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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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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 practising neonatologist as to which one to choose as a therapeutic option. Our objectives are to determine the relative merits of the available pharmacotherapeutic options for the management of PDA.

Methods and Analysis: We will conduct a systematic review of all randomised controlled trials 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, necrotising enterocolitis, gastrointestinal bleeding, time to full enteral feeds and oliguria. We will search Medline, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) as well as grey literature resources. Two reviewers will independently screen titles and abstracts, review full texts, extract information, and assess the risk of bias (ROB) and the confidence in the estimate (with Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach). Subgroup analysis according to gestational age, birth weight, different doses of interventions, time of administration of the first dose of the intervention, and echocardiographic definition of haemodynamically 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 are 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. On

Strengths and limitations of this study

- This systematic review and network meta-analysis will assess the effectiveness and safety of the interventions used to treat haemodynamically significant patent ductus arteriosus in preterm infants. It will be the first network meta-analysis 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 Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the certainty of the evidence.
- This study will, in addition to the traditional early outcomes during the hospitalisation, search for evidence related to long-term neurodevelopmental outcomes.

the basis of the nature of its design, no ethics approval is necessary for this study.
Trial registration number: CRD42015015797.

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 and 24 hours 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 with a birth weight of <1000 g, 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 comorbidities such as necrotising enterocolitis (NEC), bronchopulmonary dysplasia and intraventricular haemorrhage (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 (ECHO) 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, owing to its potent vasoconstrictive effect, it has been found to be associated with brain white matter injury, NEC, 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]

Randomised controlled trials (RCTs) comparing indomethacin with placebo, as well as oral and intravenous ibuprofen with placebo, have been conducted. The most recent Cochrane review on the use of ibuprofen for PDA has combined the aforementioned studies into a comprehensive meta-analysis which showed that ibuprofen was much safer compared with 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 summarised 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 practising neonatologist as to which one to choose as a therapeutic option. As the number of available treatment options increases, 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 such as 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 an insufficient number of participants or there were methodological flaws in the trials.

The use of network meta-analysis (NMA) 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 NMA as a highly valuable tool to evaluate and rank treatment options according to their safety and effectiveness.[20] Bayesian NMA has 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[23] in 2011 comparing indomethacin, ibuprofen and placebo using a frequentist approach. However, more evidence regarding ibuprofen and indomethacin has been generated since then, as well as 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 NMA.

METHODS AND DESIGN
This systematic review and NMA protocol has been registered on the 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 2016 the following databases: Medline and Embase through the Ovid platform, and 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 online supplementary appendix A.

We will seek registered details of selected trials in the US National Institutes of Health resource (http://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 birthweight infants (<2500 g) with a PDA diagnosed clinically or 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, their definitions and their measures are detailed in table 1.

We will exclude studies of infants with congenital structural heart disease or other congenital anomalies. The trial has 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 <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 their eligibility (SM, IDF, MET or 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 or 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 pretested and standardised Microsoft Excel data extraction form will be used to extract the data from the eligible studies. Data items to be extracted include: (1) publication year, (2) mean gestational age, (3) mean birth weight (4) number of infants randomised, (5) number of losses to follow-up, (6) mode and doses of treatment, (7) any co-interventions during treatment, (8) continuous and dichotomous outcome measures and (9) adverse effects (neurological, renal, haematological, hepatic and gastrointestinal effects). The data extraction form will be pilot tested independently by all reviewers before its use, to standardise the process. Four reviewers (SM, IDF, MET and 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 (ROB)

The 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 categorise the 'unclear risk' to ' probably low risk' or 'probably high risk'.[28] Two independent reviewers (SM, IDF, MET or DA) will assess the ROB. We will try to reach consensus in case of disagreement 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

Table 1 Characteristics of the outcome measures

Outcome	Measurement of variable (units)	Statistical estimates and measurement of association
Primary		
Failure to close the PDA	Failure to closure of the PDA. We will emphasise on 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% CrI)
Secondary		
General outcomes		
–Neonatal mortality	Death during the first 28 days of life.	OR (95% CrI)
–Reopening of the ductus arteriosus	Number of neonates with echocardiographic determination of reopening of the ductus.	
–Need for surgical closure of the PDA	Number of neonates who required surgical treatment of the PDA.	
–CLD	Total number of neonates with oxygen requirement at 28 days postnatal age in addition to compatible clinical and roentgenographic findings.	
Neurological effects		
–IVH	Number of neonates with IVH (I–IV).	OR (95% CrI)
–Severe IVH	Number of neonates with severe IVH.	
–PVL	Number of neonates with PVL.	
–Neurodevelopmental disability	Number of children with any reported disability at 1–2 years of age (eg, motor, cognitive, sensory impairments).	
Gastrointestinal and nutritional effects		
– Intestinal perforation	▶ Number of neonates with Intestinal perforation.	▶ OR (95% CrI)
– GB	▶ Number of neonates with GB.	▶ OR (95% CrI)
– NEC	▶ Number of neonates with NEC (any stage).	▶ MD (95% CrI)
– Time to full enteral feeds	▶ Postnatal age at time of achieving full enteral feeds.	▶ OR (95% CrI)
Renal effects		
– Decreased urine output	▶ Number of neonates with urine output, defined as <1 cc/kg/hour.	▶ OR (95% CrI)

CLD, chronic lung disease; ECHO, echocardiographically; GB, gastrointestinal bleed; IVH, intraventricular haemorrhage; MD, mean difference; NEC, necrotising enterocolitis; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia.

we expect clinical and methodological heterogeneity among the studies (see Rating the confidence in estimates of the effect 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 (FE) model, the RE model is conservative in the sense that it accounts for both within-study 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 OR for binary outcomes, and mean difference (MD) for continuous outcomes, if they are reported using the same scale, or standardised MD (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 a 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 (<1000; 1000–1500; >1500 g), different doses of the interventions, time of administration of 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. We hypothesise 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 either perform meta-regression or subgroup analyses 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 and Mazumdar[37] rank correlation and Egger *et al*'s test.[36]

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 Random-Effects 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 (ie, direct and indirect evidence).[38] For instance, in a triangular network ABC composed by studies that directly compare A versus B and A versus C treatments, we can indirectly estimate the effect of B versus C treatments. In case direct evidence of B versus C treatment comparison is also available, then a combined estimate of direct and indirect evidence of B versus C can be calculated using an NMA.

Evidence from an NMA may be inconsistent if the direct and indirect evidence is incompatible (loop inconsistency) or the studies involving one of the treatments are 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.[39–41] We will perform a network meta-regression or subgroup analysis using the same potential treatment effect modifiers described in the Direct comparisons and assessment of heterogeneity section to explore important

heterogeneity or inconsistency. We will also perform sensitivity analysis for different heterogeneity prior to assessing the robustness of results.[31–33]

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% 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.[42 43] We will rank the probabilities with their 95% CrIs as well as the Surface Under the Cumulative RAnking curve (SUCRA) values and cumulative probability rankograms.[44] 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 multiarm trials, and assuming a common within-network heterogeneity variance. Series of 100 000 simulations will be used to allow convergence, and after thinning of 10 and discarding the first 20 000 simulations we will produce the outputs. We will assess model convergence on the basis of the Gelman and Rubin[45] diagnostic test. The analysis will be performed in OpenBUGs (V.3.2.3).[46]

Rating the confidence in estimates of the effect

We will assess the confidence in the estimates for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.[47] For this purpose, two authors will independently do the assessment (SM, IDF, MET or 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.[48–52]

We will assess and rate the confidence in all the indirect comparisons—if available—obtained from first-order loops (FOLs) following the GRADE categories used for assessing the direct comparisons in addition to the transitivity assessment. Transitivity, also called similarity,[53] 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.[54 55] Then, when both types of evidence (direct and indirect) are present, we will rate the confidence in each NMA effect estimate using the higher rating of them.

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 FOLs, that is, 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 versus B (AB) and B

versus C (BC), we will be able to indirectly estimate the effects of A versus C (AC). The AC will be a FOL. We will choose FOL 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 judgement of confidence in the NMA estimate for any pairwise comparison will be the higher of the confidence rating among 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 assessing the incoherence (or inconsistency as described in the Network meta-analysis section) criteria, which is defined as the differences between direct and indirect estimates of effect.[56]

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 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, paediatricians, 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 the subject of future research.

Our review will have several methodological strengths. First, we will implement a wide comprehensive search that 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 summarise the likely values for the treatment effect of each intervention relative to each other.[57]

On the other hand, some challenges for this review exist. 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 may be 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 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 published evidence. No personal data of patients were required. The results of the review will be submitted to a peer-reviewed journal focusing on paediatrics or neonatology fields for publication. We also plan to present results in future conferences.

Glossary of terms Direct estimates: Estimate provided by a head-to-head comparison. Indirect estimate: Estimate provided by two or more head-to-head comparisons that share a common comparator (eg, direct comparisons: AB and BC, indirect estimation: AC). Network meta-analysis (NMA): 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 (FOLs) are those loops that involve only a single additional intervention. Heterogeneity: Differences in estimates of effect across studies that assessed the same comparison. Inconsistency:[56] The GRADE approach criterion for rating the degree of consistency among the results in the meta-analysis (heterogeneity). Incoherence:[56] 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:[56] Differences in study characteristics that may modify treatment effect in the direct comparisons, and could bias the indirect estimate.

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