 0.98 (0.23-4.01) |
| 0.73 (0.08-5.80) | 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) | 0.45 (0.08-2.65) | 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) | 0.42 (0.06-2.13) | 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) | | | | | |

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 |
|---|---|---|---|---|---|---|---|
| Mean SUCRA, 0.12 (SD, 0.22); median rank, 8 (95% CrI, 2-8) | Mean SUCRA, 0.86 (SD, 0.21); median rank, 1 (95% CrI, 1-6) | Mean SUCRA, 0.87 (SD, 0.13); median rank, 2 (95% CrI, 1-4) | Mean SUCRA, 0.61 (SD, 0.16); median rank, 4 (95% CrI, 2-6) | Mean SUCRA, 0.32 (SD, 0.22); median rank, 6 (95% CrI, 2-8) | Mean SUCRA, 0.50 (SD, 0.16); median rank, 4 (95% CrI, 2-7) | Mean SUCRA, 0.43 (SD, 0.33); median rank, 5 (95% CrI, 1-8) | Mean SUCRA, 0.29 (SD, 0.18); median rank, 6 (95% CrI, 3-8) |
| 3.73 (0.90-15.61) | 0.91 (0.38-2.15) | 3.49 (0.99-12.43) | 0.63 (0.25-1.53) | 0.68 (0.40-1.14) | 0.46 (0.17-1.27) | 0.50 (0.24-1.02) | 0.74 (0.43-1.27) | 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) | 0.88 (0.31-2.55) | 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) | 0.80 (0.48-1.32) |
| 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) | 0.90 (0.28-2.88) | | | | |

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.

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 |
|---|---|---|---|---|---|---|---|---|---|
| Mean SUCRA, 0.65 (SD, 0.31); median rank, 3 (95% CrI, 1-10) | Mean SUCRA, 0.73 (SD, 0.31); median rank, 2 (95% CrI, 1-10) | Mean SUCRA, 0.42 (SD, 0.27); median rank, 7 (95% CrI, 2-10) | Mean SUCRA, 0.49 (SD, 0.20); median rank, 6 (95% CrI, 2-9) | Mean SUCRA, 0.43 (SD, 0.22); median rank, 6 (95% CrI, 2-9) | Mean SUCRA, 0.21 (SD, 0.22); median rank, 9 (95% CrI, 3-10) | Mean SUCRA, 0.45 (SD, 0.46); median rank, 8 (95% CrI, 1-10) | Mean SUCRA, 0.52 (SD, 0.21); median rank, 5 (95% CrI, 2-9) | Mean SUCRA, 0.68 (SD, 0.31); median rank, 3 (95% CrI, 1-10) | Mean SUCRA, 0.42 (SD, 0.23); median rank, 6 (95% CrI, 2-10) |
| 1.29 (0.19-8.48) | 0.52 (0.10-2.69) | 1.09 (0.54-2.22) | 0.93 (0.51-1.66) | 0.72 (0.36-1.41) | 1.15 (0-288.80) | 1.34 (0.01-1413.00) | 1.44 (0.42-5.47) | 0.62 (0.14-2.43) | |
| 0.67 (0.17-2.48) | 0.57 (0.12-2.64) | 1.02 (0.46-2.23) | 0.68 (0.30-1.47) | 0.83 (0-207.80) | 1.54 (0.66-3.64) | 1.99 (0.01-2354.00) | 1.12 (0.61-2.04) | 1.00 (0.54-1.85) | 1.37 (0.59-3.25) |
| 0.73 (0.23-2.18) | 0.53 (0.11-2.50) | 0.74 (0.27-1.95) | 0.78 (0-199.52) | 1.04 (0.62-1.77) | 1.19 (0-1314.75) | 0.89 (0.52-1.53) | 1.50 (0.39-6.38) | 1.62 (0.40-7.01) | 2.24 (0.48-11.08) |
| 0.68 (0.19-2.34) | 0.53 (0.11-2.49) | 0.85 (0-221.80) | 0.76 (0.21-2.57) | 0.59 (0.14-2.45) | 1.10 (0.18-6.66) | 0.85 (0.13-5.98) | 1.63 (0.36-8.16) | 0.67 (0.19-2.32) | |

**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 |
|---|---|---|---|---|---|---|---|---|
| Mean SUCRA, 0.02 (SD, 0.10); median rank, 9 (95% CrI, 8-9) | Mean SUCRA, 0.40 (SD, 0.23); median rank, 6 (95% CrI, 2-8) | Mean SUCRA, 0.79 (SD, 0.16); median rank, 2 (95% CrI, 1-6) | Mean SUCRA, 0.60 (SD, 0.19); median rank, 4 (95% CrI, 2-7) | Mean SUCRA, 0.20 (SD, 0.09); median rank, 8 (95% CrI, 6-8) | Mean SUCRA, 0.61 (SD, 0.17); median rank, 4 (95% CrI, 2-7) | Mean SUCRA, 0.50 (SD, 0.35); median rank, 6 (95% CrI, 1-8) | Mean SUCRA, 0.49 (SD, 0.14); median rank, 5 (95% CrI, 3-7) | Mean SUCRA, 0.90 (SD, 0.18); median rank, 1 (95% CrI, 1-6) |
| 2.43e+10 (1.40-7.54e+17) | 4.71 (0.30-71.49) | 1.12e+11 (6.51-4.06e+18) | 2.45 (0.19-33.70) | 0.55 (0.22-1.27) | 5.71e+10 (3.48-2.2e+18) | 0.47 (0.06-3.88) | 0.10 (0.02-0.58) | 0.20 (0.04-0.92) | 1.15e+10 (0.62-4.34e+17) |
| 2.16 (0.29-17.87) | 0.48 (0.08-2.93) | 0.89 (0.16-4.66) | 4.56 (2.63-8.10) | 5.07e+10 (2.20-1.99e+18) | 1.21 (0-718.30) | 0.29 (0-91.66) | 0.53 (0-166.25) | 2.69 (0.01-1009.00) | 8.83e+10 (2.69-1.98e+18) |
| 0.59 (0-248.40) | 1.28 (0-226.60) | 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) | 4.53e+10 (1.99-1.37e+18) | 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 (0.02-36280.00) | 14.15 (0.54-1916.00) | 4.84e+11 (66.5 -2.88e+20) | | | | |

**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/no treatment group. Although standard-dose oral ibuprofen ranked best in terms of preventing mortality (SUCRA, 0.71), there was no statistically significant difference between any of the treatment modalities in the network in relation to neonatal mortality (Figure 7B;eFigures 10-11;eTables11-12).

Incidence of NEC was reported by 45 studies (3371 infants). Overall incidence of NEC was 8.7% and 6.5% in the placebo/no treatment group. Continuous infusion of IV Ibuprofen (SUCRA, 0.81) was associated with the lowest incidence of NEC (Figure 8A;eFigures 12-13;eTables13-14). Both standard and high-dose IV ibuprofen (SUCRAs, 0.42 and 0.30, respectively), and IV indomethacin (SUCRA, 0.21) ranked worse than placebo/no treatment (SUCRA, 0.50), in terms of NEC incidence, although the differences in their effect estimates failed to reach statistical significance (Figure 8A).

Standard-dose oral ibuprofen (SUCRA, 0.87) and high-dose IV ibuprofen (SUCRA, 0.73) were associated with the lowest incidences of BPD and IVH, respectively, while continuous infusion of IV ibuprofen was associated with the lowest incidence of oliguria (SUCRA, 0.90)(Figures 8B, 9A-B; eFigures14-19;eTables15-20). Heat maps depicting the hierarchy of the 10 treatment modalities according to SUCRA across all 8 outcomes are presented in Figure 10 A&B.

**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

| 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 |
|---|---|---|---|---|---|---|---|---|---|---|
| | Treatment modality | | | | | | | | | |
| 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]

| 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 |
|---|---|---|---|---|---|---|---|---|---|---|
| | Treatment modality | | | | | | | | | |
| 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.

Due to paucity of data, quantitative synthesis was not done on the remaining a priori defined outcomes (Table 1).

**Quality of Evidence Assessment**

For the primary outcome of PDA closure, there were 17 direct comparisons and 45 possible comparisons in the network. On GRADE assessment, the quality of evidence for 6 comparisons was judged to be of "high" quality, 14 "moderate", 20 "low" quality and 5 of "very low" quality (eTable 5). The quality of evidence for a number of comparisons in the secondary outcomes (especially adverse events) was rated down to "low" or "very low" in view of the imprecise effect estimates as evidenced by the wide CrIs (eTables 7, 9,11,13,15,17,19). On global assessment of network inconsistency using the design-by-treatment interaction model, only the oliguria network showed significant inconsistency (p=0.03)(Figure 9B).

**Sensitivity Analyses**

Sensitivity analyses for all outcomes were conducted taking only the high quality studies (Figure 10; eFigures20-27;eTables 21-36). High-dose oral ibuprofen still ranked the best treatment option for PDA closure (SUCRA, 0.88) and reducing surgical ligation (SUCRA, 0.97)(eTables 22,26). It also emerged as the best ranked treatment for preventing NEC (SUCRA, 0.97) over continuous infusion of IV ibuprofen (SUCRA, 0.74)(eTable30).

**Meta-regression Analysis**

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

## DISCUSSION

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

Management of PDA has evolved over 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 has ranged from targeted pharmacotherapy (based on echocardiographic or clinical criteria for hemodynamic significance) to no PDA treatment combined with co-interventions such as fluid restriction and ventilator adjustments (7). Despite ranking worst in terms of PDA closure, placebo/no treatment was not associated with a higher odds of death, NEC or IVH compared with any other treatment modality. This raises the question whether active pharmacological closure of hs-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).

With targeted PDA treatment becoming the preferred approach, the question of choice of pharmacotherapy has become more important (7,9). A number of Cochrane systematic reviews of RCTs have provided head-to-head comparisons of the various management options. They concluded that ibuprofen was as effective as indomethacin for PDA closure while the former reduced the risk of NEC and transient renal insufficiency (105). There was insufficient evidence

to suggest benefit of any of the variations of standard-dose indomethacin treatment (106). Oral acetaminophen was found to be as effective as oral ibuprofen for PDA closure based on only 2 unblinded RCTs (107). However, none of the reviews conducted an in-depth comparison of the different doses and modes of administration of the different medications with each other. With regards to multiple treatment comparisons, only 1 NMA has previously been published in 2011 that compared IV indomethacin, IV ibuprofen and placebo for hs-PDA but did not include evidence for acetaminophen (108). Recently, oral acetaminophen has emerged as a new treatment option as well as higher doses of oral ibuprofen (107,109). Use of an NMA 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 NMA, high-dose oral ibuprofen (15-20 mg/kg followed by 7.5-10 mg/kg every 12-24 h 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-dose IV ibuprofen and IV indomethacin. The ibuprofen dose that is traditionally used (10-5-5 mg/kg, each given at 24 h intervals) is based on old pharmacokinetic data in 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 showed that in infants <27 weeks gestation, the estimated minimum effective dose regimen was 20–10–10 mg/kg which 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%) (112). The results of this NMA are consistent with the above pharmacokinetic data. Apart from high-dose oral ibuprofen, oral acetaminophen also consistently ranked high across all effectiveness outcomes, suggesting that it could be an alternative to IV ibuprofen and indomethacin for hs-PDA closure. In contrast, standard-dose IV Ibuprofen generally ranked just

above placebo across all effectiveness outcomes, suggesting that the standard IV doses may be ineffective in achieving PDA closure beyond the first few days of life. In the 2015 Cochrane review, IV ibuprofen was significantly less efficacious than oral ibuprofen (RR 0.37; 95%CI,0.23-0.61) in achieving PDA closure (105). Similar findings were observed in this NMA in which the IV formulation ranked below the oral formulation across most outcomes. Although this finding may appear counterintuitive, available pharmacokinetic data support this observation (113). Pacifici et al 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 IV formulation (114).

Despite supporting pharmacokinetic evidence, clinicians have often been reluctant to use oral ibuprofen formulations due to concerns about NEC (115). In this NMA, high-dose oral ibuprofen was not associated with an increased incidence of NEC (Figure 8A). In sensitivity analysis of the high quality studies (Figure 10B), high-dose oral ibuprofen was associated with the best cumulative probability for preventing NEC, suggesting that hs-PDA in itself probably is a significant risk factor for NEC and closing it successfully when hemodynamically significant could in turn reduce the risk of NEC (2). Despite ranking lower than high-dose oral ibuprofen across the effectiveness outcomes, standard-dose oral ibuprofen ranked as the best treatment for preventing death (Figure 10). This apparent paradox in the NMA results was likely artifactual due to substantial imprecision in the effect estimates for the secondary outcomes as evidenced by the wide CrIs of the ranking statistics (Figure 7B). No statistically significant difference in mortality rates was observed with any of the interventions based on available evidence, which suggests that active pharmacological closure of an hs-PDA may not be associated with lower mortality in preterm infants.

The overall high ranking probabilities across outcomes suggest that high-dose and standard dose oral ibuprofen as well as oral acetaminophen could be effective alternatives to the standard IV ibuprofen and indomethacin regimens currently used to close an hs-PDA (Figure 10). Well-designed RCTs 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 NMA results.

***Limitations***

This study has several limitations. First, this NMA 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 co-interventions, which have changed over last 4 decades. This was accounted for in the meta-regression analysis conducted for the most important outcomes and controlling for the effect modifiers (eTables37-44). 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 one. 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 hs-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 NEC, BPD, IVH, mortality) beyond immediate PDA closure should be explored in future studies.

***Conclusions***

Oral high-dose ibuprofen was associated with a higher likelihood of hs-PDA closure compared with standard doses of intravenous ibuprofen or intravenous indomethacin. Placebo or no treatment for hs-PDA did not significantly change the likelihood of mortality, NEC or IVH.

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## Supplement 1. Network Meta-analysis Protocol

**PROSPERO**
**International prospective register of systematic reviews**

Systematic review and network meta-analysis of IV indomethacin versus IV Ibuprofen versus oral Ibuprofen versus oral acetaminophen versus placebo for treatment of symptomatic patent ductus arteriosus in preterm infants

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Citation

Souvik Mitra, Lehana Thabane, Iván D. Florez, María E. Tamayo, Dagfinn Aune. Systematic review and network meta-analysis of IV indomethacin versus IV Ibuprofen versus oral Ibuprofen versus oral acetaminophen versus placebo for treatment of symptomatic patent ductus arteriosus in preterm infants. PROSPERO 2015 CRD42015015797 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42015015797

Review question

Systematic review and network meta-analysis comparing indomethacin, ibuprofen, acetaminophen with
placebo for treatment of Patent Ductus Arteriosus in preterm infants.

Searches

A systematic literature search would be conducted from the following electronic databases:
Cochrane Central Register of Controlled Trials (CENTRAL)
MEDLINE
PubMed
EMBASE
In addition, we will seek registered details of selected trials in the U.S. National Institutes of Health resource Clinicaltrials.gov. We would obtain information by personal communication, review the reference lists of relevant articles, abstracts and conference proceedings (Society for Pediatric Research, European Society for Paediatric Research 1990–2015) and seek results of unpublished trials. No language restrictions would be imposed.
The following keywords would be used to build our search strategy for each electronic database
1. Population:
Newborn Ductus
Ductus Arteriosus, Patent
Ductus (free term)
PDA
Persistent fetal circulation
AND
Newborn (free term)
Infant
Neonate
Preterm
Premature
2. Intervention and Control:
Indomethacin
Ibuprofen

paracetamol
placebo
Acetaminophen
Cox inhibitor
Prostaglandin synthetase inhibitor
NSAID (free)
Ant-Inflammatory Agents, Non-steroidal [Mesh]
3. Design:
Randomized controlled trials as a topic [Mesh]
Randomized Controlled trial [Publication type]
Clinical Trial
Randomized Controlled trial

Types of study to be included
Randomized controlled trials
Condition or domain being studied
Management of patent ductus arteriosus (PDA) in preterm infants is one of the most controversial topics in neonatal medicine. It is associated with a number of co-morbidities like necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD) and intraventricular hemorrhage (IVH). The management dilemmas have mainly centered on when to treat and with what to treat. To increase the complexity of matters, these two aspects of PDA management are not mutually exclusive, with the modality of treatment often being dictated by the timing of treatment. There have been a large number of published studies, meta-analyses, reviews, and editorials focusing on different aspects of management dilemmas. Regarding the timing of treatment, prophylactic therapy has gradually fallen out of favor and neonatal units have shifted towards a more conservative approach by treating only the clinically and echocardiographically significant PDAs. However, the big dilemma that still persists among neonatologists is what to use as the primary modality of treatment.

Participants/population
Preterm infants with hemodynamically significant PDA

Intervention(s), exposure(s)
1. Intravenous Indomethacin
or
2. Intravenous Ibuprofen
or
3. Oral Ibuprofen
or
4. Oral Acetaminophen
or
5. IV acetaminophen

***Inclusion criteria:*** trials included in our review will have 1) Indomethacin or Ibuprofen or Acetaminophen being used for the treatment of clinically and/or echocardiographically determined hemodynamically significant PDA ; 2) have randomized infants to two intervention

arms using the above mentioned drugs or an intervention arm using one of the above mentioned drugs and a control arm.
***Exclusion criteria:*** use of any intervention for prophylaxis

Comparator(s)/control
Any of the interventions or placebo

Primary outcome(s)
Closure of PDA
Secondary outcome(s)
Incidence of necrotizing enterocolitis
Incidence of oliguria
Duration of ventilatory support

Risk of bias (quality) assessment
GRADE guidelines will be used for risk of bias assessment

Strategy for data synthesis
Network meta-analysis will be done
Data will analyzed as aggregate
Quantitative synthesis is planned

Analysis of subgroups or subsets
None planned

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Language
English
Country
England, Canada, Colombia
Stage of review
Ongoing
Subject index terms status
Subject indexing assigned by CRD
Subject index terms
Acetaminophen; Cyclooxygenase Inhibitors; Ductus Arteriosus, Patent; Humans; Ibuprofen; Indomethacin;
Infant, Newborn; Infant, Premature
Date of registration in PROSPERO
30 June 2015
Date of publication of this version
30 June 2015
Revision note for this version
Details of search strategies including keywords and database sources have been specified on section # 16

Stage of review at time of this submission
**Stage Started Completed**
Preliminary searches Yes Yes
Piloting of the study selection process Yes No
Formal screening of search results against eligibility criteria No No
Data extraction No No
Risk of bias (quality) assessment No No
Data analysis No No

Revision note
Details of search strategies including keywords and database sources have been specified on section # 16
Versions
30 June 2015
30 June 2015

**Supplement 2. Summary of changes between published protocol and manuscript**

| Sections | Published Protocol | Final systematic review manuscript | Reasons for the changes |
|---|---|---|---|
| Type of study | "We will include RCTs and quasi-RCTs" | The review only included RCTs | To improve the quality of evidence generated from synthesis of results |
| Overall risk of bias assessment for the individual outcomes for each study | Not specified | The overall RoB for each study was assessed by taking the average of the following RoB items: sequence generation, allocation concealment and blinding | Prior to data extraction, it was decided by expert consensus that the aforementioned RoB items provided the most robust assessment of the overall RoB given the nature of the population, interventions and outcomes involved in the RCTs included this systematic review |
| Primary outcome measure | "Failure of permanent PDA closure" defined as failure to close the PDA | "PDA closure" defined as closure of an hs-PDA within a week of administration of the first dose of the intervention | We intended to depict the primary effectiveness outcome as a positive outcome to make it easier for the readers to interpret |
| Secondary outcome assessment | 3 effectiveness and 11 safety outcomes were initially planned for evaluation | Quantitative synthesis of data was conducted with eight outcomes, that included all three | Paucity of data |

| | | | |
|---|---|---|---|
| | | effectiveness outcomes and five safety outcomes. The outcomes that were not explored included the following: severe intra-ventricular hemorrhage; periventricular leukomalacia; neurodevelopmental disability; intestinal perforation; gastrointestinal bleeding; time to full enteral feeds | |
| Secondary outcome definitions | • Mortality: Death during the first 28 days of life<br>• Reopening of the ductus arteriosus: Number of neonates with echocardiographically determination of reopening of the ductus<br>• Chronic lung disease (CLD): Total number of neonates with oxygen requirement at 28 days postnatal age in addition to compatible clinical and roentgenographic findings.<br>• Necrotizing enterocolitis (NEC): Number of neonates with NEC (any stage) | • Mortality: Death at 36 weeks' postmenstrual age or before discharge<br>• Need for repeat pharmacotherapy: Number of neonates who require a repeat course of pharmacotherapy following an initial course for treatment of a persistent hs-PDA<br>• Bronchopulmonary dysplasia (BPD): Number of neonates who require oxygen at 36 weeks' postmenstrual age<br>• Necrotizing enterocolitis (NEC): Number of | The definitions of some of the secondary outcomes were modified to make them more clinically relevant to clinicians and decision makers based on consensus from experts |

| | | | |
|---|---|---|---|
| | | neonates with NEC (stage 2 or higher based on Bell criteria). | |
| Network Plots | Possibility of combination of multiple treatment modalities into single nodes were not discussed in the protocol | Several variations of indomethacin that are seldom used in the current context, namely, indomethacin with furosemide, indomethacin with dopamine, high dose IV indomethacin, prolonged infusion of IV indomethacin, oral indomethacin and echocardiography-guided indomethacin infusion were condensed into a single node named 'Indomethacin, other types' (INDOTHERS). Similarly, placebo and no treatment were combined into a single node named 'Placebo/No Treatment' (PLAC_NORx). Hence the final NMA was conducted with 10 nodes, each depicting a treatment modality | To make the results more relevant in the current clinical context and for ease of analysis |
| Exploring heterogeneity | "We propose, a priori, the following potential sources of heterogeneity, which could be possible effect modifiers: gestational age (<28; 28–32; >32 weeks of gestational age), birth weight (<1000; 1000–1500; >1500 g), different doses of the interventions, time of administration of | The sources of heterogeneity that were explored included: gestational age (GA) (as a continuous variable); birth weight (BW) (as a continuous variable); time of administration of first dose (as a continuous variable). | We conducted a network meta-regression analysis (instead of subgroup analysis) using GA, BW and time of initiation of treatment as potential effect modifiers, hence we chose to use |

| | | | |
|---|---|---|---|
| | the first dose of the intervention (<3, 3–7, >7 days), echocardiographic findings (PDA size and left atrium:aortic root ratio), time of PDA assessment post pharmacotherapy (<24 hours, 24 hours to 3 days, and >7 days) and previous medical PDA medical therapy." | | continuous measures. Timing of PDA closure assessment was not explored due to paucity of data. Variation in echo findings were not included in the model as the studies were fairly uniform in their echo definition of hs-PDA |

**Supplementary Online Content**

Mitra S, Florez ID, Tamayo ME, et al. Association of placebo, indomethacin, ibuprofen, and acetaminophen with closure of hemodynamically significant patent ductus arteriosus in preterm infants: a systematic review and meta-analysis. JAMA. doi:10.1001/jama.2018.1896

This supplementary material has been provided by the authors to give readers additional information about their work.

**eTable 1. Glossary of abbreviations, acronyms (including dosage & routes of administration of medications) and terms**

| **Abbreviations** |
|---|
| • PDA: Patent ductus arteriosus<br>• Hs-PDA: hemodynamically-significant PDA<br>• CENTRAL: Cochrane Central Register of Controlled Trials<br>• NEC: Necrotizing enterocolitis<br>• BPD: bronchopulmonary dysplasia<br>• IVH: Intraventricular hemorrhage<br>• RCT: Randomized Controlled Trial<br>• OR: Odds ratio<br>• CrI: Credible interval<br>• SUCRA: Surface under the cumulative ranking<br>• PROSPERO: International prospective register of systematic reviews<br>• DA: ductus arteriosus<br>• NMA: Network meta-analysis<br>• ISPOR: International Society For Pharmacoeconomics and Outcomes Research<br>• PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses<br>• ECHO: echocardiography<br>• RoB: Risk of Bias<br>• RE: Random effects<br>• DBT: Design by treatment<br>• GRADE: Grading of Recommendations Assessment, Development and Evaluation<br>• RR: Relative Risk<br>• CI: Confidence intervals<br>• AUC: Area under the curve<br>• BW: Birth weight<br>• GA: Gestational age |
| **Acronyms for pharmacotherapeutic options (with routes & doses)** |
| • INDOIV: Intravenous (IV) indomethacin standard dose (0.1-0.3 mg/kg IV every 12-24h for a total of 3 doses)<br>• IBUIV: Intravenous ibuprofen standard dose (10 mg/kg IV followed by 5mg/kg IV every 12-24 h for a total of 3 doses)<br>• IBUPO: Oral ibuprofen standard dose (10 mg/kg oral followed by 5mg/kg oral every 12-24 h for a total of 3 doses)<br>• PARAPO: Oral acetaminophen 15 mg/kg/dose four times a day for 3-7 days<br>• IBUPOHIGHDOSE: Oral ibuprofen high dose (15-20 mg/kg oral followed by 7.5-10 mg/kg oral every 12-24 h for a total of 3 doses)<br>• IBUIVHIGHDOSE: Intravenous ibuprofen high dose (15-20 mg/kg IV followed by 7.5-10 mg/kg IV every 12-24 h for a total of 3 doses)<br>• INDOIVCONT: Intravenous indomethacin infused continuously for 36 h at a rate of 17 mcg/kg/h<br>• IBUIVCONT: Intravenous ibuprofen continuous infusions of 10mg/kg (0.416 mg/kg/h), 5 mg/kg (0.208 mg/kg/h) and 5 mg/kg(0.208 mg/kg/h), and boluses of equal volumes of 5% dextrose administered over 15 min, 24 h apart |

- INDOPO: Oral indomethacin standard dose (dose same as INDOIV)
- INDOIVHIGHDOSE: Intravenous indomethacin 0.2-0.5mg/kg every day for 3 days
- INDOIVPROLONGED: Intravenous indomethacin prolonged treatment course (0.1-0.15 mg/kg every 12-24 h for 5-7 days).
- INDOIVLATE: Intravenous indomethacin standard dose (dose same as INDOIV); late initiation of therapy (started on or beyond day 7)
- INDOIVFRU: Intravenous indomethacin standard dose (dose same as INDOIV) along with Frusemide
- INDOIVECHOGUIDED: Intravenous indomethacin standard dose (dose same as INDOIV); duration guided by echo assessment of PDA
- INDOTHERS: Indomethacin, other types (INDOPO + INDOIVLATE + INDOIVFRU + INDOIVECHOGUIDED + INDOIVHIGHDOSE + INDOIVPROLONGED)
- PLAC: Placebo
- NORX: No treatment
- PLAC_NORX: Placebo + No treatment

## eTable 2. Electronic Database Search Strategies

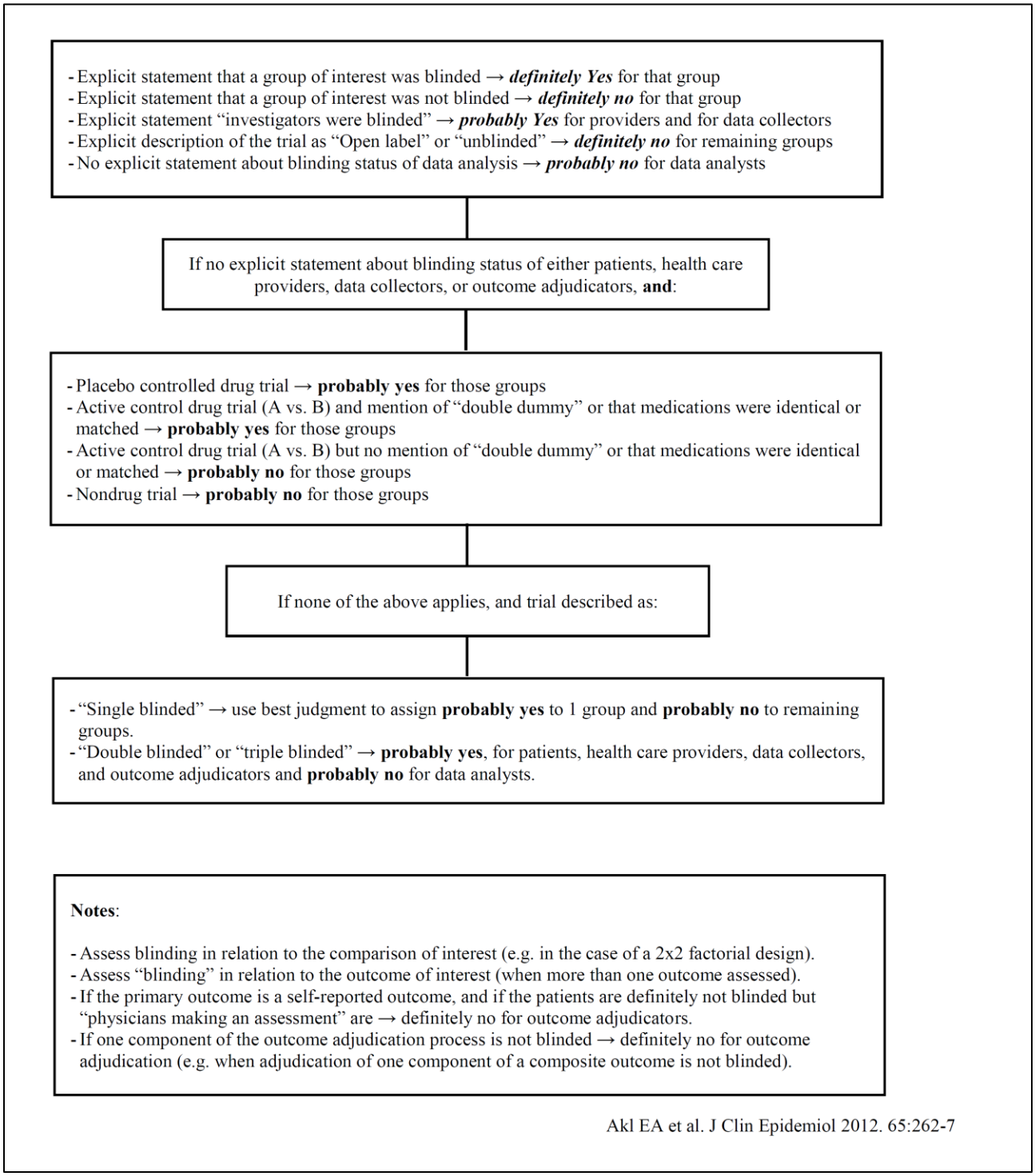
| MEDLINE (on OVID platform) | EMBASE (on OVID platform) | CENTRAL (Cochrane Central Register of Controlled Trials) |
|---|---|---|
| 1. Infant, Premature/ or Premature Birth/ or Infant, Newborn/ or Infant, Premature, Diseases/ or preterm.mp. | 1. Infant, Premature/ | #1 infant, premature |
| 2. low birth weight.mp. or Infant, Low Birth Weight/ | 2. Premature Birth/ | #2 Premature Birth |
| 3. very low birth weight.mp. or Infant, Very Low Birth Weight/ | 3. Infant, Newborn/ | #3 Infant, Newborn |
| 4. Infant, Extremely Low Birth Weight/ | 4. Infant, Premature, Diseases/ | #4 Infant, Premature, Diseases |
| 5. 1 or 2 or 3 or 4 | 5. preterm.mp. | #5 preterm.mp. |
| 6. Ductus Arteriosus, Patent/ | 6. low birth weight.mp. | #6 low birth weight.mp. |
| 7. patent ductus arteriosus.mp. | 7. Infant, Low Birth Weight/ | #7 Infant, Low Birth Weight |
| 8. ductus arteriosus.mp. or Ductus Arteriosus/ | 8. very low birth weight.mp. | #8 very low birth weight.mp. |
| 9. ductus.mp. | 9. Infant, Extremely Low Birth Weight/ | #9 Infant, Extremely Low Birth Weight |
| 10. PDA.mp. | 10. lbw.mp. | #10 lbw.mp. |
| 11. persistent ductus arteriosus.mp. | 11. vlbw.mp. | #11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 |
| 12. 6 or 7 or 8 or 9 or 10 or 11 | 12. or/1-11 | #12 Ductus Arteriosus, Patent |
| 13. indomethacin.mp. or Indomethacin/ | 13. Ductus Arteriosus, Patent/ | #13 Ductus Arteriosus |
| 14. indometacin.mp. | 14. patent ductus arteriosus.mp. | #14 PDA.mp. |
| 15. indocid.mp. | 15. ductus arteriosus.mp. | #15 #12 or #13 or #14 |
| 16. ibuprofen.mp. or Ibuprofen/ | 16. Ductus Arteriosus/ | #16 Indomethacin |
| 17. brufen.mp. | 17. ductus.mp. | #17 indomethacin.mp. |
| 18. paracetamol.mp. or Acetaminophen/ | 18. PDA.mp. | #18 indometacin.mp. |
| 19. tylenol.mp. | 19. persistent ductus arteriosus.mp. | #19 ibuprofen.mp. |
| 20. Anti-Inflammatory Agents, Non-Steroidal/ | 20. or/13-19 | #20 Ibuprofen |
| 21. Cyclooxygenase Inhibitors/ or prostaglandin synthetase inhibitor.mp. | 21. indomethacin.mp. | #21 brufen.mp. |
| 22. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 | 22. Indomethacin/ | #22 paracetamol.mp. |
| 23. 5 and 12 and 22 | 23. indometacin.mp. | #23 Acetaminophen |
| 24. Randomized Controlled Trial/ | 24. indocid.mp. | #24 tylenol.mp. |
| 25. randomized controlled trials.mp. | 25. ibuprofen.mp. | #25 Anti-Inflammatory Agents, Non-Steroidal |
| 26. Random Allocation/ | 26. Ibuprofen/ | #26 Cyclooxygenase Inhibitors |
| 27. Double-Blind Method/ | 27. brufen.mp. | #27 prostaglandin synthetase inhibitor.mp. |
| 28. Single-Blind Method/ | 28. paracetamol.mp. | #28 #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 |
| 29. Clinical Trial/ | 29. Acetaminophen/ | #29 #11 and #15 and #28 |
| 30. clinical trial,phase i.pt. | 30. tylenol.mp. | |
| 31. clinical trial,phase ii.pt. | 31. acetaminophen.mp. | |
| 32. clinical trial,phase iii.pt. | 32. Anti-Inflammatory Agents, Non-Steroidal/ | |
| 33. clinical trial,phase iv.pt. | 33. Cyclooxygenase Inhibitors/ | |
| 34. controlled clinical trial.pt. | 34. prostaglandin synthetase inhibitor.mp. | |
| 35. randomized controlled trial.pt. | 35. NSAID?.mp. | |
| 36. multicenter study.pt. | 36. or/21-35 | |
| 37. clinical trial.pt. | 37. 12 and 20 and 36 | |
| 38. Clinical Trial/ | 38. Randomized Controlled Trial/ | |
| 39. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 | 39. randomized controlled trials.mp. | |
| 40. (clinical adj trial$).tw. | 40. Random Allocation/ | |
| 41. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. | 41. Double-Blind Method/ | |
| 42. PLACEBOS/ | 42. Single-Blind Method/ | |
| 43. placebo$.tw. | 43. Clinical Trial/ | |
| 44. randomly allocated.tw. | 44. randomized controlled trial.pt. | |
| 45. allocated adj2 random$).tw. | 45. clinical trial.pt. | |
| 46. 40 or 41 or 42 or 43 or 44 or 45 | | |
| 47. 39 or 46 | | |
| 48. case report.tw. | | |

| | | |
|---|---|---|
| 49. letter/<br>50. historical article/<br>51. 48 or 49 or 50<br>52. 47 not 51<br>53. 23 and 52 | 46. Clinical Trial/<br>47. or/38-46<br>48. (clinical adj trial$).tw.<br>49. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.<br>50. PLACEBOS/<br>51. placebo$.tw.<br>52. randomly allocated.tw.<br>53. (allocated adj2 random$).tw.<br><br>54. or/48-53<br>55. 47 or 54<br>56. 37 and 55 | |

## eText 1. Risk of Bias Assessment of eligible studies

The risk of bias of eligible studies was assessed according to a modified and validated version of the Cochrane Collaboration's ROB tool (1). The six criteria that were assessed included sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, completeness of follow up, selective outcome reporting, and presence of other biases. Each domain was assigned a score of 'definitely low risk', or 'definitely high risk' or 'unclear risk'. 'Unclear risk' was further categorized to 'probably low risk', or 'probably high risk' based on specific instructions provided to the reviewers provided in the flow diagram below (eFigure 1) (2). This has been adapted from the tool validated by Akl et al (2). Two independent reviewers assessed the risk of bias. Disagreements between two reviewers when assessing the risk of bias was resolved through consensus. If a consensus was not reached, the disagreement was resolved by a third reviewer.

**eFigure 1. Specific instructions for estimating unclearly reported blinding status**



## eTable 3. LIST OF EXCLUDED STUDIES after full text screening

| No. | Study Reference | Reason for exclusion |
|---|---|---|
| 1 | Amoozgar H, Ghodstehrani M, Pishva N. Oral ibuprofen and ductus arteriosus closure in full-term neonates: A prospective case–control study. Pediatr Cardiol. 2010;1;31(1):40-3. | Not RCT |
| 2 | Bravo MD, Cabañas F, Pérez-Fernández E, Quero J, Pellicer A. 212 Randomized Clinical Trial on Echocardiographically Guided (ECHOG) Versus Standard Ibuprofen Treatment (SIBT) for Patent Ductus Arteriosus (PDA): Pilot Study. J Neonatal Perinatal Med. 2011;4(3):287-288. | Duplicate (Conference abstract of included study) |
| 3 | Brecht M, Wiese M, Hopkins AM, Wojiechowski J, Suppiah V, Garg A, Garg S, Stark MJ, Andersen CC. Pharmakokinetics And Clinical Effects Of A Novel Dosing Regimen For Intravenous Ibuprofen–A Pilot Study. J Paediatr Child Health. 2015;51:97. | Not RCT |
| 4 | Carmo KB, Evans N, Paradisis M. Duration of indomethacin treatment of the preterm patent ductus arteriosus as directed by echocardiography. J Pediatr. 2009;155(6):819-22. | Not relevant intervention |
| 5 | Clyman RI, Roman C. The effects of caffeine on the preterm sheep ductus arteriosus. Pediatr Res. 2007;62(2):167-9. | Not RCT |
| 6 | Dani C, Bertini G, Reali MF, Murru P, Fabris C, Vangi V, Rubaltelli FF. Prophylaxis of patent ductus arteriosus with ibuprofen in preterm infants. Acta Paediatr. 2000;89(11):1369-74. | Prophylactic use of Ibuprofen |
| 7 | Desfrere L, Zohar S, Morville P, Brunhes A, Chevret S, Pons G, Moriette G, Rey E, Treluyer JM. Dose-finding study of ibuprofen in patent ductus arteriosus using the continual reassessment method. J Clin Pharm Ther. 2005;30(2):121-32. | Not RCT |
| 8 | Eras Z, Gokmen T, Erdeve O, Ozyurt BM, Saridas B, Dilmen U. Impact of oral versus intravenous ibuprofen on neurodevelopmental outcome: a randomized controlled parallel study. Am J Perinat. 2013;30(10):857-62. | Duplicate (Secondary analysis of included study) |
| 9 | Eras Z, Gokmen T, Erdeve O, Sarıdas B, Canpolat E, Dilmen U. 1244 Impact of Oral Versus Intravenous Ibuprofen on Neurodevelopmental Outcome: a Randomised Controlled Parallel Study. Arch Dis Child. 2012;97(Suppl 2):A355. | Duplicate (Conference abstract of included study) |
| 10 | Lai TH, Soong WJ, Hwang B. Indomethacin for the prevention of symptomatic patent ductus arteriosus in very low birth weight infants. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi. 1990 Jan-Feb;31(1):17-23. | Prophylactic use of Indomethacin |
| 11 | Fajardo CA, Whyte RK, Steele BT. Effect of dopamine on failure of indomethacin to close the patent ductus arteriosus. J Pediatr. 1992;121(5):771-5. | Not relevant intervention |
| 12 | Gokmen T. Erdeve O, Altug N, Oguz SS, Uras N, Dilmen U. Efficacy and safety of oral versus intravenous ibuprofen in very-low-birth-weight preterms with patent ductus arteriosus. 2010;86:S38. | Duplicate (Conference abstract of included study) |
| 13 | Hammerman C, Aramburo MJ. Prolonged indomethacin therapy for the prevention of recurrences of patent ductus arteriosus. 1990. 117(5):771-776. | Not relevant intervention |
| 14 | Jannatdoust A, Samadi M, Yeganehdoust S, et al. Effects of intravenous indomethacin on reduction of symptomatic patent ductus arteriosus cases and decreasing the need for prolonged mechanical ventilation. J Cardiovasc Thorac Res. 2014;6(4):257-259. | Prophylactic use of Indomethacin |
| 15 | Kluckow M, Evans N, Gill A, Jeffery M. Ductal echocardiographic targeting and early closure trial (DETECT): A pilot randomised controlled trial. 2012;48:43-44. | Duplicate (Conference abstract of included study) |
| 16 | Gimeno A, Modesto,V. Comparison of ibuprofen and indomethacin therapy for the treatment of patent ductus arteriosus. Anales de Pediatria Continuada. 2007;5(2):100-104. | Not RCT |

**eTable 3. LIST OF EXCLUDED STUDIES after full text screening (continued)**

| No. | Study Reference | Reason for exclusion |
|---|---|---|
| 17 | Gournay V, Roze JC, Kuster A, et al. Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial. Lancet. 2004;364(9449):1939-44. | Prophylactic use of Ibuprofen |
| 18 | Hammerman C, Shchors I, Schimmel MS, Bromiker R, Kaplan M, Nir A. N-terminal-pro-B-type natriuretic peptide in premature patent ductus arteriosus: a physiologic biomarker, but is it a clinical tool? Pediatr Cardiol. 2010;31(1):62-5. | Duplicate (Secondary analysis of included study) |
| 19 | Mahony L, Carnero V, Brett C, Heymann MA, Clyman RI. Prophylactic indomethacin therapy for patent ductus arteriosus in very-low-birth-weight infants. N Engl J Med. 1982;306(9):506-10. | Prophylactic use of Indomethacin |
| 20 | Mardoum R, Bejar R, Merritt TA, Berry C. Controlled study of the effects of indomethacin on cerebral blood flow velocities in newborn infants. J Pediatr. 1991;118(1):112-5. | Not relevant outcome |
| 21 | Maruyama K, Fujiu T. Effects of prophylactic indomethacin on renal and intestinal blood flows in premature infants. Pediatr Int. 2012;54(4):480-5. | Prophylactic use of Indomethacin |
| 22 | Nestrud R. Hil D. Arrington,R. A double blind controlled study on the efficacy of indomethacin (Ind) in closure of patent ductus arteriosus (PDA) in premature infants. Ped Res. 1979;13(4, Part II):14. | Duplicate (Conference abstract of included study) |
| 23 | Van Overmeire B, Allegaert K, Casaer A, et al. Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2004;364(9449):1945-9. | Prophylactic use of Ibuprofen |
| 24 | Schmidt B, Roberts RS, Fanaroff A, et al. TIPP Investigators. Indomethacin prophylaxis, patent ductus arteriosus, and the risk of bronchopulmonary dysplasia: further analyses from the Trial of Indomethacin Prophylaxis in Preterms (TIPP). J Pediatr. 2006;148(6):730-734. | Not RCT |
| 25 | Supapannachart S, Khowsathit P, Patchakapati B. Indomethacin prophylaxis for patent ductus arteriosus (PDA) in infants with a birth weight of less than 1250 grams. J Med Assoc Thai. 1999;82 Suppl 1:S87-92. | Prophylactic use of Indomethacin |
| 26 | Valaes T, Moylan F, Cohn H. Incidence and significance of PDA in preterm infants (PTI) and controlled blind trial of indomethacin (IND). Ped Res. 1980;14(4, Part II):15. | Not relevant population |
| 27 | Van Overmeire B. The use of ibuprofen in neonates in the treatment of patent ductus arteriosus. Int J Clin Pract Suppl. 2003;(135):23-7. | Duplicate (Commentary on included study) |
| 28 | Vargas-Origel A, Cruz-Anguiano V, López-Montaño E. [Indomethacin and furosemide in closure of ductus arteriosus]. Bol Med Hosp Infant Mex. 1986;43(8):482-8. [Spanish] | Not relevant outcome |
| 29 | Yanowitz TD, Reese J, Gillam-Krakauer M, et al. Superior mesenteric artery blood flow velocities following medical treatment of a patent ductus arteriosus. J Pediatr. 2014;164(3):661-3. | Not relevant intervention/outocme |
| 30 | Yanowitz TD, Baker RW, Sobchak Brozanski B. Prophylactic indomethacin reduces grades III and IV intraventricular hemorrhages when compared to early indomethacin treatment of a patent ductus arteriosus. J Perinatol. 2003;23(4):317-22. | Prophylactic use of Indomethacin |
| 31 | Yeh TF, Raval D, Lilien LD, Srinivasan G, Pildes RS. Decreased plasma glucose after indomethacin therapy in premature infants with patent ductus anteriosus. Lancet. 1982;2(8289):104-5. | Duplicate (Secondary analysis from included study) |
| 32 | Yeh TF, Thalji A, Luken,J. Intravenous indocin therapy in premature infants with PDA: A double-blind control study. Ped Res. 1979; 13(4, Part II):17. | Duplicate (Conference abstract of included study) |
| 33 | Zanardo V, Trevisanuto D, Dani C, et al. "Silent" patent ductus arteriosus and bronchopulmonary dysplasia in low birth weight infants. J Perinat Med. 1995;23(6):493-9. | Not RCT |

**eTable 3. LIST OF EXCLUDED STUDIES after full text screening (continued)**

| No. | Study Reference | Reason for exclusion |
|---|---|---|
| 34 | Peckham GJ, Miettinen OS, Ellison RC, et al. Clinical course to 1 year of age in premature infants with patent ductus arteriosus: results of a multicenter randomized trial of indomethacin. J Pediatr. 1984;105(2):285-91. | Duplicate (Secondary analysis from included study) |
| 35 | Prifti E, Enkeleda P, Rubena M, Alketa H. The impact of antenatal corticosteroids on PDA in low birth weight preterm infants. J Perinatal Med. 2013;41(s1) | Not relevant outcome |
| 36 | Weesner KM, Dillard RG, Boyle RJ, Block SM. Prophylactic treatment of asymptomatic patent ductus arteriosus in premature infants with respiratory distress syndrome. South Med J. 1987;Jun;80(6):706-8. | Prophylactic use of Indomethacin |
| 37 | Yeh TF, Goldbarg HR, Henek T, Thalji A, Pildes RS. Intravenous indomethacin therapy in premature infants with patent ductus arteriosus. Causes of death and one-year follow-up. Am J Dis Child. 1982;136(9):803-7. | Duplicate (Secondary analysis from included study) |
| 38 | Yeh TF, Raval D, Pyati S, Pildes RS. Retinopathy of prematurity (ROP) and indomethacin therapy in premature infants with patent ductus arteriosus (PDA). Prostaglandins. 1983;25(3):385-91. | Not relevant outcome |
| 39 | Yeh TF, Thalji A, Luken L, Lilien L, Carr I, Pildes RS. Improved lung compliance following indomethacin therapy in premature infants with persistent ductus arteriosus. Chest. 1981;80(6):698-700. | Duplicate (Secondary analysis from included study) |
| 40 | Satar M, Yapicioğlu H, Narli N, Ozbarlas N, Küçükosmanoğlu O, Tutak E. Is oral indomethacin effective in treatment of preterm infants with patent ductus arteriosus? Turk J Pediatr. 2004;46(2):137-41. | Not RCT |
| 41 | Zanardo V, Vedovato S, Chiozza L, Faggian D, Favaro F, Trevisanuto D. Pharmacological closure of patent ductus arteriosus: effects on pulse pressure and on endothelin-1 and vasopressin excretion. Am J Perinatol. 2008;25(6):353-8. | Not relevant outcome |
| 42 | Alipour MR, Mozaffari Shamsi M, Namayandeh SM, Pezeshkpour Z, Rezaeipour F, Sarebanhassanabadi M. The Effects of Oral Ibuprofen on Medicinal Closure of Patent Ductus Arteriosus in Full-Term Neonates in the Second Postnatal Week. Iran J Pediatr. 2016;26(4):e5807. | Not relevant population (full term infants) |
| 43 | Demir N, Peker E, Ece İ, Balahoroğlu R, Tuncer O. Efficacy and safety of rectal ibuprofen for patent ductus arteriosus closure in very low birth weight preterm infants. J Matern Fetal Neonatal Med. 2017;30(17):2119-2125. | Not relevant intervention |
| 44 | Dorval VG, Martin B, Brassard M, Miro J, Chemtob S, Payot,A. The evolution of serum PGE2 during oral and intravenous ibuprofen treatment in preterm infants with patent ductus arteriosus (PDA). Pediatr Child Health. 2010;15:46A. | Not relevant outcome |
| 45 | Knight D, Alkindi S, Buksh M, Kuschel C, Skinner,J. Placebo-controlled pilot trial of indomethacin in preterm infants with a patent ductus arteriosus. J Pediatr Child Health. 2011;47(s1):88 | Not relevant outcome |
| 46 | Hoxha A, Kola E, Kuneshka N, Tushe E. Oral versus intravenous ibuprofen for the early closure of patent ductus arteriosus in low birth weight preterm infants. European Medical, Health and Pharmaceutical Journal. 2013;6. | Duplicate publication |
| 47 | Akbari Asbagh P, Zarkesh MR, Nili F, Nayeri FS, Tofighi Naeem AT. Prophylactic teatment with oral paracetamol for patent ductus arteriosus in preterm infants: A randomized clinical trial. Tehran U Med J. 2015;73(2)86-92. | Prophylactic use of acetaminophen |
| 48 | Jasani B, Kabra N, Nanavati RN. Oral paracetamol in treatment of closure of patent ductus arteriosus in preterm neonates. J Postgrad Med. 2013;59(4):312-4. | Not RCT |
| 49 | Görk AS, Ehrenkranz RA, Bracken MB. Continuous infusion versus intermittent bolus doses of indomethacin for patent ductus arteriosus closure in symptomatic preterm infants. Cochrane Database Syst Rev. 2008 Jan 23;(1). | Not RCT |

## eTable 4. Clinical & Methodological Characteristics of Included Studies

eTable 4. Clinical & Methodological Characteristics of Included Studies

| Ref No | Author & year of publication | Language of publication | # of infants enrolled | Gestational age at birth (in weeks) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])] | Birth weight (in grams) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])] | Age at start of treatment (days) [Mean [a] (SD [c] )]/ [Median [b] (IQR [d]/ Range [e])] | Overall assessment of risk of bias | Criteria for diagnosis of hs-PDA | Intervention characteristics (drug: route & dose) | |
|---|---|---|---|---|---|---|---|---|---|---|
| 37 | Adamska 2005 | Polish | 35 | INDO 27.6 [a] (2) [c]<br>IBU 27.7 [a] (1.8) [c] | INDO 1003 [a] (192) [c]<br>IBU 1074 [a] (264) [c] | NR | Probably Low | PDA size >1.5mm; LA:AO ratio>1.3 | IV Indomethacin 0.2 mg/kg every 12 h x 3doses | IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h |
| 38 | Akisu 2001 | Turkish | 23 | INDO 31.9 [a] (1.3)[c]<br>IBU 32.1 [a] (1.2) [c] | INDO 1645 [a] (190) [c]<br>IBU 1706 [a] (187) [c] | INDO 3.5 [a] (0.6) [c]<br>IBU 3.9 [a] (0.5) [c] | Probably High | Echo confirmed hs-PDA; criteria not specified | Oral Indomethacin 0.2 mg/kg every 12 h x 3doses | Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h |
| 39 | Aly 2007 | English | 21 | INDO 32.9 [a] (1.6) [c]<br>IBU 31.2 [a] (2.5) [c] | INDO1884 [a] (485) [c]<br>IBU 1521 [a] (398) [c] | NR | Probably Low | Shunting across PDA graded as mild, moderate, and severe according PDA diameter (<1.5, 1.5 to 2, and >2 mm, respectively); treatment criteria not specified | Intravenous indomethacin (3 doses of IV indomethacin 0.2 mg/kg at 12-hour intervals) | Oral Ibuprofen (Initial dose of 10 mg/kg, followed by two doses of 5 mg/kg each) |
| 40 | Aranda 2009 | English | 136 | IBU 26.1 [a] (1.3) [c]<br>PLAC 26.2 [a] (1.4) [c] | IBU 798.5 [a] (128.7) [c]<br>PLAC 797.3 [a] (132.8) [c] | IBU 1.5 [a] (0.74)[c]<br>PLAC 1.4 [a] (0.73) [c] | Low | PDA>1.5mm<br>LA/AO ratio of >1.4:1<br>LV/AO ratio of >2.1:1 | Intravenous Ibuprofen 10 mg/kg loading dose followed by 5 mg/kg/d on the 2nd and 3rd day) | Placebo |
| 41 | Baenziger 1999 | English | 32 | INDO 28 [a] (3.1) [c]<br>INDO + dopamine 28.5 [a] ( 2.3) [c] | INDO1220 [a] (305) [c]<br>INDO + dopamine 1115 [a] (252) [c] | INDO 13 [a] (8.3) [c]<br>INDO+ dopamine 11 [a] (7.56) [c] | Probably High | Clinical signs of hs-PDA along with following echo criteria were: (A) Diastolic or systolic-diastolic reverse flow in the main pulmonary artery, PDA, or both, (B) reversed diastolic flow within the descending aorta below the PDA, (C) diastolic anterograde flow in the branches of the pulmonary arteries; (D) LA/AO ratio of >1.3:1 | IV Indomethacin 0.2 mg/kg/dose | IV indomethacin 0.2 mg/kg/dose intravenously + Dopamine 4 mcg/kg/min |
| 42 | Bagheri 2016 | English | 129 | IBU 31.7 [a] (2.2) [c]<br>PARA 31.5 [a] ( 2.3) [c] | IBU 1642 [a] (58.5) [c]<br>PARA 1646 (59.1) [c] | IBU 3.4 [a] (2.1) [c]<br>PARA 2.9 [a] (1.3) [c] | Probably Low | PDA>1.5 mm; LA:AO>1.2 | Oral high dose Ibuprofen at 20 mg/kg followed by two 10 mg/kg doses at 24h interval | Oral acetaminophen 15 mg/kg every 6 h for 3 days |
| 43 | Bagnoli 2013 | English | 134 | IBU 27.4 [a] (2.5) [c]<br>PLAC 27.8 [a] (4) [c] | IBU 989 [a] (326) [c]<br>PLAC 1197 [a] (835) [c] | NR | Probably High | LA/AO ratio of ≥1.4:1<br>LV/AO ratio of 2.1:1; and/or narrowest PDA diameter >1.5mm<br>Left-to-right shunting of blood and diastolic reversal of blood flow in the aorta. | IV Ibuprofen 10 mg/kg loading doses, followed by 5 mg/kg/d on the 2nd & 3rd day | Placebo |
| 44 | Betkerur 1981 | English | 21 | IND 31.1 [a] (0.6) [c]<br>PLAC 29.6 [a] (0.7) [c] | INDO 1395.2 [a] (92.2) [c]<br>PLAC 1134.3 [a] (150.3) [c] | INDO 7.4 [a] (0.6) [c]<br>PLAC 11.9 [a] (2.6) [c] | Probably High | LA:AO ≥ 1.3 | IV Indomethacin 0.3 mg/kg/dose | Placebo (IV saline) |
| 45 | Cherif 2008 | English | 64 | IBU oral 29.3 [a] (1.2) [c]<br>IBU IV 28.3 [a] (1.1) [c] | IBU oral 1227.2 [b] (188) [d] (600-1470)<br>IBU IV 1197.7 [b] (158) [d] (630-1420) | NR | Low | A left-to-right ductal shunting; LA:AO > 1.6 | IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h | Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h |
| 46 | Chotigeat 2003 | English | 30 | INDO 29.86 [a] (2.92) [c]<br>IBU 30.8 [a] (2.3) [c] | INDO 1434 [a] (421) [c]<br>IBU 1412 [a] (354) [c] | NR | Probably High | 3 of 5 criteria that includes clinical signs and Doppler echo | IV indomethacin (3 doses of IV indomethacin 0.2 mg/kg at 12-hour intervals) | Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h |
| 47 | Christmann 2002 | English | 32 | INDO bolus 30.5 [a] (0.5) [c]<br>INDO continuous 29.4 [a] (0.5) [c] | INDO bolus 1424 [a] (150) [c]<br>INDO continuous 1150 [a] (77) [c] | NR | Probably Low | Left to right PDA shunting on Doppler echo along with the following clinical criteria: Unexplained respiratory insufficiency and/or a persistent need of oxygen, bounding peripheral pulses and cardiac enlargement | IV Indomethacin (0.4mg/kg) (Initial dose was 0.2 mg/kg followed by two doses of 0.1 mg/kg at 12 and 36 h ) | IV Indomethacin 0.4 mg/kg continuous infusion |
| 48 | Dang 2013 | English | 160 | IBU 30.9 [a] (2.2) [c]<br>PARA 31.2 [a] (1.8) [c] | IBU 1531 [a] (453.5) [c]<br>PARA 1591.9 [a] (348.6) [c] | NR | Probably Low | Any one of the following:<br>1) LA:AO of ≥1.4 in the parasternal long-axis view<br>2) PDA diameter of ≥1.4 mm/kg body weight<br>3) left ventricular enlargement<br>4) Holodiastolic flow reversal in the descending aorta. | Oral Ibuprofen 10 mg/kg followed by 5 mg/kg after 24 and 48 h | Oral acetaminophen 15 mg/kg every 6 h for 3 days |

## eTable 4. Clinical & Methodological Characteristics of Included Studies (cont'd….)

| Ref No | Author & year of publication | Language of publication | # of infants enrolled | Gestational age at birth (in weeks) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])] | Birth weight (in grams) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])] | Age at start of treatment (days) [Mean [a] (SD [c] )]/ [Median [b] (IQR [d]/ Range [e])] | Overall assessment of risk of bias | Criteria for diagnosis of hs-PDA | Intervention characteristics (drug: route & dose) | |
|---|---|---|---|---|---|---|---|---|---|---|
| 49 | Dani 2012 | English | 70 | IBU standard dose 26 [a] (1.7) [c]<br>IBU high dose 25.6 [a] (1.8) [c] | IBU standard dose 835 [a] (215) [c]<br>IBU high dose 781 [a] (225) [c] | NR | Low | Echocardiographic demonstration of a ductal left-to-right shunt, with a LA:AO >1.3 or a PDA >1.5 mm | IV Ibuprofen 20 mg/kg, followed by two doses of 10 mg/kg each, after 24 and 48h | IV Ibuprofen initial dose of 10 mg/kg followed by two doses of 5 mg/kg at 24-h intervals |
| 50 | Dash 2015 | English | 73 | PARA 28.5 [a] (2.7) [c]<br>INDO 28.9 [a] (2.6) [c] | PARA 989 [a] (299) [c]<br>INDO 1027 [a] (262) [c] | NR | Low | PDA size ≥1.5 mm; Left to right PDA shunt<br>LA:AO ratio > 1.5:1. | IV Indomethacin 0.2 mg/kg/dose once daily for 3 days | Oral Acetaminophen 15 mg/kg/dose four times daily for 7 days (28 doses) |
| 51 | Ding 2014 | English | 72 | 30.24 [a] (1.49) [c] | 1468.64 [a] (447.62) [c] | NR | Probably High | Echo confirmed hs-PDA; criteria not specified | Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg after 24 and 48 h. | Placebo (Oral 5% glucose) |
| 52 | Erdeve 2012 | English | 70 | IBU oral 26.4 [a] (1.1) [c]<br>IBU IV 26.3 [a] (1.3) [c] | IBU oral 892 [a] (117) [c]<br>IBU IV 872 [a] (123) [c] | NR | Low | PDA >1.5 mm;<br>LA:AO >1.5;<br>Left-to-right shunting of blood;<br>End-diastolic reversal of blood flow in the aorta or poor cardiac function | IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h | Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h |
| 53 | Fakhraee 2007 | English | 36 | INDO 30.9 [a] (2) [c]<br>IBU 31.5 [a] (1.4) [c] | INDO 1522.1 [a] (357.7) [c]<br>IBU 1658.3 [a] (386.6) [c] | NR | Probably High | Left to right shunt; PDA> 1.5 mm; LA:AO>1.6; severe diastolic backflow in the pulmonary trunk and in the aorta | Oral Indomethacin; 3 doses of 0.2 mg/kg at 24 hour intervals | Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h |
| 54 | Fesharaki 2012 | Persian | 60 | IBU high dose 29.77 [a]<br>IBU standard dose 30.88 [a] | IBU high dose 1300.2 [a]<br>IBU standard dose 1324.3 [a] | NR | Probably Low | Echo confirmed hs-PDA; criteria not specified | Oral high dose Ibuprofen at 15 mg/kg followed by two 7.5 mg/kg doses at 24h interval | Oral Ibuprofen 10 mg/kg followed by 5 mg/kg after 24 and 48 h |
| 55 | Gersony 1983 | English | 405 | NR | NR | NR | Low | Clinical signs of hs-PDA & LA:AO>1.15 on echocardiography | IV Indomethacin 3 doses; 1st 0.2mg/kg; Infants less than 48 hours of age at the time of trial entry received 0.1 mg/kg body weight for the second and third doses of the drug. Infants who were 2-7 days of age at the time of the first dose received 0.2 mg/kg for the second and third doses, and those infants 8 days or older received 0.25 mg/kg body weight for their second and third doses | Placebo (IV colorless solution) |
| 56 | Ghanem 2010 | English | 66 | IBU 28.8 [a] (2.8) [c]<br>PLAC 28.9 [a] (2.7) [c] | IBU 1035 [a] (353) [c]<br>PLAC 1047 [a] (403) [c] | NR | Probably High | LA:AO >1.4 or PDA >1.5 mm | Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h | Placebo |
| 57 | Gimeno Navarro 2005 | Spanish | 47 | INDO 28.5 [b] (27-30) [d]<br>IBU 28 [b] (24-31) [d] | INDO 1205.8 [a] (512.9) [c]<br>IBU 1169 [a] (489.5) [c] | NR | Probably Low | PDA/Pulmonary root ratio >0.3; Diastolic reverse flow in the abdominal aorta | IV Indomethacin 0.2 mgkg every 12 h x 3doses | IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h |
| 58 | Gokmen 2011 | English | 102 | IBU oral 28.5 [a] ( 1.9) [c]<br>IBU IV 28.7 [a] (2.1) [c] | IBU oral 1170 [a] (297) [c]<br>IBU IV 1205 [a] (366) [c] | NR | Low | PDA >1.5 mm;<br>LA:AO >1.5;<br>Left-to-right shunting of blood across PDA;<br>End-diastolic reversal of blood flow in the aorta or poor cardiac function | IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h | Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h |

## eTable 4. Clinical & Methodological Characteristics of Included Studies (cont'd….)

| Ref No | Author & year of publication | Language of publication | # of infants enrolled | Gestational age at birth (in weeks) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])] | Birth weight (in grams) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])] | Age at start of treatment (days) [Mean [a] (SD [c] )]/ [Median [b] (IQR [d]/ Range [e])] | Overall assessment of risk of bias | Criteria for diagnosis of hs-PDA | Intervention characteristics (drug: route & dose) | |
|---|---|---|---|---|---|---|---|---|---|---|
| 59 | Hammerman 1990 | English | 39 | INDO 28 [a] (3) [c]<br>PLAC 27 [a] (7) [c] | INDO 1099 [a] (435) [c]<br>PLAC 1040 [a] (394) [c] | INDO 9 [a] (4) [c]<br>PLAC 10 [a] (5) [c] | Probably Low | The presence of an infraclavicular and precordial systolic murmur consistent with PDA, plus any two of the following: bounding pulse rate, diastolic pressure of ≤25 mm Hg, and pulmonary plethora or cardiomegaly on chest radiographs. The clinical diagnosis was confirmed by pulsed Doppler echocardiography; echo criteria not specified | IV Indomethacin (3 initial doses, 0.2 mg/kg/dose every 12 hours followed by 5 more doses 0.2 mg/kg/dose every 24 hours) | Placebo (IV saline) |
| 60 | Hammerman 1995 | English | 18 | INDO bolus 29 [a] (2) [c]<br>INDO continuous 28 [a] (2) [c] | INDO bolus 1200 [a] (0.3) [c]<br>INDO continuous 1100 [a] (0.2) [c] | NR | Probably Low | Measurements of maximal systolic pressure gradient and % filling of the pulmonary artery were recorded as reflections of severity of ductal shunting | IV Indomethacin 0.2 mg/kg by a 1-minute rapid injection for the first dose and then 0.1 mg/kg again by rapid injection, every 12 hours for two additional doses (total indomethacin dose 400 mcg/kg) | IV Indomethacin infusion at 11 mcg/kg/hour to run for 36 hours (total dose 396 mcg/kg) |
| 61 | Hammerman 2008 | English | 63 | INDO continuous 27.8 [a] (2.8) [c]<br>IBU IV 27.8 [a] (2.6) [c] | INDO continuous 1100 [a] (0.45) [c]<br>IBU IV 1060 [a] (0.35) [c] | INDO continuous 4.5 [b] (2.3-7.7) [d]<br>IBU IV 3.7 [b] (2.5-5.5) [d] | Low | Left to right PDA shunting on Doppler echo | IV Indomethacin infused continuously for 36 h at a rate of 17 mcg/kg/h | IV Ibuprofen initial dose of 10 mg/kg followed by two doses of 5 mg/kg at 24-h intervals |
| 62 | Jegatheesan 2008 | English | 105 | INDO low dose 25.8 [a] (1.2) [c]<br>INDO high dose 25.5 [a] (1.2) [c] | INDO low dose 816 [a] (177) [c]<br>INDO high dose 791 [a] (158) [c] | NR | Probably High | Hs-PDA on echo; criteria not specified | IV Indomethacin 0.1mg/Kg/d x 3d | IV Indomethacin 0.2-0.5mg/Kg/d x3d |
| 63 | Kluckow 2014 | English | 92 | INDO 26 [a] (1.4) [c]<br>PLAC 26 [a] (1.4) [c] | INDO 892 [a] (205) [c]<br>PLAC 876 [a] (203) [c] | INDO 0.34 [a] (0.12) [c]<br>PLAC 0.37 [a] (0.14) [c] | Low | The PDA diameters used were >1.8 mm at postnatal age 3–5 h, >1.6 mm at post- natal age 6–8 h and >1.3 mm at postnatal age 9–12h | IV Indomethacin 0.2 mg/kg followed by 0.1 mg/kg | Placebo |
| 64 | Krauss 1989 | English | 27 | NR | INDO 1183 [a] (266) [c]<br>No treatment 1022 [a] (224) [c] | NR | Probably High | Clinical signs of PDA along with PDA diameter and LA:AO ratio on echocardiography; criteria not specified | 3 doses of IV Indomethacin 0.2 mg/kg/dose between 72-96 h of age | No treatment |
| 65 | Lago 2002 | English | 175 | INDO 29 [a] (3) [c]<br>IBU 28 [a] (2) [c] | INDO 1214 [a] (427) [c]<br>IBU 1126 [a] (412) [c] | NR | Probably High | Typical PDA flow pattern obtained by colour Doppler echocardiography. Shunting was defined as haemodynamically significant if a disturbed diastolic flow was easily detectable in the main pulmonary artery with a diastolic backflow in the aorta immediately below the ductus arteriosus and a forward flow above the ductal insertion | IV Indomethacin 3 doses of 0.2 mg/kg at 12 h intervals | IV Ibuprofen initial dose of 10 mg/kg followed by two doses of 5 mg/kg each after 24 and 48h |
| 66 | Lago 2014 | English | 111 | INDO bolus 27.4 [a] (2.7) [c]<br>INDO continuous 27.3 [a] (2.1) [c] | INDO bolus 1027.1 [a] (346.1) [c]<br>INDO continuous 1012.1 [a] (315.4) [c] | INDO bolus 3.3 [a] (1) [c]<br>INDO continuous 2.7 [a] (0.7) [c] | Low | Shunting was hemodynamically significant if 2 or more of the following conditions were met: (1) transductal PDA diameter > 1.4 mm/kg; (2) unrestrictive pulsatile transductal flow [PDA maximum velocity (Vmax) <2.0 m/s]; (3) mild-to-moderate left heart volume loading [ LA/Ao ratio >1.4]; (4) increased pulmonary perfusion, i.e. mean and end-diastolic flow velocity in the left pulmonary artery ≥0.42 and ≥0.20 m/s, respectively, and (5) increased left ventricular output and consistent peripheral hypoperfusion in the superior vena cava, i.e. left ventricular output/superior vena cava (LVO/SVC) flow ratio ≥4 | IV Ibuprofen bolus (Daily continuous infusions of 5% dextrose and IBU boluses of 10, 5 and 5 mg/kg administered over 15 min, 24h apart) | IV Ibuprofen continuous infusions of 10mg/kg (0.416 mg/kg/h), 5 mg/kg (0.208 mg/kg/h) and 5 mg/kg(0.208 mg/kg/h), and boluses of equal volumes of 5% dextrose administered over 15 min, 24 h apart |

## eTable 4. Clinical & Methodological Characteristics of Included Studies (cont'd….)

| Ref No | Author & year of publication | Language of publication | # of infants enrolled | Gestational age at birth (in weeks) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])] | Birth weight (in grams) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])] | Age at start of treatment (days) [Mean [a] (SD [c] ]/ [Median [b] (IQR [d]/ Range [e])] | Overall assessment of risk of bias | Criteria for diagnosis of hs-PDA | Intervention characteristics (drug: route & dose) | |
|---|---|---|---|---|---|---|---|---|---|---|
| 67 | Lee 2003 | English | 140 | 27.4 [a] (2.7) [c] | 955 [a] (264) [c] | 2.2 [b] (1.58-3.08) [d] | Low | Clinical criteria (murmur, hyperactive precordium, hypotension, apnea, high $FiO_2$ along with PDA: >1.5mm on echo | IV Indomethacin 0.1mg/Kg every 12h x 3doses infused over 30 mins | IV Indomethacin 0.1 mg/kg every 24 h x 6 doses infused over 30 min |
| 68 | Lee 2008 | Korean | 34 | INDO 29.4 [a] (2.6) [c]<br>IBU 30.2 [a] (3.0) [c] | INDO 1290 [a] (360) [c]<br>IBU 1480 [a] (560) [c] | INDO 3.9 [a] (1.8) [c]<br>IBU 3.9 [a] (1.4) [c] | Probably Low | PDA >1.5mm; LA:AO >1.3 | IV Indomethacin 0.2 mgkg every 12 h x 3doses | Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h |
| 69 | Lin 2017 | English | 144 | INDO 26.3 [a] (1.6) [c]<br>IBU 26.2 [a] (1.7) [c] | INDO 812 [a] (160) [c]<br>IBU 801 [a] (156) [c] | INDO 3.3 [a] (1.4) [c]<br>IBU 3.2 [a] (2) [c] | Low | Cardiovascular dysfunction score>3 & LA:Ao > 1.3 | IV Indomethacin 0.2 mg/kg followed by 0.1 mg/kg q 24h x 2 doses | IV Ibuprofen: Initial dose of 10 mg/kg, followed by two doses of 5 mg/kg each at 24h interval |
| 70 | Lin 2012 | Chinese | 64 | IBU 31.2 [a] (2.4) [c]<br>PLAC 30.8 [a] (2.3) [c] | IBU 1301 [a] (260) [c]<br>PLAC 1350 [a] (221) [c] | IBU 23 [a] (4) [c]<br>PLAC 20 [a] (5) [c] | Probably Low | Clinical signs of hs-PDA along with following echo criteria: PDA ≥1.5mm & Left-right PDA shunt | Oral Ibuprofen 10 mg/kg followed by 5 mg/kg after 24 and 48 h | Placebo (Oral saline) |
| 71 | Merrit 1981 | English | 24 | NR | NR<br>NR | NR | High | Clinical signs of hs-PDA along with LA:AO >1.2 on echo | IV Indomethacin 0.2 mg/kg every 24h x 3days | No treatment |
| 72 | Monset-Couchard 1983 | French | 24 | INDO 30.6 [a] (NR)<br>No treatment 30.6 [a] (NR) | INDO 1434 [a] (361) [c]<br>No treatment 1398 [a] (471) | NR | High | Clinical signs of hs-PDA & increased LA:AO on echo | IV Indomethacin 0.2 mg/kg single dose | No treatment |
| 73 | Mosca 1997 | English | 16 | INDO 28 [b] (25-30) [e]<br>IBU 29 [b] (27-31) [e] | INDO 820 [b] (600-1390) [e]<br>IBU 855 [b] (620-1620) [e] | NR | Probably High | Mechanically ventilated for RDS & LA:AO >1.4 on echo | IV Indomethacin 0.2 mg/kg every 24h x 3days | IV Ibuprofen 10mg/kg every 24h x 3days |
| 74 | Mullett 1982 | English | 47 | PLAC 29.5 [a] (NR)<br>INDO 30.1 [a] (NR) | PLAC 1212 [a] (NR)<br>INDO 1237 [a] (NR) | PLAC 7.5 [a]<br>INDO 7.4 [a] | Probably Low | Enrolment criterion: Heart murmur consistent with PDA<br>PDA closure criteria: complete cessation of the PDA murmur or a decrease in intensity by II of VI grades, resting heart rate of less than 145 beats per minute, improvement in respiratory status (removal from assistance or 30% decrease in Fi02), and LA/AO ratio of > 1.2:1 on echo | Oral Indomethacin 0.2 mg/kg every 24h x 2days | Placebo (Oral cornstarch) |
| 75 | Nestrud 1980 | English | 23 | INDO 30.8 [a] (1.8) [c]<br>PLAC 28.1 [a] (2.0) [c] | INDO 1287 [a] (325) [c]<br>PLAC 1189 [a] ( 376) [c] | INDO 20.1 [a] (16.7) [c]<br>PLAC 14.4 [a] (10) [c] | Low | Presence of a large left-right shunt on echo; LA:AO<1.3 did not exclude patient from the study if there was overwhelming clinical signs of congestive cardiac failure | Oral Indomethacin 0.2 mg/kg every 12h x 3 doses | Placebo (Oral saline) |
| 76 | Neu 1981 | English | 21 | 29.3 [a] (0.6) [c] | 1142 [a] (80) [c] | NR | Low | Clinical signs of hs-PDA and increased LA:AO ratio on echo; cut-off not specified | Oral Indomethacin 0.25mg/kg every 24h x 2doses | Placebo |
| 77 | Oncel 2014 | English | 80 | IBU 27.3 [a] (2.1) [c]<br>PARA 27.3 [a] (1.7) [c] | IBU 973 [a] (224) [c]<br>PARA 931 [a] (217) [c] | NR | Probably Low | PDA >1.5 mm, LA:AO >1.5, end diastolic reversal of blood flow in the aorta, or poor cardiac function in addition to clinical signs of PDA. | Oral Ibuprofen 10 mg/kg followed by 5 mg/kg after 24 and 48 h | Oral acetaminophen 15 mg/kg every 6 h for 3 days |
| 78 | Osborn 2003 | English | 70 | PLAC 26.9 [a] (1.8) [c]<br>INDO 26.7 [a] (1.6) [c] | PLAC 1002 [a] (288) [c]<br>INDO 958 [a] (237.2) [c] | 4.3 [b] (2-12) [e] | Probably Low | PDA>1.6mm | IV Indomethacin 0.2mg/kg single dose | Placebo |
| 79 | Patel 2000 | English | 33 | INDO 26.7 [b] (23.2-30) [e]<br>IBU 26.0 [b] (23.9-35.0) [e] | INDO 838 [b] (458-1377) [e]<br>IBU 790 [b] (620-2780) [e] | INDO 7 [b] (3-21) [e]<br>IBU 8 [b] (3-20) [e] | Probably Low | Clinical signs of hs-PDA & left-right PDA shunt on echo | IV Indomethacin 0.2 mg/kg every 12 h x 3doses | IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h |
| 80 | Pezzati 1999 | English | 17 | INDO 29.5 [a] (2.6) [c]<br>IBU 29.1 [a] (2.1) [c] | INDO 1277 [a] (440) [c]<br>IBU 1151 [a] (426) [c] | INDO 1.38 [a] (0.22) [c]<br>IBU 1.33 [a] (0.18) [c] | Probably High | LA:AO>1.4 | IV Indomethacin 0.2 mg/kg followed by two doses of 0.1mg/kg every 24 hours | IV Ibuprofen 10 mg/kg followed by 5 mg/kg at 24 and 48 h |
| 81 | Pistulli 2014 | English | 68 | NR | NR | NR | Probably High | PDA >1.5 mm, LA:AO >1.4, and a left-to-right shunting of blood in addition to clinical signs of hs-PDA. | IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h | IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h |

## eTable 4. Clinical & Methodological Characteristics of Included Studies (cont'd….)

| Ref No | Author & year of publication | Language of publication | # of infants enrolled | Gestational age at birth (in weeks) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])] | Birth weight (in grams) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])] | Age at start of treatment (days) [Mean [a] (SD [c] )]/ [Median [b] (IQR [d]/ Range [e])] | Overall assessment of risk of bias | Criteria for diagnosis of hs-PDA | Intervention characteristics (drug: route & dose) | |
|---|---|---|---|---|---|---|---|---|---|---|
| 82 | Pourarian 2008 | English | 20 | INDO 33.2 [a] (3.1) [c]<br>IBU 31.3 [a] (4.4) [c] | INDO 1720 [a] (6302) [c]<br>IBU 1860 [a] (402) [c] | INDO 6.4 [a]<br>IBU 5.5 [a] | Probably Low | Presence of hs-PDA on echo; criteria not specified | Oral Indomethacin 0.2 mg/kg every 24h x 3days (Administration of 2nd and 3rd doses was dependent on achievement of ductal closure after the initial dose) | Oral Ibuprofen 10 mg/kg, followed by 5 mg/kg after 24 and 48 h |
| 83 | Pourarian 2015 | English | 30 | IBU high dose 2.6 [a] (30) [c]<br>IBU standard dose 2.1 [a] (31.4) [c] | IBU high dose 1339 [a] (542) [c]<br>IBU standard dose 1493 [a] (346) [c] | NR | Probably Low | Presence of hs-PDA on echo; criteria not specified | Oral high dose Ibuprofen at 20 mg/kg followed by two 10 mg/kg doses at 24h interval | Oral Ibuprofen 10 mg/kg followed by 5 mg/kg after 24 and 48 h |
| 84 | Rennie 1991 | English | 121 | INDOIVPROLONGED 27 [a] (2.2) [c]<br>INDOIV 27 [a] (2.2) [c] | INDOIVPROLONGED 1116 [a] (340) [c]<br>INDOIV 1135 [a] (340) [c] | NR | Probably High | Clinical signs of hs-PDA | IV Indomethacin 0.1mg/kg every 24 hours x 6days | IV Indomethacin 0.2 mg/kg every 12 h x 3 doses |
| 85 | Rhodes 1988 | English | 70 | INDOIVPROLONGED 27 [a] (2.3) [c]<br>INDOIV 27 [a] (2.2) [c] | INDOIVPROLONGED 975 [a] (234) [c]<br>INDOIV 972 [a] (245) [c] | <1 | Probably High | Left-to-right shunting through PDA on echo | IV Indomethacin initial two doses of 0.15 mg/kg given 12h apart followed by 0.1 mg/kg every day for 5 days | IV Indomethacin two doses of 0.15 mg/kg given 12h apart |
| 86 | Romagnoli 1997 | English | 34 | INDOIVFRU 27.9 [a] (2.0) [c]<br>INDOIV 28.9 [a] (1.9) [c] | INDOIVFRU 1088 [a] (300) [c]<br>INDOIV 1159 [a] (238) [c] | INDOIVFRU 3.0 [a] (1.7) [c]<br>INDOIV 3.9 [a] (3.4) [c] | Probably High | Clinical criteria: appearance of systolic or continuous murmur, respiratory "step-up" with increased ventilatory pattern, progressive increase of basal heart rate, and presence of bounding radial pulses. The clinical diagnosis was confirmed by color Doppler echocardiography. | IV Indomethacin 0.2 mg/kg every 12 h x 3doses PLUS IV Frusemide 0.1mg/kg every 12h x 3 doses | IV Indomethacin 0.2 mg/kg every 12 h x 3doses |
| 87 | Rudd 1983 | English | 30 | PLAC 29.0 [a] (1.7) [c]<br>INDO 28.9 [a] (1.2) [c] | PLAC 1170 [a] (211) [c]<br>INDO 1105 [a] (251) [c] | PLAC 10.2 [a] (5.3) [c]<br>INDO 11.0 [a] (8.1) [c] | Probably Low | LA:AO Ratio ≥ 1.2 | Oral Indomethacin 0.2 mg/kg every 12h x 3 doses (maximum) | Placebo |
| 88 | Sangtawesin 2008 | English | 62 | IBU 29.3 [a] (1.94) [c]<br>PLAC 29.3 [a] (2.16) [c] | IBU 1156.9 [a] (263.6) [c]<br>PLAC 1162.9 [a] (261.0) [c] | IBU 0.75 [a] (0.25) [c]<br>PLAC 0.84 [a] (0.24) [c] | Probably Low | PDA> 1.5mm<br>LA:AO>1.4 | Oral Ibuprofen 10 mg/kg followed by 5 mg/kg after 24 and 48 h | Placebo (oral orange starch) |
| 89 | Sosenko 2012 | English | 105 | IBU 26 [b] (23-28) [d]<br>PLAC 25 [b] (24-29) [d] | IBU 854 [a] (204) [c]<br>PLAC 842 [a] (203) [c] | 3 | Low | Presence of PDA with either predominantly left-to-right or bidirectional shunt | IV Ibuprofen initial dose of 10 mg/kg followed by two doses of 5 mg/kg each after 24 and 48 h | Placebo (5% Dextrose IV) |
| 90 | Su BH 1999 | English | 93 | INDO 27.8 [a] (2.5) [c]<br>INDOIVECHOGUIDED 27.2 [a] (2.6) [c] | INDO 1039 [a] (244) [c]<br>INDOIVECHOGUIDED 955 [a] (271) | NR | Probably High | Pulsatile or growing pattern of left-right PDA shunt on Doppler echo | IV Indomethacin 0.2 mg/kg for the first dose, then 0.1 mg/kg in infants less than 48 hours old, 0.2 mg/kg in infants over 48 hours, every 12 hours for another two doses | IV Indomethacin: one unique dose of 0.2 mg/kg initially followed by subsequent doses as per the standard IV Indomethacin regimen only if echocardiography shows hs-PDA |

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| Ref No | Author & year of publication | Language of publication | # of infants enrolled | Gestational age at birth (in weeks) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])] | Birth weight (in grams) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])] | Age at start of treatment (days) [Mean [a] (SD [c] )]/ [Median [b] (IQR [d]/ Range [e])] | Overall assessment of risk of bias | Criteria for diagnosis of hs-PDA | Intervention characteristics (drug: route & dose) | |
|---|---|---|---|---|---|---|---|---|---|---|
| 91 | Su BH 2008 | English | 119 | IBU 25 [b] (23-28) [d]<br>INDO 25 [b] (23-28) [d] | IBU 825 [b] (550-990) [d]<br>INDO 762 [b] (540-980) [d] | IBU 0.33 [b] (0.17-0.88) [d]<br>INDO 0.33 [b] (0.12-1.0) [d] | Probably Low | Pulsatile or growing pattern of left-right PDA shunt on Doppler echo | IV Indomethacin 0.2mg/kg as the initial dose followed by 0.1 mg/ kg in infants less than 48 hours old, 0.2 mg/kg in infants over 48 hours at 24-hour intervals as indicated by PDA flow pattern | IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h as indicated by the PDA flow pattern |
| 92 | Su PH 2003 | English | 63 | IBU 28.7 [a] ( 2.2) [c]<br>INDO 28.2 [a] (2.4) [c] | IBU 1133.9 [a] (200.0) [c]<br>INDO 1109.5 [a] (244.1) [c] | IBU 4.1 [a] (1.3) [c]<br>INDO 4.9 [a] (3.7) [c] | Probably High | Left-right PDA shunt; LA:AO> 1:3; PDA>1.5 mm. | IV Indomethacin 0.2 mgkg every 12 h x 3doses | IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h |
| 93 | Supapannachart 2002 | English | 18 | IBU 30.1 [a] (2.7) [c]<br>INDO 30.4 [a] (2.6) [c] | IBU 1446.7 [a] (38.5) [c]<br>INDO 1431.7 [a] (1431.7) [c] | IBU 3.0 [a] (1.1) [c]<br>INDO 3.4 [a] (2.2) [c] | High | Clinical Criteria: (a) Systolic murmur at left upper parasternal border; (b) Continuous murmur at left upper parasternal border; (c) Active precordium; (d) Bounding pulse, wide pulse pressure (pulse pressure >35 mmHg) (e) Tachycardia (heart rate >170/min) (f)Hepatomegaly (g) Chest X-ray with cardiomegaly (CT ratio>0.6) or increased pulmonary vasculature. Any infant with more than 3 of the above criteria was diagnosed with symptomatic PDA. | IV Indomethacin 0.2 mgkg every 12 h x 3doses | Oral Ibuprofen 10mg/kg daily for 3 consecutive days |
| 94 | Tammela 1999 | English | 61 | INDOIV 27.9 [a] (2.3) [c]<br>INDOIVPROLONGED 27.3 [a] (1.94) [c] | INDOIV 1154 [a] (388) [c]<br>INDOIVPROLONGED 2094 [a] (298) [c] | INDOIV 4.3 [a] (4.4) [c]<br>INDOIVPROLONGED 3.1 [a] (1.7) [c] | Probably High | Clinical signs & left-right PDA shunt on Doppler echo | IV Indomethacin 0.2 mg/kg followed by 2 doses of 0.1 mg/kg at 12-hour intervals | IV Indomethacin: 7 doses of 0.1mg/kg at 24 h intervals |
| 95 | Van Overmeire 1995 | English | 75 | INDO 29.6 [a] (2.5) [c]<br>ASA 29.7 [a] (2.5) [c] | INDO 1292 [a] (434) [c]<br>ASA 1298 [a] (494) [c] | INDO 3.45 [a] (0.69) [c]<br>ASA 3.43 [a] (0.65) [c] | Probably High | 1) Moderate PDA: Disturbed diastolic flow easily detectable at all sites of the pulmonary trunk, a diastolic back flow was present in the aorta immediately beneath the PDA and a forward flow above the PDA; 2) Large (severe) PDA: If a diastolic back flow was detectable in the abdominal aorta at the level of the celiac arterial trunk and if dilatation of the left atrium was present expressed as a LA:AO> 1.7 | IV Indomethacin 0.2 mg/kg every 12 h x 3doses | IV Aspirin 15mg/kg/dose every 6h x 4doses |
| 96 | Van Overmeire 1997 | English | 40 | INDO 28.7 [a] (1.9) [c]<br>IBU 29.0 [a] (2.4) [c] | INDO 1210 [a] (360) [c]<br>IBU 1270 [a] (450) | INDO 3.1 [a] (0.5) [c]<br>IBU 3.2 [a] (0.4) [c] | Probably Low | (1) Moderate PDA shunt: if a disturbed diastolic flow was easily detectable at all sites of the pulmonary trunk, a diastolic back flow was present in the aorta immediately beneath the PDA and a forward flow above the PDA; (2) Severe PDA shunt: If a diastolic back flow was detectable in the aorta and if dilatation of the left atrium was present and expressed as a LA:AO>1.6 | IV Indomethacin 0.2 mg/kg every 12 h x 3doses | IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h |
| 97 | Van Overmeire 2000 | English | 148 | INDO 29.0 [a] (2.1) [c]<br>IBU 29.0 [a] (2.3) [c] | INDO 1230 [a] (380) [c]<br>IBU 1230 [a] (390) [c] | INDO 3.1 [a] (0.5) [c]<br>IBU 3.1 [a] (0.6) [c] | Probably Low | (1) Moderate PDA shunt: If a disturbed diastolic flow was easily detected in the main pulmonary artery with a diastolic reversed flow in the aorta beneath the ductus and a forward flow above the ductal insertion; (2) Severe PDA shunt: If a diastolic backflow in the aorta was straightforward and if dilatation of the left atrium was present (LA:AO > 1.6) | IV Indomethacin 0.2 mgkg every 12 h x 3 doses | IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h |

## eTable 4. Clinical & Methodological Characteristics of Included Studies (cont'd….)

| Ref No | Author & year of publication | Language of publication | # of infants enrolled | Gestational age at birth (in weeks) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])] | Birth weight (in grams) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])] | Age at start of treatment (days) [Mean [a] (SD [c] )]/ [Median [b] (IQR [d]/ Range [e])] | Overall assessment of risk of bias | Criteria for diagnosis of hs-PDA | Intervention characteristics (drug: route & dose) | |
|---|---|---|---|---|---|---|---|---|---|---|
| 98 | Van Overmeire 2001 | English | 127 | INDO 28.9 [a] (2.0) [c]<br>INDOLATE 29.2 [a] (2.1) [c] | INDO 1210 [a] (370) [c]<br>INDOLATE 1270 [a] (365) [c] | NR | Probably Low | (1) Moderate PDA shunt: If a disturbed diastolic flow was easily detected in the main pulmonary artery with a diastolic reversed flow in the aorta beneath the ductus and a forward flow above the ductal insertion; (2) Severe PDA shunt: If a diastolic backflow in the aorta was straightforward and if dilatation of the left atrium was present (LA:AO > 1.5). | IV Indomethacin 0.2 mgkg every 12 h x 3doses started on day 3 | IV Indomethacin 0.2 mgkg every 12 h x 3doses started on day 7 |
| 99 | Yadav 2014 | English | 83 | IBU 29.65 [a] (3.15) [c]<br>INDO 30.29 [a] (3.14) [c] | IBU 1440 [a] (450) [c]<br>INDO 1380 [a] (450) [c] | IBU 10.1 [a] (6.1) [c]<br>INDO 9.8 [a] (6.0) [c] | Probably Low | PDA> 1.5mm LA:AO>1.4 | Oral Indomethacin three doses (0.20–0.25 mg/kg every 24 h) depending on the gestational age (initial dose was 0.2 mg/kg, subsequent doses 2–7 days of age were 0.2mg/kg/dose every 24 h for two doses; >7 days of age 0.25mg/kg/dose every 24 h for two doses) | Oral Ibuprofen 10 mg/kg followed by 5 mg/kg after 24 and 48 h |
| 100 | Yanagi 1981 | English | 43 | PLAC 30.4 [a] (1.0) [c]<br>INDO 29.4 [a] (1.0) [c] | PLAC 1500 [a] (200) [c]<br>INDO 1200 [a] (100) [c] | PLAC 9.1 [a] (6.6) [c]<br>INDO 8.6 [a] (9.8) [c] | Probably Low | LA:AO ≥1.3 and continuous requirement of ventilator support | Oral Indomethacin was administered in 2 phases: In phase 1, 2 mg/kg of indomethacin was administered as the first dose, second and third doses were administered 24 and 48 hours following the first dose as long as the clinical and echocardiographic criteria of sPDA persisted. In phase 2, the dose interval was decreased to eight rather than 24 hours and the second and third doses were thus administered at eight and 16 hours after the first dose. Digitalis and furosemide were used as cointerventions | Oral placebo was used. Small amount of cornstarch was added to 250 mg of lactose to achieve an appearance similar to that of the indomethacin vials. Just prior to administration, 9.5 ml of normal saline was added to each vial and 0.4 ml/kg of this suspension (0.2 mg/kg of indomethacin or placebo) was administered |
| 101 | Yang 2016 | English | 87 | IBU 33.4 [a] (2.1) [c]<br>PARA 33.6 [a] (2.1) [c] | IBU 2091 [a] (657) [c]<br>PARA 2219 [a] (606) [c] | IBU 5.8 [a] (2) [c]<br>PARA 6.4 [a] (1.8) [c] | Probably High | PDA > 1.4 mm; LA:AO>1.4 | Oral Ibuprofen 10 mg/kg followed by 5 mg/kg after 24 and 48 h | Oral acetaminophen 15 mg/kg every 6 h for 5 days |

## eTable 4. Clinical & Methodological Characteristics of Included Studies (cont'd….)

| Ref No | Author & year of publication | Language of publication | # of infants enrolled | Gestational age at birth (in weeks) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])] | Birth weight (in grams) [Mean [a] (SD [c])]/ [Median [b] (IQR [d] /Range [e])] | Age at start of treatment (days) [Mean [a] (SD [c] ]/ [Median [b] (IQR [d]/ Range [e])] | Overall assessment of risk of bias | Criteria for diagnosis of hs-PDA | Intervention characteristics (drug: route & dose) | |
|---|---|---|---|---|---|---|---|---|---|---|
| 102 | Yeh 1981 | English | 55 | PLAC 30.2 [a] (2.3) [c]<br>INDO 31.5 [a] (2.3) [c] | PLAC 1167 [a] (354) [c]<br>INDO 1233 [a] (408) [c] | PLAC 10.9 [a] (6.1) [c]<br>INDO 8.9 [a] (5.3) [c] | Low | Cardiovascular dysfunction score ≥ 3 or LA:AO ≥ 1.3 on echo | IV Indomethacin: One dose of 0.3 mg/kg was administered intravenously and was repeated at intervals of about 24 hours up to a maximum of three doses, unless the PDA murmur disappeared. IV Frusemide (1mg/kg) and fluid restriction were used as cointerventions in both groups | IV Placebo: Identical syringes containing either indomethacin 1 mg in 1 ml saline diluent or a placebo consisting of 1 ml of saline only were prepared. A dose of 0.3 ml/kg was administered intravenously and was repeated at intervals of about 24 hours up to a maximum of three doses, unless the PDA murmur disappeared. |
| 103 | Yeh 1982 | English | 19 | INDO 30.4 [a] (0.9) [c]<br>INDOIVFRU 30.7 [a] (0.8) [c] | INDO 1120 [a] (390) [c]<br>INDOIVFRU 1190 [a] (100) [c] | INDO 10.7 [a] (3.4) [c]<br>INDOIVFRU 9.5 [a] (1.7) [c] | Probably Low | Clinical criteria: (1) evidence of PDA, and (2) evidence of significant clinical cardiovascular Dysfunction along with echocardiographic left atrium/aortic root dimension ratio (LA:AO) ≥ 1.30 | IV Indomethacin 0.3mg/kg every 24h up to 3 doses | IV Indomethacin 0.3mg/kg followed immediately IV Frusemide (1mg/kg) every 24h up to 3 doses |
| 104 | Zanardo 2005 | English | 46 | IBU 26 [b] (23-34) [e]<br>INDO 27.5 [b] (23-33) [e] | IBU 857.5 [b] (500-2110) [e]<br>INDO 977.5 [b] (616-2450) [e] | IBU 3 [b] (2-17) [e]<br>INDO 2.5 [b] (2-12) [e] | Probably Low | Infants with RDS who required ventilator support along with typical flow pattern of hs-PDA on Doppler echo | IV Indomethacin 0.2 mg/kg every 12 h x 3doses | IV Ibuprofen 10 mg/kg, followed by 5 mg/kg at 24 and 48 h |

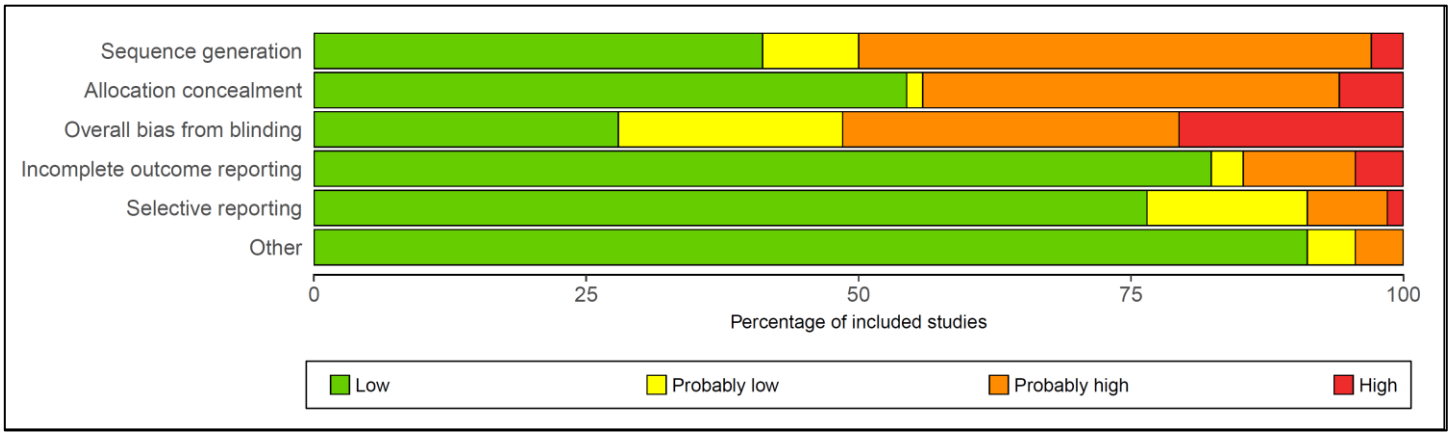
***Abbreviations:***

- SD: Standard deviation
- IQR: Interquartile range
- INDO: Indomethacin
- IBU: Ibuprofen
- PLAC: Placebo
- PARA: Acetaminophen
- NR: Not reported
- ASA: Acetylsalicylic acid (aspirin)
- INDOLATE: Intravenous indomethacin standard dose; late initiation of therapy (started on or beyond day 7)
- INDOIVPROLONGED: Intravenous indomethacin prolonged treatment course
- INDOIVFRU: Intravenous indomethacin standard dose along with Frusemide
- INDOIVECHOGUIDED: Intravenous indomethacin standard dose; duration guided by echo assessment of PDA
- hs-PDA: hemodynamically significant patent ductus arteriosus
- LA:AO: Left atrium to aortic root ratio on echocardiography
- LV:AO: Left ventricle to aortic root ratio on echocardiography

## eFigure 2. Detailed risk of Bias assessment of individual studies


- ***Risk of Bias (RoB) assessment items:*** Sequence generation; Allocation concealment; Blinding; Incomplete outcome data; Selective reporting of outcomes; other biases
- ***RoB categories:*** Low; Probably low; Probably High; High

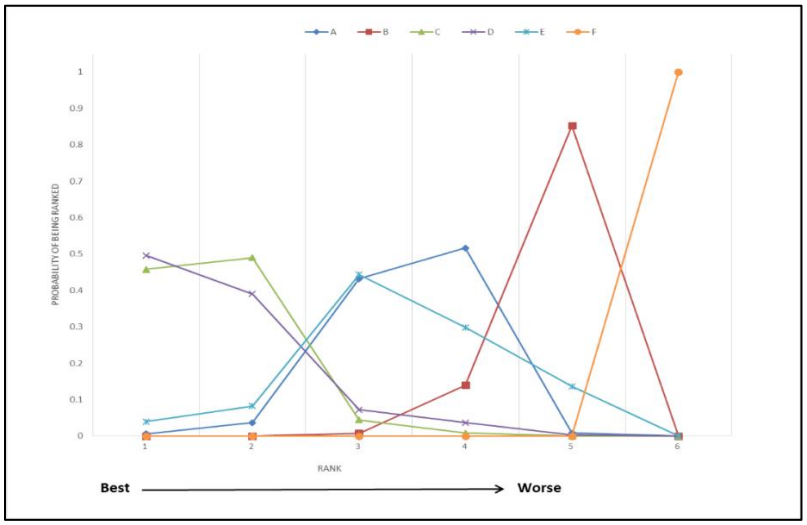
**eFigure 3. Assessment summary across the risk of bias items**




- ***Risk of Bias (RoB) assessment items:*** Sequence generation; Allocation concealment; Blinding; Incomplete outcome data; Selective reporting of outcomes; other biases
- ***RoB categories:*** Low; Probably low; Probably High; High
- ***Number of studies included in the summary:*** 68

## eText 2. Guide to interpreting NMA results (rankograms; SUCRA; Network GRADE)

### eText 2(a). Rankograms examples and interpretation




***eText 2(a):rankogram example figure***

The figure above displays an example of a rankogram in a hypothetical study comparing 6 interventions for a specific outcome. The figure shows each intervention with a different color and symbol. The horizontal axis displays the ranking from 1 to 6. Ranking should be interpreted from best (rank 1), to worst (rank 6), for this specific outcome. The vertical axis displays the probability of being ranked in any specific ranking position, from 0 to 1. In order to systematically interpret a rankogram, one should start by focusing on rank 1 first, establish which intervention might be the best and then follow the same for each rank. As shown in the figure above, in rank 1, the treatment D showed slightly more than 0.5 probability of being ranked the best, or being ranked in the first position. After treatment D, treatment C had a probability of approximately 0.46 of being ranked in the first place, while treatment E had a probability of approximately 0.05 of being ranked the first. Of note, treatments A, B and F only had probabilities of around 0 of being best ranked. Similarly, the last position on the right of the curve, rank 6, shows the probability of being ranked as the worst treatment. In this case, intervention F had the highest probability of being in rank 6 (approximately 0.99).

In summary, rankograms allow the reader to see for each treatment, the probability of being ranked in the first, second, third position, and so on, until the worst (depending on the number of interventions analyzed) (3). In this case, treatment D was found to be the one with the highest probability of being the best while treatment F had the highest probability of being the worst treatment.

### eText 2(b). SUCRA examples and interpretation

Surface under the cumulative ranking curve (SUCRA) summarizes the information from the rankograms as a single number. Its calculation is based on the cumulative probabilities of the treatments being ranked in each position, and the SUCRA is the final area under the curve of the graph for these probabilities. This is a simple numerical summary to supplement the graphical display. SUCRA would be 1 when a treatment is certain to be the best and 0 when a treatment is certain to be the worst (4). If a treatment always ranks first, then SUCRA=1, and if it always ranks last, it will have SUCRA=0. For example, if cumulative probabilities are computed using the information from the rankogram above, we would obtain the mean SUCRA value for each intervention, as presented in the SUCRA example table below. The median ranks for each treatment option are also provided along with. This enables overall ranking of the treatments based on the mean SUCRA value. In this case, treatment C emerges as the best (SUCRA, 0.88), followed by D, E, A, B and lastly F (SUCRA, 0). Thus, SUCRA simplifies the information on the ranking distribution of each treatment into a single number, which helps to summarize the ranking statistics in a complex network meta-analysis.

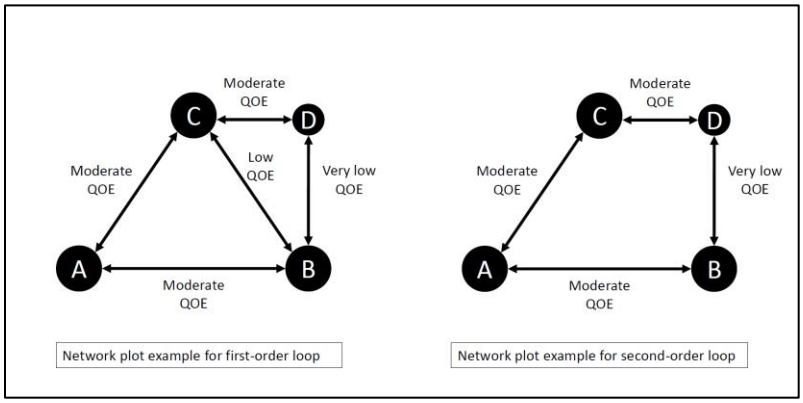
**eText 2(b):SUCRA example table**

| Treatment | Mean SUCRA (standard deviation) | Median rank (95% credible intervals) |
|---|---|---|
| A | 0.50 (0.12) | 4 (2-4) |
| B | 0.23 (0.08) | 5 (4-5) |
| C | 0.88 (0.12) | 2 (1-3) |
| D | 0.87 (0.16) | 2 (1-4) |
| E | 0.52 (0.19) | 3 (1-5) |
| F | 0 | 6 (6-6) |

## eText 2(c). Network GRADE Assessment Strategy

The assessment of the confidence in the estimates (quality of evidence) for each reported outcome was performed according to the GRADE approach (5). To assess GRADE quality of evidence in a network meta-analysis, both direct and indirect comparisons are taken into account. A ***direct comparison*** between two treatment options is defined as a comparison based on head-to-head RCTs between the two treatment options. An ***indirect comparison*** between two treatment options is computed when no head-to-head RCTs have been conducted between the two respective treatment options (described in detail below). Initially, direct comparisons were assessed and rated based on the following categories: risk of bias; indirectness; inconsistency (which is determined based on the heterogeneity); imprecision and publication bias (6-9). This was followed by assessment of confidence from indirect estimates and the final step was assessment of confidence in the NMA estimates (10). The final confidence was rated based on four levels: high, moderate, low and very low.

For rating confidence in the indirect comparisons, information obtained from the first and second order loops in the network was used as shown in the example figure below.




In the above networks, each node indicates a treatment strategy and each of two-way arrows indicates a direct comparison between two strategies. In the first figure above *(network plot example for first-order loop),* for the comparison of A vs. B, the pathway of A-C-B is a first-order loop and the pathway of A-C-D-B is a second-order loop. The quality of evidence of indirect comparisons was derived from the quality of evidence of the first order loops. The quality of evidence of a first-order loop was derived from the lowest quality of evidence among direct comparisons within the first-order loop. In the first example figure, the quality of evidence of the indirect comparison of A vs. B was the lower quality of evidence among 2 direct comparisons of A vs. C (moderate) and B vs. C (low), which was low quality of evidence. When an indirect comparison had two or more first-order loops, the highest quality of evidence among its first-order loops were used for the quality of evidence of the indirect comparison. For example, the quality of evidence for the indirect comparison of B vs. C was the highest quality of evidence of the 2 first order loops of B-A-C (moderate) and B-D-C (very low), which was moderate quality of evidence. When no first order loop was available, the quality of evidence for an indirect comparison was derived from the second-order loops. In the second figure above *(network plot example for second-order loop),* the quality of evidence for the indirect comparison between A vs. B was derived from the lowest quality of evidence among the 3 direct comparisons within the 2nd order loops including A vs. C (moderate), C vs. D (moderate) and D vs. B (very low). So the final quality of evidence for the indirect comparison of A vs B was adjudged to be very low. In

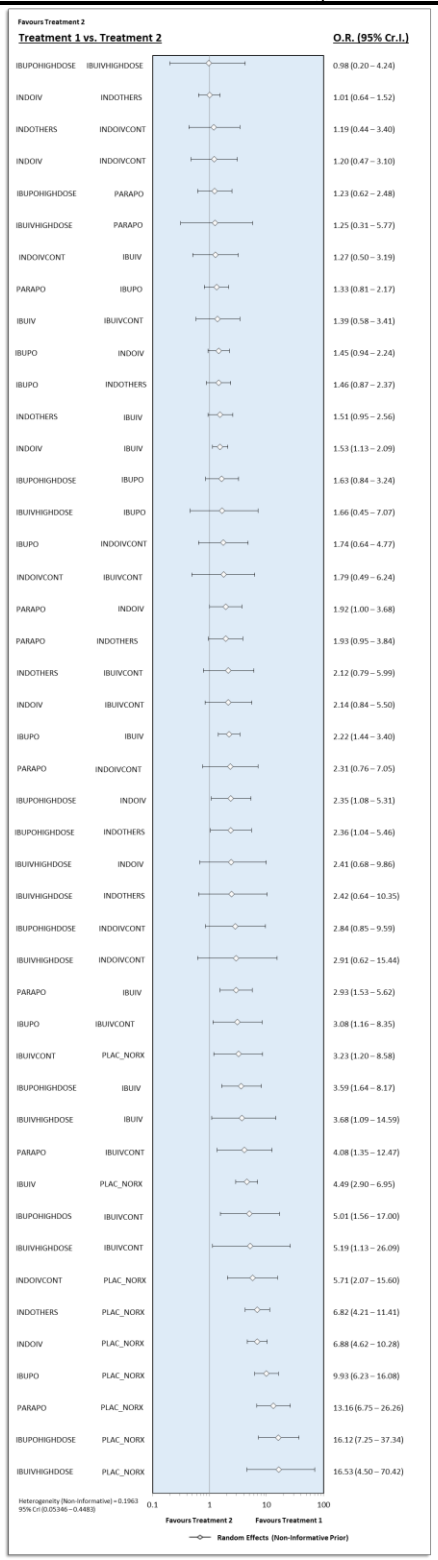
addition, the final indirect confidence rating was rated down by one level, if there was a strong suspicion that the transitivity assumption was violated for this loop (11) Transitivity is the assumption that an indirect comparison is a valid method to compare two treatments, because the studies are sufficiently similar in important clinical and methodological characteristics, or in other words, that they are similar in their distributions of effect modifiers (12, 13).

The overall confidence in the NMA estimates for any paired comparison was rated using the higher of the confidence rating amongst the contributing direct and indirect comparisons. For example, if a NMA estimate was obtained from combining direct evidence of A vs. B that was rated as moderate, and indirect evidence of A vs. B that was rated as Low, the final A vs B NMA estimate would be rated as moderate.

Additionally, this confidence in the NMA estimate was rated down if it was found that the direct and indirect estimates had incoherence (also called inconsistency), which was defined as the differences between direct and indirect estimates of effect (10).

Inconsistency was quantitatively computed using the **node-splitting model**. In a node-splitting analysis a treatment comparison is split into a parameter for direct evidence and a parameter for indirect evidence in order to assess whether there is significant disagreement between the two parameters (14). In this NMA, a node-splitting analysis was performed separately for each of the comparisons in the treatment network on which both direct and indirect evidence were available, to assess evidence consistency. A p value less than 0.05 indicated significant inconsistency between the direct and indirect comparisons. This was computed using the GeMTC GUI 0.14.3 package (15).

**eFigure 4. Network meta-analysis forest plots for outcome: *PDA closure***




eFigure 4: Forest plot showing network effect estimates (OR with 95% credible intervals) for each possible treatment comparison in the network for PDA closure computed using Bayesian RE model with non-informative priors; the horizontal axis denotes network odds ratios (with 95% credible intervals)

## eTable 5. GRADE assessment of the Quality of Evidence (QoE) for the network for PDA closure

| *eTable 5. GRADE assessment of the Quality of Evidence (QoE) for the network for PDA closure* | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Comparison | No. of direct comparisons | Events in intervention group (n/N) | Events in comparison group (n/N) | Direct OR (95% CrI) | QoE (GRADE) based on direct comparisons | QoE (GRADE) based on indirect comparisons | Network OR (95% CrI) | Inconsistency assessment (based on node splitting p value) | Changes in GRADE assessment based on precision & effect size | Network QoE | Network absolute risk difference per 1000 infants (95% CrI) |
| versus INDOIV | | | (INDOIV) | | | | | | | | ACR INDO IV 849/1125 (75.5%) |
| IBUIV | 12 | 327/447 | 329/436 | 0.86(0.59-1.24) | MODERATE | MODERATE | 0.65(0.48-0.89) | <0.01 | Rated down (network inconsistency) | LOW | 88 fewer (from 22 fewer to 158 fewer) |
| IBUPO | 4 | 38/52 | 41/51 | 0.63(0.22-1.74) | LOW | MODERATE | 1.45(0.94-2.24) | 0.14 | None | MODERATE | 62 more (from 12 fewer to 119 more) |
| PARAPO | 1 | 35/36 | 35/37 | 2.42(0.17-83.51) | MODERATE | LOW | 1.92(1.00-3.68) | 0.06 | None | MODERATE | 101 more (from 0 fewer to 164 more) |
| IBUIVHIGHDOSE | ——— | ——— | ——— | ——— | ——— | MODERATE | 2.41(0.68-9.86) | ——— | Rated down (imprecision) | LOW | 126 more (from 78 fewer to 213 more) |
| IBUPOHIGHDOSE | ——— | ——— | ——— | ——— | ——— | LOW | 2.35(1.08-5.31) | ——— | None | LOW | 124 more (from 14 more to 188 more) |
| IBUIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.47(0.18-1.19) | ——— | None | LOW | 164 fewer (from 31 more to 398 fewer) |
| INDOIVCONT | 2 | 18/27 | 19/23 | 0.39(0.09-1.74) | LOW | LOW | 0.83(0.32-2.11) | 0.3 | None | LOW | 36 fewer (from 112 more to 259 fewer) |
| INDOTHERS | 10 | 270/403 | 285/399 | 0.81(0.43-1.51) | LOW | MODERATE | 0.99(0.66-1.57) | 0.14 | None | MODERATE | 2 fewer (from 74 more to 85 fewer) |
| PLAC_NORX | 4 | 112/316 | 140/179 | 0.14(0.07-0.23) | MODERATE | MODERATE | 0.15(0.10-0.22) | 0.94 | Rated up (high precision) | HIGH | 439 fewer (from 351 fewer to 519 fewer) |
| versus IBUIV | | | (IBUIV) | | | | | | | | ACR IBUIV 542/786 (68.9%) |
| IBUPO | 4 | 133/156 | 95/148 | 3.25(1.77-6.26) | HIGH | LOW | 2.22(1.44-3.40) | 0.11 | None | HIGH | 142 more (from 72 more to 194 more) |
| PARAPO | ——— | ——— | ——— | ——— | ——— | MODERATE | 2.93(1.53-5.62) | ——— | None | MODERATE | 177 more (from 83 more to 236 more) |
| IBUIVHIGHDOSE | 1 | 30/35 | 22/35 | 3.82(1.07-14.71) | MODERATE | NOT ESTIMABLE | 3.68(1.09-14.59) | NA | None | MODERATE | 201 more (from 18 more to 281 more) |
| IBUPOHIGHDOSE | ——— | ——— | ——— | ——— | ——— | MODERATE | 3.59(1.64-8.17) | ——— | Rated up (large effect) | HIGH | 199 more (from 95 more to 258 more) |
| IBUIVCONT | 1 | 27/55 | 32/56 | 0.72(0.29-1.79) | LOW | NOT ESTIMABLE | 0.72(0.29-1.73) | NA | None | LOW | 74 fewer (from 104 more to 298 fewer) |
| INDOIVCONT | 1 | 23/31 | 19/32 | 2.02(0.61-7.00) | LOW | LOW | 1.27(0.50-3.19) | 0.3 | None | LOW | 49 more (from 163 fewer to 187 more) |
| INDOTHERS | ——— | ——— | ——— | ——— | ——— | LOW | 1.51(0.95-2.56) | ——— | None | LOW | 81 more (from 11 fewer to 161 more) |
| PLAC_NORX | 1 | 32/68 | 47/68 | 0.39(0.16-0.93) | MODERATE | MODERATE | 0.22(0.14-0.34) | 0.16 | None | MODERATE | 361 fewer (from 259 fewer to 452 fewer) |
| versus IBUPO | | | (IBUPO) | | | | | | | | ACR IBUPO 486/650 (74.8%) |
| PARAPO | 3 | 105/164 | 102/163 | 1.03(0.58-1.77) | MODERATE | MODERATE | 1.33(0.81-2.17) | 0.02 | Rated down (network inconsistency) | LOW | 50 more (from 42 fewer to 118 more) |
| IBUIVHIGHDOSE | ——— | ——— | ——— | ——— | ——— | MODERATE | 1.66(0.45-7.07) | ——— | None | MODERATE | 83 more (from 176 fewer to 207 more) |
| IBUPOHIGHDOSE | 2 | 45/60 | 31/60 | 3.02(1.23-7.77) | MODERATE | MODERATE | 1.63(0.84-3.24) | 0.16 | None | MODERATE | 81 more (from 34 fewer to 158 more) |
| IBUIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.32(0.12-0.86) | ——— | None | LOW | 261 fewer (from 29 fewer to 485 fewer) |
| INDOIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.58(0.21-1.56) | ——— | None | LOW | 116 fewer (from 74 more to 364 fewer) |

***eTable 5. GRADE assessment of the Quality of Evidence (QoE) for the network for PDA closure***

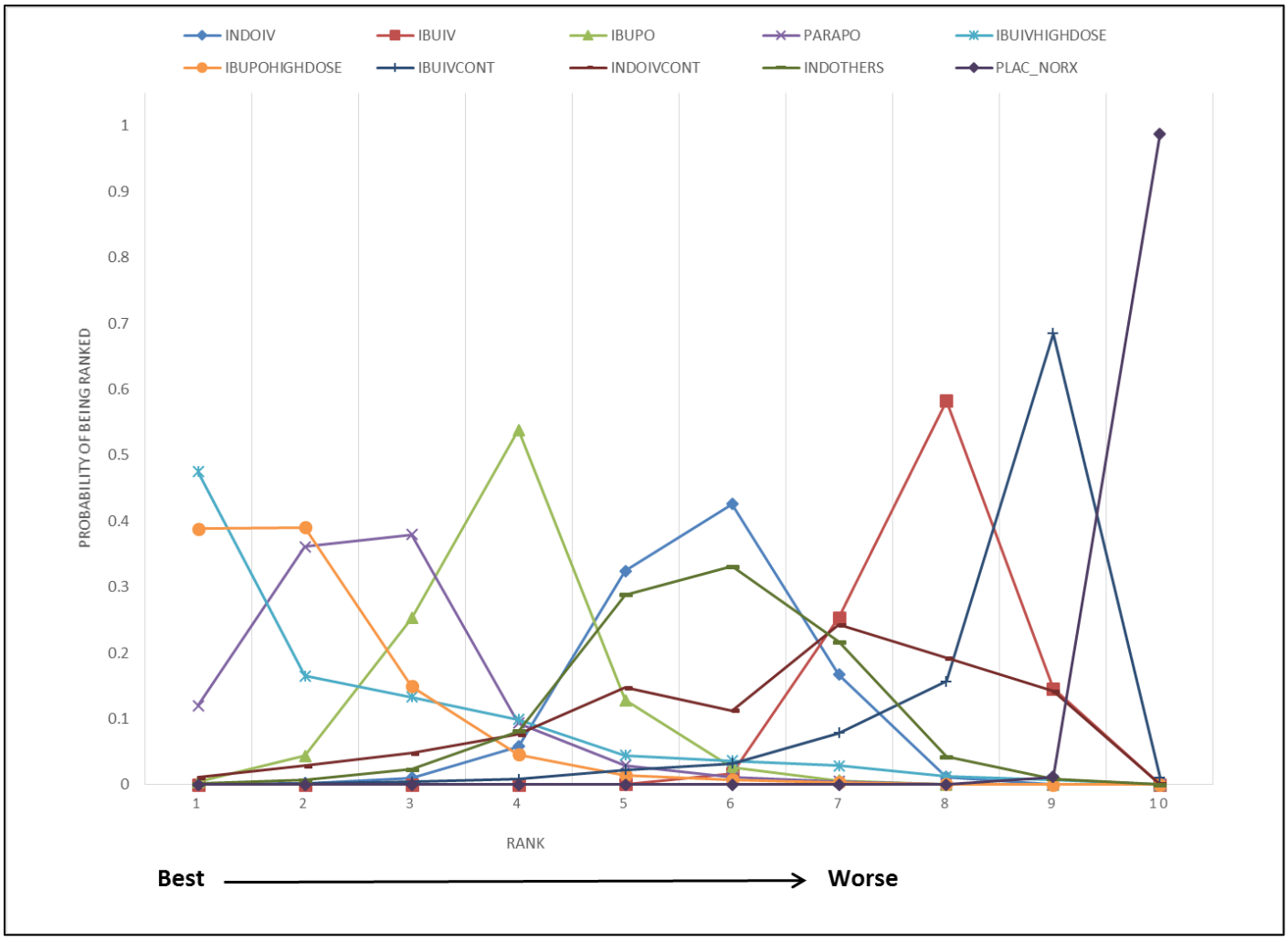
| Treatment Comparison | No. of direct comparisons | Events in intervention group (n/N) | Events in comparison group (n/N) | Direct OR (95% CrI) | QoE (GRADE) based on direct comparisons | QoE (GRADE) based on indirect comparisons | Network OR (95% CrI) | Inconsistency assessment (based on node splitting p value) | Changes in GRADE assessment based on precision & effect size | Network QoE | Network absolute risk difference per 1000 infants (95% CrI) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | ***(Continued…)*** |
| INDOTHERS | 4 | 53/74 | 65/88 | 0.75(0.32-1.69) | LOW | VERY LOW | 0.69(0.42-1.15) | 0.99 | None | LOW | 76 fewer (from 25 more to 193 fewer) |
| PLAC_NORX | 4 | 70/133 | 117/131 | 0.11(0.05-0.22) | VERY LOW | LOW | 0.10(0.06-0.16) | 0.54 | Rated up (high precision) | MODERATE | 519 fewer (from 426 fewer to 597 fewer) |
| versus PARAPO | | | (PARAPO) | | | | | | | | ACR PARAPO 195/267 (73%) |
| IBUIVHIGHDOSE | ——— | ——— | ——— | ——— | ——— | MODERATE | 1.25(0.31-5.77) | ——— | None | MODERATE | 42 more (from 210 more to 274 fewer) |
| IBUPOHIGHDOSE | 1 | 45/62 | 55/67 | 0.57(0.21-1.55) | MODERATE | MODERATE | 1.23(0.62-2.48) | 0.88 | None | MODERATE | 39 more (from 104 fewer to 140 more) |
| IBUIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.24(0.08-0.74) | ——— | None | LOW | 336 fewer (from 63 fewer to 552 fewer) |
| INDOIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.43(0.14-1.32) | ——— | None | LOW | 192 fewer (from 51 more to 455 fewer) |
| INDOTHERS | ——— | ——— | ——— | ——— | ——— | LOW | 0.52(0.26-1.05) | ——— | None | LOW | 146 fewer (from 10 more to 317 fewer) |
| PLAC_NORX | ——— | ——— | ——— | ——— | ——— | MODERATE | 0.08(0.04-0.15) | ——— | Rated up (high precision; large effect) | HIGH | 552 fewer (441 fewer to 633 fewer) |
| versus IBUIVHIGHDOSE | | | (IBUIVHIGHDOSE) | | | | | | | | ACR IBUIVHIGHDOSE 30/35 (85.7%) |
| IBUPOHIGHDOSE | ——— | ——— | ——— | ——— | ——— | MODERATE | 0.98(0.20-4.24) | ——— | None | MODERATE | 2 fewer (from 105 more to 312 fewer) |
| IBUIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.19(0.04-0.89) | ——— | None | LOW | 324 fewer (from 15 fewer to 664 fewer) |
| INDOIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.34(0.06-1.60) | ——— | Rated down (imprecision) | VERY LOW | 186 fewer (from 49 more to 592 fewer) |
| INDOTHERS | ——— | ——— | ——— | ——— | ——— | LOW | 0.41(0.10-1.57) | ——— | Rated down (imprecision) | VERY LOW | 146 fewer (from 47 more to 482 fewer) |
| PLAC_NORX | ——— | ——— | ——— | ——— | ——— | MODERATE | 0.06(0.01-0.22) | ——— | Rated up (large effect) | HIGH | 592 fewer (from 288 fewer to 801 fewer) |
| versus IBUPOHIGHDOSE | | | (IBUPOHIGHDOSE) | | | | | | | | ACR IBUPOHIGHDOSE 90/122 (73.8%) |
| IBUIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.20(0.06-0.64) | ——— | Rated down (imprecision) | VERY LOW | 378 fewer (from 95 fewer to 593 fewer) |
| INDOIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.35(0.10-1.17) | ——— | Rated down (imprecision) | VERY LOW | 242 fewer (from 29 more to 518 fewer) |
| INDOTHERS | ——— | ——— | ——— | ——— | ——— | LOW | 0.42(0.18-0.96) | ——— | None | LOW | 190 fewer (from 8 fewer to 441 fewer) |
| PLAC_NORX | ——— | ——— | ——— | ——— | ——— | LOW | 0.06(0.03-0.14) | ——— | Rated up (large effect) | MODERATE | 593 fewer (from 455 fewer to 660 fewer) |
| versus IBUIVCONT | | | (IBUIVCONT) | | | | | | | | ACR IBUIVCONT 27/55 (49.1%) |
| INDOIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 1.79(0.49-6.24) | ——— | None | LOW | 142 more (from 170 fewer to 367 more) |
| INDOTHERS | ——— | ——— | ——— | ——— | ——— | LOW | 2.12(0.79-5.99) | ——— | None | LOW | 181 more (from 59 fewer to 362 more) |
| PLAC_NORX | ——— | ——— | ——— | ——— | ——— | LOW | 0.31(0.12-0.84) | ——— | Rated down (imprecision) | VERY LOW | 261 fewer (from 43 more to 387 fewer) |
| versus INDOIVCONT | | | (INDOIVCONT) | | | | | | | | ACR INDOIVCONT 41/58 (70.7%) |

| ***eTable 5. GRADE assessment of the Quality of Evidence (QoE) for the network for PDA closure*** | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Comparison | No. of direct comparisons | Events in intervention group (n/N) | Events in comparison group (n/N) | Direct OR (95% CrI) | QoE (GRADE) based on direct comparisons | QoE (GRADE) based on indirect comparisons | Network OR (95% CrI) | Inconsistency assessment (based on node splitting p value) | Changes in GRADE assessment based on precision & effect size | Network QoE | Network absolute risk difference per 1000 infants (95% CrI) |
| | | | | | | | | | | | ***(Continued…)*** |
| INDOTHERS | ____ | ——— | ——— | ——— | ——— | LOW | 1.19(0.44-3.40) | ——— | None | LOW | 35 more (from 184 more to 192 fewer) |
| PLAC_NORX | ——— | ——— | ——— | ——— | ——— | LOW | 0.18(0.06-0.48) | ——— | Rated up (high precision) | MODERATE | 404 fewer (from 170 fewer to 580 fewer) |
| versus INDOTHERS | | | (INDOTHERS) | | | | | | | | ACR INDOTHERS 380/561 (67.7%) |
| PLAC_NORX | 5 | 13/80 | 57/84 | 0.09(0.04-0.22) | HIGH | LOW | 0.15(0.09-0.24) | 0.07 | Rated up (high precision) | HIGH | 438 fewer (from 342 fewer to 518 fewer) |

Abbreviations: NA: Not Applicable; QoE: Quality of Evidence; OR: Odds Ratio; Crl: Credible Intervals; ACR: Assumed control risk

## eFigure 5. Ranking probability (rankogram) of each treatment modality for PDA closure

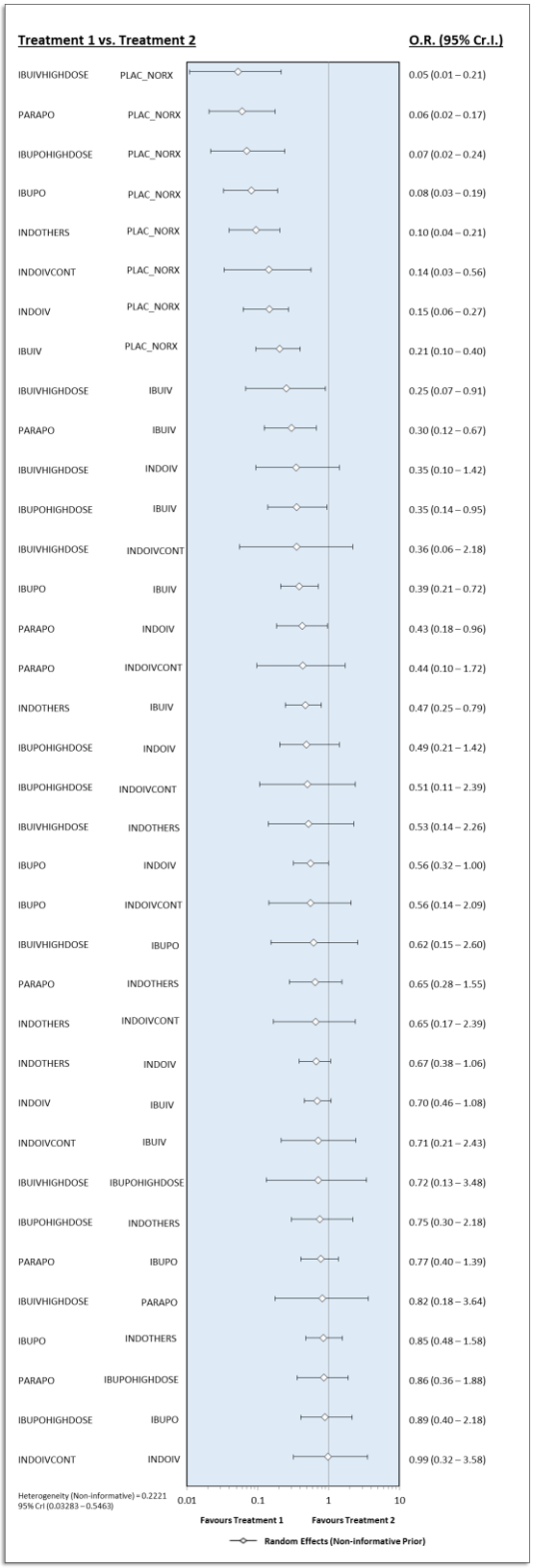
eFigure 5. Each line indicates a treatment modality. The horizontal x-axis represents the ranking of strategies in which the first through 10th modalities are ranked in numerical order, with the first representing the best strategy. The vertical y-axis represents the probability of each ranking.




## eTable 6. Ranking statistics for each treatment modality for outcome *PDA closure*

| PDA closure | | |
|---|---|---|
| **Treatment** | **SUCRA mean (Standard Deviation)** | **Median rank (95% Credible Intervals)** |
| INDOIV | 0.48 (0.10) | 6 (4-7) |
| IBUIV | 0.24 (0.07) | 8 (7-9) |
| IBUPO | 0.68 (0.10) | 4 (2-6) |
| PARAPO | 0.82 (0.12) | 3 (1-5) |
| IBUIVHIGHDOSE | 0.84 (0.20) | 2 (1-7) |
| IBUPOHIGHDOSE | 0.89 (0.12) | 2 (1-5) |
| IBUIVCONT | 0.17 (0.13) | 9 (5-9) |
| INDOIVCONT | 0.40 (0.21) | 7 (2-9) |
| INDOTHERS | 0.47 (0.13) | 6 (3-8) |
| PLAC_NORX | 0.001 (0.012) | 10 (10-10) |

**eFigure 6. Network meta-analysis forest plots for outcome: N*eed for repeat pharmacotherapy***




eFigure 6. Forest plot showing network effect estimates (OR with 95% credible intervals) for each possible treatment comparison in the network for need for repeat treatment computed using Bayesian RE model with non-informative priors; the horizontal axis denotes network odds ratios (with 95% credible intervals)

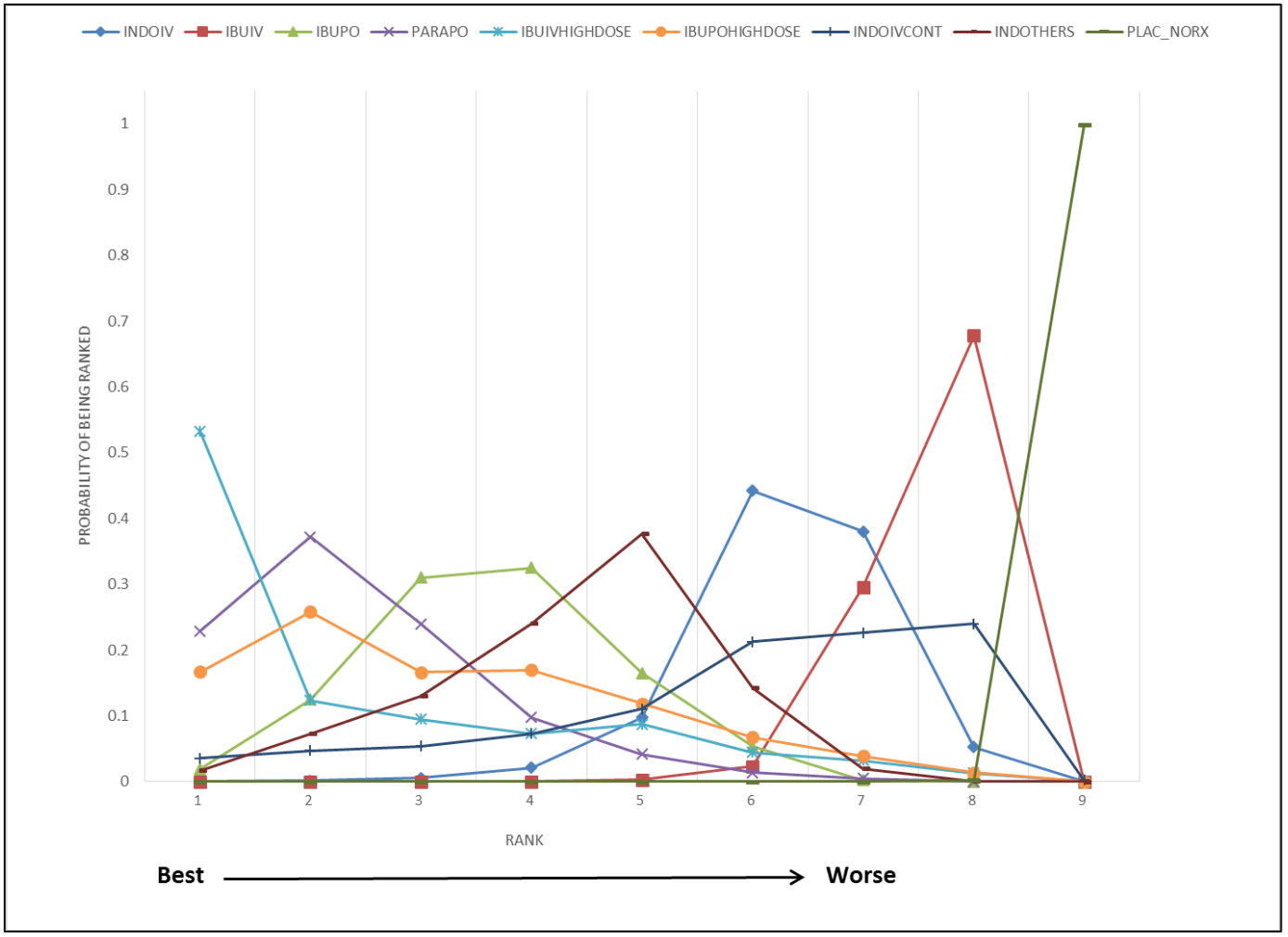
## eTable 7. GRADE assessment of the Quality of Evidence (QoE) for the network for need for repeat pharmacotherapy

| *eTable 7. GRADE assessment of the Quality of Evidence (QoE) for the network for need for repeat pharmacotherapy* | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Comparison | No. of direct comparisons | Events in intervention group (n/N) | Events in comparison group (n/N) | Direct OR (95% CrI) | QoE (GRADE) based on direct comparisons | QoE (GRADE) based on indirect comparisons | Network OR (95% CrI) | Inconsistency assessment (based on node splitting p value) | Changes in GRADE assessment based on precision & effect size | Network QoE | Network absolute risk difference per 1000 infants (95% CrI) |
| *versus* INDOIV | | | (INDOIV) | | | | | | | | ACR INDOIV 108/601 (18%) |
| IBUIV | 7 | 63/237 | 50/281 | 1.36(0.80-2.15) | MODERATE | MODERATE | 1.43(0.92-2.18) | 0.09 | None | MODERATE | 59 more (from 12 fewer to 144 more) |
| IBUPO | 3 | 7/43 | 7/42 | 0.96(0.34-3.65) | LOW | MODERATE | 0.56(0.32-1.00) | 0.18 | None | MODERATE | 70 fewer (from 0 fewer to 114 fewer) |
| PARAPO | ——— | | | ——— | ——— | LOW | 0.43(0.18-0.96) | ——— | None | LOW | 94 fewer (from 6 fewer to 142 fewer) |
| IBUIVHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 0.35(0.10-1.42) | ——— | None | MODERATE | 108 fewer (from 58 more to 158 fewer) |
| IBUPOHIGHDOSE | ——— | | | ——— | ——— | LOW | 0.49(0.21-1.42) | ——— | None | LOW | 83 fewer (from 58 more to 136 fewer) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 0.99(0.32-3.58) | ——— | None | LOW | 1 fewer (from 114 fewer to 260 more) |
| INDOTHERS | 5 | 30/235 | 42/235 | 0.64(0.33-1.20) | LOW | MODERATE | 0.67(0.38-1.06) | ——— | None | MODERATE | 52 fewer (from 9 more to 103 fewer) |
| PLAC_NORX | 3 | 30/44 | 9/43 | 10.02(3.73-38.24) | MODERATE | MODERATE | 6.87(3.66-16.03) | 0.88 | Rated up (large effect) | HIGH | 421 more (from 265 more to 599 more) |
| *versus* IBUIV | | | (IBUIV) | | | | | | | | ACR IBUIV 138/534 (25.8%) |
| IBUPO | 3 | 18/124 | 41/116 | 0.34(0.16-0.61) | HIGH | LOW | 0.39(0.21-0.72) | 0.03 | Rated down (network inconsistency) | MODERATE | 139 fewer (from 58 fewer to 190 fewer) |
| PARAPO | ——— | | | ——— | ——— | MODERATE | 0.30(0.12-0.67) | ——— | None | MODERATE | 164 fewer (from 69 fewer to 218 fewer) |
| IBUIVHIGHDOSE | 1 | 5/35 | 13/35 | 0.24(0.07-0.78) | MODERATE | NOT ESTIMABLE | 0.25(0.07-0.91) | NA | None | MODERATE | 178 fewer (from 18 fewer to 235 fewer) |
| IBUPOHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 0.35(0.14-0.95) | ——— | None | MODERATE | 150 fewer (from 10 fewer to 212 fewer) |
| INDOIVCONT | 1 | 9/31 | 12/32 | 0.74(0.21-2.05) | LOW | NOT ESTIMABLE | 0.71(0.21-2.43) | NA | None | LOW | 60 fewer (from 190 fewer to 200 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 0.47(0.25-0.79) | ——— | None | LOW | 118 fewer (from 43 fewer to 178 fewer) |
| PLAC_NORX | 1 | 24/51 | 9/54 | 5.06(1.58-14.27) | MODERATE | MODERATE | 4.86(2.50-10.52) | 0.26 | Rated up (large effect) | HIGH | 370 more (from 207 more to 527 more) |
| *versus* IBUPO | | | (IBUPO) | | | | | | | | ACR IBUPO 104/395 (26.3%) |
| PARAPO | 2 | 31/120 | 34/120 | 0.92(0.47-1.76) | MODERATE | MODERATE | 0.77(0.40-1.39) | 0.99 | None | MODERATE | 47 fewer (from 69 more to 138 fewer) |
| IBUIVHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 0.62(0.15-2.60) | ——— | None | MODERATE | 82 fewer (from 212 fewer to 218 more) |
| IBUPOHIGHDOSE | 1 | 6/30 | 10/30 | 0.47(0.16-1.93) | MODERATE | MODERATE | 0.89(0.40-2.18) | 0.38 | None | MODERATE | 22 fewer (from 138 fewer to 175 more) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 1.79(0.48-7.00) | ——— | None | LOW | 127 more (from 117 fewer to 451 more) |
| INDOTHERS | 3 | 26/64 | 35/78 | 0.91(0.45-2.54) | LOW | VERY LOW | 1.18(0.63-2.08) | 0.89 | None | LOW | 33 more (from 80 fewer to 163 more) |
| PLAC_NORX | ——— | | | ——— | ——— | LOW | 12.24(5.25-30.54) | ——— | Rated up (large effect) | MODERATE | 551 more (from 389 more to 653 more) |
| *versus* PARAPO | | | (PARAPO) | | | | | | | | ACR PARAPO 43/187 (23%) |
| IBUIVHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 0.82(0.18-3.64) | ——— | None | MODERATE | 33 fewer (from 179 fewer to 291 more) |
| IBUPOHIGHDOSE | 1 | 17/62 | 12/67 | 1.95(0.69-4.69) | MODERATE | MODERATE | 1.16(0.53-2.76) | 0.62 | None | MODERATE | 27 more (from 93 fewer to 222 more) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 2.30(0.58-10.14) | ——— | Rated down (imprecision) | VERY LOW | 177 more (from 82 fewer to 522 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 1.53(0.64-3.55) | ——— | None | LOW | 84 more (from 69 fewer to 285 more) |
| PLAC_NORX | ——— | | | ——— | ——— | MODERATE | 16.58(5.72-48.36) | ——— | Rated up (large effect) | HIGH | 602 more (from 401 more to 705 more) |
| *versus* IBUIVHIGHDOSE | | | (IBUIVHIGHDOSE) | | | | | | | | ACR IBUIVHIGHDOSE 5/35 (14.3%) |
| IBUPOHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 1.39(0.29-7.61) | ——— | None | MODERATE | 45 more (from 97 fewer to 416 more) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 2.80(0.46-18.15) | ——— | Rated down (imprecision) | VERY LOW | 175 more (from 72 fewer to 609 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 1.90(0.44-7.08) | ——— | None | LOW | 98 more (from 75 fewer to 398 more) |
| PLAC_NORX | ——— | | | ——— | ——— | MODERATE | 18.97(4.69-92.05) | ——— | Rated up (large effect) | HIGH | 617 more (from 296 more to 796 more) |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | ***(Continued…)*** |
| *versus* IBUPOHIGHDOSE | | | (IBUPOHIGHDOSE) | | | | | | | | ACR IBUPOHIGHDOSE 23/92 (25%) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 1.98(0.42-9.38) | ——— | None | LOW | 148 more (from 127 fewer to 508 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 1.33(0.46-3.34) | ——— | None | LOW | 57 more (from 117 fewer to 277 more) |
| PLAC_NORX | ——— | | | ——— | ——— | LOW | 14.17(4.16-46.11) | ——— | Rated up (large effect) | MODERATE | 575 more (from 331 more to 689 more) |
| *versus* INDOIVCONT | | | (INDOIVCONT) | | | | | | | | ACR INDOIVCONT 9/31 (29%) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 0.65(0.17-2.39) | ——— | None | LOW | 80 fewer (from 204 more to 225 fewer) |
| PLAC_NORX | ——— | | | ——— | ——— | LOW | 6.98(1.77-29.85) | ——— | Rated up (large effect) | MODERATE | 450 more (from 130 more to 634 more) |
| *versus* INDOTHERS | | | (INDOTHERS) | | | | | | | | ACR INDOTHERS 62/326 (19%) |
| PLAC_NORX | 2 | 15/26 | 6/27 | 4.92(1.68-21.35) | HIGH | LOW | 10.52(4.86-25.32) | 0.1 | None | HIGH | 522 more (from 343 more to 666 more) |

Abbreviations: NA: Not Applicable; QoE: Quality of Evidence; OR: Odds Ratio; Crl: Credible Intervals; ACR: Assumed control risk

**eFigure 7. Ranking probability (rankogram) of each treatment modality for need for repeat pharmacotherapy**

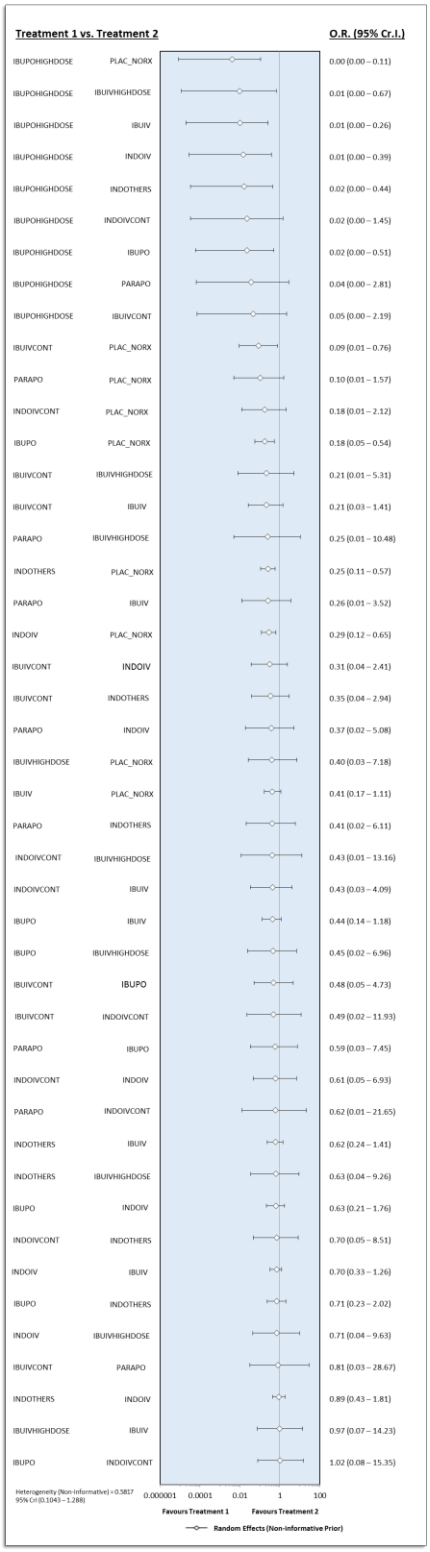



eFigure 7. Each line indicates a treatment modality. The horizontal x-axis represents the ranking of strategies in which the first through 9th modalities are ranked in numerical order, with the first representing the best strategy. The vertical y-axis represents the probability of each ranking.

**eTable 8. Ranking statistics for each treatment modality for outcome need for repeat pharmacotherapy**

| Need for repeat pharmacotherapy | | |
|---|---|---|
| **Treatment** | **SUCRA mean (Standard Deviation)** | **Median rank (95% Credible Intervals)** |
| INDOIV | 0.33 (0.11) | 6 (4-8) |
| IBUIV | 0.17 (0.07) | 8 (6-8) |
| IBUPO | 0.67 (0.14) | 4 (2-6) |
| PARAPO | 0.82 (0.15) | 2 (1-5) |
| IBUIVHIGHDOSE | 0.83 (0.24) | 1 (1-7) |
| IBUPOHIGHDOSE | 0.72 (0.22) | 3 (1-7) |
| INDOIVCONT | 0.38 (0.24) | 6 (1-8) |
| INDOTHERS | 0.58 (0.16) | 5 (2-6) |
| PLAC_NORX | 0.0003 (0.0056) | 9 (9-9) |

## eFigure 8. Network meta-analysis forest plots for outcome: N*eed for surgical PDA ligation*




eFigure 8: Forest plot showing network effect estimates (OR with 95% credible intervals) for each possible treatment comparison in the network for need for surgical PDA ligation computed using Bayesian RE model with non-informative priors; the horizontal axis denotes network odds ratios (with 95% credible intervals)

## eTable 9. GRADE assessment of the Quality of Evidence (QoE) for the network for need for surgical PDA ligation

***eTable 9.*** **GRADE assessment of the Quality of Evidence (QoE) for the network for need for surgical PDA ligation**

| Treatment Comparison | No. of direct comparisons | Events in the intervention group (n/N) | Events in the comparison group (n/N) | Direct OR (95% CrI) | QoE (GRADE) based on direct comparisons | QeE (GRADE) based on indirect comparisons | Network OR (95% CrI) | Inconsistency assessment (based on node splitting p value) | Changes in GRADE assessment based on precision & effect size | Network QoE | Network absolute risk difference per 1000 infants (95% CrI) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *versus* INDOIV | | | (INDOIV) | | | | | | | | ACR INDOIV 92/767 (12%) |
| IBUIV | 8 | 52/376 | 50/365 | 1.15 (0.61-2.77) | MODERATE | MODERATE | 1.42(0.79-3.01) | 0.56 | None | MODERATE | 42 more (from 23 fewer to 171 more) |
| IBUPO | 1 | 1/16 | 2/18 | 0.47 (0.01-8.65) | LOW | MODERATE | 0.62(0.20-1.76) | 0.43 | None | MODERATE | 42 fewer (from 74 more to 93 fewer) |
| PARAPO | 1 | 0/36 | 0/37 | 0.93 (0.00-541) | MODERATE | LOW | 0.37(0.01-5.08) | 0.72 | Rated down (imprecision) | LOW | 72 fewer (from 119 fewer to 289 more) |
| IBUIVHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 1.40(0.10-22.8) | ——— | Rated down (imprecision) | LOW | 40 more (from 107 fewer to 637 more) |
| IBUPOHIGHDOSE | ——— | | | ——— | ——— | LOW | 0.014(0.00-0.38) | ——— | None | LOW | 118 fewer (up to 71 fewer)* |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 0.30(0.03-2.41) | ——— | None | LOW | 81 fewer (from 115 fewer to 127 more) |
| INDOIVCONT | ——— | | | ——— | LOW | LOW | 0.61(0.04-6.92) | ——— | None | LOW | 43 fewer (from 115 fewer to 365 more) |
| INDOTHERS | 5 | 42/237 | 37/232 | 1.14 (0.47-2.73) | LOW | MODERATE | 0.88(0.43-1.81) | 0.56 | None | MODERATE | 13 fewer (from 65 fewer to 78 more) |
| PLAC_NORX | 5 | 10/119 | 3/115 | 4.10 (0.83-23.68) | MODERATE | MODERATE | 3.49(1.53-8.34) | 0.17 | None | MODERATE | 202 more (from 53 more to 412 more) |
| *versus* IBUIV | | | (IBUIV) | | | | | | | | ACR IBUIV 86/715 (12%) |
| IBUPO | 4 | 3/156 | 9/148 | 0.26 (0.04-1.25) | HIGH | LOW | 0.44(0.13-1.17) | 0.73 | None | HIGH | 64 fewer (from 18 more to 103 fewer) |
| PARAPO | ——— | | | ——— | ——— | MODERATE | 0.25(0.01-3.51) | ——— | Rated down (imprecision) | LOW | 87 fewer (from 119 fewer to 204 more) |
| IBUIVHIGHDOSE | 1 | 2/35 | 2/35 | 0.98 (0.06-14.73) | MODERATE | NOT ESTIMABLE | 0.97(0.07-14.2) | NA | Rated down (imprecision) | LOW | 3 fewer (from 111 fewer to 540 more) |
| IBUPOHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 0.01(0.00-0.26) | ——— | None | MODERATE | 119 fewer (up to 86 fewer)* |
| IBUIVCONT | 1 | 3/55 | 11/56 | 0.21 (0.03-1.42) | LOW | NOT ESTIMABLE | 0.21(0.02-1.41) | NA | Rated down (imprecision) | VERY LOW | 92 fewer (from 41 more to 118 fewer) |
| INDOIVCONT | 1 | 2/31 | 4/32 | 0.43 (0.03-4.33) | LOW | NOT ESTIMABLE | 0.42(0.03-4.09) | NA | Rated down (imprecision) | VERY LOW | 66 fewer (from 116 fewer to 238 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 0.62(0.23-1.41) | ——— | None | LOW | 42 fewer (from 41 more to 90 fewer) |
| PLAC_NORX | 1 | 9/68 | 8/68 | 1.10 (0.19-6.78) | MODERATE | MODERATE | 2.44(0.9-6.0) | 0.7 | None | MODERATE | 130 more (from 11 fewer to 330 more) |
| *versus* IBUPO | | | (IBUPO) | | | | | | | | ACR IBUPO 26/354 (7.3%) |
| PARAPO | 1 | 1/40 | 2/40 | 0.39 (0.00-7.69) | MODERATE | LOW | 0.59(0.03-7.45) | 0.78 | Rated down (imprecision) | LOW | 29 fewer (from 71 fewer to 298 more) |
| IBUIVHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 2.22(0.14-42.88) | ——— | None | MODERATE | 76 more (from 62 fewer to 699 more) |
| IBUPOHIGHDOSE | 1 | 0/30 | 7/30 | 0.02 (0.00 - 0.47) | MODERATE | NOT ESTIMABLE | 0.02(0.00-0.50) | NA | None | MODERATE | 72 fewer (up to 35 fewer)* |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 0.48(0.05-4.72) | ——— | Rated down (imprecision) | VERY LOW | 37 fewer (from 69 fewer to 199 more) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 0.97(0.06-12.96) | ——— | Rated down (imprecision) | VERY LOW | 2 fewer (from 69 fewer to 433 more) |
| INDOTHERS | 1 | 7/35 | 12/48 | 0.73 (0.12-4.42) | LOW | VERY LOW | 1.40(0.49-4.31) | 0.11 | None | LOW | 26 more (from 36 fewer to 181 more) |
| PLAC_NORX | 2 | 8/64 | 1/64 | 11.52 (1.05-307) | VERY LOW | LOW | 5.54(1.86-18.2) | 0.99 | Rated down (imprecision) | VERY LOW | 232 more (from 55 more to 517 more) |
| *versus* PARAPO | | | (PARAPO) | | | | | | | | ACR PARAPO 1/76 (1.3%) |
| IBUIVHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 3.96(0.09-199.3) | ——— | Rated down (imprecision) | LOW | 37 more (from 12 fewer to 713 more) |
| IBUPOHIGHDOSE | ——— | | | ——— | ——— | LOW | 0.03(0.00-2.80) | ——— | Rated down (imprecision) | VERY LOW | 13 fewer (from – to 23 more)* |

***eTable 9.*** **GRADE assessment of the Quality of Evidence (QoE) for the network for need for surgical PDA ligation**

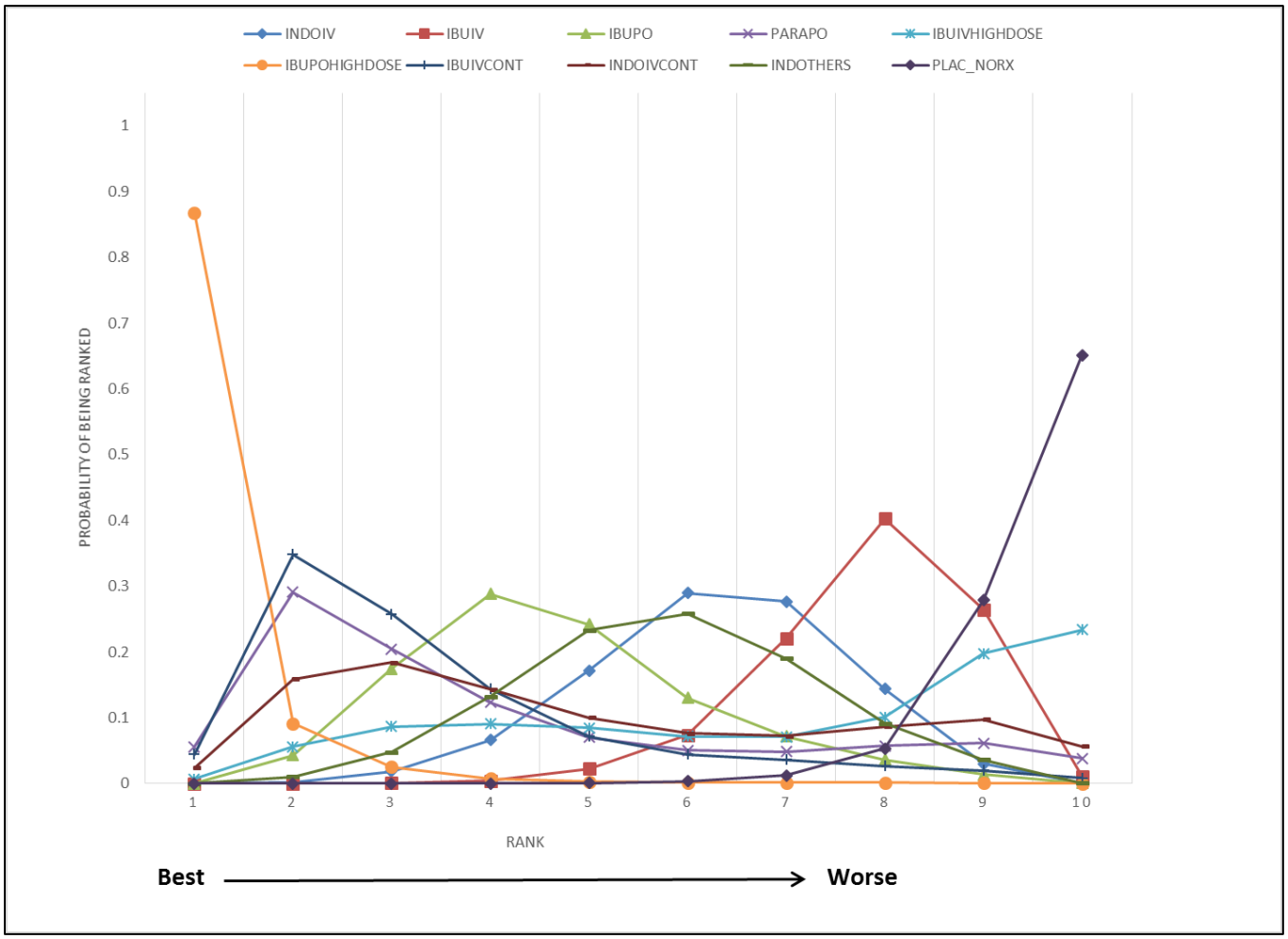
| Treatment Comparison | No. of direct comparisons | Events in the intervention group (n/N) | Events in the comparison group (n/N) | Direct OR (95% CrI) | QoE (GRADE) based on direct comparisons | QeE (GRADE) based on indirect comparisons | Network OR (95% CrI) | Inconsistency assessment (based on node splitting p value) | Changes in GRADE assessment based on precision & effect size | Network QoE | Network absolute risk difference per 1000 infants (95% CrI) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***(…..Continued)*** | | | | | | | | | | | |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 0.81(0.03-28.6) | ——— | Rated down (imprecision) | VERY LOW | 2 fewer (from 13 fewer to 263 more) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 1.61(0.04-77.34) | ——— | Rated down (imprecision) | VERY LOW | 8 more (from 13 fewer to 495 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 2.41(0.16-48.33) | ——— | Rated down (imprecision) | VERY LOW | 18 more (from 11 fewer to 379 more) |
| PLAC_NORX | ——— | | | ——— | ——— | MODERATE | 9.54(0.63-197.9) | ——— | Rated down (imprecision) | LOW | 100 more (from 5 fewer to 712 more) |
| *versus* IBUIVHIGHDOSE | | | (IBUIVHIGHDOSE) | | | | | | | | ACR IBUIVHIGHDOSE 2/35 (5.7%) |
| IBUPOHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 0.01(0.00-0.67) | ——— | None | MODERATE | 57 fewer (up to 18 fewer)* |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 0.20(0.00-5.3) | ——— | Rated down (imprecision) | VERY LOW | 45 fewer (from – to 186 more)* |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 0.421(0.01-13.16) | ——— | Rated down (imprecision) | VERY LOW | 32 fewer (from 57 fewer to 387 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 0.62(0.03-9.25) | ——— | Rated down (imprecision) | VERY LOW | 21 fewer (from 55 fewer to 302 more) |
| PLAC_NORX | ——— | | | ——— | ——— | MODERATE | 2.49(0.13-37.36) | ——— | Rated down (imprecision) | LOW | 74 more (from 49 fewer to 637 more) |
| *versus* IBUPOHIGHDOSE | | | (IBUPOHIGHDOSE) | | | | | | | | ACR IBUPOHIGHDOSE 0/30 (0%) ** |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 21.75(0.456-14340) | ——— | Rated down (imprecision) | VERY LOW | 253 more (from 9 fewer to 979 more) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 44.04(0.68-30690) | ——— | Rated down (imprecision) | VERY LOW | 411 more (from 5 fewer to 981 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 61.43(2.27-30340) | ——— | Rated up (large effect) | MODERATE | 493 more (from 20 more to 981 more) |
| PLAC_NORX | ——— | | | ——— | ——— | LOW | 242.4(9.11-122400) | ——— | Rated up (large effect) | MODERATE | 788 more (from 117 more to 983 more) |
| *versus* IBUIVCONT | | | (IBUIVCONT) | | | | | | | | ACR IBUIVCONT 3/55 (5.5%) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 2.042(0.08-43.79) | ——— | Rated down (imprecision) | VERY LOW | 51 more (from 50 fewer to 662 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 2.894(0.33-25.56) | ——— | Rated down (imprecision) | VERY LOW | 88 more (from 36 fewer to 541 more) |
| PLAC_NORX | ——— | | | ——— | ——— | LOW | 11.55(1.32-106.2) | ——— | Rated down (imprecision) | VERY LOW | 354 more (from 16 more to 805 more) |
| *versus* INDOIVCONT | | | (INDOIVCONT) | | | | | | | | ACR INDOIVCONT 2/31 (6.5%) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 1.428(0.11-21.0) | ——— | Rated down (imprecision) | VERY LOW | 25 more (from 57 fewer to 527 more) |
| PLAC_NORX | ——— | | | ——— | ——— | LOW | 5.677(0.47-81.8) | ——— | Rated down (imprecision) | VERY LOW | 217 more (from 33 fewer to 785 more) |
| *versus* INDOTHERS | | | (INDOTHERS) | | | | | | | | ACR INDOTHERS 61/345 (17.7%) |
| PLAC_NORX | 4 | 33/70 | 12/73 | 5.15 (1.64-14.61) | HIGH | LOW | 3.96 (1.75-9.0) | 0.14 | None | VERY LOW | 283 more (from 96 more to 482 more) |

Abbreviations: NA: Not Applicable; QoE: Quality of Evidence; OR: Odds Ratio; Crl: Credible Intervals; ACR: Assumed control risk

*The lower limit of the 95% credible interval for absolute risk difference could not be computed due to the very low (tending to zero) lower limit of the 95% credible interval for the corresponding network odds ratio

**In view of zero event rate for the particular outcome in the control group, a continuity correction of 0.5 has been applied to calculate the assumed control risk in order to compute the absolute risk difference (16).

**eFigure 9. Ranking probability (rankogram) of each treatment modality for need for surgical PDA ligation**

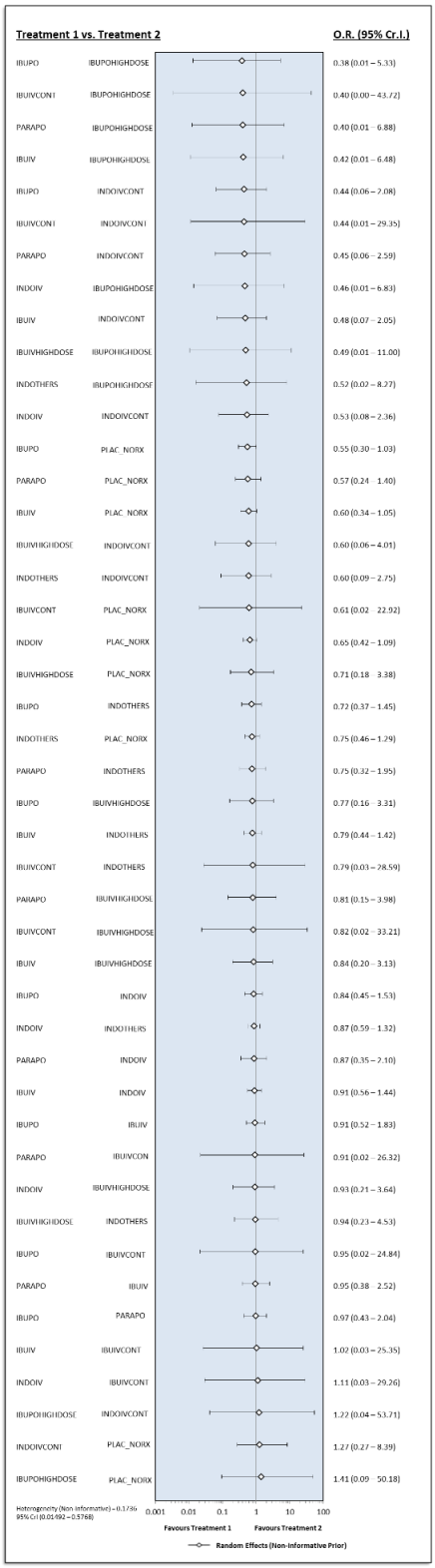



eFigure 9. Each line indicates a treatment modality. The horizontal x-axis represents the ranking of strategies in which the first through 10th modalities are ranked in numerical order, with the first representing the best strategy. The vertical y-axis represents the probability of each ranking.

**eTable 10. Ranking statistics for each treatment modality for need for surgical PDA ligation**

| Need for surgical PDA ligation | | |
|---|---|---|
| **Treatment** | **SUCRA mean (Standard Deviation)** | **Median rank (95% Credible intervals)** |
| INDOIV | 0.41 (0.14) | 6 (4-9) |
| IBUIV | 0.24 (0.12) | 8 (5-9) |
| IBUPO | 0.59 (0.17) | 4 (2-8) |
| PARAPO | 0.65 (0.28) | 3 (1-10) |
| IBUIVHIGHDOSE | 0.33 (0.30) | 8 (2-10) |
| IBUPOHIGHDOSE | 0.98 (0.08) | 1 (1-3) |
| IBUIVCONT | 0.73 (0.21) | 3 (1-9) |
| INDOIVCONT | 0.55 (0.29) | 4 (2-10) |
| INDOTHERS | 0.47 (0.17) | 6 (3-9) |
| PLAC_NORX | 0.05 (0.08) | 10 (8-10) |

## eFigure 10. Network meta-anlaysis forest plots for outcome: *Neonatal Mortality*




eFigure 10. Forest plot showing network effect estimates (OR with 95% credible intervals) for each possible treatment comparison in the network for neonatal mortality computed using Bayesian RE model with non-informative priors; the horizontal axis denotes network odds ratios (with 95% credible intervals)

## eTable 11. GRADE assessment of the Quality of Evidence (QoE) for the network for Neonatal Mortality

**eTable 11. GRADE assessment of the Quality of Evidence (QoE) for the network for Neonatal Mortality**

| Treatment Comparison | No. of direct comparisons | Events in the intervention group (n/N) | Events in the comparison group (n/N) | Direct OR (95% CrI) | QoE (GRADE) based on direct comparisons | QoE (GRADE) based on indirect comparisons | Network OR (95% CrI) | Inconsistency assessment (based on node splitting p value) | Changes in GRADE assessment based on precision & effect size | Network QoE | Network absolute risk difference per 1000 infants (95% CrI) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *versus* INDOIV | | | (INDOIV) | | | | | | | | ACR INDO IV 111/904 (12.3%) |
| IBUIV | 6 | 29/303 | 29/289 | 0.90 (0.49-1.65) | MODERATE | MODERATE | 0.91(0.56-1.44) | 0.56 | None | MODERATE | 10 fewer (from 45 more to 50 fewer) |
| IBUPO | 3 | 4/40 | 5/42 | 0.68(0.12-3.57) | LOW | MODERATE | 0.84(0.45-1.53) | 0.43 | None | MODERATE | 18 fewer (from 54 more to 64 fewer) |
| PARAPO | 1 | 8/38 | 8/39 | 0.99 (0.28-3.49) | MODERATE | LOW | 0.87(0.35-2.10) | 0.72 | None | MODERATE | 14 fewer (from 76 fewer to 104 more) |
| IBUIVHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 1.07(0.27-4.81) | ——— | None | MODERATE | 7 more (from 86 fewer to 280 more) |
| IBUPOHIGHDOSE | ——— | | | ——— | ——— | LOW | 2.19(0.15-72.38) | ——— | Rated down (Imprecision) | VERY LOW | 112 more (from 102 fewer to 787 more) |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 0.90(0.03-33.65) | ——— | Rated down (Imprecision) | VERY LOW | 11 fewer (from 119 fewer to 702 more) |
| INDOIVCONT | 1 | 2/18 | 0/14 | 1.89 (0.74-8.89) | LOW | LOW | 1.89(0.42-12.82) | 0.66 | Rated down (Imprecision) | VERY LOW | 86 more (from 67 fewer to 519 more) |
| INDOTHERS | 7 | 52/359 | 42/358 | 1.31(0.79-2.13) | LOW | MODERATE | 1.15(0.76-1.70) | 0.2 | None | MODERATE | 16 more (from 27 fewer to 69 more) |
| PLAC_NORX | 7 | 30/169 | 27/162 | 1.11 (0.58-2.11) | MODERATE | MODERATE | 1.53(0.92-2.36) | 0.17 | None | MODERATE | 54 more (from 9 fewer to 126 more) |
| *versus* IBUIV | | | (IBUIV) | | | | | | | | ACR IBUIV 60/664 (9%) |
| IBUPO | 3 | 13/120 | 10/116 | 1.41 (0.51-3.99) | HIGH | LOW | 0.91(0.52-1.83) | 0.73 | None | LOW | 7 fewer (from 41 fewer to 63 more) |
| PARAPO | ——— | | | ——— | ——— | MODERATE | 0.95(0.38-2.52) | ——— | None | MODERATE | 4 fewer (from 54 fewer to 110 more) |
| IBUIVHIGHDOSE | 1 | 6/35 | 5/35 | 1.24 (0.31-5.35) | MODERATE | NOT ESTIMABLE | 1.20(0.32-5.06) | NA | None | MODERATE | 16 more (from 60 fewer to 244 more) |
| IBUPOHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 2.39(0.15-88.03) | ——— | Rated down (Imprecision) | LOW | 102 more (from 76 fewer to 807 more) |
| IBUIVCONT | 1 | 1/55 | 1/56 | 0.93 (0.03-24.45) | LOW | NOT ESTIMABLE | 0.98(0.04-38.00) | NA | Rated down (Imprecision) | VERY LOW | 2 fewer (from 86 fewer to 700 more) |
| INDOIVCONT | 1 | 4/31 | 3/32 | 1.36 (0.26-8.44) | LOW | LOW | 2.09(0.49-14.65) | 0.78 | Rated down (Imprecision) | VERY LOW | 82 more (from 44 fewer to 502 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 1.27(0.70-2.25) | ——— | None | LOW | 22 more (from 25 fewer to 92 more) |
| PLAC_NORX | 2 | 16/119 | 12/122 | 1.45 (0.59-3.46) | MODERATE | MODERATE | 1.67(0.95-2.92) | 0.7 | None | MODERATE | 52 more (from 4 fewer to 134 more) |
| *versus* IBUPO | | | (IBUPO) | | | | | | | | ACR IBUPO 43/484 (8.9%) |
| PARAPO | 2 | 13/120 | 14/120 | 0.92 (0.36-2.49) | MODERATE | LOW | 1.03(0.49-2.34) | 0.78 | None | LOW | 2 more (from 43 fewer to 97 more) |
| IBUIVHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 1.30(0.30-6.08) | ——— | None | MODERATE | 24 more (from 60 fewer to 283 more) |
| IBUPOHIGHDOSE | 1 | 2/30 | 1/30 | 2.59 (0.25-42.94) | MODERATE | NOT ESTIMABLE | 2.61(0.19-76.13) | NA | Rated down (Imprecision) | LOW | 114 more (from 71 fewer to 792 more) |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 1.05(0.04-46.64) | ——— | Rated down (Imprecision) | VERY LOW | 4 more (from 85 fewer to 731 more) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 2.30(0.48-15.43) | ——— | Rated down (Imprecision) | VERY LOW | 94 more (from 44 fewer to 512 more) |
| INDOTHERS | 3 | 8/64 | 3/78 | 3.92 (1.03-17.37) | LOW | VERY LOW | 1.38(0.69-2.70) | 0.01 | Rated down (Incoherence) | VERY LOW | 30 more (from 26 fewer to 120 more) |
| PLAC_NORX | 3 | 12/96 | 8/96 | 1.62 (0.60-4.68) | VERY LOW | LOW | 1.81(0.97-3.31) | 0.99 | None | LOW | 61 more (from 2 fewer to 155 more) |
| *versus* PARAPO | | | (PARAPO) | | | | | | | | ACR PARAPO 21/158 (13.3%) |

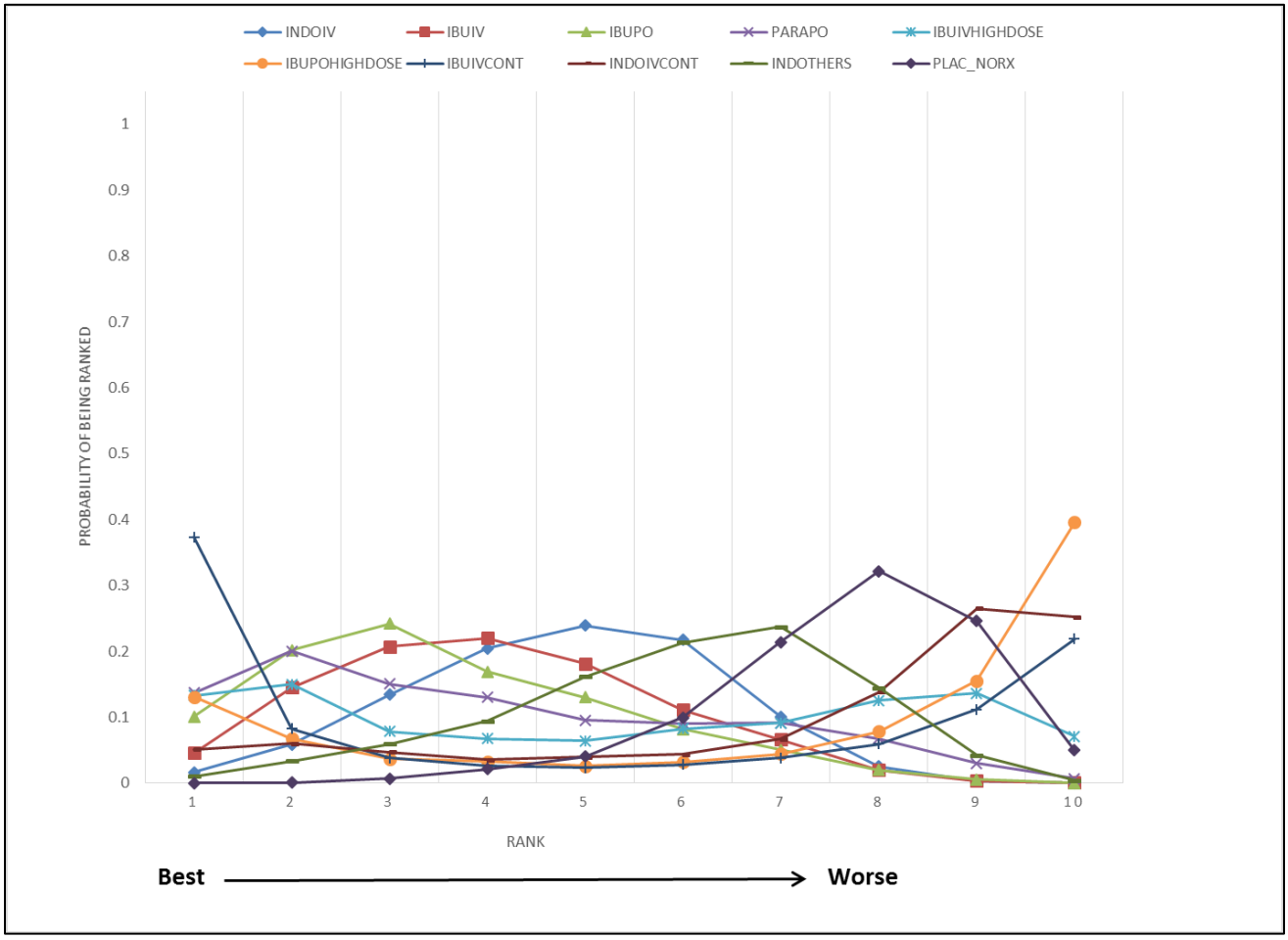
**eTable 11. GRADE assessment of the Quality of Evidence (QoE) for the network for Neonatal Mortality**

| Treatment Comparison | No. of direct comparisons | Events in the intervention group (n/N) | Events in the comparison group (n/N) | Direct OR (95% CrI) | QoE (GRADE) based on direct comparisons | QoE (GRADE) based on indirect comparisons | Network OR (95% CrI) | Inconsistency assessment (based on node splitting p value) | Changes in GRADE assessment based on precision & effect size | Network QoE | Network absolute risk difference per 1000 infants (95% CrI) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | ***(…continued)*** |
| IBUIVHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 1.24(0.25-6.83) | ——— | None | MODERATE | 27 more (from 96 fewer to 379 more) |
| IBUPOHIGHDOSE | ——— | | | ——— | ——— | LOW | 2.47(0.15-80.63) | ——— | Rated down (Imprecision) | VERY LOW | 142 more (from 110 fewer to 792 more) |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 1.09(0.04-45.81) | ——— | Rated down (Imprecision) | VERY LOW | 10 more (from 127 fewer to 742 more) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 2.20(0.39-16.46) | ——— | Rated down (Imprecision) | VERY LOW | 119 more (from 77 fewer to 583 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 1.33(0.51-3.09) | ——— | None | LOW | 36 more (from 60 fewer to 189 more) |
| PLAC_NORX | ——— | | | ——— | ——— | MODERATE | 1.74(0.72-4.16) | ——— | None | MODERATE | 78 more (from 34 fewer to 256 more) |
| *versus* IBUIVHIGHDOSE | | | (IBUIVHIGHDOSE) | | | | | | | | ACR IBUIVHIGHDOSE 6/35 (17.1%) |
| IBUPOHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 2.04(0.09-92.38) | ——— | Rated down (Imprecision) | LOW | 125 more (from 153 fewer to 779 more) |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 0.82(0.02-33.21) | ——— | Rated down (Imprecision) | VERY LOW | 26 fewer (from 167 fewer to 702 more) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 1.67(0.25-16.18) | ——— | Rated down (Imprecision) | VERY LOW | 85 more (from 122 fewer to 599 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 1.07(0.22-4.31) | ——— | None | VERY LOW | 10 more (from 128 fewer to 300 more) |
| PLAC_NORX | ——— | | | ——— | ——— | MODERATE | 1.40(0.30-5.71) | ——— | None | MODERATE | 53 more (from 113 fewer to 370 more) |
| *versus* IBUPOHIGHDOSE | | | (IBUPOHIGHDOSE) | | | | | | | | ACR IBUPOHIGHDOSE 2/30 (6.7%) |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 0.40(0.00-43.72) | ——— | Rated down (Imprecision) | VERY LOW | 39 fewer (from – to 691 more)* |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 0.82(0.02-24.35) | ——— | Rated down (Imprecision) | VERY LOW | 11 fewer (from 65 fewer to 568 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 0.52(0.02-8.27) | ——— | None | LOW | 31 fewer (from 65 fewer to 305 more) |
| PLAC_NORX | ——— | | | ——— | ——— | LOW | 0.71(0.02-10.63) | ——— | Rated down (Imprecision) | VERY LOW | 18 fewer (from 65 fewer to 365 more) |
| *versus* IBUIVCONT | | | (IBUIVCONT) | | | | | | | | ACR IBUIVCONT 1/55 (1.8%) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 2.26(0.03-87.92) | ——— | Rated down (Imprecision) | VERY LOW | 22 more (from 18 fewer to 601 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 1.27(0.03-36.40) | ——— | Rated down (Imprecision) | VERY LOW | 5 more (from 18 fewer to 384 more) |
| PLAC_NORX | ——— | | | ——— | ——— | LOW | 1.64(0.04-48.25) | ——— | Rated down (Imprecision) | VERY LOW | 11 more (from 17 fewer to 454 more) |
| *versus* INDOIVCONT | | | (INDOIVCONT) | | | | | | | | ACR INDOIVCONT 6/49 (12.2%) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 0.60(0.09-2.75) | ——— | None | LOW | 7 fewer (from 17 fewer to 30 more) |
| PLAC_NORX | ——— | | | ——— | ——— | LOW | 0.78(0.12-3.71) | ——— | None | LOW | 4 fewer (from 16 fewer to 46 more) |
| *versus* INDOTHERS | | | (INDOTHERS) | | | | | | | | ACR INDOTHERS 69/496 (13.9%) |
| PLAC_NORX | 4 | 21/70 | 9/73 | 3.15 (1.24-8.26) | HIGH | LOW | 1.33(0.78-2.19) | 0.14 | None | LOW | 38 more (from 27 fewer to 122 more) |

Abbreviations: NA: Not Applicable; QoE: Quality of Evidence; OR: Odds Ratio; Crl: Credible Intervals; ACR: Assumed control risk

*The lower limit of the 95% credible interval for absolute risk difference could not be computed due to the very low (tending to zero) lower limit of the 95% credible interval for the corresponding network odds ratio

## eFigure 11. Ranking probability (rankogram) of each treatment modality for Neonatal Mortality

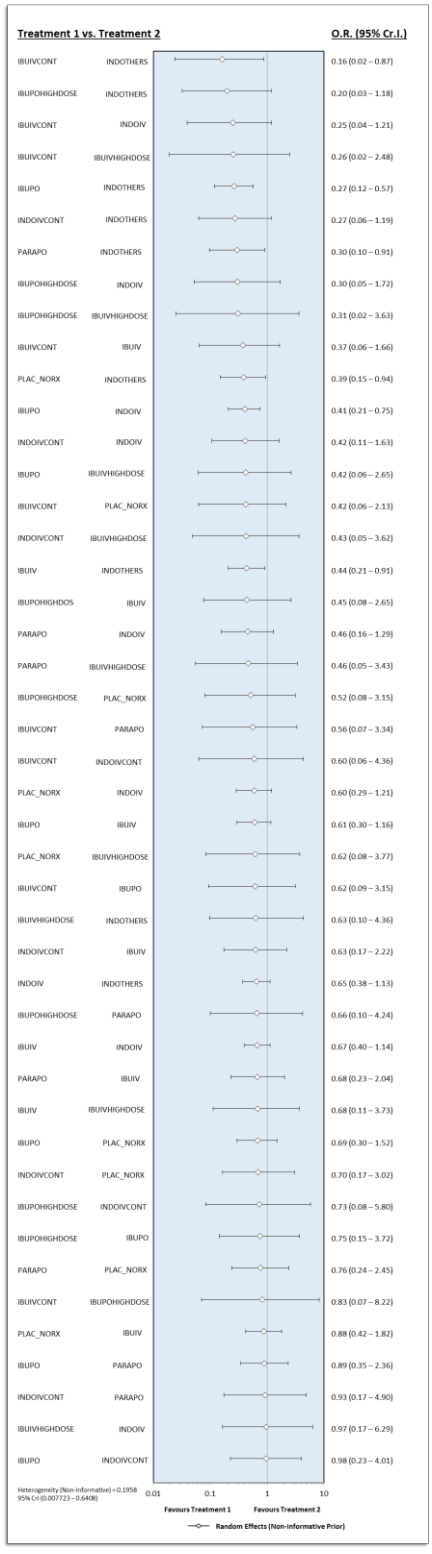



eFigure 11. Each line indicates a treatment modality. The horizontal x-axis represents the ranking of strategies in which the first through 10th modalities are ranked in numerical order, with the first representing the best strategy. The vertical y-axis represents the probability of each ranking.

## eTable 12. Ranking statistics for each treatment modality for Neonatal Mortality

| Neonatal Mortality | | |
|---|---|---|
| **Treatment** | **SUCRA mean (Standard Deviation)** | **Median rank (95% Credible Intervals)** |
| INDOIV | 0.58 (0.17) | 5 (2-8) |
| IBUIV | 0.66 (0.19) | 4 (1-7) |
| IBUPO | 0.71 (0.20) | 3 (1-8) |
| PARAPO | 0.66 (0.26) | 4 (1-9) |
| IBUIVHIGHDOSE | 0.52 (0.34) | 6 (1-10) |
| IBUPOHIGHDOSE | 0.32 (0.38) | 9 (1-10) |
| IBUIVCONT | 0.56 (0.43) | 4 (1-10) |
| INDOIVCONT | 0.29 (0.31) | 9 (1-10) |
| INDOTHERS | 0.45 (0.20) | 6 (2-9) |
| PLAC_NORX | 0.26 (0.15) | 8 (4-10) |

**eFigure 12. Network meta-analysis forest plots for outcome: *Risk of Necrotizing Enterocolitis (NEC)***




eFigure 12. Forest plot showing network effect estimates (OR with 95% credible intervals) for each possible treatment comparison in the network for risk of NEC computed using Bayesian RE model with non-informative priors; the horizontal axis denotes network odds ratios (with 95% credible intervals)

## eTable 13. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of NEC

**eTable 13. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of NEC**

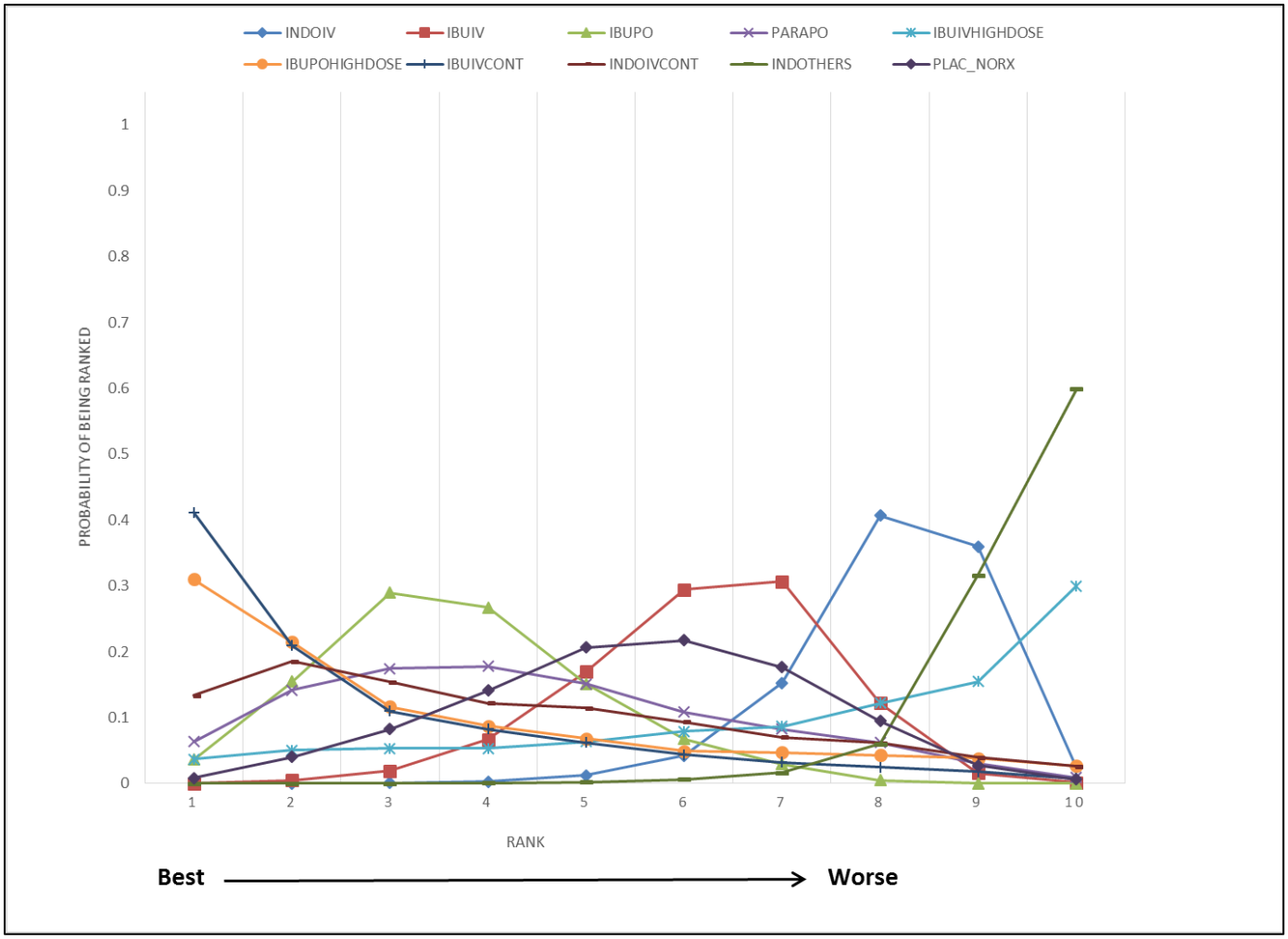
| Treatment Comparison | No. of direct comparisons | Events in the intervention group (n/N) | Events in the comparison group (n/N) | Direct OR (95% CrI) | QoE (GRADE) based on direct comparisons | QoE (GRADE) based on indirect comparisons | Network OR (95% CrI) | Inconsistency assessment (based on node splitting p value) | Changes in GRADE assessment based on precision & effect size | Network QoE | Network absolute risk difference per 1000 infants (95% CrI) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *versus* INDOIV | | | (INDOIV) | | | | | | | | ACR INDOIV 86/931 (9.2%) |
| IBUIV | 10 | 22/417 | 29/404 | 0.73(0.39-1.41) | MODERATE | MODERATE | 0.67(0.40-1.14) | 0.64 | None | MODERATE | 29 fewer (from 12 more to 53 fewer) |
| IBUPO | 4 | 8/52 | 14/51 | 0.38(0.11-1.29) | LOW | MODERATE | 0.41(0.21-0.75) | 0.69 | None | MODERATE | 52 fewer (from 21 fewer to 71 fewer) |
| PARAPO | 1 | 2/38 | 4/39 | 0.43(0.04-2.98) | MODERATE | LOW | 0.46(0.16-1.29) | 0.6 | None | MODERATE | 48 fewer (from 24 more to 76 fewer) |
| IBUIVHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 0.97(0.17-6.29) | ——— | None | MODERATE | 3 fewer (from 75 fewer to 298 more) |
| IBUPOHIGHDOSE | ——— | | | ——— | ——— | LOW | 0.30(0.05-1.72) | ——— | Rated down (imprecision) | VERY LOW | 63 fewer (from 57 more to 87 fewer) |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 0.25(0.04-1.21) | ——— | Rated down (imprecision) | VERY LOW | 68 fewer (from 17 more to 88 fewer) |
| INDOIVCONT | 1 | 0/18 | 1/14 | 0.00(0.00-0.08) | LOW | LOW | 0.42(0.11-1.63) | 0.01 | Rated down (inconsistency) | VERY LOW | 51 fewer (from 50 more to 81 fewer) |
| INDOTHERS | 6 | 40/300 | 30/296 | 1.40(0.76-2.62) | LOW | MODERATE | 1.54(0.89-2.65) | 0.58 | None | MODERATE | 43 more (from 9 fewer to 120 more) |
| PLAC_NORX | 4 | 6/129 | 8/127 | 0.71(0.21-2.66) | MODERATE | MODERATE | 0.60(0.29-1.21) | 0.71 | None | MODERATE | 35 fewer (from 17 more to 64 fewer) |
| *versus* IBUIV | | | (IBUIV) | | | | | | | | ACR IBUIV 64/778 (8.2%) |
| IBUPO | 3 | 8/120 | 9/116 | 0.85(0.27-2.46) | HIGH | LOW | 0.61(0.30-1.16) | 0.89 | None | HIGH | 30 fewer (from 12 more to 56 fewer) |
| PARAPO | ——— | | | ——— | ——— | MODERATE | 0.68(0.23-2.04) | ——— | None | MODERATE | 25 fewer (from 62 fewer to 72 more) |
| IBUIVHIGHDOSE | 1 | 4/35 | 3/35 | 1.47(0.24-11.01) | MODERATE | Not estimable | 1.46(0.27-8.94) | NA | None | MODERATE | 33 more (from 59 fewer to 363 more) |
| IBUPOHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 0.45(0.08-2.65) | ——— | Rated down (imprecision) | LOW | 43 fewer (from 75 fewer to 110 more) |
| IBUIVCONT | 1 | 3/55 | 7/56 | 0.36(0.06-1.99) | LOW | Not estimable | 0.37(0.06-1.66) | NA | Rated down (imprecision) | VERY LOW | 50 fewer (from 47 more to 77 fewer) |
| INDOIVCONT | 1 | 7/31 | 9/32 | 0.71(0.18-2.77) | LOW | Not estimable | 0.63(0.17-2.22) | 0.21 | None | LOW | 29 fewer (from 67 fewer to 84 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 2.30(1.10-4.81) | ——— | None | LOW | 89 more (from 7 more to 219 more) |
| PLAC_NORX | 2 | 11/119 | 14/122 | 0.73(0.26-2.02) | MODERATE | MODERATE | 0.88(0.42-1.82) | 0.75 | None | MODERATE | 9 fewer (from 46 fewer to 58 more) |
| *versus* IBUPO | | | (IBUPO) | | | | | | | | ACR IBUPO 36/537 (6.7%) |
| PARAPO | 3 | 10/164 | 9/163 | 1.10(0.39-3.34) | MODERATE | LOW | 1.12(0.42-2.88) | 0.7 | None | MODERATE | 7 more (from 38 fewer to 104 more) |
| IBUIVHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 2.39(0.38-16.16) | ——— | Rated down (imprecision) | LOW | 80 more (from 40 fewer to 470 more) |
| IBUPOHIGHDOSE | 1 | 4/30 | 5/30 | 0.75(0.14-3.79) | MODERATE | Not estimable | 0.75(0.15-3.72) | NA | None | MODERATE | 16 fewer (from 56 fewer to 144 more) |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 0.62(0.09-3.15) | ——— | Rated down (imprecision) | VERY LOW | 24 fewer (from 61 fewer to 118 more) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 1.02(0.25-4.43) | ——— | None | LOW | 1 more (from 49 fewer to 174 more) |
| INDOTHERS | 3 | 8/63 | 2/76 | 5.55(1.20-41.14) | LOW | Very low | 3.77(1.77-8.47) | 0.67 | None | LOW | 146 more (from 46 more to 311 more) |
| PLAC_NORX | 3 | 7/96 | 4/96 | 1.99(0.50-9.54) | VERY LOW | LOW | 1.46(0.66-3.36) | 0.76 | None | LOW | 28 more (from 22 fewer to 127 more) |
| *versus* PARAPO | | | (PARAPO) | | | | | | | | ACR PARAPO 12/202 (5.9%) |
| IBUIVHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 2.16(0.29-18.21) | ——— | Rated down (imprecision) | LOW | 61 more (from 41 fewer to 476 more) |
| IBUPOHIGHDOSE | ——— | | | ——— | ——— | LOW | 0.66(0.10-4.24) | ——— | None | LOW | 19 fewer (from 53 fewer to 152 more) |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 0.56(0.07-3.34) | ——— | Rated down (imprecision) | VERY LOW | 25 fewer (from 55 fewer to 115 more) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 0.93(0.17-4.90) | ——— | None | LOW | 4 fewer (from 49 fewer to 177 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 3.36(1.10-10.38) | ——— | Rated down (imprecision) | VERY LOW | 116 more (from 6 more to 337 more) |
| PLAC_NORX | ——— | | | ——— | ——— | MODERATE | 1.31(0.41-4.17) | ——— | None | MODERATE | 17 more (from 34 fewer to 149 more) |
| *versus* IBUIVHIGHDOSE | | | (IBUIVHIGHDOSE) | | | | | | | | ACR IBUIVHIGHDOSE 4/35 (11.4%) |

**eTable 13. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of NEC**

| Treatment Comparison | No. of direct comparisons | Events in the intervention group (n/N) | Events in the comparison group (n/N) | Direct OR (95% CrI) | QoE (GRADE) based on direct comparisons | QoE (GRADE) based on indirect comparisons | Network OR (95% CrI) | Inconsistency assessment (based on node splitting p value) | Changes in GRADE assessment based on precision & effect size | Network QoE | Network absolute risk difference per 1000 infants (95% CrI) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | ***(…continued)*** |
| IBUPOHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 0.31(0.02-3.63) | ——— | Rated down (imprecision) | LOW | 76 fewer (from 112 fewer to 205 more) |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 0.26(0.02-2.48) | ——— | Rated down (imprecision) | VERY LOW | 82 fewer (from 112 fewer to 128 more) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 0.43(0.05-3.62) | ——— | Rated down (imprecision) | VERY LOW | 62 fewer (from 108 fewer to 204 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 1.59(0.23-10.27) | ——— | Rated down (imprecision) | VERY LOW | 56 more (from 85 fewer to 456 more) |
| PLAC_NORX | ——— | | | ——— | ——— | MODERATE | 0.62(0.08-3.77) | ——— | Rated down (imprecision) | LOW | 40 fewer (from 104 fewer to 213 more) |
| *versus* IBUPOHIGHDOSE | | | (IBUPOHIGHDOSE) | | | | | | | | ACR IBUPOHIGHDOSE 4/30 (13.3%) |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 0.83(0.07-8.22) | ——— | Rated down (imprecision) | VERY LOW | 20 fewer (from 123 fewer to 425 more) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 1.36(0.17-12.04) | ——— | Rated down (imprecision) | VERY LOW | 40 more (from 108 fewer to 516 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 5.06(0.85-31.10) | ——— | Rated down (imprecision) | VERY LOW | 304 more (from 18 fewer to 694 more) |
| PLAC_NORX | ——— | | | ——— | ——— | LOW | 1.93(0.32-12.39) | ——— | Rated down (imprecision) | VERY LOW | 96 more (from 86 fewer to 523 more) |
| *versus* IBUIVCONT | | | (IBUIVCONT) | | | | | | | | ACR IBUIVCONT 3/55 (5.5%) |
| INDOIVCONT | ——— | | | ——— | ——— | LOW | 1.67(0.23-16.00) | ——— | Rated down (imprecision) | VERY LOW | 33 more (from 41 fewer to 425 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 6.18(1.15-42.37) | ——— | Rated up (large effect) | MODERATE | 208 more (from 8 more to 655 more) |
| PLAC_NORX | ——— | | | ——— | ——— | LOW | 2.36(0.47-16.10) | ——— | Rated down (imprecision) | VERY LOW | 65 more (from 28 fewer to 427 more) |
| *versus* INDOIVCONT | | | (INDOIVCONT) | | | | | | | | ACR INDOIVCONT 7/49 (14.3%) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 3.68(0.84-15.96) | ——— | Rated down (imprecision) | VERY LOW | 237 more (from 20 fewer to 584 more) |
| PLAC_NORX | ——— | | | ——— | ——— | LOW | 1.43(0.33-6.03) | ——— | None | LOW | 50 more (from 91 fewer to 358 more) |
| *versus* INDOTHERS | | | (INDOTHERS) | | | | | | | | ACR INDOTHERS 49/387 (12.7%) |
| PLAC_NORX | 1 | 0/23 | 1/24 | 0.00(0.00-.08) | HIGH | LOW | 0.38(0.15-0.94) | 0.28 | None | HIGH | 74 fewer (from 7 fewer to 105 fewer) |

Abbreviations: NA: Not Applicable; QoE: Quality of Evidence; OR: Odds Ratio; Crl: Credible Intervals; ACR: Assumed control risk

## eFigure 13. Ranking probability (rankogram) of each treatment modality for risk of NEC

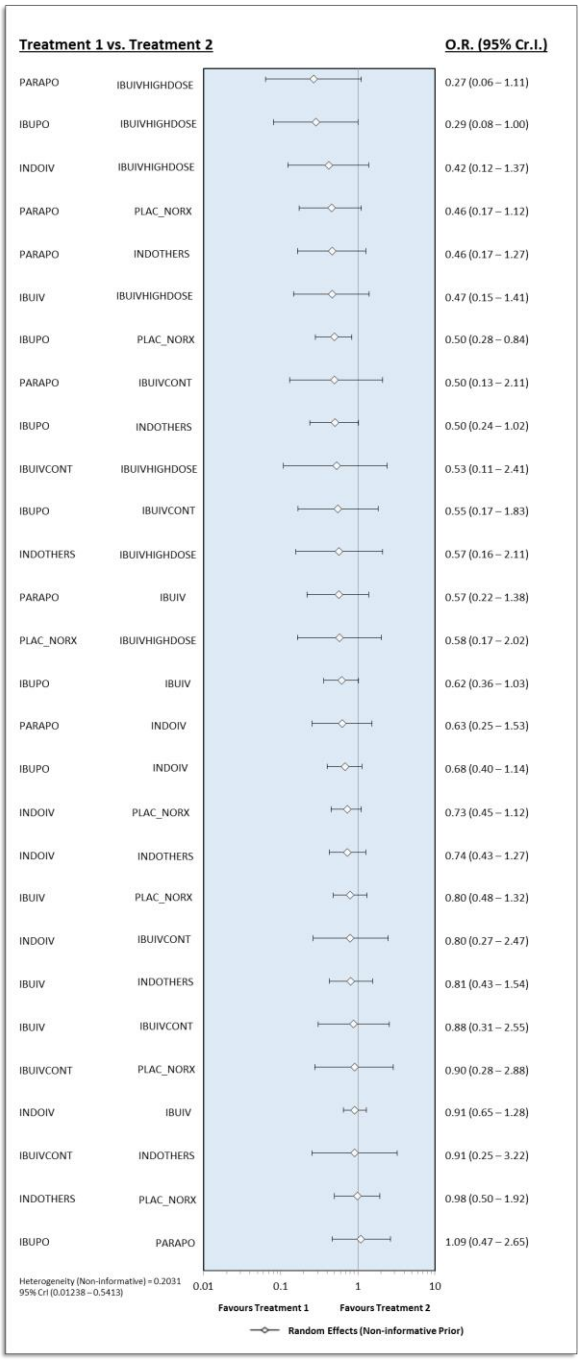



eFigure 13. Each line indicates a treatment modality. The horizontal x-axis represents the ranking of strategies in which the first through 10th modalities are ranked in numerical order, with the first representing the best strategy. The vertical y-axis represents the probability of each ranking.

## eTable 14. Ranking statistics for each treatment modality for risk of NEC

| Risk of Necrotizing Enterocolitis | | |
|---|---|---|
| **Treatment** | **SUCRA mean (Standard Deviation)** | **Median rank (95% Credible Intervals)** |
| INDOIV | 0.21 (0.11) | 8 (6-9) |
| IBUIV | 0.42 (0.14) | 6 (4-8) |
| IBUPO | 0.70 (0.15) | 4 (1-7) |
| PARAPO | 0.62 (0.24) | 4 (1-9) |
| IBUIVHIGHDOSE | 0.30 (0.31) | 8 (1-10) |
| IBUPOHIGHDOSE | 0.74 (0.29) | 2 (1-10) |
| IBUIVCONT | 0.81 (0.24) | 2 (1-9) |
| INDOIVCONT | 0.65 (0.27) | 4 (1-10) |
| INDOTHERS | 0.06 (0.09) | 10 (7-10) |
| PLAC_NORX | 0.50 (0.19) | 6 (2-9) |

**eFigure 14. Network meta-analysis forest plots for outcome: *Risk of Bronchopulmonary Dysplasia (BPD)***




eFigure 14. Forest plot showing network effect estimates (OR with 95% credible intervals) for each possible treatment comparison in the network for risk of BPD computed using Bayesian RE model with non-informative priors; the horizontal axis denotes network odds ratios (with 95% credible intervals)

## eTable 15. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of BPD

**eTable 15. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of BPD**

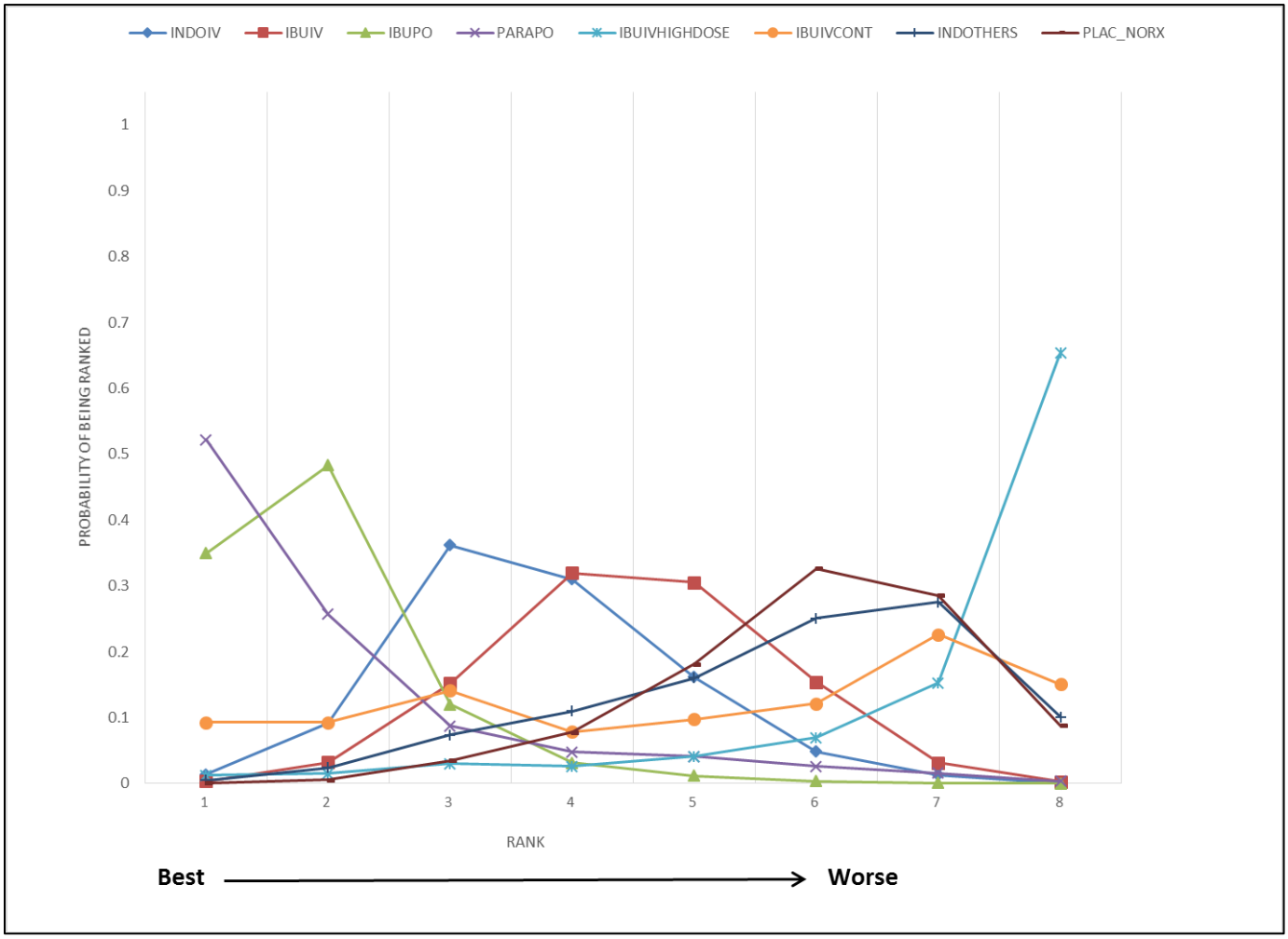
| Treatment Comparison | No. of direct comparisons | Events in the intervention group (n/N) | Events in the comparison group(n/N) | Direct OR (95% CrI) | QoE (GRADE) based on direct comparisons | QoE (GRADE) based on indirect comparisons | Network OR (95% CrI) | Inconsistency assessment (based on node splitting p value) | Changes in GRADE assessment based on precision & effect size | Network QoE | Network absolute risk difference per 1000 infants (95% CrI) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *versus* INDOIV | | | (INDOIV) | | | | | | | | ACR INDOIV 307/810 (37.9%) |
| IBUIV | 8 | 152/392 | 143/385 | 1.10(0.73-1.61) | MODERATE | MODERATE | 1.10(0.78-1.55) | 0.41 | None | MODERATE | 23 more (from 56 fewer to 107 more) |
| IBUPO | 2 | 12/24 | 13/24 | 0.80(0.23-2.92) | LOW | MODERATE | 0.68(0.40-1.14) | 0.65 | None | MODERATE | 86 fewer (from 31 more to 183 fewer) |
| PARAPO | 1 | 5/38 | 6/39 | 0.82(0.18-3.60) | MODERATE | LOW | 0.63(0.25-1.53) | 0.81 | None | MODERATE | 101 fewer (from 104 more to 247 fewer) |
| IBUIVHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 2.37(0.73-8.02) | ——— | None | MODERATE | 212 more (from 71 fewer to 451 more) |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 1.25(0.40-3.76) | ——— | None | LOW | 54 more (from 183 fewer to 317 more) |
| INDOTHERS | 4 | 72/195 | 58/191 | 1.39(0.81-2.45) | LOW | MODERATE | 1.36(0.78-2.32) | 0.89 | None | MODERATE | 75 more (from 56 fewer to 207 more) |
| PLAC_NORX | 5 | 95/175 | 87/171 | 1.30(0.75-2.34) | MODERATE | MODERATE | 1.37(0.89-2.20) | 0.58 | None | MODERATE | 76 more (from 27 fewer to 194 more) |
| *versus* IBUIV | | | (IBUIV) | | | | | | | | ACR IBUIV 226/653 (34.6%) |
| IBUPO | 3 | 30/120 | 35/116 | 0.72(0.34-1.48) | HIGH | LOW | 0.62(0.36-1.03) | 0.55 | None | HIGH | 99 fewer (from 7 more to 186 fewer) |
| PARAPO | ——— | | | ——— | ——— | MODERATE | 0.57(0.22-1.38) | ——— | None | MODERATE | 114 fewer (from 76 more to 242 fewer) |
| IBUIVHIGHDOSE | 1 | 16/35 | 10/35 | 2.06(0.65-6.62) | MODERATE | NOT ESTIMABLE | 2.14(0.71-6.86) | NA | None | MODERATE | 185 more (from 73 fewer to 438 more) |
| IBUIVCONT | 1 | 13/55 | 12/56 | 1.12(0.39-3.39) | LOW | NOT ESTIMABLE | 1.13(0.39-3.26) | NA | None | LOW | 28 more (from 175 fewer to 287 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 1.23(0.65-2.35) | ——— | None | LOW | 48 more (from 90 fewer to 208 more) |
| PLAC_NORX | 1 | 16/51 | 17/54 | 1.00(0.36-2.75) | MODERATE | MODERATE | 1.25(0.76-2.09) | 0.4 | None | MODERATE | 52 more (from 59 fewer to 179 more) |
| *versus* IBUPO | | | (IBUPO) | | | | | | | | ACR IBUPO 72/363 (19.8%) |
| PARAPO | 2 | 9/124 | 11/123 | 0.79(0.25-2.51) | MODERATE | LOW | 0.92(0.38-2.15) | 0.85 | None | MODERATE | 13 fewer (from 112 fewer to 149 more) |
| IBUIVHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 3.49(1.00-12.43) | ——— | None | MODERATE | 265 more (from 0 fewer to 556 more) |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 1.82(0.55-5.91) | ——— | None | LOW | 112 more (from 79 fewer to 396 more) |
| INDOTHERS | ——— | | | ——— | ——— | VERY LOW | 1.99(0.98-4.16) | ——— | None | VERY LOW | 132 more (from 3 fewer to 309 more) |
| PLAC_NORX | 3 | 35/96 | 19/96 | 2.96(1.29-7.05) | VERY LOW | LOW | 2.01(1.19-3.56) | 0.32 | None | LOW | 134 more (from 29 more to 270 more) |
| *versus* PARAPO | | | (PARAPO) | | | | | | | | ACR PARAPO 14/162 (8.6%) |
| IBUIVHIGHDOSE | ——— | | | ——— | ——— | MODERATE | 3.74(0.90-15.61) | ——— | Rated down (imprecision) | LOW | 175 more (from 8 fewer to 510 more) |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 2.01(0.47-7.68) | ——— | None | LOW | 73 more (from 44 fewer to 334 more) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 2.16(0.79-6.01) | ——— | None | LOW | 83 more (from 17 fewer to 276 more) |
| PLAC_NORX | ——— | | | ——— | ——— | MODERATE | 2.17(0.89-5.76) | ——— | None | MODERATE | 84 more (from 9 fewer to 266 more) |
| *versus* IBUIVHIGHDOSE | | | (IBUIVHIGHDOSE) | | | | | | | | ACR IBUIVHIGHDOSE 16/35 (45.7%) |
| IBUIVCONT | ——— | | | ——— | ——— | LOW | 0.53(0.11-2.41) | ——— | None | LOW | 149 fewer (from 213 more to 372 fewer) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 0.57(0.16-2.11) | ——— | None | LOW | 133 fewer (from 183 more to 338 fewer) |
| PLAC_NORX | ——— | | | ——— | ——— | MODERATE | 0.58(0.17-2.02) | ——— | None | MODERATE | 129 fewer (from 173 more to 332 fewer) |
| *versus* IBUIVCONT | | | (IBUIVCONT) | | | | | | | | ACR IBUIVCONT 13/55 (23.6%) |
| INDOTHERS | ——— | | | ——— | ——— | LOW | 1.10(0.31-3.93) | ——— | None | LOW | 18 more (from 149 fewer to 312 more) |
| PLAC_NORX | ——— | | | ——— | ——— | LOW | 1.11(0.35-3.63) | ——— | None | LOW | 19 more (from 139 fewer to 293 more) |
| *versus* INDOTHERS | | | (INDOTHERS) | | | | | | | | ACR INDOTHERS 73/207 (35.3%) |

**eTable 15. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of BPD**

| Treatment Comparison | No. of direct comparisons | Events in the intervention group (n/N) | Events in the comparison group(n/N) | Direct OR (95% CrI) | QoE (GRADE) based on direct comparisons | QoE (GRADE) based on indirect comparisons | Network OR (95% CrI) | Inconsistency assessment (based on node splitting p value) | Changes in GRADE assessment based on precision & effect size | Network QoE | Network absolute risk difference per 1000 infants (95% CrI) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PLAC_NORX | 1 | 1/11 | 1/12 | 0.99(0.02-71.31) | HIGH | LOW | 1.02(0.52-2.00) | 0.21 | None | HIGH | 5 more (from 132 fewer to 169 more) |

Abbreviations: NA: Not Applicable; QoE: Quality of Evidence; OR: Odds Ratio; Crl: Credible Intervals; ACR: Assumed control risk

## eFigure 15. Ranking probability (rankogram) of each treatment modality for risk of BPD

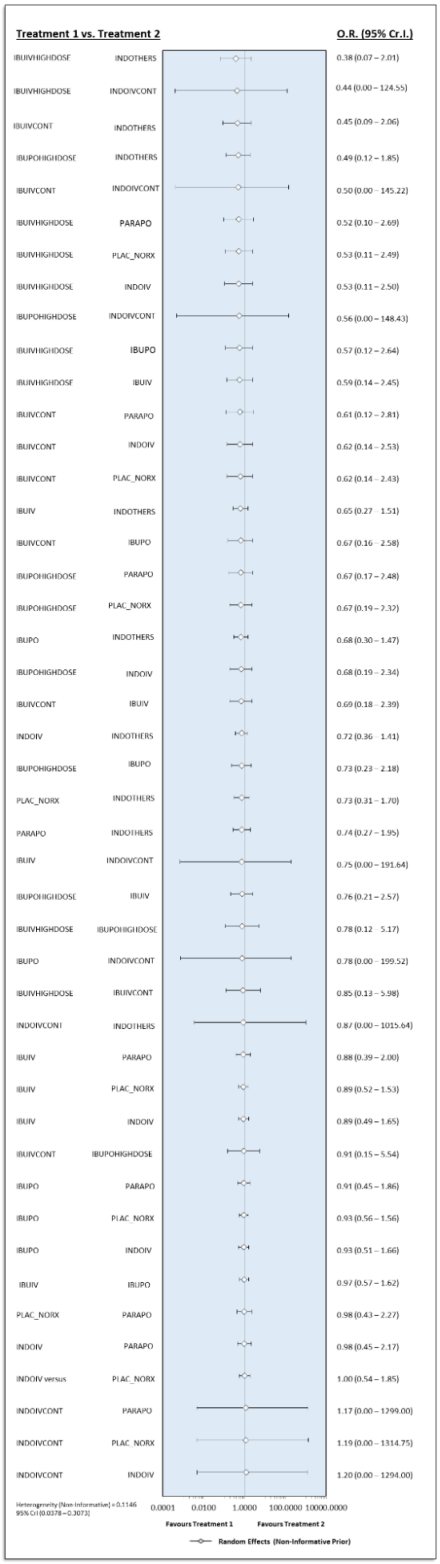



eFigure 15. Each line indicates a treatment modality. The horizontal x-axis represents the ranking of strategies in which the first through 8th modalities are ranked in numerical order, with the first representing the best strategy. The vertical y-axis represents the probability of each ranking.

## eTable 16. Ranking statistics for each treatment modality for risk of BPD

| **Risk of Bronchopulmonary Dysplasia** | | |
|---|---|---|
| **Treatment** | **SUCRA mean (Standard Deviation)** | **Median rank (95 % Credible Intervals)** |
| INDOIV | 0.61 (0.16) | 4 (2-6) |
| IBUIV | 0.50 (0.16) | 4 (2-7) |
| IBUPO | 0.87 (0.13) | 2 (1-4) |
| PARAPO | 0.86 (0.21) | 1 (1-6) |
| IBUIVHIGHDOSE | 0.12 (0.22) | 8 (2-8) |
| IBUIVCONT | 0.43 (0.33) | 5 (1-8) |
| INDOTHERS | 0.32 (0.22) | 6 (2-8) |
| PLAC_NORX | 0.29 (0.18) | 6 (3-8) |

**eFigure 16. Network meta-analysis forest plots for outcome: *Risk of Intraventricular Hemorrhage (IVH)***




eFigure 16. Forest plot showing network effect estimates (OR with 95% credible intervals) for each possible treatment comparison in the network for risk of IVH computed using Bayesian RE model with non-informative priors; the horizontal axis denotes network odds ratios (with 95% credible intervals)

## eTable 17. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of IVH

| eTable 17. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of IVH | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment Comparison | No. of direct comparisons | Events in the intervention group (n/N) | Events in the control group (n/N) | Direct OR (95% CrI) | QoE (GRADE) based on direct comparisons | QoE (GRADE) based on indirect comparisons | Network OR (95% CrI) | Inconsistency assessment (based on node splitting p value) | Changes in GRADE assessment based on precision & effect size | Network QoE | Network absolute risk difference per 1000 (95% CrI) infants |
| *versus* INDOIV | | | (INDOIV) | | | | | | | | ACR INDOIV 53/285 (18.6%) |
| IBUIV | 3 | 11/74 | 13/75 | 0.84(0.32-2.15) | MODERATE | MODERATE | 0.89(0.49-1.65) | 0.8 | None | MODERATE | 17 fewer (from 85 fewer to 88 more) |
| IBUPO | 2 | 6/31 | 3/33 | 2.62(0.57-15.12) | LOW | MODERATE | 0.93(0.51-1.66) | 0.18 | None | MODERATE | 11 fewer (from 82 fewer to 89 more) |
| PARAPO | 1 | 8/38 | 7/39 | 1.21(0.32-4.61) | MODERATE | LOW | 1.02(0.46-2.23) | 0.64 | None | MODERATE | 3 more (from 91 fewer to 152 more) |
| IBUIVHIGHDOSE | ——— | ——— | ——— | ——— | ——— | MODERATE | 0.53(0.11-2.50) | ——— | None | MODERATE | 78 fewer (from 161 fewer to 178 more) |
| IBUPOHIGHDOSE | ——— | ——— | ——— | ——— | ——— | LOW | 0.68(0.19-2.34) | ——— | None | LOW | 52 fewer (from 144 fewer to 162 more) |
| IBUIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.62(0.14-2.53) | ——— | None | LOW | 62 fewer (from 155 fewer to 180 more) |
| INDOIVCONT | 1 | 0/18 | 0/14 | 1.21(0.00-1562) | LOW | NOT ESTIMABLE | 1.20(0.00-1294) | NA | Rated down (imprecision) | VERY LOW | 29 more (from – to 811 more)* |
| INDOTHERS | 2 | 20/77 | 16/77 | 1.38(0.59-3.63) | LOW | MODERATE | 1.38(0.71-2.77) | 0.92 | None | MODERATE | 54 more (from 46 fewer to 202 more) |
| PLAC_NORX | 2 | 10/47 | 14/47 | 0.63(0.22-1.84) | MODERATE | MODERATE | 1.00(0.54-1.85) | 0.21 | None | MODERATE | 0 fewer (from 76 fewer to 111 more) |
| *versus* IBUIV | | | (IBUIV) | | | | | | | | ACR IBUIV 72/349 (20.6%) |
| IBUPO | 3 | 25/120 | 23/116 | 1.10(0.52-2.34) | HIGH | LOW | 1.04(0.62-1.77) | 0.83 | None | HIGH | 6 more (from 68 fewer to 109 more) |
| PARAPO | ——— | ——— | ——— | ——— | ——— | MODERATE | 1.14(0.50-2.59) | ——— | None | MODERATE | 22 more (from 91 fewer to 196 more) |
| IBUIVHIGHDOSE | 1 | 4/35 | 6/35 | 0.60(0.13-2.73) | MODERATE | NOT ESTIMABLE | 0.59(0.14-2.45) | NA | None | MODERATE | 73 fewer (from 171 fewer to 183 more) |
| IBUPOHIGHDOSE | ——— | ——— | ——— | ——— | ——— | MODERATE | 0.76(0.21-2.57) | ——— | None | MODERATE | 41 fewer (from 155 fewer to 194 more) |
| IBUIVCONT | 1 | 5/55 | 7/56 | 0.70(0.17-2.75) | LOW | NOT ESTIMABLE | 0.69(0.18-2.39) | NA | None | LOW | 54 fewer (from 162 fewer to 177 more) |
| INDOIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 1.34(0.01-1413) | ——— | Rated down (imprecision) | VERY LOW | 52 more (from 204 fewer to 791 more) |
| INDOTHERS | ——— | ——— | ——— | ——— | ——— | LOW | 1.54(0.66-3.64) | ——— | None | LOW | 80 more (from 60 fewer to 280 more) |
| PLAC_NORX | 1 | 25/68 | 25/68 | 0.99(0.40-2.50) | MODERATE | MODERATE | 1.12(0.65-1.94) | 0.69 | None | MODERATE | 19 more (from 62 fewer to 129 more) |
| *versus* IBUPO | | | (IBUPO) | | | | | | | | ACR IBUPO 90/430 (20.9%) |
| PARAPO | 2 | 14/124 | 14/123 | 1.01(0.41-2.51) | MODERATE | LOW | 1.09(0.54-2.22) | 0.74 | None | MODERATE | 15 more (from 84 fewer to 161 more) |
| IBUIVHIGHDOSE | ——— | ——— | ——— | ——— | ——— | MODERATE | 0.57(0.12-2.64) | ——— | None | MODERATE | 78 fewer (from 179 fewer to 202 more) |
| IBUPOHIGHDOSE | 1 | 9/30 | 11/30 | 0.74(0.21-2.58) | MODERATE | NOT ESTIMABLE | 0.73(0.23-2.18) | NA | None | MODERATE | 47 fewer (from 152 fewer to 157 more) |
| IBUIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.67(0.16-2.58) | ——— | None | LOW | 59 fewer (from 169 fewer to 196 more) |
| INDOIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 1.28(0.01-1343) | ——— | Rated down (imprecision) | VERY LOW | 44 more (from 207 fewer to 788 more) |
| INDOTHERS | 2 | 8/29 | 6/30 | 1.55(0.38-6.17) | LOW | VERY LOW | 1.47(0.68-3.36) | 0.96 | None | VERY LOW | 71 more (from 57 fewer to 261 more) |
| PLAC_NORX | 3 | 35/96 | 28/96 | 1.44(0.70-3.00) | VERY LOW | LOW | 1.08(0.64-1.79) | 0.25 | None | LOW | 13 more (from 64 fewer to 112 more) |
| *versus* PARAPO | | | (PARAPO) | | | | | | | | ACR PARAPO 22/162 (13.6%) |
| IBUIVHIGHDOSE | ——— | ——— | ——— | ——— | ——— | MODERATE | 0.52(0.10-2.69) | ——— | None | MODERATE | 60 fewer (from 120 fewer to 161 more) |
| IBUPOHIGHDOSE | ——— | ——— | ——— | ——— | ——— | LOW | 0.67(0.17-2.48) | ——— | None | LOW | 41 fewer (from 110 fewer to 145 more) |
| IBUIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.61(0.12-2.81) | ——— | None | LOW | 48 fewer (from 117 fewer to 171 more) |
| INDOIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 1.17(0.00-1299) | ——— | Rated down (imprecision) | VERY LOW | 20 more (from – to 859 more)* |
| INDOTHERS | ——— | ——— | ——— | ——— | ——— | LOW | 1.35(0.51-3.64) | ——— | None | LOW | 39 more (from 62 fewer to 228 more) |
| PLAC_NORX | ——— | ——— | ——— | ——— | ——— | MODERATE | 0.98(0.43-2.27) | ——— | None | MODERATE | 2 fewer (from 73 fewer to 127 more) |

**eTable 17. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of IVH**

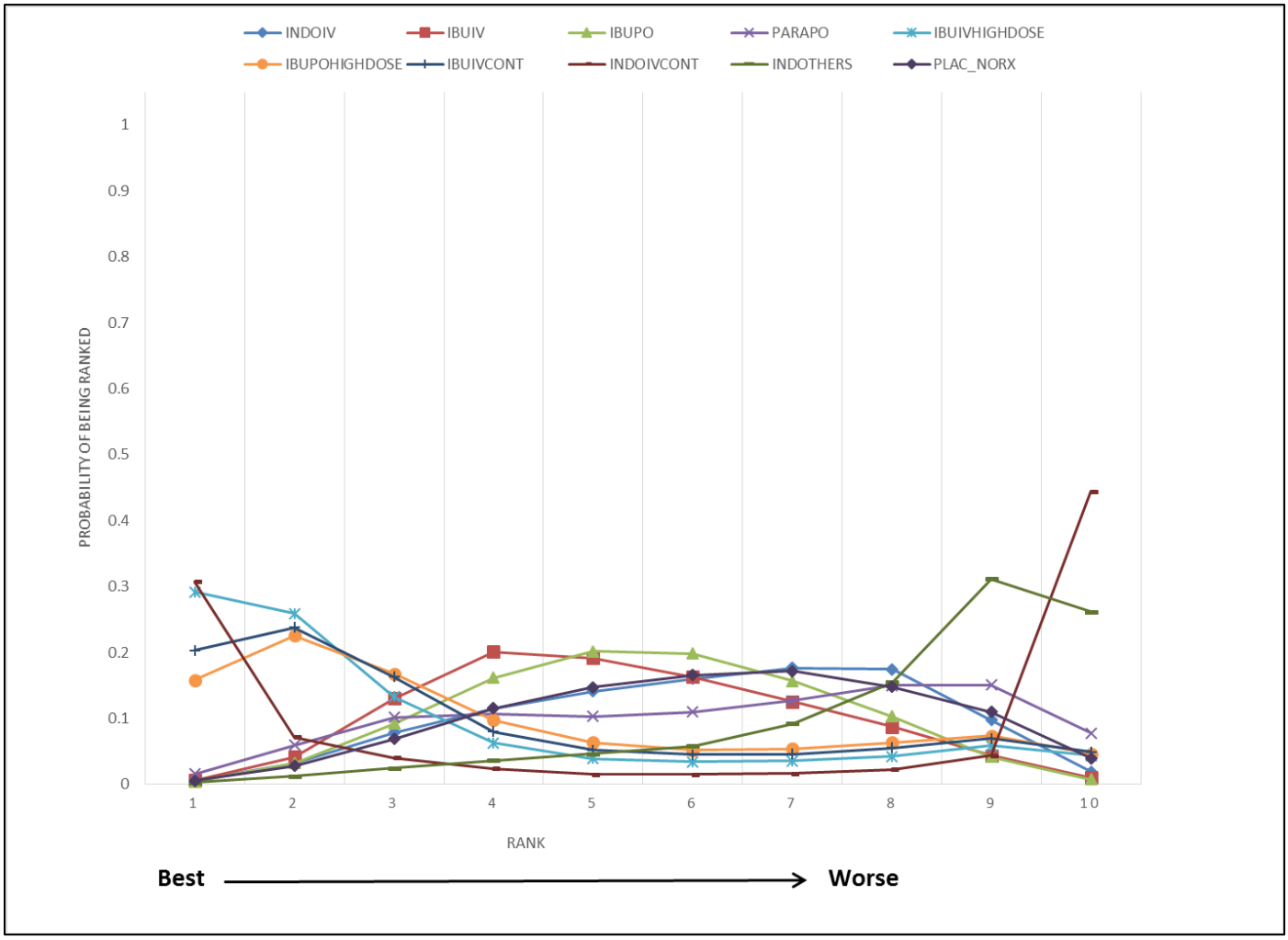
| Treatment Comparison | No. of direct comparisons | Events in the intervention group (n/N) | Events in the control group (n/N) | Direct OR (95% CrI) | QoE (GRADE) based on direct comparisons | QoE (GRADE) based on indirect comparisons | Network OR (95% CrI) | Inconsistency assessment (based on node splitting p value) | Changes in GRADE assessment based on precision & effect size | Network QoE | Network absolute risk difference per 1000 (95% CrI) infants |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***(Continued……)*** | | | | | | | | | | | |
| *versus* IBUIVHIGHDOSE | | | (IBUIVHIGHDOSE) | | | | | | | | ACR IBUIVHIGHDOSE 4/35 (11.4%) |
| IBUPOHIGHDOSE | ——— | ——— | ——— | ——— | ——— | MODERATE | 1.29(0.19-8.48) | ——— | None | MODERATE | 28 more (from 90 fewer to 408 more) |
| IBUIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 1.17(0.17-8.00) | ——— | None | LOW | 17 more (from 93 fewer to 394 more) |
| INDOIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 2.29(0.01-2484) | ——— | Rated down (imprecision) | VERY LOW | 114 more (from 113 fewer to 883 more) |
| INDOTHERS | ——— | ——— | ——— | ——— | ——— | LOW | 2.61(0.50-14.24) | ——— | Rated down (imprecision) | VERY LOW | 138 more (from 54 fewer to 533 more) |
| PLAC_NORX | ——— | ——— | ——— | ——— | ——— | MODERATE | 1.90(0.40-9.17) | ——— | None | MODERATE | 83 more (from 65 fewer to 428 more) |
| *versus* IBUPOHIGHDOSE | | | (IBUPOHIGHDOSE) | | | | | | | | ACR IBUPOHIGHDOSE 9/30 (30%) |
| IBUIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.91(0.15-5.54) | ——— | None | LOW | 19 fewer (from 240 fewer to 404 more) |
| INDOIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 1.78(0.01-2077) | ——— | Rated down (imprecision) | VERY LOW | 133 more (from 296 fewer to 699 more) |
| INDOTHERS | ——— | ——— | ——— | ——— | ——— | LOW | 2.04(0.54-8.06) | ——— | None | LOW | 166 more (from 112 fewer to 475 more) |
| PLAC_NORX | ——— | ——— | ——— | ——— | ——— | LOW | 1.48(0.43-5.22) | ——— | None | LOW | 88 more (from 144 fewer to 391 more) |
| *versus* IBUIVCONT | | | (IBUIVCONT) | | | | | | | | ACR IBUIVCONT 5/55 (9.1%) |
| INDOIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 1.99(0.01-2354) | ——— | Rated down (imprecision) | VERY LOW | 75 more (from 90 fewer to 905 more) |
| INDOTHERS | ——— | ——— | ——— | ——— | ——— | LOW | 2.24(0.48-11.08) | ——— | Rated down (imprecision) | VERY LOW | 92 more (from 45 fewer to 435 more) |
| PLAC_NORX | ——— | ——— | ——— | ——— | ——— | LOW | 1.61(0.41-6.95) | ——— | None | LOW | 48 more (from 52 fewer to 319 more) |
| *versus* INDOIVCONT | | | (INDOIVCONT) | | | | | | | | ACR INDOIVCONT 0/18 (0%) ** |
| INDOTHERS | ——— | ——— | ——— | ——— | ——— | LOW | 1.15(0.00-288) | ——— | Rated down (imprecision) | VERY LOW | 4 more (from – to 864 more)* |
| PLAC_NORX | ——— | ——— | ——— | ——— | ——— | LOW | 0.84(0.00-218) | ——— | Rated down (imprecision) | VERY LOW | 4 fewer (from – to 834 more)* |
| *versus* INDOTHERS | | | (INDOTHERS) | | | | | | | | ACR INDOTHERS 28/106 (26.4%) |
| PLAC_NORX | ——— | ——— | ——— | ——— | ——— | LOW | 0.73(0.31-1.70) | ——— | None | LOW | 57 fewer (from 115 more to 164 fewer) |

Abbreviations: NA: Not Applicable; QoE: Quality of Evidence; OR: Odds Ratio; Crl: Credible Intervals; ACR: Assumed control risk

*The lower limit of the 95% credible interval for absolute risk difference could not be computed due to the very low (tending to zero) lower limit of the 95% credible interval for the corresponding network odds ratio

**In view of zero event rate for the particular outcome in the control group, a continuity correction of 0.5 has been applied to calculate the assumed control risk in order to compute the absolute risk difference

## eFigure 17. Ranking probability (rankogram) of each treatment modality for risk of IVH

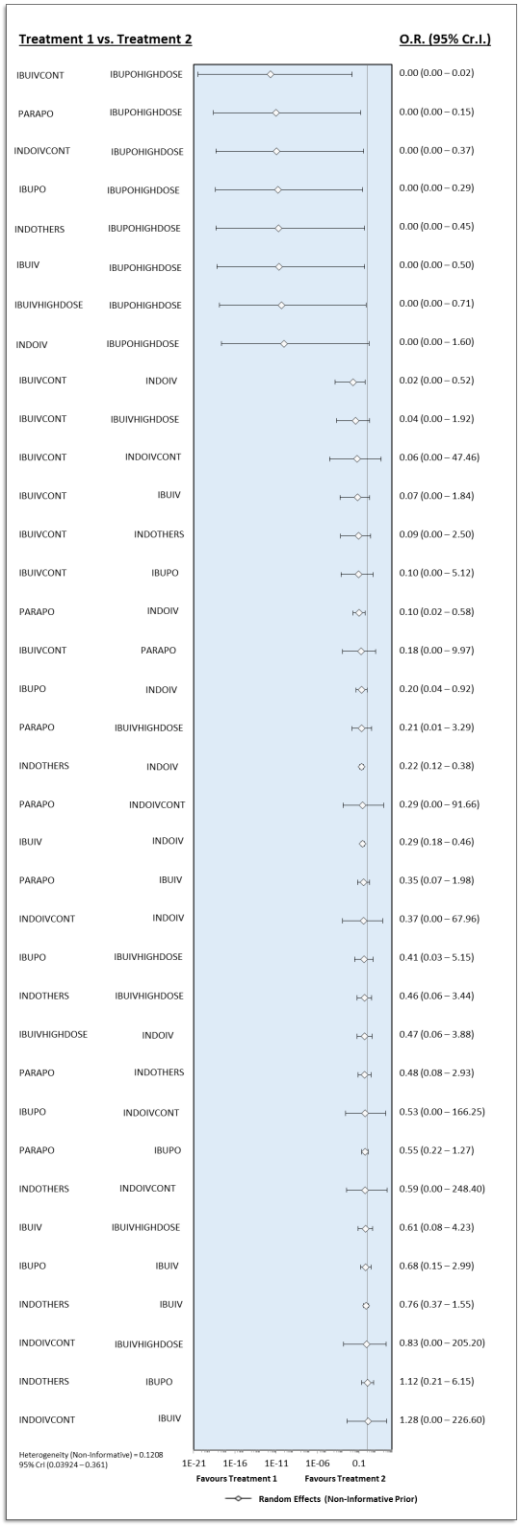



eFigure 17. Each line indicates a treatment modality. The horizontal x-axis represents the ranking of strategies in which the first through 10th modalities are ranked in numerical order, with the first representing the best strategy. The vertical y-axis represents the probability of each ranking.

## eTable 18. Ranking statistics for each treatment modality for risk of IVH

| Risk of Intra-ventricular Hemorrhage | | |
|---|---|---|
| **Treatment** | **SUCRA mean (Standard Deviation)** | **Median rank (95% Credible Intervals)** |
| INDOIV | 0.43 (0.22) | 6 (2-9) |
| IBUIV | 0.52 (0.21) | 5 (2-9) |
| IBUPO | 0.49 (0.20) | 6 (2-9) |
| PARAPO | 0.42 (0.27) | 7 (2-10) |
| IBUIVHIGHDOSE | 0.73 (0.31) | 2 (1-10) |
| IBUPOHIGHDOSE | 0.65 (0.31) | 3 (1-10) |
| IBUIVCONT | 0.68 (0.31) | 3 (1-10) |
| INDOIVCONT | 0.45 (0.46) | 8 (1-10) |
| INDOTHERS | 0.21 (0.22) | 9 (3-10) |
| PLAC_NORX | 0.42 (0.23) | 6 (2-10) |

## eFigure 18. Network meta-analysis forest plots for outcome: *Risk of Oliguria*




eFigure 18. Forest plot showing network effect estimates (OR with 95% credible intervals) for each possible treatment comparison in the network for risk of oliguria computed using Bayesian RE model with non-informative priors; the horizontal axis denotes network odds ratios (with 95% credible intervals)

## eTable 19. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of oliguria

**eTable 19. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of oliguria**

| Treatment Comparison | No. of direct comparisons | Events in the intervention group (n/N) | Events in the comparison group (n/N) | Direct OR (95% CrI) | QoE (GRADE) based on direct comparisons | QoE (GRADE) based on indirect comparisons | Network OR (95% CrI) | Inconsistency assessment (based on node splitting p value) | Changes in GRADE assessment based on precision & effect size | Network QoE | Network absolute risk difference per 1000 (95% CrI) infants |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *versus* INDOIV | | | (INDOIV) | | | | | | | | ACR INDOIV 143/734 (19.5%) |
| IBUIV | 9 | 27/384 | 75/373 | 0.25(0.13-0.48) | MODERATE | MODERATE | 0.29(0.18-0.46) | <0.01 | High precision; network inconsistency ; no change in GRADE | MODERATE | 129 fewer (from 95 fewer to 153 fewer) |
| IBUPO | ——— | ——— | ——— | ——— | LOW | MODERATE | 0.20(0.04-0.92) | ——— | None | MODERATE | 149 fewer (from 13 fewer to 185 fewer) |
| PARAPO | 1 | 1/38 | 0/39 | 9.54E+17 (34.2-8.3E+40) | MODERATE | LOW | 0.10(0.02-0.58) | <0.01 | network inconsistency | VERY LOW | 171 fewer (from 72 fewer to 190 fewer) |
| IBUIVHIGHDOSE | ——— | ——— | ——— | ——— | ——— | MODERATE | 0.47(0.06-3.88) | ——— | Rated down (imprecision) | LOW | 93 fewer (from 181 fewer to 289 more) |
| IBUPOHIGHDOSE | ——— | ——— | ——— | ——— | ——— | LOW | 1.15E+10(0.62-4.34E+17) | ——— | Rated down (imprecision) | VERY LOW | 805 more (from 64 fewer to 805 more) |
| IBUIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.02(0.00-0.52) | ——— | None | LOW | 190 fewer (up to 83 fewer)* |
| INDOIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.37(0.00-67.96) | ——— | Rated down (imprecision) | VERY LOW | 113 fewer (from – to 748 more)* |
| INDOTHERS | 6 | 23/325 | 68/322 | 0.22 (0.10-0.44) | LOW | MODERATE | 0.22(0.12-0.38) | 0.8 | Rated up (high precision; large effect) | HIGH | 144 fewer (from 111 fewer to 167 fewer) |
| *versus* IBUIV | | | (IBUIV) | | | | | | | | ACR IBUIV 34/655 (5.2%) |
| IBUPO | 4 | 0/156 | 3/148 | 0.26(0.02-2.34) | HIGH | LOW | 0.68(0.15-2.99) | <0.01 | network inconsistency | VERY LOW | 16 fewer (from 44 fewer to 89 more) |
| PARAPO | ——— | ——— | ——— | ——— | ——— | MODERATE | 0.35(0.07-1.98) | ——— | Rated down (imprecision) | LOW | 33 fewer (from 46 more to 48 fewer) |
| IBUIVHIGHDOSE | 1 | 3/35 | 2/35 | 1.70(0.21-17.03) | MODERATE | NOT ESTIMABLE | 1.64(0.24-11.85) | NA | Rated down (imprecision) | LOW | 30 more (from 39 fewer to 342 more) |
| IBUPOHIGHDOSE | ——— | ——— | ——— | ——— | ——— | MODERATE | 4.53E+10(1.99-1.37E+18) | ——— | Rated up (large effect) | HIGH | 948 more (from 46 more to 948 more) |
| IBUIVCONT | 1 | 0/55 | 2/56 | 0.10(0.00-3.43) | LOW | NOT ESTIMABLE | 0.07(0.00-1.84) | NA | Rated down (imprecision) | VERY LOW | 48 fewer (from – to 40 more)* |
| INDOIVCONT | 1 | 0/31 | 0/32 | 0.92(0.00-246) | LOW | NOT ESTIMABLE | 1.28(0.00-226.60) | NA | Rated down (imprecision) | VERY LOW | 14 more (from – to 874 more)* |
| INDOTHERS | ——— | ——— | ——— | ——— | ——— | LOW | 0.76(0.37-1.55) | ——— | None | LOW | 12 fewer (from 26 more to 32 fewer) |
| *versus* IBUPO | | | (IBUPO) | | | | | | | | ACR IBUPO 15/367 (4.1%) |
| PARAPO | 3 | 7/164 | 15/163 | 0.42(0.12-1.21) | MODERATE | LOW | 0.55(0.22-1.27) | <0.01 | None | LOW | 18 fewer (from 10 more to 32 fewer) |
| IBUIVHIGHDOSE | ——— | ——— | ——— | 3.676642604 | ——— | MODERATE | 2.45(0.19-33.70) | ——— | Rated down (imprecision) | LOW | 54 more (from 33 fewer to 549 more) |
| IBUPOHIGHDOSE | 1 | 1/30 | 0/30 | 1.02E+14(178-6.59E+36) | MODERATE | NOT ESTIMABLE | 5.71E+10(3.48-2.20E+18) | NA | Rated up (large effect) | HIGH | 959 more (from 88 more to 959 more) |
| IBUIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.10(0.00-5.12) | ——— | Rated down (imprecision) | VERY LOW | 37 fewer (from – 138 more)* |
| INDOIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 1.87(0.01-415.80) | ——— | Rated down (imprecision) | VERY LOW | 33 more (from 40 fewer to 906 more) |
| INDOTHERS | 1 | 0/18 | 0/18 | 0.78(0.00-303) | LOW | VERY LOW | 1.12(0.21-6.15) | 0.25 | None | VERY LOW | 5 more (from 32 fewer to 167 more) |
| *versus* PARAPO | | | (PARAPO) | | | | | | | | ACR PARAPO 8/202 (4%) |
| IBUIVHIGHDOSE | ——— | ——— | ——— | ——— | ——— | MODERATE | 4.71(0.30-71.49) | ——— | Rated down (imprecision) | LOW | 123 more (from 27 fewer to 707 more) |
| IBUPOHIGHDOSE | ——— | ——— | ——— | ——— | ——— | LOW | 1.12E+11(6.51-4.06E+18) | ——— | Rated up (large effect) | MODERATE | 960 more (from 172 more to 960 more) |
| IBUIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.18(0.00-9.97) | ——— | Rated down (imprecision) | VERY LOW | 32 fewer (from – to 252 more)* |
| INDOIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 3.43(0.01-866.40) | ——— | Rated down (imprecision) | VERY LOW | 84 more (from 39 fewer to 933 more) |

**eTable 19. GRADE assessment of the Quality of Evidence (QoE) for the network for risk of oliguria**

| Treatment Comparison | No. of direct comparisons | Events in the intervention group (n/N) | Events in the comparison group (n/N) | Direct OR (95% CrI) | QoE (GRADE) based on direct comparisons | QoE (GRADE) based on indirect comparisons | Network OR (95% CrI) | Inconsistency assessment (based on node splitting p value) | Changes in GRADE assessment based on precision & effect size | Network QoE | Network absolute risk difference per 1000 (95% CrI) infants |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | ***(Continued…..)*** |
| INDOTHERS | ——— | ——— | ——— | ——— | ——— | LOW | 2.10(0.34-13.05) | ——— | Rated down (imprecision) | VERY LOW | 40 more (from 26 fewer to 310 more) |
| *versus* IBUIVHIGHDOSE | | | (IBUIVHIGHDOSE) | | | | | | | | ACR IBUIVHIGHDOSE 3/35 (8.6%) |
| IBUPOHIGHDOSE | ——— | ——— | ——— | ——— | ——— | MODERATE | 2.43E+10(1.40-7.54E+17) | ——— | Rated up (large effect) | HIGH | 914 more (from 30 more to 914 more) |
| IBUIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.04(0.00-1.92) | ——— | Rated down (imprecision) | VERY LOW | 82 fewer (from – to 67 more)* |
| INDOIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.83(0.00-205.20) | ——— | Rated down (imprecision) | VERY LOW | 14 fewer (from – to 865 more)* |
| INDOTHERS | ——— | ——— | ——— | ——— | ——— | LOW | 0.46(0.06-3.44) | ——— | Rated down (imprecision) | VERY LOW | 44 fewer (from 80 fewer to 158 more) |
| *versus* IBUPOHIGHDOSE | | | (IBUPOHIGHDOSE) | | | | | | | | ACR IBUPOHIGHDOSE 1/30 (3.3%) |
| IBUIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.00(0.00-0.02) | ——— | Rated up (large effect) | MODERATE | -- (up to 33 fewer)*** |
| INDOIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 0.00(0.00-0.37) | ——— | Rated up (large effect) | MODERATE | -- (up to 21 fewer)*** |
| INDOTHERS | ——— | ——— | ——— | ——— | ——— | LOW | 0.00(0.00-0.45) | ——— | Rated up (large effect) | MODERATE | -- (up to 18 fewer)*** |
| *versus* IBUIVCONT | | | (IBUIVCONT) | | | | | | | | ACR IBUIVCONT 0/55 (0%) ** |
| INDOIVCONT | ——— | ——— | ——— | ——— | ——— | LOW | 17.44(0.02-36280.00) | ——— | Rated down (imprecision) | VERY LOW | 129 more (from 9 fewer to 988 more) |
| INDOTHERS | ——— | ——— | ——— | ——— | ——— | LOW | 11.13(0.40-1693.00) | ——— | Rated down (imprecision) | VERY LOW | 84 more (from 5 fewer to 930 more) |
| *versus* INDOIVCONT | | | (INDOIVCONT) | | | | | | | | ACR INDOIVCONT 0/31 (0%) ** |
| INDOTHERS | ——— | ——— | ——— | ——— | ——— | LOW | 0.59(0.00-248.40) | ——— | Rated down (imprecision) | VERY LOW | 7 fewer (from – to 787 more)* |

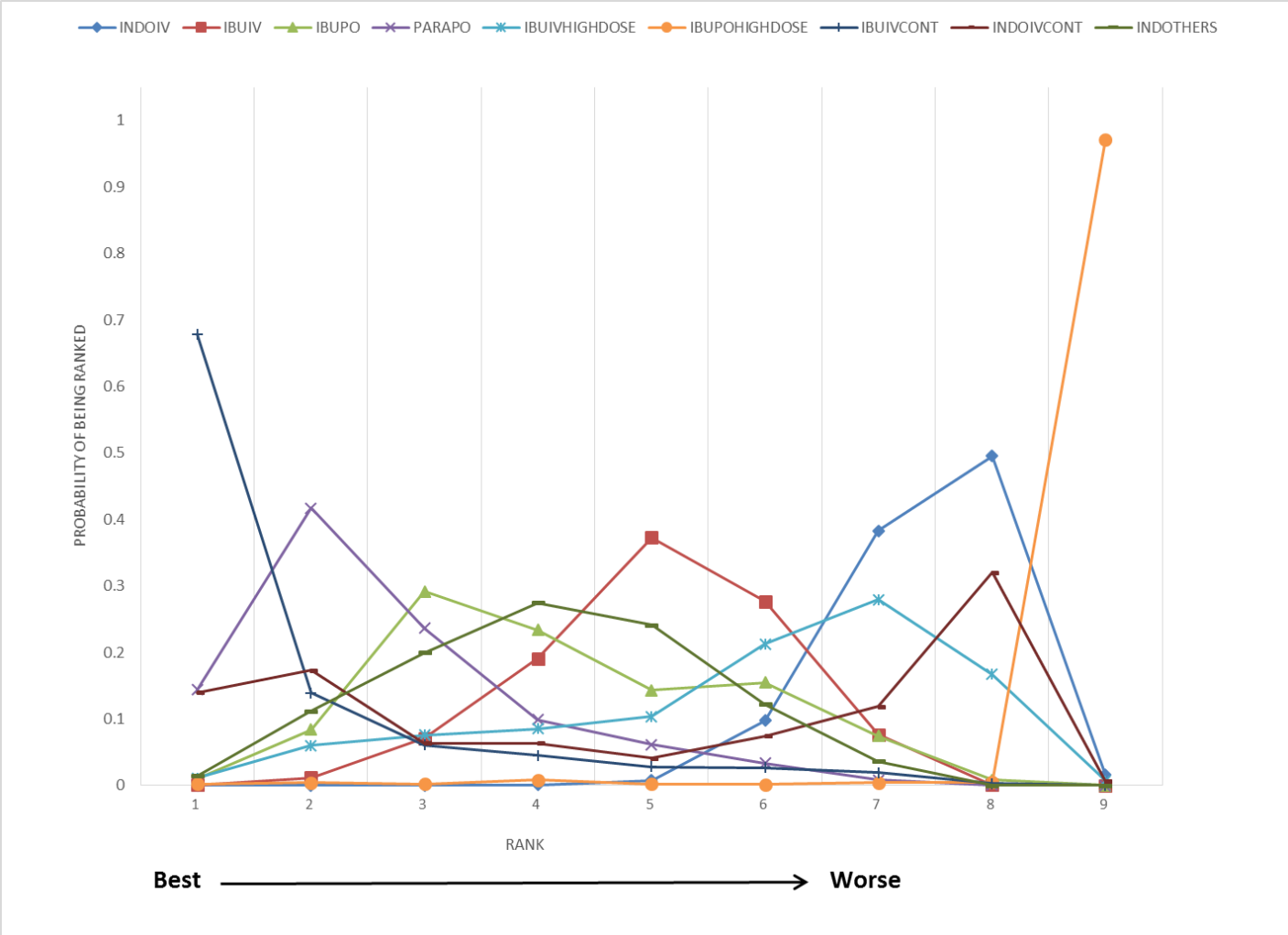
Abbreviations: NA: Not Applicable; QoE: Quality of Evidence; OR: Odds Ratio; Crl: Credible Intervals; ACR: Assumed control risk

*The lower limit of the 95% credible interval for absolute risk difference could not be computed due to the very low (tending to zero) lower limit of the 95% credible interval for the corresponding network odds ratio

**In view of zero event rate for the particular outcome in the control group, a continuity correction of 0.5 has been applied to calculate the assumed control risk in order to compute the absolute risk difference

***The absolute risk difference could not be computed due to very low (tending to zero) network odds ratio

## eFigure 19. Ranking probability (rankogram) of each treatment modality for risk of oliguria




eFigure 19. Each line indicates a treatment modality. The horizontal x-axis represents the ranking of strategies in which the first through 9th modalities are ranked in numerical order, with the first representing the best strategy. The vertical y-axis represents the probability of each ranking.

## eTable 20. Ranking statistics for each treatment modality for risk of oliguria

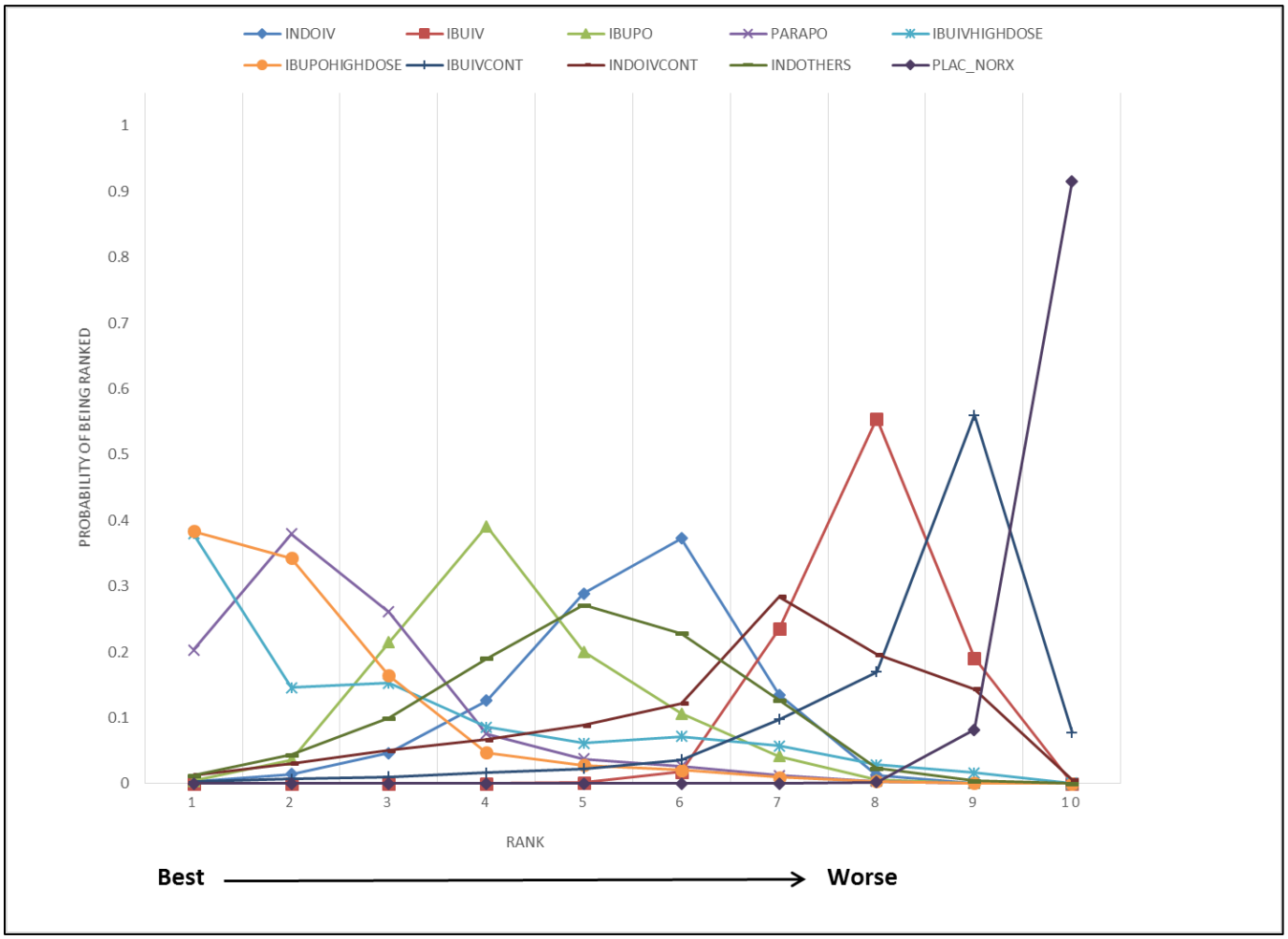
| Risk of oliguria | | |
|---|---|---|
| **Treatment** | **SUCRA mean (Standard Deviation)** | **Median rank (95% Credible Intervals)** |
| INDOIV | 0.20 (0.09) | 8 (6-8) |
| IBUIV | 0.49 (0.14) | 5 (3-7) |
| IBUPO | 0.60 (0.19) | 4 (2-7) |
| PARAPO | 0.79 (0.16) | 2 (1-6) |
| IBUIVHIGHDOSE | 0.40 (0.23) | 6 (2-8) |
| IBUPOHIGHDOSE | 0.02 (0.10) | 9 (8-9) |
| IBUIVCONT | 0.90 (0.18) | 1 (1-6) |
| INDOIVCONT | 0.50 (0.35) | 6 (1-8) |
| INDOTHERS | 0.61 (0.17) | 4 (2-7) |

## eTable 21. Network effect estimates for PDA closure on sensitivity analysis ('low' & 'probably low' risk of bias studies)

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **IBUPOHIGHDOSE** | | | | | | | | | |
| 1.15 (0.46 – 2.97) | **PARAPO** | | | | | | | | |
| 1.15 (0.17 – 7.55) | 1.00 (0.16 – 6.24) | **IBUIVHIGHDOSE** | | | | | | | |
| 1.81 (0.77 – 4.46) | 1.58 (0.74 – 3.46) | 1.58 (0.30 – 8.53) | **IBUPO** | | | | | | |
| 2.18 (0.70 – 6.49) | 1.88 (0.67 – 5.03) | 1.86 (0.34 – 10.23) | 1.18 (0.57 – 2.36) | **INDOTHERS** | | | | | |
| 2.33 (0.80 – 6.91) | 2.02 (0.78 – 5.32) | 2.01 (0.41 – 10.48) | 1.28 (0.66 – 2.42) | 1.08 (0.60 – 2.02) | **INDOIV** | | | | |
| 3.23 (0.75 – 14.95) | 2.82 (0.70 – 12.03) | 2.86 (0.43 – 19.72) | 1.78 (0.54 – 6.23) | 1.51 (0.45 – 5.44) | 1.40 (0.47 – 4.33) | **INDOIVCONT** | | | |
| 4.34 (1.52 – 12.78) | 3.77 (1.47 – 10.04) | 3.76 (0.83 – 18.23) | 2.39 (1.30 – 4.49) | 2.01 (1.04 – 4.12) | 1.86 (1.19 – 3.01) | 1.33 (0.44 – 3.92) | **IBUIV** | | |
| 6.00 (1.21 – 31.95) | 5.18 (1.12 – 25.40) | 5.21 (0.76 – 38.40) | 3.32 (0.83 – 13.23) | 2.77 (0.70 – 11.91) | 2.59 (0.69 – 9.71) | 1.86 (0.36 – 9.53) | 1.39 (0.40 – 4.75) | **IBUIVCONT** | |
| 15.85 (5.34 – 49.75) | 13.82 (5.07 – 38.65) | 13.78 (2.66 – 77.16) | 8.72 (4.44 – 17.47) | 7.36 (3.98 – 14.56) | 6.82 (3.81 – 12.75) | 4.88 (1.44 – 16.32) | 3.67 (1.93 – 6.95) | 2.63 (0.66 – 10.75) | **PLAC_NORX** |

*Network effect estimates (Odds ratio with 95% credible intervals) for each possible treatment comparison in the network for PDA closure computed using Bayesian random effects model with non-informative priors. For each outcome, the treatment on the top left corner indicates the best treatment option and the one on the bottom right indicates the worst treatment option based on mean SUCRA values*

**eFigure 20. Rankogram for PDA closure on sensitivity analysis ('low' & 'probably low' risk of bias studies)**




**eTable 22. Ranking statistics for PDA closure on sensitivity analysis ('low' & 'probably low' risk of bias studies)**

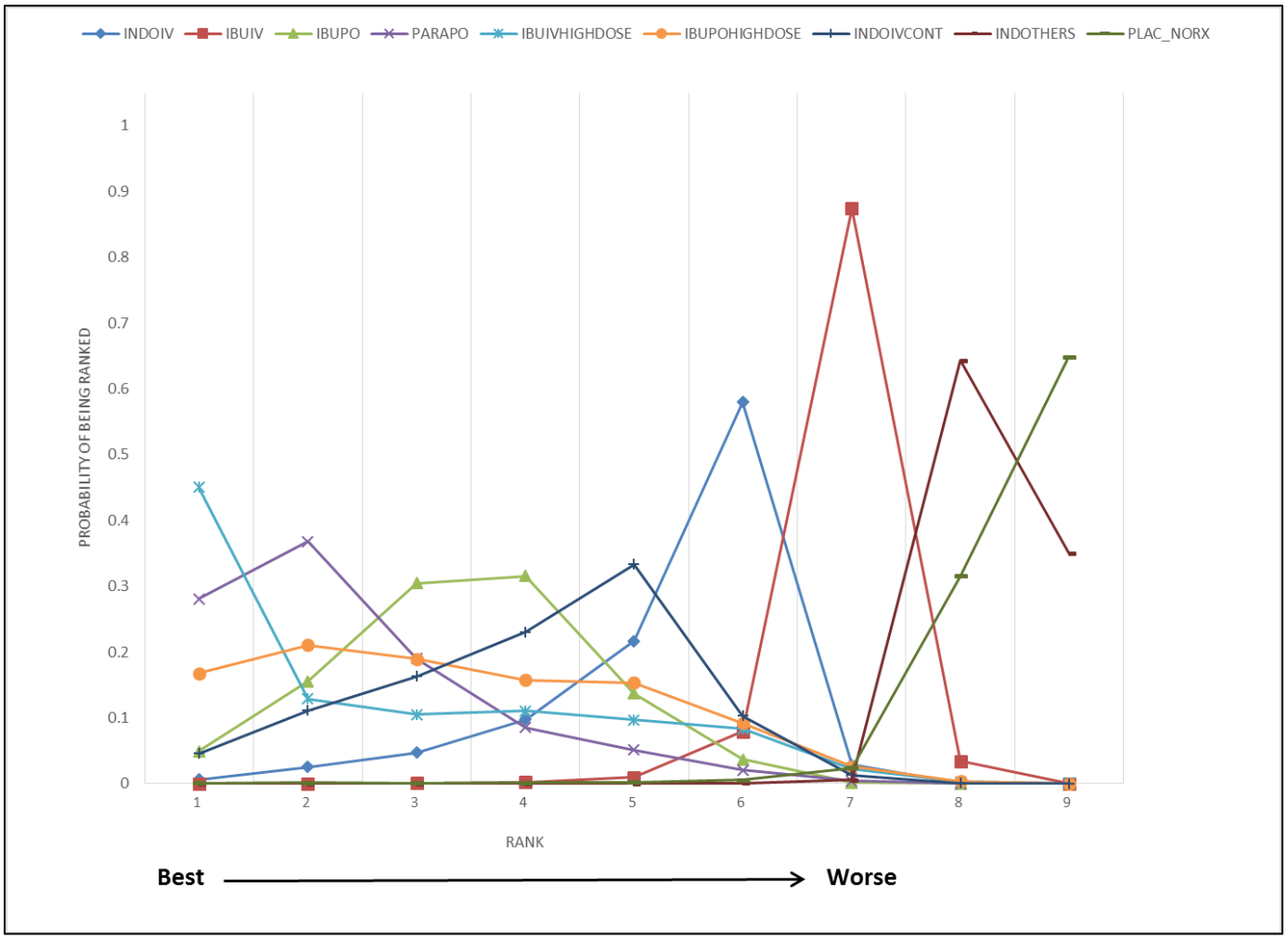
| PDA closure | | |
|---|---|---|
| **Treatment** | **SUCRA mean (Standard Deviation)** | **Median rank (95% Credible Intervals)** |
| INDOIV | 0.51 (0.13) | 6 (3-7) |
| IBUIV | 0.23 (0.08) | 8 (7-9) |
| IBUPO | 0.64 (0.13) | 4 (2-7) |
| PARAPO | 0.83 (0.15) | 2 (1-6) |
| IBUIVHIGHDOSE | 0.78 (0.25) | 2 (1-8) |
| IBUPOHIGHDOSE | 0.88 (0.15) | 2 (1-6) |
| IBUIVCONT | 0.19 (0.16) | 9 (4-10) |
| INDOIVCONT | 0.38 (0.22) | 7 (2-9) |
| INDOTHERS | 0.56 (0.16) | 5 (2-8) |
| PLAC_NORX | 0.01 (0.03) | 10 (9-10) |

**eTable 23. Network effect estimates for need for repeat pharmacotherapy on sensitivity analysis ('low' & 'probably low' risk of bias studies)**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **PARAPO** | | | | | | | | |
| 1.05 (0.20 – 5.93) | **IBUIVHIGHDOSE** | | | | | | | |
| 0.81 (0.34 – 2.04) | 0.78 (0.12 – 4.71) | **IBUPOHIGHDOSE** | | | | | | |
| 0.77 (0.38 – 1.59) | 0.74 (0.15 – 3.33) | 0.95 (0.37 – 2.30) | **IBUPO** | | | | | |
| 0.66 (0.22 – 1.74) | 0.63 (0.12 – 2.77) | 0.81 (0.23 – 2.48) | 0.84 (0.38 – 1.81) | **INDOIVCONT** | | | | |
| 0.47 (0.17 – 1.34) | 0.45 (0.09 – 1.92) | 0.58 (0.17 – 1.90) | 0.61 (0.27 – 1.38) | 0.72 (0.35 – 1.58) | **INDOIV** | | | |
| 0.28 (0.10 – 0.73) | 0.27 (0.06 – 1.00) | 0.34 (0.10 – 1.06) | 0.36 (0.18 – 0.72) | 0.43 (0.22 – 0.89) | 0.60 (0.32 – 1.02) | **IBUIV** | | |
| 0.07 (0.02 – 0.28) | 0.07 (0.01 – 0.37) | 0.09 (0.02 – 0.37) | 0.10 (0.04 – 0.29) | 0.12 (0.05 – 0.31) | 0.16 (0.06 – 0.45) | 0.27 (0.11 – 0.68) | **INDOTHERS** | |
| 0.05 (0.00 – 0.38) | 0.05 (0.00 – 0.45) | 0.06 (0.00 – 0.51) | 0.07 (0.01 – 0.43) | 0.08 (0.01 – 0.52) | 0.11 (0.01 – 0.58) | 0.18 (0.02 – 1.14) | 0.67 (0.06 – 4.89) | **PLAC_NORX** |

*Network effect estimates (Odds ratio with 95% credible intervals) for each possible treatment comparison in the network for need for repeat pharmacotherapy computed using Bayesian random effects model with non-informative priors. For each outcome, the treatment on the top left corner indicates the best treatment option and the one on the bottom right indicates the worst treatment option based on mean SUCRA values*

**eFigure 21. Rankogram for need for repeat pharmacotherapy on sensitivity analysis ('low' & 'probably low' risk of bias studies)**




**eTable 24. Ranking statistics for need for repeat pharmacotherapy on sensitivity analysis ('low' & 'probably low' risk of bias studies)**

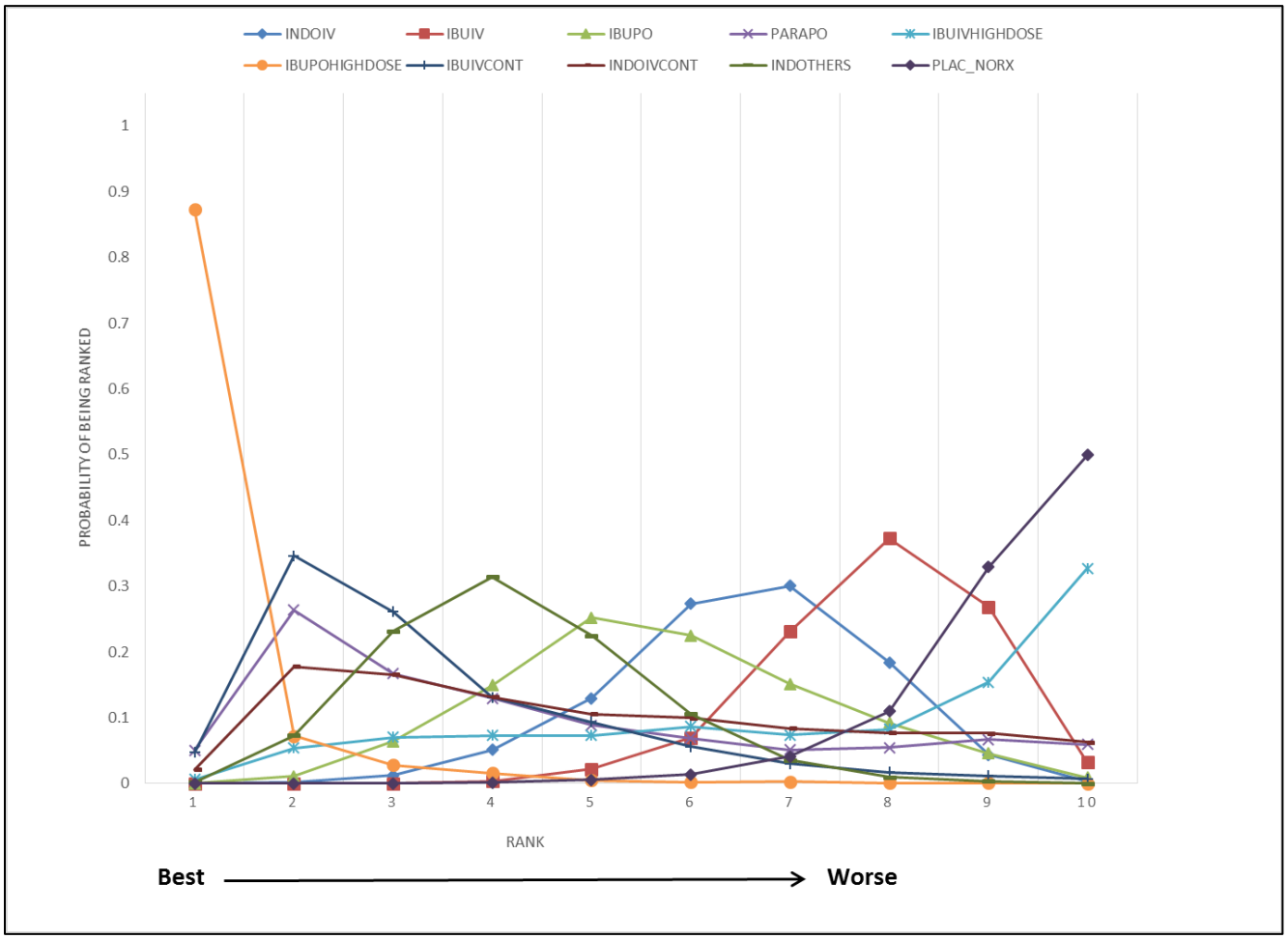
| Need for repeat pharmacotherapy | | |
|---|---|---|
| **Treatment** | **SUCRA mean (Standard Deviation)** | **Median rank (95% Credible Intervals)** |
| INDOIV | 0.46 (0.14) | 6 (2-7)) |
| IBUIV | 0.26 (0.05) | 7 (6-8) |
| IBUPO | 0.69 (0.15) | 3 (1-6) |
| PARAPO | 0.83 (0.16) | 2 (1-5) |
| IBUIVHIGHDOSE | 0.80 (0.23) | 2 (1-7) |
| IBUPOHIGHDOSE | 0.71 (0.21) | 3 (1-7) |
| INDOIVCONT | 0.62 (0.17) | 4 (1-6) |
| INDOTHERS | 0.08 (0.06) | 8 (8-9) |
| PLAC_NORX | 0.05 (0.09) | 9 (7-9) |

**eTable 25. Network effect estimates for need for surgical PDA ligation on sensitivity analysis ('low' & 'probably low' risk of bias studies)**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| IBUPOHIGHDOSE | | | | | | | | | |
| 0.05 (0.00 – 2.60) | IBUIVCONT | | | | | | | | |
| 0.03 (0.00 – 0.87) | 0.57 (0.08 – 3.85) | INDOTHERS | | | | | | | |
| 0.03 (0.00 – 2.95) | 0.71 (0.03 – 16.93) | 1.16 (0.10 – 18.05) | PARAPO | | | | | | |
| 0.02 (0.00 – 1.83) | 0.54 (0.03 – 7.74) | 0.89 (0.09 – 11.48) | 0.72 (0.02 – 22.85) | INDOIVCONT | | | | | |
| 0.02 (0.00 – 0.47) | 0.38 (0.04 – 2.59) | 0.65 (0.21 – 1.90) | 0.56 (0.04 – 5.50) | 0.75 (0.05 – 7.10) | IBUPO | | | | |
| 0.01 (0.00 – 0.44) | 0.29 (0.05 – 1.80) | 0.50 (0.21 – 1.31) | 0.42 (0.03 – 5.19) | 0.56 (0.05 – 4.98) | 0.77 (0.26 – 2.51) | INDOIV | | | |
| 0.01 (0.00 – 0.61) | 0.20 (0.01 – 4.09) | 0.35 (0.03 – 4.77) | 0.31 (0.01 – 9.35) | 0.40 (0.01 – 9.22) | 0.54 (0.04 – 7.59) | 0.70 (0.06 – 8.19) | IBUIVHIGHDOSE | | |
| 0.01 (0.00 – 0.33) | 0.22 (0.03 – 1.07) | 0.37 (0.14 – 0.92) | 0.30 (0.02 – 3.64) | 0.42 (0.04 – 3.15) | 0.57 (0.19 – 1.66) | 0.75 (0.35 – 1.27) | 1.08 (0.09 – 10.90) | IBUIV | |
| 0.01 (0.00 – 0.24) | 0.13 (0.02 – 0.82) | 0.22 (0.10 – 0.48) | 0.18 (0.01 – 2.49) | 0.24 (0.02 – 2.28) | 0.34 (0.10 – 1.10) | 0.43 (0.17 – 1.01) | 0.62 (0.05 – 7.72) | 0.59 (0.24 – 1.52) | PLAC_NORX |

*Network effect estimates (Odds ratio with 95% credible intervals) for each possible treatment comparison in the network for need for surgical PDA ligation computed using Bayesian random effects model with non-informative priors. For each outcome, the treatment on the top left corner indicates the best treatment option and the one on the bottom right indicates the worst treatment option based on mean SUCRA values*

**eFigure 22. Rankogram for need for surgical PDA ligation on sensitivity analysis ('low' & 'probably low' risk of bias studies)**




**eTable 26. Ranking statistics for need for surgical PDA ligation on sensitivity analysis ('low' & 'probably low' risk of bias studies)**

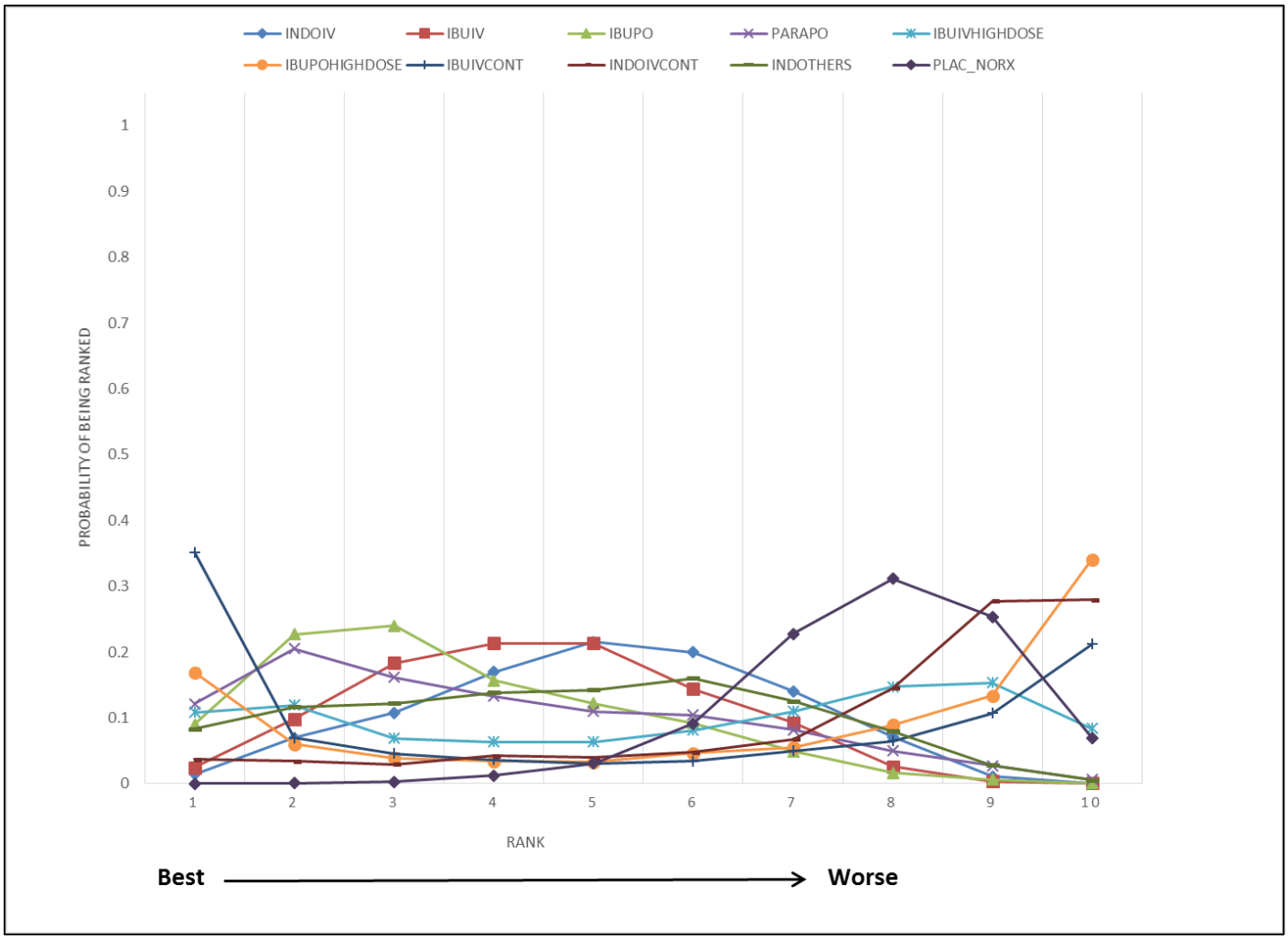
| Need for surgical PDA ligation | | |
|---|---|---|
| **Treatment** | **SUCRA mean (Standard Deviation)** | **Median rank (95% Credible intervals)** |
| INDOIV | 0.39 (0.14) | 7 (4-9) |
| IBUIV | 0.24 (0.12) | 8 (5-10) |
| IBUPO | 0.48 (0.18) | 6 (3-9) |
| PARAPO | 0.62 (0.29) | 4 (1-10) |
| IBUIVHIGHDOSE | 0.30 (0.30) | 8 (2-10) |
| IBUPOHIGHDOSE | 0.97 (0.09) | 1 (1-4) |
| IBUIVCONT | 0.74 (0.19) | 3 (1-8) |
| INDOIVCONT | 0.55 (0.29) | 5 (2-10) |
| INDOTHERS | 0.64 (0.14) | 4 (2-7) |
| PLAC_NORX | 0.08 (0.11) | 9 (7-10) |

**eTable 27. Network effect estimates for neonatal mortality on sensitivity analysis ('low' & 'probably low' risk of bias studies)**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **IBUPO** | | | | | | | | | |
| 0.96 (0.41 – 2.07) | **PARAPO** | | | | | | | | |
| 0.85 (0.41 – 1.81) | 0.90 (0.35 – 2.32) | **IBUIV** | | | | | | | |
| 0.83 (0.33 – 2.25) | 0.85 (0.30 – 2.68) | 0.97 (0.42 – 2.19) | **INDOTHERS** | | | | | | |
| 0.86 (0.01 – 27.31) | 0.87 (0.02 – 29.74) | 1.00 (0.02 – 30.42) | 1.02 (0.02 – 33.02) | **IBUIVCONT** | | | | | |
| 0.78 (0.36 – 1.76) | 0.82 (0.33 – 2.04) | 0.91 (0.50 – 1.70) | 0.94 (0.46 – 2.03) | 0.92 (0.03 – 64.11) | **INDOIV** | | | | |
| 0.66 (0.12 – 3.32) | 0.69 (0.12 – 3.94) | 0.77 (0.18 – 3.27) | 0.81 (0.14 – 4.48) | 0.80 (0.02 – 41.76) | 0.84 (0.17 – 4.06) | **IBUIVHIGHDOSE** | | | |
| 0.42 (0.01 – 5.24) | 0.45 (0.02 – 6.09) | 0.51 (0.02 – 7.33) | 0.49 (0.02 – 7.70) | 0.40 (0.00 – 85.48) | 0.54 (0.02 – 7.83) | 0.62 (0.02 – 13.66) | **IBUPOHIGHDOSE** | | |
| 0.36 (0.05 – 1.96) | 0.39 (0.04 – 2.33) | 0.42 (0.06 – 2.01) | 0.43 (0.06 – 2.34) | 0.46 (0.01 – 31.39) | 0.45 (0.07 – 2.25) | 0.57 (0.05 – 4.24) | 0.79 (0.03 – 33.66) | **INDOIVCONT** | |
| 0.50 (0.22 – 1.07) | 0.51 (0.20 – 1.32) | 0.58 (0.30 – 1.09) | 0.59 (0.29 – 1.18) | 0.56 (0.02 – 37.85) | 0.62 (0.36 – 1.07) | 0.73 (0.15 – 3.81) | 1.14 (0.08 – 34.40) | 1.37 (0.26 – 9.96) | **PLAC_NORX** |

*Network effect estimates (Odds ratio with 95% credible intervals) for each possible treatment comparison in the network for neonatal mortality computed using Bayesian random effects model with non-informative priors. For each outcome, the treatment on the top left corner indicates the best treatment option and the one on the bottom right indicates the worst treatment option based on mean SUCRA values*

**eFigure 23. Rankogram for neonatal mortality on sensitivity analysis ('low' & 'probably low' risk of bias studies)**




**eTable 28. Ranking statistics for neonatal mortality on sensitivity analysis ('low' & 'probably low' risk of bias studies)**

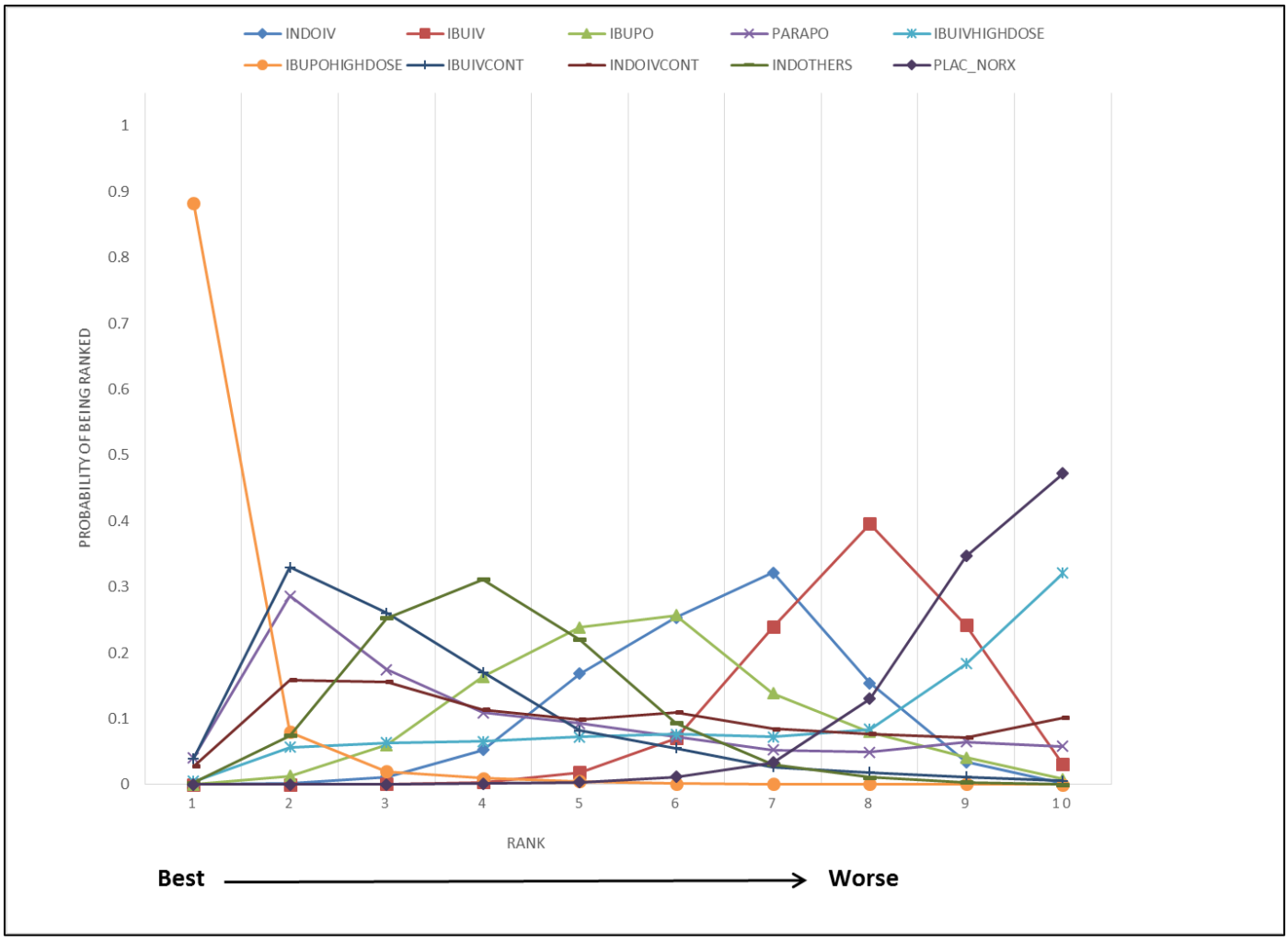
| Neonatal Mortality | | |
|---|---|---|
| **Treatment** | **SUCRA mean (Standard Deviation)** | **Median rank (95 % Credible intervals)** |
| INDOIV | 0.55 (0.19) | 5 (2-8) |
| IBUIV | 0.62 (0.18) | 4 (2-8) |
| IBUPO | 0.71 (0.20) | 3 (1-7) |
| PARAPO | 0.67 (0.25) | 4 (1-9) |
| IBUIVHIGHDOSE | 0.47 (0.33) | 6 (1-10) |
| IBUPOHIGHDOSE | 0.37 (0.39) | 8 (1-10) |
| IBUIVCONT | 0.55 (0.42) | 4 (1-10) |
| INDOIVCONT | 0.25 (0.28) | 9 (1-10) |
| INDOTHERS | 0.59 (0.25) | 5 (1-9) |
| PLAC_NORX | 0.24 (0.14) | 8 (5-10) |

**eTable 29. Network effect estimates for risk of necrotizing enterocolitis on sensitivity analysis ('low' & 'probably low' risk of bias studies)**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **IBUPOHIGHDOSE** | | | | | | | | | |
| 0.05 (0.00 – 2.60) | **IBUIVCONT** | | | | | | | | |
| 0.03 (0.00 – 0.87) | 0.57 (0.08 – 3.85) | **INDOTHERS** | | | | | | | |
| 0.03 (0.00 – 2.95) | 0.71 (0.03 – 16.93) | 1.16 (0.10 – 18.05) | **PARAPO** | | | | | | |
| 0.02 (0.00 – 1.83) | 0.54 (0.03 – 7.74) | 0.89 (0.09 – 11.48) | 0.72 (0.02 – 22.85) | **INDOIVCONT** | | | | | |
| 0.02 (0.00 – 0.47) | 0.38 (0.04 – 2.59) | 0.65 (0.21 – 1.90) | 0.56 (0.04 – 5.50) | 0.75 (0.05 – 7.10) | **IBUPO** | | | | |
| 0.01 (0.00 – 0.44) | 0.29 (0.05 – 1.80) | 0.50 (0.21 – 1.31) | 0.42 (0.03 – 5.19) | 0.56 (0.05 – 4.98) | 0.77 (0.26 – 2.51) | **INDOIV** | | | |
| 0.01 (0.00 – 0.61) | 0.20 (0.01 – 4.09) | 0.35 (0.03 – 4.77) | 0.31 (0.01 – 9.35) | 0.40 (0.01 – 9.22) | 0.54 (0.04 – 7.59) | 0.70 (0.06 – 8.19) | **IBUIVHIGHDOSE** | | |
| 0.01 (0.00 – 0.33) | 0.22 (0.03 – 1.07) | 0.37 (0.14 – 0.92) | 0.30 (0.02 – 3.64) | 0.42 (0.04 – 3.15) | 0.57 (0.19 – 1.66) | 0.75 (0.35 – 1.27) | 1.08 (0.09 – 10.90) | **IBUIV** | |
| 0.01 (0.00 – 0.24) | 0.13 (0.02 – 0.82) | 0.22 (0.10 – 0.48) | 0.18 (0.01 – 2.49) | 0.24 (0.02 – 2.28) | 0.34 (0.10 – 1.10) | 0.43 (0.17 – 1.01) | 0.62 (0.05 – 7.72) | 0.59 (0.24 – 1.52) | **PLAC_NORX** |

*Network effect estimates (Odds ratio with 95% credible intervals) for each possible treatment comparison in the network for risk of necrotizing enterocolitis computed using Bayesian random effects model with non-informative priors. For each outcome, the treatment on the top left corner indicates the best treatment option and the one on the bottom right indicates the worst treatment option based on mean SUCRA values*

**eFigure 24. Rankogram for risk of necrotizing enterocolitis on sensitivity analysis ('low' & 'probably low' risk of bias studies)**




**eTable 30. Ranking statistics for risk of necrotizing enterocolitis on sensitivity analysis ('low' & 'probably low' risk of bias studies)**

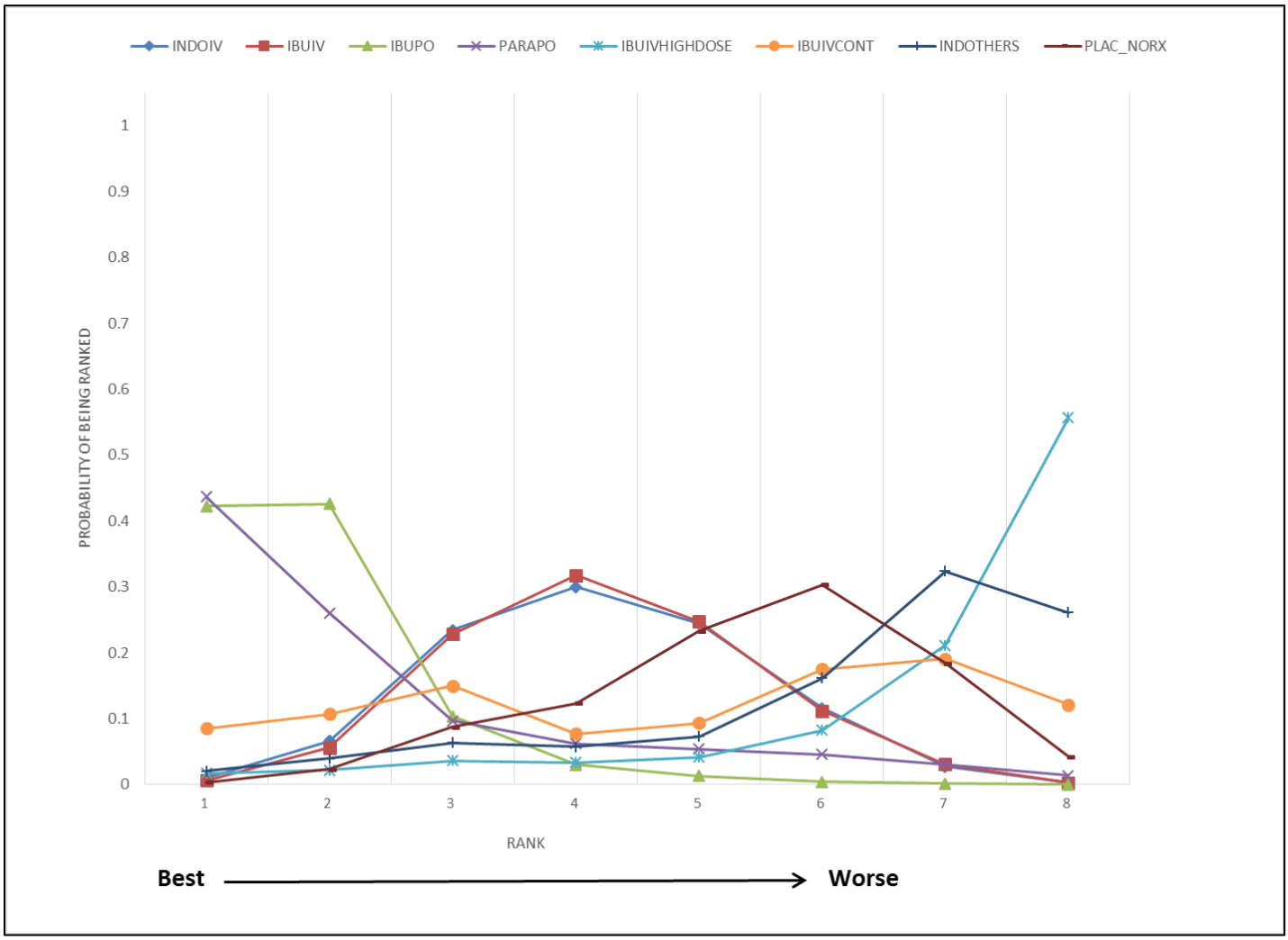
| Risk of Necrotizing Enterocolitis | | |
|---|---|---|
| **Treatment** | **SUCRA mean (Standard Deviation)** | **Median rank (95% Credible intervals)** |
| INDOIV | 0.39 (0.14) | 7 (4-9) |
| IBUIV | 0.24(0.12) | 8 (5-10) |
| IBUPO | 0.48 (0.18) | 6 (3-9) |
| PARAPO | 0.62 (0.29) | 4 (1-10) |
| IBUIVHIGHDOSE | 0.30 (0.30) | 8 (2-10) |
| IBUPOHIGHDOSE | 0.97 (0.09) | 1 (1-4) |
| IBUIVCONT | 0.74 (0.19) | 3 (1-8) |
| INDOIVCONT | 0.55 (0.29) | 5 (2-10) |
| INDOTHERS | 0.64 (0.14) | 4 (2-7) |
| PLAC_NORX | 0.08 (0.11) | 9 (7-10) |

**eTable 31. Network effect estimates for risk of bronchopulmonary dysplasia on sensitivity analysis ('low' & 'probably low' risk of bias studies)**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **IBUPO** | | | | | | | |
| 0.98 (0.34 – 3.01) | **PARAPO** | | | | | | |
| 0.60 (0.31 – 1.11) | 0.60 (0.20 – 1.75) | **INDOIV** | | | | | |
| 0.59 (0.33 – 1.06) | 0.60 (0.20 – 1.81) | 1.00 (0.67 – 1.51) | **IBUIV** | | | | |
| 0.51 (0.15 – 1.83) | 0.52 (0.11 – 2.54) | 0.86 (0.28 – 2.93) | 0.86 (0.30 – 2.66) | **IBUIVCONT** | | | |
| 0.49 (0.25 – 0.91) | 0.50 (0.16 – 1.53) | 0.83 (0.50 – 1.36) | 0.83 (0.47 – 1.45) | 0.96 (0.26 – 3.17) | **PLAC_NORX** | | |
| 0.37 (0.12 – 1.22) | 0.39 (0.09 – 1.68) | 0.64 (0.23 – 1.74) | 0.64 (0.22 – 1.83) | 0.72 (0.16 – 3.43) | 0.76 (0.26 – 2.33) | **INDOTHERS** | |
| 0.27 (0.07 – 1.09) | 0.28 (0.05 – 1.49) | 0.46 (0.13 – 1.70) | 0.46 (0.14 – 1.58) | 0.53 (0.10 – 2.74) | 0.55 (0.16 – 2.16) | 0.74 (0.15 – 3.51) | **IBUIVHIGHDOSE** |

*Network effect estimates (Odds ratio with 95% credible intervals) for each possible treatment comparison in the network for risk of bronchopulmonary dysplasia computed using Bayesian random effects model with non-informative priors. For each outcome, the treatment on the top left corner indicates the best treatment option and the one on the bottom right indicates the worst treatment option based on mean SUCRA values*

**eFigure 25. Rankogram for risk of bronchopulmonary dysplasia on sensitivity analysis ('low' & 'probably low' risk of bias studies)**




**eTable 32. Ranking statistics for risk of bronchopulmonary dysplasia on sensitivity analysis ('low' & 'probably low' risk of bias studies)**

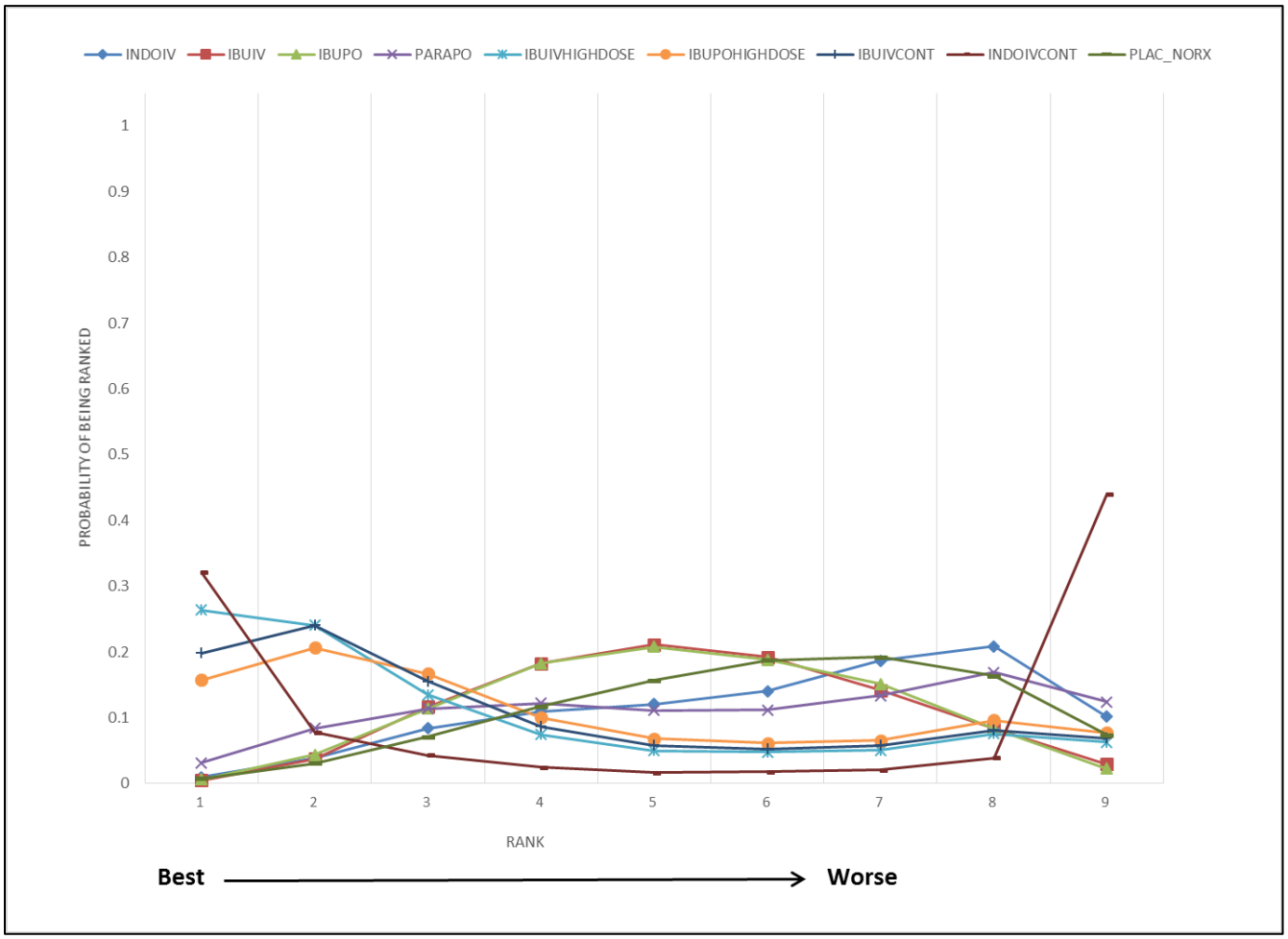
| Risk of Bronchopulmonary Dysplasia | | |
|---|---|---|
| **Treatment** | **SUCRA mean (Standard Deviation)** | **Median rank (95% Credible intervals)** |
| INDOIV | 0.55 (0.18) | 4 (2-7) |
| IBUIV | 0.54 (0.17) | 4 (2-7) |
| IBUPO | 0.89 (0.13) | 2 (1-4) |
| PARAPO | 0.81 (0.25) | 2 (1-7) |
| IBUIVHIGHDOSE | 0.15 (0.24) | 8 (2-8) |
| IBUIVCONT | 0.45 (0.32) | 5 (1-8) |
| INDOTHERS | 0.26 (0.26) | 7 (2-8) |
| PLAC_NORX | 0.37 (0.20) | 6 (2-8) |

**eTable 33. Network effect estimates for risk of intraventricular hemorrhage on sensitivity analysis ('low' & 'probably low' risk of bias studies)**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **IBUIVHIGHDOSE** | | | | | | | | |
| 0.90 (0.10 – 7.36) | **IBUIVCONT** | | | | | | | |
| 0.81 (0.09 – 7.05) | 0.89 (0.12 – 6.74) | **IBUPOHIGHDOSE** | | | | | | |
| 0.60 (0.11 – 3.27) | 0.67 (0.14 – 3.07) | 0.74 (0.20 – 2.69) | **IBUPO** | | | | | |
| 0.60 (0.12 – 2.89) | 0.68 (0.16 – 2.71) | 0.74 (0.18 – 3.06) | 1.00 (0.55 – 1.87) | **IBUIV** | | | | |
| 0.50 (0.00 – 209.16) | 0.57 (0.00 – 178.25) | 0.65 (0.00 – 168.55) | 0.85 (0.00 – 239.52) | 0.86 (0.00 – 226.35) | **INDOIVCONT** | | | |
| 0.55 (0.08 – 3.80) | 0.63 (0.11 – 3.67) | 0.69 (0.14 – 3.41) | 0.93 (0.36 – 2.40) | 0.93 (0.32 – 2.63) | 1.09 (0.00 – 941.60) | **PARAPO** | | |
| 0.54 (0.09 – 2.96) | 0.60 (0.13 – 2.89) | 0.67 (0.16 – 2.73) | 0.90 (0.49 – 1.66) | 0.90 (0.46 – 1.72) | 1.05 (0.00 – 949.67) | 0.97 (0.34 – 2.81) | **PLAC_NORX** | |
| 0.52 (0.09 – 3.06) | 0.58 (0.11 – 2.94) | 0.65 (0.14 – 2.92) | 0.87 (0.39 – 1.99) | 0.87 (0.39 – 1.96) | 1.03 (0.00 – 850.70) | 0.93 (0.35 – 2.57) | 0.96 (0.43 – 2.21) | **INDOIV** |

*Network effect estimates (Odds ratio with 95% credible intervals) for each possible treatment comparison in the network for risk of intraventricular hemorrhage computed using Bayesian random effects model with non-informative priors. For each outcome, the treatment on the top left corner indicates the best treatment option and the one on the bottom right indicates the worst treatment option based on mean SUCRA values*

**eFigure 26. Rankogram for risk of intraventricular hemorrhage on sensitivity analysis ('low' & 'probably low' risk of bias studies)**




**eTable 34. Ranking statistics for risk of intraventricular hemorrhage on sensitivity analysis ('low' & 'probably low' risk of bias studies)**

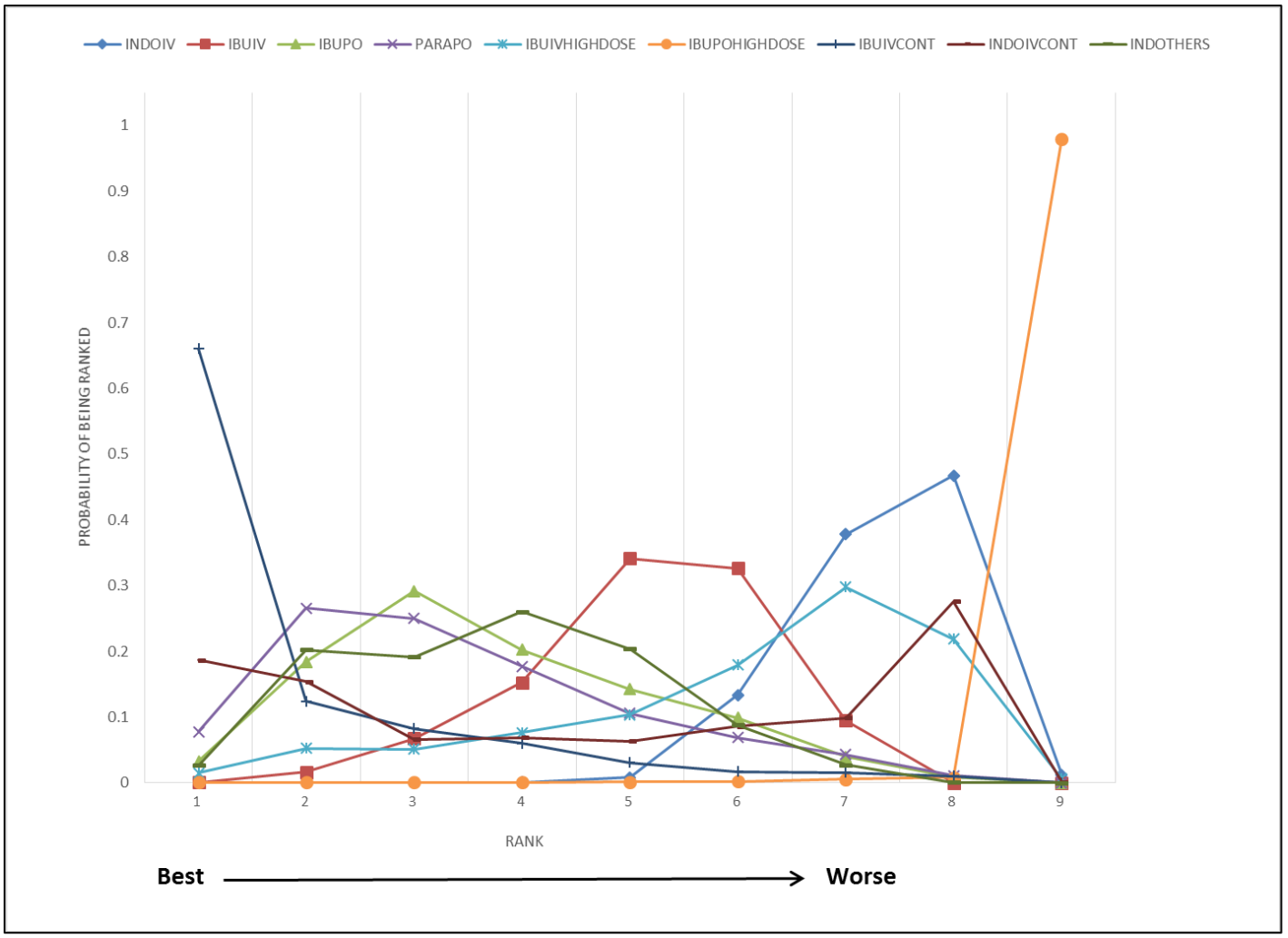
| Risk of Intraventricular Hemorrhage | | |
|---|---|---|
| **Treatment** | **SUCRA mean (Standard Deviation)** | **Median rank (95% Credible intervals)** |
| INDOIV | 0.36 (0.25) | 6 (2-9) |
| IBUIV | 0.46 (0.21) | 5 (2-9) |
| IBUPO | 0.47 (0.22) | 5 (2-8) |
| PARAPO | 0.42 (0.29) | 6 (1-9) |
| IBUIVHIGHDOSE | 0.69 (0.32) | 2 (1-9) |
| IBUPOHIGHDOSE | 0.61(0.33) | 3 (1-9) |
| IBUIVCONT | 0.65 (0.32) | 3 (1-9) |
| INDOIVCONT | 0.46 (0.46) | 6 (1-9) |
| PLAC_NORX | 0.38 (0.23) | 6 (2-9) |

**eTable 35. Network effect estimates for risk of oliguria on sensitivity analysis ('low' & 'probably low' risk of bias studies)**

| IBUIVCONT | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 0.13 (0.00 – 9.06) | PARAPO | | | | | | | |
| 0.12 (0.00 – 6.47) | 0.87 (0.31 – 2.35) | IBUPO | | | | | | |
| 0.11 (0.00 – 3.68) | 0.74 (0.07 – 6.78) | 0.81 (0.09 – 6.93) | INDOTHERS | | | | | |
| 0.04 (0.00 – 231.80) | 0.51 (0.00 – 342.58) | 0.56 (0.00 – 471.92) | 0.66 (0.00 – 1621.00) | INDOIVCONT | | | | |
| 0.06 (0.00 – 1.88) | 0.43 (0.04 – 2.85) | 0.48 (0.06 – 2.59) | 0.57 (0.21 – 1.57) | 0.87 (0.00 – 584.40) | IBUIV | | | |
| 0.03 (0.00 – 2.54) | 0.22 (0.01 – 4.44) | 0.25 (0.01 – 4.43) | 0.32 (0.02 – 3.59) | 0.51 (0.00 – 307.80) | 0.56 (0.05 – 4.75) | IBUIVHIGHDOSE | | |
| 0.02 (0.00 – 0.61) | 0.14 (0.01 – 0.96) | 0.15 (0.02 – 0.93) | 0.19 (0.08 – 0.41) | 0.28 (0.00 – 197.70) | 0.33 (0.19 – 0.55) | 0.58 (0.06 – 7.20) | INDOIV | |
| 0.00 (0.00 – 0.04) | 0.00 (0.00 – 0.09) | 0.00 (0.00 – 0.10) | 0.00 (0.00 – 0.12) | 0.00 (0.00 – 0.12) | 0.00 (0.00 – 0.17) | 0.00 (0.00 – 0.26) | 0.00 (0.00 – 0.57) | IBUPOHIGHDOSE |

*Network effect estimates (Odds ratio with 95% credible intervals) for each possible treatment comparison in the network for risk of oliguria computed using Bayesian random effects model with non-informative priors. For each outcome, the treatment on the top left corner indicates the best treatment option and the one on the bottom right indicates the worst treatment option based on mean SUCRA values*

**eFigure 27. Rankogram for risk of oliguria on sensitivity analysis ('low' & 'probably low' risk of bias studies)**




**eTable 36. Ranking statistics for risk of oliguria on sensitivity analysis ('low' & 'probably low' risk of bias studies)**

| Risk of Oliguria | | |
|---|---|---|
| **Treatment** | **SUCRA mean (Standard Deviation)** | **Median rank (95% Credible intervals)** |
| INDOIV | 0.21 (0.09) | 7 (6-8) |
| IBUIV | 0.48 (0.14) | 5 (3-7) |
| IBUPO | 0.66 (0.19) | 3 (1-7) |
| PARAPO | 0.70 (0.20) | 3 (1-7) |
| IBUIVHIGHDOSE | 0.37(0.23) | 7 (2-8) |
| IBUPOHIGHDOSE | 0.006 (0.054) | 9 (9-9) |
| IBUIVCONT | 0.89 (0.19) | 1 (1-7) |
| INDOIVCONT | 0.54 (0.34) | 5 (1-8) |
| INDOTHERS | 0.65 (0.18) | 4 (1-7) |

## eText 3. Guide to interpreting meta-regression results

With a meta-regression model, the pooled relative treatment effect for a certain comparison can be estimated on the basis of available studies, adjusted for differences in the level of the effect modifier between studies. This allows readers to identify the potential effect of some key variables in the results. Usually the approach with meta-regression is, after running the network meta-analysis and obtaining the effect estimates and rankings, a new model is generated adjusting for additional variables that could be effect modifiers (17).

In the following hypothetical example, an NMA of four interventions A, B, C and D, for the treatment of diarrhea in children, was conducted. The outcome of interest was the proportion of children who had diarrhea at day 3 of treatment. Odds ratios (OR) were interpreted as follows: for OR below 1.0, the first displayed intervention was protective (less children with diarrhea at day 3); for OR above 1.0, the opposite. A meta-regression analysis was run adjusting for age and days with diarrhea before recruitment as they were thought to play a role as effect modifiers. The results of this analysis have been displayed in the example tables below (etext3: Example tables A & B). It was found that on adjustment by days with diarrhea before recruitment, estimates for comparisons with treatment D changed substantially, and its SUCRA values changed as well. This suggested that the days with diarrhea had an impact on the effect of treatment D on the presence of diarrhea at day 3. In other words, the more days with diarrhea the child had, the less was the effect of D.

**eText3: Example Table A: Hypothetical example of network meta-regression results**

| Treatment comparison | Meta-regression for Age | Meta-regression for Days of diarrhea before recruitment |
|---|---|---|
| A vs B | 0.48 (0.18-0.9) | 0.48 (0.18-0.82) |
| B vs C | 0.6 (0.4-0.9) | 0.6 (0.4-0.9) |
| A vs C | 0.32 (021-0.81) | 0.32 (021-0.81) |
| A vs D | 1.05 (0.9-1.4) | **0.58 (0.39-0.89)** |
| D vs B | 0.7 (0.40-0.86) | **1.0 (0.88-1.46)** |
| D vs C | 0.24 (0.2 -0.60) | 0.55 (0.35-0.85) |

**eText3: Example Table B: Hypothetic example of corresponding mean SUCRA values (with SD) in the meta-regression Analysis**

| Treatment | Meta-regression for Age | Meta-regression for Days of diarrhea before recruitment |
|---|---|---|
| A | 0.96 (0.12) | 0.96 (0.12) |
| D | **0.95 (0.08)** | **0.28 (0.03)** |
| B | 0.23 (0.04) | 0.33 (0.06) |
| C | 0.08 (0.01) | 0.09 (0.01) |

**eTable 37. Meta-regression Analysis Results for Outcome: PDA Closure**

| *Meta-regression NMA Results For Mean Gestational Age* | | *Meta-regression NMA Results For Mean Birth Weight* | | *Meta-regression NMA Results For Year of Publication* | | *Meta-regression NMA Results For Age of Initiation of Treatment* | |
|---|---|---|---|---|---|---|---|
| **Treatment Comparison** | **Network Meta-regression OR (95% CrI)** | **Treatment Comparison** | **Network Meta-regression OR (95% CrI)** | **Treatment Comparison** | **Network Meta-regression OR (95% CrI)** | **Treatment Comparison** | **Network Meta-regression OR (95% CrI)** |
| PARAPO *versus* | | PARAPO *versus* | | PARAPO *versus* | | PARAPO *versus* | |
| INDOTHERS | 1.99 (0.80-4.86) | INDOTHERS | 2.24 (0.93-5.50) | INDOTHERS | 1.42 (0.62-3.27) | INDOTHERS | 0.95 (0.34-2.73) |
| INDOIVCONT | 2.31 (0.60-9.17) | INDOIVCONT | 2.48 (0.66-9.51) | INDOIVCONT | 1.43 (0.38-5.47) | INDOIVCONT | 0.65 (0.11-3.55) |
| INDOIV | 1.79 (0.77-4.15) | INDOIV | 1.97 (0.85-4.55) | INDOIV | 1.25 (0.54-2.86) | INDOIV | 0.93 (0.30-2.82) |
| IBUPOHIGHDOSE | 0.47 (0.12-1.78) | IBUPOHIGHDOSE | 0.53 (0.15-1.93) | IBUPOHIGHDOSE | 0.24 (0.06-0.88) | IBUPO | 1.11 (0.50-2.47) |
| IBUPO | 1.32 (0.66-2.65) | IBUPO | 1.47 (0.75-2.94) | IBUPO | 0.93 (0.48-1.81) | IBUIVCONT | 2.21 (0.48-9.97) |
| IBUIVHIGHDOSE | 0.91 (0.13-5.84) | IBUIVHIGHDOSE | 1.13 (0.18-7.19) | IBUIVHIGHDOSE | 0.64 (0.12-3.32) | IBUIV | 1.38 (0.43-4.30) |
| IBUIVCONT | 4.40 (0.91-21.77) | IBUIVCONT | 5.26 (1.16-24.64) | IBUIVCONT | 3.53 (0.91-13.95) | PLAC/NORX | 5.89 (2.03-17.91) |
| IBUIV | 3.01 (1.26-7.32) | IBUIV | 3.38 (1.44-8.25) | IBUIV | 1.94 (0.85-4.56) | INDOTHERS *versus* | |
| PLAC/NORX | 15.92 (6.50-41.74) | PLAC/NORX | 18.58 (7.40-48.49) | PLAC/NORX | 8.86 (3.60-22.98) | INDOIVCONT | 0.68 (0.15-2.75) |
| INDOTHERS *versus* | | INDOTHERS *versus* | | INDOTHERS *versus* | | INDOIV | 0.96 (0.58-1.59) |
| INDOIVCONT | 1.16 (0.36-3.88) | INDOIVCONT | 1.10 (0.36-3.53) | INDOIVCONT | 1.01 (0.33-3.14) | IBUPO | 1.16 (0.60-2.30) |
| INDOIV | 0.90 (0.59-1.37) | INDOIV | 0.87 (0.58-1.31) | INDOIV | 0.88 (0.59-1.29) | IBUIVCONT | 2.32 (0.69-7.66) |
| IBUPOHIGHDOSE | 0.24 (0.07-0.80) | IBUPOHIGHDOSE | 0.24 (0.07-0.78) | IBUPOHIGHDOSE | 0.17 (0.05-0.54) | IBUIV | 1.46 (0.77-2.69) |
| IBUPO | 0.67 (0.38-1.18) | IBUPO | 0.66 (0.37-1.14) | IBUPO | 0.65 (0.38-1.12) | PLAC/NORX | 6.10 (3.39-11.95) |
| IBUIVHIGHDOSE | 0.46 (0.08-2.41) | IBUIVHIGHDOSE | 0.51 (0.10-2.56) | IBUIVHIGHDOSE | 0.45 (0.09-2.11) | INDOIVCONT *versus* | |
| IBUIVCONT | 2.24 (0.57-8.87) | IBUIVCONT | 2.34 (0.64-8.69) | IBUIVCONT | 2.47 (0.72-8.95) | INDOIV | 1.42 (0.38-5.76) |
| IBUIV | 1.52 (0.90-2.62) | IBUIV | 1.51 (0.91-2.57) | IBUIV | 1.37 (0.83-2.32) | IBUPO | 1.71 (0.38-8.35) |
| PLAC/NORX | 8.05 (4.48-15.14) | PLAC/NORX | 8.24 (4.70-15.27) | PLAC/NORX | 6.25 (3.61-11.34) | IBUIVCONT | 3.39 (0.67-18.43) |
| INDOIVCONT *versus* | | INDOIVCONT *versus* | | INDOIVCONT *versus* | | IBUIV | 2.13 (0.62-8.09) |
| INDOIV | 0.78 (0.25-2.30) | INDOIV | 0.79 (0.27-2.28) | INDOIV | 0.87 (0.30-2.46) | PLAC/NORX | 9.05 (2.18-42.52) |
| IBUPOHIGHDOSE | 0.20 (0.04-1.04) | IBUPOHIGHDOSE | 0.22 (0.04-1.02) | IBUPOHIGHDOSE | 0.17 (0.04-0.74) | INDOIV *versus* | |
| IBUPO | 0.58 (0.17-1.89) | IBUPO | 0.59 (0.18-1.89) | IBUPO | 0.65 (0.21-1.99) | IBUPO | 1.20 (0.57-2.59) |
| IBUIVHIGHDOSE | 0.39 (0.05-2.86) | IBUIVHIGHDOSE | 0.46 (0.06-2.97) | IBUIVHIGHDOSE | 0.44 (0.07-2.72) | IBUIVCONT | 2.39 (0.78-7.49) |
| IBUIVCONT | 1.92 (0.34-10.43) | IBUIVCONT | 2.12 (0.40-10.52) | IBUIVCONT | 2.44 (0.49-12.00) | IBUIV | 1.50 (0.97-2.38) |
| IBUIV | 1.31 (0.43-3.95) | IBUIV | 1.37 (0.47-3.91) | IBUIV | 1.35 (0.48-3.83) | PLAC/NORX | 6.34 (3.32-12.90) |
| PLAC/NORX | 6.95 (1.95-24.51) | PLAC/NORX | 7.46 (2.29-24.73) | PLAC/NORX | 6.17 (2.02-19.16) | IBUPO *versus* | |
| INDOIV *versus* | | INDOIV *versus* | | INDOIV *versus* | | IBUIVCONT | 2.00 (0.54-7.17) |
| IBUPOHIGHDOSE | 0.26 (0.08-0.90) | IBUPOHIGHDOSE | 0.27 (0.08-0.87) | IBUPOHIGHDOSE | 0.19 (0.06-0.59) | IBUIV | 1.25 (0.55-2.79) |
| IBUPO | 0.74 (0.43-1.28) | IBUPO | 0.75 (0.44-1.28) | IBUPO | 0.74 (0.46-1.22) | PLAC/NORX | 5.24 (2.60-11.22) |
| IBUIVHIGHDOSE | 0.51 (0.09-2.65) | IBUIVHIGHDOSE | 0.58 (0.11-2.88) | IBUIVHIGHDOSE | 0.51 (0.11-2.30) | IBUIVCONT *versus* | |
| IBUIVCONT | 2.47 (0.64-9.66) | IBUIVCONT | 2.67 (0.76-9.53) | IBUIVCONT | 2.80 (0.84-9.98) | IBUIV | 0.62 (0.23-1.74) |
| IBUIV | 1.69 (1.12-2.59) | IBUIV | 1.72 (1.17-2.61) | IBUIV | 1.56 (1.08-2.30) | PLAC/NORX | 2.66 (0.77-9.62) |
| PLAC/NORX | 8.91 (4.82-17.22) | PLAC/NORX | 9.41 (5.36-17.51) | PLAC/NORX | 7.08 (4.35-12.34) | IBUIV *versus* | |
| IBUPOHIGHDOSE *versus* | | IBUPOHIGHDOSE *versus* | | IBUPOHIGHDOSE *versus* | | PLAC/NORX | 4.24 (2.16-8.83) |
| IBUPO | 2.84 (0.95-8.52) | IBUPO | 2.75 (0.97-7.93) | IBUPO | 3.91 (1.40-10.87) | | |
| IBUIVHIGHDOSE | 1.93 (0.26-14.06) | IBUIVHIGHDOSE | 2.13 (0.30-14.60) | IBUIVHIGHDOSE | 2.70 (0.40-17.60) | | |
| IBUIVCONT | 9.52 (1.66-55.73) | IBUIVCONT | 9.76 (1.85-52.78) | IBUIVCONT | 14.73 (2.90-77.76) | | |
| IBUIV | 6.46 (1.90-22.01) | IBUIV | 6.31 (1.98-20.49) | IBUIV | 8.21 (2.69-25.46) | | |
| PLAC/NORX | 34.15 (10.00-121.90) | PLAC/NORX | 34.60 (10.74-117.80) | PLAC/NORX | 37.47 (12.32-119.00) | | |
| IBUPO *versus* | | IBUPO *versus* | | IBUPO *versus* | | | |
| IBUIVHIGHDOSE | 0.68 (0.12-3.71) | IBUIVHIGHDOSE | 0.77 (0.14-3.96) | IBUIVHIGHDOSE | 0.69 (0.14-3.17) | | |
| IBUIVCONT | 3.37 (0.83-13.66) | IBUIVCONT | 3.56 (0.95-13.75) | IBUIVCONT | 3.79 (1.09-13.44) | | |
| IBUIV | 2.28 (1.31-4.01) | IBUIV | 2.30 (1.35-4.03) | IBUIV | 2.10 (1.29-3.46) | | |
| PLAC/NORX | 12.03 (6.64-23.25) | PLAC/NORX | 12.56 (7.00-23.66) | PLAC/NORX | 9.56 (5.52-17.29) | | |
| IBUIVHIGHDOSE *versus* | | IBUIVHIGHDOSE *versus* | | IBUIVHIGHDOSE *versus* | | | |
| IBUIVCONT | 4.87 (0.68-37.63) | IBUIVCONT | 4.66 (0.67-33.94) | IBUIVCONT | 5.55 (0.87-37.28) | | |
| IBUIV | 3.32 (0.68-17.00) | IBUIV | 2.98 (0.65-14.78) | IBUIV | 3.04 (0.71-13.99) | | |
| PLAC/NORX | 17.68 (3.29-103.90) | PLAC/NORX | 16.15 (3.19-91.47) | PLAC/NORX | 13.86 (2.93-71.25) | | |
| IBUIVCONT *versus* | | IBUIVCONT *versus* | | IBUIVCONT *versus* | | | |
| IBUIV | 0.68 (0.19-2.42) | IBUIV | 0.64 (0.20-2.12) | IBUIV | 0.55 (0.17-1.77) | | |
| PLAC/NORX | 3.60 (0.88-15.19) | PLAC/NORX | 3.53 (0.93-13.95) | PLAC/NORX | 2.52 (0.68-9.46) | | |
| IBUIV *versus* | | IBUIV *versus* | | IBUIV *versus* | | | |
| PLAC/NORX | 5.30 (2.81-10.22) | PLAC/NORX | 5.47 (3.02-10.38) | PLAC/NORX | 4.55 (2.69-8.01) | | |
| Common within-network between-study variance | 0.23 (0.04-0.57) | Common within-network between-study variance | 0.20 (0.02-0.50) | Common within-network between-study variance | 0.17 (0.01-0.45) | Common within-network between-study variance | 0.06 (0.00-0.48) |
| Regression coefficient (log OR scale) | -0.039 (-0.172-0.096) | Regression coefficient (log OR scale) | -0.001 (-0.001-0.000) | Regression coefficient (log OR scale) | 0.022 (-0.002-0.047) | Regression coefficient (log OR scale) | -0.045 (-0.102-0.014) |

**eTable 38. Meta-regression Analysis Corresponding SUCRA values: PDA Closure**

| Mean Gestational Age | | Mean Birth Weight | | Year of Publication | | Age initiation of Treatment | |
|---|---|---|---|---|---|---|---|
| **Treatment** | **Mean SUCRA (SD)** | **Treatment** | **Mean SUCRA (SD)** | **Treatment** | **Mean SUCRA (SD)** | **Treatment** | **Mean SUCRA (SD)** |
| PARAPO | 0.79 (0.15) | PARAPO | 0.82 (0.13) | PARAPO | 0.65 (0.19) | PARAPO | 0.63 (0.28) |
| INDOTHERS | 0.45 (0.13) | INDOTHERS | 0.44 (0.13) | INDOTHERS | 0.44 (0.14) | INDOTHERS | 0.68 (0.19) |
| INDOIVCONT | 0.41 (0.23) | INDOIVCONT | 0.42 (0.22) | INDOIVCONT | 0.47 (0.24) | INDOIVCONT | 0.81 (0.27) |
| INDOIV | 0.52 (0.12) | INDOIV | 0.53 (0.11) | INDOIV | 0.54 (0.12) | INDOIV | 0.72 (0.18) |
| IBUPOHIGHDOSE | 0.95 (0.10) | IBUPOHIGHDOSE | 0.95 (0.10) | IBUPOHIGHDOSE | 0.98 (0.05) | IBUPO | 0.55 (0.22) |
| IBUPO | 0.68 (0.11) | IBUPO | 0.68 (0.11) | IBUPO | 0.72 (0.11) | IBUIVCONT | 0.23 (0.20) |
| IBUIVHIGHDOSE | 0.76 (0.24) | IBUIVHIGHDOSE | 0.72 (0.25) | IBUIVHIGHDOSE | 0.77 (0.23) | IBUIV | 0.38 (0.16) |
| IBUIVCONT | 0.20 (0.17) | IBUIVCONT | 0.18 (0.15) | IBUIVCONT | 0.16 (0.14) | PLAC/NORX | 0.01 (0.03) |
| IBUIV | 0.24 (0.08) | IBUIV | 0.24 (0.08) | IBUIV | 0.26 (0.09) | | |
| PLAC/NORX | 0.00 (0.02) | PLAC/NORX | 0.00 (0.02) | PLAC/NORX | 0.01 (0.03) | | |

**eTable 39. Meta-regression Analysis Results for Outcome: Need for repeat pharmacotherapy**

| *Meta-regression NMA Results For Mean Gestational Age* | | *Meta-regression NMA Results For Mean Birth Weight* | | *Meta-regression NMA Results For Year of Publication* | | *Meta-regression NMA Results For Age of Initiation of Treatment* | |
|---|---|---|---|---|---|---|---|
| **Treatment Comparison** | **Network Meta-regression OR (95% CrI)** | **Treatment Comparison** | **Network Meta-regression OR (95% CrI)** | **Treatment Comparison** | **Network Meta-regression OR (95% CrI)** | **Treatment Comparison** | **Network Meta-regression OR (95% CrI)** |
| PARAPO *versus* | | PARAPO *versus* | | PARAPO *versus* | | PARAPO *versus* | |
| INDOTHERS | 0.77 (0.29-2.21) | INDOTHERS | 0.79 (0.28-2.24) | INDOTHERS | 0.78 (0.27-2.29) | INDOTHERS | 0.67 (0.11-3.45) |
| INDOIVCONT | 0.44 (0.10-2.06) | INDOIVCONT | 0.46 (0.10-2.17) | INDOIVCONT | 0.58 (0.09-3.99) | INDOIVCONT | 0.35 (0.02-3.78) |
| INDOIV | 0.47 (0.19-1.25) | INDOIV | 0.48 (0.19-1.26) | INDOIV | 0.54 (0.17-1.85) | INDOIV | 0.34 (0.04-1.93) |
| IBUPOHIGHDOSE | 1.97 (0.42-9.94) | IBUPOHIGHDOSE | 1.86 (0.41-8.92) | IBUPOHIGHDOSE | 1.93 (0.38-11.04) | IBUPO | 0.51 (0.12-1.94) |
| IBUPO | 0.85 (0.45-1.67) | IBUPO | 0.87 (0.44-1.72) | IBUPO | 0.87 (0.42-1.88) | IBUIV | 0.25 (0.03-1.56) |
| IBUIVHIGHDOSE | 1.37 (0.25-8.51) | IBUIVHIGHDOSE | 1.39 (0.24-8.72) | IBUIVHIGHDOSE | 1.27 (0.25-7.02) | PLAC/NORX | 0.06 (0.01-0.39) |
| IBUIV | 0.32 (0.13-0.79) | IBUIV | 0.32 (0.12-0.83) | IBUIV | 0.37 (0.11-1.32) | INDOTHERS *versus* | |
| PLAC/NORX | 0.08 (0.02-0.28) | PLAC/NORX | 0.07 (0.02-0.23) | PLAC/NORX | 0.08 (0.02-0.37) | INDOIVCONT | 0.52 (0.06-3.16) |
| INDOTHERS *versus* | | INDOTHERS *versus* | | INDOTHERS *versus* | | INDOIV | 0.50 (0.15-1.29) |
| INDOIVCONT | 0.58 (0.14-2.37) | INDOIVCONT | 0.59 (0.14-2.35) | INDOIVCONT | 0.75 (0.17-3.50) | IBUPO | 0.75 (0.25-2.48) |
| INDOIV | 0.61 (0.35-1.05) | INDOIV | 0.61 (0.36-1.07) | INDOIV | 0.69 (0.40-1.23) | IBUIV | 0.37 (0.10-1.09) |
| IBUPOHIGHDOSE | 2.56 (0.59-11.58) | IBUPOHIGHDOSE | 2.35 (0.56-10.71) | IBUPOHIGHDOSE | 2.47 (0.59-11.33) | PLAC/NORX | 0.09 (0.02-0.28) |
| IBUPO | 1.10 (0.56-2.21) | IBUPO | 1.10 (0.56-2.20) | IBUPO | 1.12 (0.59-2.15) | INDOIVCONT *versus* | |
| IBUIVHIGHDOSE | 1.77 (0.42-8.09) | IBUIVHIGHDOSE | 1.76 (0.42-8.35) | IBUIVHIGHDOSE | 1.63 (0.39-7.12) | INDOIV | 0.96 (0.18-5.03) |
| IBUIV | 0.41 (0.21-0.77) | IBUIV | 0.41 (0.21-0.78) | IBUIV | 0.48 (0.24-0.96) | IBUPO | 1.45 (0.21-13.99) |
| PLAC/NORX | 0.10 (0.04-0.23) | PLAC/NORX | 0.09 (0.04-0.20) | PLAC/NORX | 0.10 (0.04-0.26) | IBUIV | 0.72 (0.15-3.13) |
| INDOIVCONT *versus* | | INDOIVCONT *versus* | | INDOIVCONT *versus* | | PLAC/NORX | 0.17 (0.03-0.99) |
| INDOIV | 1.06 (0.28-3.85) | INDOIV | 1.04 (0.29-3.93) | INDOIV | 0.93 (0.23-3.50) | INDOIV *versus* | |
| IBUPOHIGHDOSE | 4.44 (0.62-31.52) | IBUPOHIGHDOSE | 4.08 (0.57-29.66) | IBUPOHIGHDOSE | 3.27 (0.48-21.76) | IBUPO | 1.51 (0.45-7.35) |
| IBUPO | 1.92 (0.47-7.35) | IBUPO | 1.90 (0.46-7.46) | IBUPO | 1.48 (0.31-6.64) | IBUIV | 0.76 (0.33-1.60) |
| IBUIVHIGHDOSE | 3.08 (0.49-21.79) | IBUIVHIGHDOSE | 2.97 (0.45-20.26) | IBUIVHIGHDOSE | 2.19 (0.32-14.91) | PLAC/NORX | 0.18 (0.06-0.49) |
| IBUIV | 0.71 (0.20-2.33) | IBUIV | 0.70 (0.20-2.35) | IBUIV | 0.64 (0.18-2.16) | IBUPO *versus* | |
| PLAC/NORX | 0.17 (0.04-0.77) | PLAC/NORX | 0.15 (0.03-0.64) | PLAC/NORX | 0.13 (0.03-0.55) | IBUIV | 0.50 (0.09-1.87) |
| INDOIV *versus* | | INDOIV *versus* | | INDOIV *versus* | | PLAC/NORX | 0.12 (0.02-0.46) |
| IBUPOHIGHDOSE | 4.16 (0.96-19.01) | IBUPOHIGHDOSE | 3.86 (0.91-16.92) | IBUPOHIGHDOSE | 3.56 (0.87-15.28) | IBUIV *versus* | |
| IBUPO | 1.80 (0.94-3.44) | IBUPO | 1.80 (0.95-3.41) | IBUPO | 1.61 (0.78-3.18) | PLAC/NORX | 0.24 (0.08-0.68) |
| IBUIVHIGHDOSE | 2.92 (0.69-13.38) | IBUIVHIGHDOSE | 2.86 (0.67-12.89) | IBUIVHIGHDOSE | 2.35 (0.58-9.96) | | |
| IBUIV | 0.68 (0.42-1.03) | IBUIV | 0.67 (0.41-1.03) | IBUIV | 0.69 (0.43-1.08) | | |
| PLAC/NORX | 0.17 (0.07-0.37) | PLAC/NORX | 0.15 (0.07-0.30) | PLAC/NORX | 0.15 (0.07-0.32) | | |
| IBUPOHIGHDOSE *versus* | | IBUPOHIGHDOSE *versus* | | IBUPOHIGHDOSE *versus* | | | |
| IBUPO | 0.44 (0.11-1.68) | IBUPO | 0.47 (0.12-1.74) | IBUPO | 0.45 (0.11-1.71) | | |
| IBUIVHIGHDOSE | 0.69 (0.09-5.64) | IBUIVHIGHDOSE | 0.74 (0.10-5.70) | IBUIVHIGHDOSE | 0.65 (0.09-4.73) | | |
| IBUIV | 0.16 (0.03-0.70) | IBUIV | 0.17 (0.04-0.75) | IBUIV | 0.19 (0.05-0.78) | | |
| PLAC/NORX | 0.04 (0.01-0.20) | PLAC/NORX | 0.04 (0.01-0.18) | PLAC/NORX | 0.04 (0.01-0.20) | | |
| IBUPO *versus* | | IBUPO *versus* | | IBUPO *versus* | | | |
| IBUIVHIGHDOSE | 1.63 (0.36-7.98) | IBUIVHIGHDOSE | 1.59 (0.35-7.87) | IBUIVHIGHDOSE | 1.46 (0.35-6.29) | | |
| IBUIV | 0.37 (0.19-0.69) | IBUIV | 0.37 (0.19-0.69) | IBUIV | 0.43 (0.21-0.90) | | |
| PLAC/NORX | 0.09 (0.04-0.24) | PLAC/NORX | 0.08 (0.03-0.20) | PLAC/NORX | 0.09 (0.03-0.27) | | |
| IBUIVHIGHDOSE *versus* | | IBUIVHIGHDOSE *versus* | | IBUIVHIGHDOSE *versus* | | | |
| IBUIV | 0.23 (0.05-0.90) | IBUIV | 0.24 (0.05-0.90) | IBUIV | 0.30 (0.07-1.15) | | |
| PLAC/NORX | 0.06 (0.01-0.26) | PLAC/NORX | 0.05 (0.01-0.23) | PLAC/NORX | 0.06 (0.01-0.31) | | |
| IBUIV *versus* | | IBUIV *versus* | | IBUIV *versus* | | | |
| PLAC/NORX | 0.25 (0.11-0.56) | PLAC/NORX | 0.22 (0.10-0.46) | PLAC/NORX | 0.21 (0.10-0.45) | | |
| Common within-network between-study variance | 0.05 (0.00-0.40) | Common within-network between-study variance | 0.04 (0.00-0.39) | Common within-network between-study variance | 0.04 (0.00-0.36) | Common within-network between-study variance | 0.10 (0.00-1.42) |
| Regression coefficient (log OR scale) | -0.052 (-0.223-0.106) | Regression coefficient (log OR scale) | 0.000 (-0.002-0.001) | Regression coefficient (log OR scale) | -0.009 (-0.053-0.032) | Regression coefficient (log OR scale) | -0.047 (-0.197-0.088) |

**eTable 40. Meta-regression Analysis Corresponding SUCRA values: Need for repeat pharmacotherapy**

| Mean Gestational Age | | Mean Birth Weight | | Year of Publication | | Age of initiation of Treatment | |
|---|---|---|---|---|---|---|---|
| Treatment | Mean SUCRA (SD) | Treatment | Mean SUCRA (SD) | Treatment | Mean SUCRA (SD) | Treatment | Mean SUCRA (SD) |
| PARAPO | 0.71 (0.19) | PARAPO | 0.71 (0.19) | PARAPO | 0.68 (0.24) | PARAPO | 0.87 (0.21) |
| INDOTHERS | 0.59 (0.16) | INDOTHERS | 0.60 (0.16) | INDOTHERS | 0.57 (0.17) | INDOTHERS | 0.78 (0.17) |
| INDOIVCONT | 0.36 (0.23) | INDOIVCONT | 0.37 (0.24) | INDOIVCONT | 0.44 (0.28) | INDOIVCONT | 0.49 (0.29) |
| INDOIV | 0.34 (0.10) | INDOIV | 0.34 (0.10) | INDOIV | 0.36 (0.13) | INDOIV | 0.45 (0.18) |
| IBUPOHIGHDOSE | 0.89 (0.17) | IBUPOHIGHDOSE | 0.88 (0.18) | IBUPOHIGHDOSE | 0.88 (0.18) | IBUPO | 0.62 (0.21) |
| IBUPO | 0.64 (0.13) | IBUPO | 0.64 (0.13) | IBUPO | 0.63 (0.14) | IBUIV | 0.29 (0.16) |
| IBUIVHIGHDOSE | 0.79 (0.22) | IBUIVHIGHDOSE | 0.79 (0.23) | IBUIVHIGHDOSE | 0.75 (0.25) | PLAC/NORX | 0.01 (0.04) |
| IBUIV | 0.17 (0.07) | IBUIV | 0.17 (0.07) | IBUIV | 0.18 (0.08) | | |
| PLAC/NORX | 0.00 (0.02) | PLAC/NORX | 0.00 (0.01) | PLAC/NORX | 0.00 (0.01) | | |

**eTable 41. Meta-regression Analysis Results for Outcome: Neonatal Mortality**

| *Meta-regression NMA Results For Mean Gestational Age* | | *Meta-regression NMA Results For Mean Birth Weight* | | *Meta-regression NMA Results For Year of Publication* | | *Meta-regression NMA Results For Age of Initiation of Treatment* | |
|---|---|---|---|---|---|---|---|
| **Treatment Comparison** | **Network Meta-regression OR (95% CrI)** | **Treatment Comparison** | **Network Meta-regression OR (95% CrI)** | **Treatment Comparison** | **Network Meta-regression OR (95% CrI)** | **Treatment Comparison** | **Network Meta-regression OR (95% CrI)** |
| PARAPO *versus* | | PARAPO *versus* | | PARAPO *versus* | | INDOTHERS *versus* | |
| INDOTHERS | 0.75 (0.29-1.91) | INDOTHERS | 0.80 (0.32-2.01) | INDOTHERS | 0.78 (0.31-1.98) | INDOIVCONT | 0.77 (0.09-6.22) |
| INDOIVCONT | 0.40 (0.06-2.44) | INDOIVCONT | 0.42 (0.06-2.32) | INDOIVCONT | 0.44 (0.06-2.86) | INDOIV | 0.94 (0.46-1.85) |
| INDOIV | 0.86 (0.37-2.01) | INDOIV | 0.88 (0.39-2.04) | INDOIV | 0.91 (0.36-2.30) | IBUPO | 2.33 (0.80-7.46) |
| IBUPOHIGHDOSE | 0.37 (0.01-6.53) | IBUPOHIGHDOSE | 0.45 (0.01-7.33) | IBUPOHIGHDOSE | 0.43 (0.01-8.05) | IBUIVCONT | 1.17 (0.02-55.69) |
| IBUPO | 1.00 (0.46-2.24) | IBUPO | 1.05 (0.49-2.27) | IBUPO | 1.07 (0.47-2.55) | IBUIV | 1.12 (0.47-2.73) |
| IBUIVHIGHDOSE | 0.72 (0.12-4.73) | IBUIVHIGHDOSE | 0.86 (0.15-5.03) | IBUIVHIGHDOSE | 0.79 (0.15-4.47) | PLAC/NORX | 0.65 (0.32-1.26) |
| IBUIVCONT | 0.91 (0.02-37.98) | IBUIVCONT | 1.03 (0.02-58.09) | IBUIVCONT | 0.89 (0.02-29.27) | INDOIVCONT *versus* | |
| IBUIV | 0.94 (0.38-2.40) | IBUIV | 0.97 (0.41-2.40) | IBUIV | 1.03 (0.37-2.97) | INDOIV | 1.19 (0.16-9.46) |
| PLAC/NORX | 0.56 (0.22-1.39) | PLAC/NORX | 0.61 (0.25-1.49) | PLAC/NORX | 0.61 (0.23-1.70) | IBUPO | 3.04 (0.31-30.75) |
| INDOTHERS *versus* | | INDOTHERS *versus* | | INDOTHERS *versus* | | IBUIVCONT | 1.55 (0.02-95.81) |
| INDOIVCONT | 0.54 (0.08-2.84) | INDOIVCONT | 0.53 (0.08-2.59) | INDOIVCONT | 0.57 (0.09-2.97) | IBUIV | 1.45 (0.23-9.84) |
| INDOIV | 1.15 (0.74-1.82) | INDOIV | 1.11 (0.71-1.73) | INDOIV | 1.18 (0.73-1.88) | PLAC/NORX | 0.82 (0.11-6.57) |
| IBUPOHIGHDOSE | 0.50 (0.01-7.63) | IBUPOHIGHDOSE | 0.56 (0.02-8.37) | IBUPOHIGHDOSE | 0.57 (0.01-9.35) | INDOIV *versus* | |
| IBUPO | 1.35 (0.71-2.56) | IBUPO | 1.31 (0.67-2.55) | IBUPO | 1.38 (0.70-2.71) | IBUPO | 2.48 (0.84-8.16) |
| IBUIVHIGHDOSE | 0.97 (0.19-4.90) | IBUIVHIGHDOSE | 1.07 (0.23-5.25) | IBUIVHIGHDOSE | 1.02 (0.21-4.92) | IBUIVCONT | 1.26 (0.02-58.52) |
| IBUIVCONT | 1.19 (0.03-46.44) | IBUIVCONT | 1.28 (0.03-70.42) | IBUIVCONT | 1.14 (0.02-37.29) | IBUIV | 1.20 (0.62-2.45) |
| IBUIV | 1.28 (0.69-2.41) | IBUIV | 1.21 (0.66-2.32) | IBUIV | 1.33 (0.67-2.60) | PLAC/NORX | 0.69 (0.39-1.24) |
| PLAC/NORX | 0.74 (0.44-1.28) | PLAC/NORX | 0.75 (0.45-1.32) | PLAC/NORX | 0.79 (0.43-1.47) | IBUPO *versus* | |
| INDOIVCONT *versus* | | INDOIVCONT *versus* | | INDOIVCONT *versus* | | IBUIVCONT | 0.50 (0.01-25.72) |
| INDOIV | 2.14 (0.42-13.28) | INDOIV | 2.10 (0.47-12.92) | INDOIV | 2.07 (0.43-11.65) | IBUIV | 0.48 (0.13-1.63) |
| IBUPOHIGHDOSE | 0.95 (0.02-25.30) | IBUPOHIGHDOSE | 1.05 (0.03-29.01) | IBUPOHIGHDOSE | 0.95 (0.02-25.98) | PLAC/NORX | 0.28 (0.09-0.79) |
| IBUPO | 2.51 (0.45-16.41) | IBUPO | 2.51 (0.51-15.12) | IBUPO | 2.42 (0.48-14.84) | IBUIVCONT *versus* | |
| IBUIVHIGHDOSE | 1.78 (0.19-18.14) | IBUIVHIGHDOSE | 2.11 (0.25-21.54) | IBUIVHIGHDOSE | 1.81 (0.21-17.39) | IBUIV | 0.97 (0.02-56.04) |
| IBUIVCONT | 2.23 (0.04-136.70) | IBUIVCONT | 2.56 (0.05-179.90) | IBUIVCONT | 1.98 (0.03-86.87) | PLAC/NORX | 0.54 (0.01-36.77) |
| IBUIV | 2.37 (0.48-13.56) | IBUIV | 2.29 (0.54-13.45) | IBUIV | 2.30 (0.51-12.69) | IBUIV *versus* | |
| PLAC/NORX | 1.39 (0.25-8.66) | PLAC/NORX | 1.43 (0.31-8.98) | PLAC/NORX | 1.38 (0.29-7.86) | PLAC/NORX | 0.58 (0.28-1.16) |
| INDOIV *versus* | | INDOIV *versus* | | INDOIV *versus* | | | |
| IBUPOHIGHDOSE | 0.43 (0.01-6.88) | IBUPOHIGHDOSE | 0.51 (0.02-7.81) | IBUPOHIGHDOSE | 0.47 (0.01-8.00) | | |
| IBUPO | 1.17 (0.65-2.11) | IBUPO | 1.18 (0.65-2.17) | IBUPO | 1.17 (0.65-2.17) | | |
| IBUIVHIGHDOSE | 0.84 (0.17-4.36) | IBUIVHIGHDOSE | 0.97 (0.21-4.67) | IBUIVHIGHDOSE | 0.87 (0.19-4.05) | | |
| IBUIVCONT | 1.04 (0.03-39.00) | IBUIVCONT | 1.16 (0.03-62.43) | IBUIVCONT | 0.97 (0.02-30.28) | | |
| IBUIV | 1.10 (0.68-1.81) | IBUIV | 1.10 (0.67-1.80) | IBUIV | 1.13 (0.69-1.87) | | |
| PLAC/NORX | 0.65 (0.40-1.04) | PLAC/NORX | 0.68 (0.42-1.09) | PLAC/NORX | 0.67 (0.42-1.07) | | |
| IBUPOHIGHDOSE *versus* | | IBUPOHIGHDOSE *versus* | | IBUPOHIGHDOSE *versus* | | | |
| IBUPO | 2.72 (0.18-90.56) | IBUPO | 2.31 (0.16-65.91) | IBUPO | 2.48 (0.16-103.90) | | |
| IBUIVHIGHDOSE | 2.00 (0.08-90.59) | IBUIVHIGHDOSE | 1.94 (0.09-74.02) | IBUIVHIGHDOSE | 1.84 (0.07-86.77) | | |
| IBUIVCONT | 2.50 (0.02-350.10) | IBUIVCONT | 2.59 (0.03-426.10) | IBUIVCONT | 2.22 (0.02-254.30) | | |
| IBUIV | 2.55 (0.15-90.95) | IBUIV | 2.15 (0.14-65.74) | IBUIV | 2.40 (0.15-105.50) | | |
| PLAC/NORX | 1.52 (0.09-49.98) | PLAC/NORX | 1.33 (0.09-40.32) | PLAC/NORX | 1.43 (0.08-64.01) | | |
| IBUPO *versus* | | IBUPO *versus* | | IBUPO *versus* | | | |
| IBUIVHIGHDOSE | 0.72 (0.13-3.79) | IBUIVHIGHDOSE | 0.82 (0.16-4.15) | IBUIVHIGHDOSE | 0.73 (0.15-3.60) | | |
| IBUIVCONT | 0.89 (0.03-33.53) | IBUIVCONT | 0.97 (0.02-51.56) | IBUIVCONT | 0.82 (0.02-25.78) | | |
| IBUIV | 0.95 (0.50-1.82) | IBUIV | 0.92 (0.48-1.78) | IBUIV | 0.97 (0.49-1.85) | | |
| PLAC/NORX | 0.55 (0.29-1.02) | PLAC/NORX | 0.58 (0.31-1.07) | PLAC/NORX | 0.57 (0.30-1.09) | | |
| IBUIVHIGHDOSE *versus* | | IBUIVHIGHDOSE *versus* | | IBUIVHIGHDOSE *versus* | | | |
| IBUIVCONT | 1.19 (0.03-62.65) | IBUIVCONT | 1.19 (0.02-83.28) | IBUIVCONT | 1.07 (0.02-43.68) | | |
| IBUIV | 1.31 (0.29-6.19) | IBUIV | 1.14 (0.25-5.07) | IBUIV | 1.30 (0.30-5.91) | | |
| PLAC/NORX | 0.78 (0.15-4.06) | PLAC/NORX | 0.70 (0.15-3.31) | PLAC/NORX | 0.77 (0.16-3.87) | | |
| IBUIVCONT *versus* | | IBUIVCONT *versus* | | IBUIVCONT *versus* | | | |
| IBUIV | 1.05 (0.03-35.26) | IBUIV | 0.95 (0.02-40.48) | IBUIV | 1.18 (0.04-54.37) | | |
| PLAC/NORX | 0.63 (0.02-21.65) | PLAC/NORX | 0.59 (0.01-26.33) | PLAC/NORX | 0.69 (0.02-33.84) | | |
| IBUIV *versus* | | IBUIV *versus* | | IBUIV *versus* | | | |
| PLAC/NORX | 0.59 (0.33-1.03) | PLAC/NORX | 0.62 (0.35-1.11) | PLAC/NORX | 0.59 (0.33-1.03) | | |
| Common within-network between-study variance | 0.04 (0.00-0.36) | Common within-network between-study variance | 0.04 (0.00-0.36) | Common within-network between-study variance | 0.04 (0.00-0.36) | Common within-network between-study variance | 0.06 (0.00-0.71) |
| Regression coefficient (log OR scale) | 0.013 (-0.142-0.160) | Regression coefficient (log OR scale) | 0.000 (-0.001-0.001) | Regression coefficient (log OR scale) | -0.004 (-0.034-0.025) | Regression coefficient (log OR scale) | 0.017 (-0.064-0.099) |

**eTable 42. Meta-regression Analysis Corresponding SUCRA values: Neonatal Mortality**

| Mean Gestational Age | | Mean Birth Weight | | Year of Publication | | Age of initiation of Treatment | |
|---|---|---|---|---|---|---|---|
| **Treatment** | **Mean SUCRA (SD)** | **Treatment** | **Mean SUCRA (SD)** | **Treatment** | **Mean SUCRA (SD)** | **Treatment** | **Mean SUCRA (SD)** |
| PARAPO | 0.67 (0.26) | PARAPO | 0.64 (0.27) | PARAPO | 0.63 (0.28) | INDOTHERS | 0.50 (0.23) |
| INDOTHERS | 0.47 (0.20) | INDOTHERS | 0.48 (0.21) | INDOTHERS | 0.45 (0.21) | INDOIVCONT | 0.39 (0.36) |
| INDOIVCONT | 0.26 (0.29) | INDOIVCONT | 0.24 (0.28) | INDOIVCONT | 0.27 (0.30) | INDOIV | 0.45 (0.20) |
| INDOIV | 0.59 (0.18) | INDOIV | 0.57 (0.18) | INDOIV | 0.59 (0.18) | IBUPO | 0.87 (0.17) |
| IBUPOHIGHDOSE | 0.32 (0.38) | IBUPOHIGHDOSE | 0.34 (0.38) | IBUPOHIGHDOSE | 0.34 (0.39) | IBUIVCONT | 0.53 (0.43) |
| IBUPO | 0.70 (0.20) | IBUPO | 0.70 (0.20) | IBUPO | 0.71 (0.19) | IBUIV | 0.59 (0.21) |
| IBUIVHIGHDOSE | 0.49 (0.34) | IBUIVHIGHDOSE | 0.54 (0.35) | IBUIVHIGHDOSE | 0.50 (0.34) | PLAC/NORX | 0.17 (0.16) |
| IBUIVCONT | 0.55 (0.42) | IBUIVCONT | 0.57 (0.42) | IBUIVCONT | 0.53 (0.42) | | |
| IBUIV | 0.67 (0.19) | IBUIV | 0.65 (0.20) | IBUIV | 0.69 (0.19) | | |
| PLAC/NORX | 0.27 (0.15) | PLAC/NORX | 0.26 (0.15) | PLAC/NORX | 0.28 (0.16) | | |

**eTable 43. Meta-regression Analysis Results for Outcome: Risk of Necrotizing Enterocolitis**

| *Meta-regression NMA Results For Mean Gestational Age* | | *Meta-regression NMA Results For Mean Birth Weight* | | *Meta-regression NMA Results For Year of Publication* | | *Meta-regression NMA Results For Age of Initiation of Treatment* | |
|---|---|---|---|---|---|---|---|
| **Treatment Comparison** | **Network Meta-regression OR (95% CrI)** | **Treatment Comparison** | **Network Meta-regression OR (95% CrI)** | **Treatment Comparison** | **Network Meta-regression OR (95% CrI)** | **Treatment Comparison** | **Network Meta-regression OR (95% CrI)** |
| PARAPO *versus* | | PARAPO *versus* | | PARAPO *versus* | | PARAPO *versus* | |
| INDOTHERS | 0.29 (0.08-1.02) | INDOTHERS | 0.27 (0.07-0.91) | INDOTHERS | 0.27 (0.08-0.92) | INDOTHERS | 0.10 (0.01-0.79) |
| INDOIVCONT | 1.06 (0.20-5.76) | INDOIVCONT | 1.03 (0.19-5.65) | INDOIVCONT | 0.94 (0.18-5.59) | INDOIVCONT | 0.57 (0.04-6.52) |
| INDOIV | 0.45 (0.15-1.32) | INDOIV | 0.43 (0.13-1.29) | INDOIV | 0.42 (0.14-1.29) | INDOIV | 0.32 (0.04-2.36) |
| IBUPOHIGHDOSE | 1.62 (0.23-13.13) | IBUPOHIGHDOSE | 1.46 (0.21-11.53) | IBUPOHIGHDOSE | 1.47 (0.21-10.29) | IBUPO | 0.73 (0.14-3.69) |
| IBUPO | 1.16 (0.44-3.16) | IBUPO | 1.12 (0.39-2.99) | IBUPO | 1.08 (0.42-2.97) | IBUIVCONT | 1.10 (0.07-15.26) |
| IBUIVHIGHDOSE | 0.49 (0.05-4.82) | IBUIVHIGHDOSE | 0.43 (0.04-3.88) | IBUIVHIGHDOSE | 0.46 (0.05-3.44) | IBUIV | 0.42 (0.04-3.30) |
| IBUIVCONT | 1.81 (0.27-14.88) | IBUIVCONT | 1.69 (0.25-13.47) | IBUIVCONT | 1.70 (0.28-12.97) | PLAC/NORX | 0.49 (0.06-3.75) |
| IBUIV | 0.66 (0.22-2.11) | IBUIV | 0.65 (0.20-1.98) | IBUIV | 0.63 (0.20-2.09) | INDOTHERS *versus* | |
| PLAC/NORX | 0.75 (0.21-2.69) | PLAC/NORX | 0.71 (0.19-2.77) | PLAC/NORX | 0.72 (0.21-2.53) | INDOIVCONT | 5.51 (0.95-32.44) |
| INDOTHERS *versus* | | INDOTHERS *versus* | | INDOTHERS *versus* | | INDOIV | 3.00 (1.31-7.42) |
| INDOIVCONT | 3.54 (0.82-16.15) | INDOIVCONT | 3.81 (0.89-16.83) | INDOIVCONT | 3.49 (0.80-16.74) | IBUPO | 7.02 (2.00-29.92) |
| INDOIV | 1.51 (0.84-2.77) | INDOIV | 1.57 (0.90-2.74) | INDOIV | 1.54 (0.89-2.78) | IBUIVCONT | 10.59 (1.60-78.09) |
| IBUPOHIGHDOSE | 5.44 (0.91-37.59) | IBUPOHIGHDOSE | 5.43 (0.90-35.52) | IBUPOHIGHDOSE | 5.30 (0.88-34.53) | IBUIV | 4.01 (1.38-12.33) |
| IBUPO | 3.92 (1.75-9.10) | IBUPO | 4.03 (1.83-9.26) | IBUPO | 4.04 (1.80-9.27) | PLAC/NORX | 4.64 (1.52-14.91) |
| IBUIVHIGHDOSE | 1.66 (0.23-11.82) | IBUIVHIGHDOSE | 1.57 (0.21-12.14) | IBUIVHIGHDOSE | 1.68 (0.23-12.04) | INDOIVCONT *versus* | |
| IBUIVCONT | 6.08 (1.14-41.00) | IBUIVCONT | 6.20 (1.17-38.04) | IBUIVCONT | 6.25 (1.16-43.54) | INDOIV | 0.56 (0.12-2.57) |
| IBUIV | 2.25 (1.07-4.94) | IBUIV | 2.33 (1.14-5.04) | IBUIV | 2.32 (1.07-5.06) | IBUPO | 1.30 (0.19-9.64) |
| PLAC/NORX | 2.51 (1.05-6.33) | PLAC/NORX | 2.61 (1.07-6.53) | PLAC/NORX | 2.66 (1.06-6.77) | IBUIVCONT | 1.92 (0.23-17.03) |
| INDOIVCONT *versus* | | INDOIVCONT *versus* | | INDOIVCONT *versus* | | IBUIV | 0.74 (0.18-2.89) |
| INDOIV | 0.42 (0.11-1.68) | INDOIV | 0.41 (0.10-1.58) | INDOIV | 0.45 (0.11-1.72) | PLAC/NORX | 0.85 (0.17-4.41) |
| IBUPOHIGHDOSE | 1.54 (0.17-15.10) | IBUPOHIGHDOSE | 1.46 (0.16-12.39) | IBUPOHIGHDOSE | 1.51 (0.17-12.82) | INDOIV *versus* | |
| IBUPO | 1.11 (0.26-4.62) | IBUPO | 1.07 (0.24-4.54) | IBUPO | 1.15 (0.26-4.57) | IBUPO | 2.33 (0.65-9.44) |
| IBUIVHIGHDOSE | 0.47 (0.05-4.49) | IBUIVHIGHDOSE | 0.41 (0.04-3.71) | IBUIVHIGHDOSE | 0.47 (0.05-4.61) | IBUIVCONT | 3.46 (0.61-21.64) |
| IBUIVCONT | 1.72 (0.23-15.09) | IBUIVCONT | 1.68 (0.21-13.13) | IBUIVCONT | 1.80 (0.23-14.99) | IBUIV | 1.32 (0.68-2.59) |
| IBUIV | 0.63 (0.17-2.23) | IBUIV | 0.63 (0.17-2.14) | IBUIV | 0.67 (0.18-2.32) | PLAC/NORX | 1.53 (0.70-3.45) |
| PLAC/NORX | 0.71 (0.17-3.20) | PLAC/NORX | 0.70 (0.15-2.97) | PLAC/NORX | 0.75 (0.17-3.28) | IBUPO *versus* | |
| INDOIV *versus* | | INDOIV *versus* | | INDOIV *versus* | | IBUIVCONT | 1.48 (0.19-12.80) |
| IBUPOHIGHDOSE | 3.65 (0.61-23.87) | IBUPOHIGHDOSE | 3.46 (0.62-21.59) | IBUPOHIGHDOSE | 3.39 (0.58-20.85) | IBUIV | 0.56 (0.14-2.23) |
| IBUPO | 2.62 (1.34-5.29) | IBUPO | 2.58 (1.34-5.13) | IBUPO | 2.60 (1.31-5.19) | PLAC/NORX | 0.66 (0.17-2.47) |
| IBUIVHIGHDOSE | 1.11 (0.16-7.34) | IBUIVHIGHDOSE | 1.00 (0.14-7.39) | IBUIVHIGHDOSE | 1.08 (0.15-7.41) | IBUIVCONT *versus* | |
| IBUIVCONT | 4.06 (0.82-24.84) | IBUIVCONT | 3.96 (0.80-22.86) | IBUIVCONT | 3.98 (0.82-25.51) | IBUIV | 0.38 (0.07-1.87) |
| IBUIV | 1.50 (0.86-2.57) | IBUIV | 1.50 (0.90-2.61) | IBUIV | 1.49 (0.85-2.59) | PLAC/NORX | 0.45 (0.07-2.73) |
| PLAC/NORX | 1.68 (0.79-3.55) | PLAC/NORX | 1.66 (0.81-3.53) | PLAC/NORX | 1.70 (0.81-3.62) | IBUIV *versus* | |
| IBUPOHIGHDOSE *versus* | | IBUPOHIGHDOSE *versus* | | IBUPOHIGHDOSE *versus* | | PLAC/NORX | 1.16 (0.53-2.62) |
| IBUPO | 0.72 (0.13-3.61) | IBUPO | 0.75 (0.14-3.81) | IBUPO | 0.76 (0.15-3.90) | | |
| IBUIVHIGHDOSE | 0.31 (0.02-3.52) | IBUIVHIGHDOSE | 0.29 (0.02-3.27) | IBUIVHIGHDOSE | 0.32 (0.02-3.74) | | |
| IBUIVCONT | 1.12 (0.10-12.50) | IBUIVCONT | 1.15 (0.11-13.03) | IBUIVCONT | 1.21 (0.11-14.20) | | |
| IBUIV | 0.41 (0.06-2.35) | IBUIV | 0.43 (0.07-2.51) | IBUIV | 0.44 (0.07-2.50) | | |
| PLAC/NORX | 0.46 (0.07-2.82) | PLAC/NORX | 0.48 (0.07-2.89) | PLAC/NORX | 0.50 (0.08-3.11) | | |
| IBUPO *versus* | | IBUPO *versus* | | IBUPO *versus* | | | |
| IBUIVHIGHDOSE | 0.43 (0.06-2.95) | IBUIVHIGHDOSE | 0.38 (0.05-2.75) | IBUIVHIGHDOSE | 0.42 (0.06-2.82) | | |
| IBUIVCONT | 1.55 (0.30-9.83) | IBUIVCONT | 1.52 (0.30-9.33) | IBUIVCONT | 1.55 (0.29-10.41) | | |
| IBUIV | 0.57 (0.28-1.15) | IBUIV | 0.58 (0.29-1.15) | IBUIV | 0.58 (0.28-1.14) | | |
| PLAC/NORX | 0.64 (0.28-1.45) | PLAC/NORX | 0.64 (0.28-1.46) | PLAC/NORX | 0.66 (0.28-1.49) | | |
| IBUIVHIGHDOSE *versus* | | IBUIVHIGHDOSE *versus* | | IBUIVHIGHDOSE *versus* | | | |
| IBUIVCONT | 3.68 (0.33-47.36) | IBUIVCONT | 4.02 (0.39-50.24) | IBUIVCONT | 3.68 (0.35-46.45) | | |
| IBUIV | 1.34 (0.22-8.78) | IBUIV | 1.49 (0.24-10.33) | IBUIV | 1.37 (0.21-9.41) | | |
| PLAC/NORX | 1.50 (0.22-10.76) | PLAC/NORX | 1.65 (0.23-13.45) | PLAC/NORX | 1.60 (0.23-12.08) | | |
| IBUIVCONT *versus* | | IBUIVCONT *versus* | | IBUIVCONT *versus* | | | |
| IBUIV | 0.37 (0.06-1.66) | IBUIV | 0.38 (0.07-1.66) | IBUIV | 0.38 (0.06-1.71) | | |
| PLAC/NORX | 0.41 (0.06-2.20) | PLAC/NORX | 0.42 (0.07-2.10) | PLAC/NORX | 0.43 (0.06-2.16) | | |
| IBUIV *versus* | | IBUIV *versus* | | IBUIV *versus* | | | |
| PLAC/NORX | 1.12 (0.55-2.35) | PLAC/NORX | 1.11 (0.54-2.29) | PLAC/NORX | 1.15 (0.55-2.33) | | |
| Common within-network between-study variance | 0.05 (0.00-0.45) | Common within-network between-study variance | 0.04 (0.00-0.46) | Common within-network between-study variance | 0.04 (0.00-0.44) | Common within-network between-study variance | 0.05 (0.00-0.73) |
| Regression coefficient (log OR scale) | -0.022 (-0.192-0.143) | Regression coefficient (log OR scale) | 0.000 (-0.001-0.001) | Regression coefficient (log OR scale) | 0.003 (-0.039-0.048) | Regression coefficient (log OR scale) | 0.008 (-0.086-0.106) |

**eTable 44. Meta-regression Analysis Corresponding SUCRA values: Risk of Necrotizing Enterocolitis**

| Mean Gestational Age | | Mean Birth Weight | | Year of Publication | | Age of initiation of Treatment | |
|---|---|---|---|---|---|---|---|
| **Treatment** | **Mean SUCRA (SD)** | **Treatment** | **Mean SUCRA (SD)** | **Treatment** | **Mean SUCRA (SD)** | **Treatment** | **Mean SUCRA (SD)** |
| PARAPO | 0.61 (0.25) | PARAPO | 0.64 (0.24) | PARAPO | 0.64 (0.24) | PARAPO | 0.75 (0.29) |
| INDOTHERS | 0.06 (0.09) | INDOTHERS | 0.06 (0.08) | INDOTHERS | 0.06 (0.09) | INDOTHERS | 0.01 (0.05) |
| INDOIVCONT | 0.63 (0.27) | INDOIVCONT | 0.64 (0.27) | INDOIVCONT | 0.61 (0.28) | INDOIVCONT | 0.57 (0.29) |
| INDOIV | 0.20 (0.11) | INDOIV | 0.21 (0.11) | INDOIV | 0.21 (0.11) | INDOIV | 0.27 (0.16) |
| IBUPOHIGHDOSE | 0.76 (0.27) | IBUPOHIGHDOSE | 0.75 (0.28) | IBUPOHIGHDOSE | 0.74 (0.28) | IBUPO | 0.68 (0.23) |
| IBUPO | 0.72 (0.14) | IBUPO | 0.71 (0.15) | IBUPO | 0.71 (0.15) | IBUIVCONT | 0.79 (0.25) |
| IBUIVHIGHDOSE | 0.33 (0.32) | IBUIVHIGHDOSE | 0.30 (0.31) | IBUIVHIGHDOSE | 0.32 (0.31) | IBUIV | 0.43 (0.17) |
| IBUIVCONT | 0.80 (0.24) | IBUIVCONT | 0.80 (0.24) | IBUIVCONT | 0.80 (0.24) | PLAC/NORX | 0.51 (0.20) |
| IBUIV | 0.41 (0.14) | IBUIV | 0.42 (0.13) | IBUIV | 0.41 (0.14) | | |
| PLAC/NORX | 0.48 (0.19) | PLAC/NORX | 0.48 (0.19) | PLAC/NORX | 0.49 (0.19) | | |

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# CHAPTER FOUR

# CONCLUSION

Management of the PDA in preterm infants has remained one of the most controversial topics in neonatal intensive care (1). In spite of numerous randomized controlled trials over the last 40 years and a number of Cochrane reviews, debate still exists on whether treatment is at all required and if yes what is the best modality of treatment (2). The availability of newer pharmacotherapeutic agents like acetaminophen along with different doses and routes of established pharmacotherapeutic agents like ibuprofen has further contributed to the dilemma among clinicians. With the help of Bayesian random-effects network meta-analysis, our systematic review puts available evidence into perspective with respect to all the important effectiveness and safety outcomes. Furthermore, assessment of the strength of evidence using the GRADE guidelines will help clinicians make evidence-based decisions when it comes to management of the PDA in preterm infants. This will also help identify important gaps in knowledge that will drive further research on this topic.

*Major findings from the network meta-analysis*

In this systematic review and network meta-analysis, 68 RCTs including 4802 infants were evaluated to compare the relative effectiveness and safety of ten different modalities of pharmacotherapy using indomethacin, ibuprofen and acetaminophen to treat a hemodynamically significant PDA in preterm infants (3). Oral high dose ibuprofen ranked the best pharmacotherapeutic option to close a hemodynamically significant PDA and prevent surgical PDA ligation. Oral standard dose ibuprofen was associated with lowest odds of death and BPD. Continuous infusion of IV ibuprofen and oral high dose ibuprofen were associated with the lowest odds of NEC. The quality of evidence was high or moderate for 20 of 45 comparisons for the primary outcome while it was uniformly lower for most of the secondary outcomes in view

of the imprecision resulting from wide CrIs on the NMA. The SUCRA values marginally varied on sensitivity analysis of the high quality studies with the best ranked options remaining unchanged across all outcomes. The only notable exception was NEC where oral high dose ibuprofen ranked best among the high quality studies. The overall high ranking probabilities across outcomes suggest that high-dose and standard dose oral ibuprofen as well as oral acetaminophen could be effective alternatives to the standard IV ibuprofen and indomethacin regimens currently used to close an hs-PDA. Interestingly, placebo or no treatment for hs-PDA did not significantly change the likelihood of mortality, NEC or IVH. No statistically significant difference in mortality or IVH rates was observed with any of the interventions based on available evidence, which suggests that active pharmacological closure of a hemodynamically significant PDA may not be associated with lower mortality or IVH in preterm infants (3).

*Strengths of the study*

To our knowledge this network meta-analysis is the largest yet performed in neonatal medicine. The protocol for the study was published in an open access journal to ensure there were no major deviations from the protocol in the final analysis (4). Minor protocol deviations have been elaborated in detail in the supplementary information in chapter 3 (3). Use of a NMA framework has enabled comparisons among currently used PDA pharmacotherapy modalities, which has increased the statistical power by taking advantage of direct and indirect treatment comparisons. This NMA followed the ISPOR guidelines, used novel methods for assessing the quality of evidence recently recommended by the GRADE working group and employed network meta-regression to account for potential sources of heterogeneity (5). Heat-maps based on SUCRA values have been used to provide clinical decision makers with a visual guide to choose the right pharmacotherapeutic agent based on their effectiveness and safety priorities.

*Limitations of the study*

The limitations of the study are as follows. First, this NMA 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 co-interventions, which have changed over last 4 decades. This was accounted for in the meta-regression analysis conducted for the most important outcomes and controlling for the effect modifiers (3). 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 one. 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 a 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.

*Future directions*

As the results suggest that higher doses of oral and IV ibuprofen as well as oral acetaminophen could be better alternatives to the currently used standard ibuprofen and indomethacin regimens, well-designed trials with optimal sample sizes using oral acetaminophen, oral and IV high dose ibuprofen are needed to establish their effectiveness and safety in order to replace current regimens. The heat maps show that there is dearth of data on need for repeat pharmacotherapy with continuous infusion of IV ibuprofen; BPD with oral high dose ibuprofen and continuous infusion of IV indomethacin; and oliguria with placebo/no treatment. If further studies are done

with the said modalities then data on the above mentioned outcomes should be obtained to generate novel evidence that could guide clinicians in their decision making. This underscores the need to explore clinical outcomes (such as NEC, BPD, IVH, mortality) beyond immediate PDA closure in future studies.

On the other hand, as it was interestingly noted that placebo or no treatment for PDA did not significantly change the odds of mortality, NEC or IVH, it raises some very pertinent questions: Does active pharmacological closure of a hemodynamically significant PDA necessarily improve clinical outcomes? Should we stop treating all PDAs or is there a specific subgroup of preterm infants with PDA based on the degree of hemodynamic significance who will benefit from effective pharmacotherapy? This emphasizes the need to better define PDA treatment criteria with precise echocardiographic measurements in future studies. And with increasing emphasis on conservative management of PDA in recent times, these results may encourage researchers to revisit placebo controlled randomized trials against established pharmacotherapeutic options. A number of such RCTs are under way that should provide answers to these clinically relevant questions. For example, the BeNeDuctus Trial (https://clinicaltrials.gov/ct2/show/results/NCT02884219) and the BabyOSCAR trial (EudraCT No: 2013-005336-23) explores whether early treatment of the PDA with ibuprofen within the first 72 hours after birth as compared to conservative management affects clinical outcomes such as mortality, BPD and NEC (6,7). The TOLERATE trial (https://clinicaltrials.gov/ct2/show/NCT01958320) also explores this research question with early treatment being defined as within 5 days instead of 72 hours (8). Another similar trial, known as ‘Management of the PDA trial (PDA)’ (https://clinicaltrials.gov/ct2/show/NCT03456336) is a pragmatic randomized multicenter, effectiveness study comparing active treatment of a

symptomatic patent ductus arteriosus (sPDA) to expectant management (9). Hopefully the results of these and similar studies would help to answer some of the questions generated through our systematic review.

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