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Efficacy and safety of pharmacological treatments for Patent Ductus Arteriosus closure: a systematic review and network meta-analysis of clinical trials and observational studies

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ABSTRACT

Efficacy and safety profiles of different pharmacological interventions used to treat patent ductus arteriosus (PDA) are relatively unexplored. Integrating the findings of randomized clinical trials (RCTs) with those from observational studies may provide key evidence on this important issue. We aimed at estimating the relative likelihood of failure to close the PDA, need for surgical closure, and occurrence of adverse events among preterm and full-term infants treated with indomethacin, ibuprofen, or acetaminophen, placebo, or no treatment including both RCTs and observational studies.

We searched PubMed, Embase, and the Register of Controlled Trials from inception to October 30, 2018. We first estimated proportions of subjects with failure to close the PDA, subjects in whom surgical closure was performed after pharmacological treatment, death, and subjects with selected adverse events (AEs). These estimates were obtained using frequentist random-effect meta-analysis of arm-specific proportions. We then compared active drugs with each other and with control (either placebo or no treatment) by summarizing results at the end of treatment reported in the papers, regardless of number of administration(s), dose, route and type of administration, and study design and quality. We also summarized primary outcome results separately at first, second and third cycles of treatment. These estimates were obtained using Bayesian random-effects network meta-analysis for mixed comparisons, and frequentist random-effect pairwise meta-analysis for direct comparisons.

We included 64 RCTs and 24 observational studies including 14,568 subjects (5339 in RCTs and 9229 in observational studies, 8292 subjects received indomethacin, 4761 ibuprofen, 574 acetaminophen, and 941 control (including placebo or no intervention).The proportion of subjects with failure to close the PDA was 0.24 (95% Confidence Interval, CI: 0.20, 0.29) for indomethacin, 0.18 (0.14, 0.22) for ibuprofen, 0.19 (0.09, 0.30) for acetaminophen, and 0.59 (0.48, 0.69) for

control . At end of treatment, compared to control, we found inverse associations between all active drugs and failure to close PDA (for indomethacin Odds Ratio, OR, was 0.17 [95% Credible Interval, CrI: 0.11-0.24], ibuprofen 0.19 [0.12-0.28], and acetaminophen 0.15 [0.09-0.26]), without differences among active drugs. We showed inverse associations between effective drugs and need for surgical closure, as compared to control (for indomethacin OR was 0.28 [0.15-0.50], ibuprofen 0.30 [0.16-0.54], and acetaminophen 0.19 [0.07-0.46]), without differences among drugs. Indomethacin was directly associated with intraventricular hemorrhage (IVH) (1.27; 1.00, 1.62) compared to ibuprofen, and to oliguria as compared to ibuprofen (3.92; 1.69, 9.82) or acetaminophen (10.8; 1.86, 93.1).

In conclusion, active pharmacological treatment, with indomethacin, ibuprofen, or acetaminophen, is inversely associated with failure to close the PDA compared to non-treatment. Quality of evidence was moderate, high and low, respectively. Ibuprofen should be preferred to indomethacin to avoid occurrence of IVH or oliguria, acetaminophen should be preferred to indomethacin to avoid oliguria.

Keywords

adverse events; intraventricular hemorrhage; network meta-analysis; observational studies; oliguria; patent ductus arteriosus.

Chemical compounds

Chemical compounds studied in this article were: Indomethacin (PubChem CID: 3715); Ibuprofen (PubChem CID: 1983); Paracetamol/Acetaminophen (PubChem CID: 1983)

Abbreviations

AEs: adverse events

BPD: bronchopulmonary dysplasia

CI: confidence interval

CrI: credible interval

ECHO: echocardiographic

IV: intravenous

IVH: intraventricular hemorrhage

NMA: network meta-analysis

NSAIDs : non-steroidal anti-inflammatory drugs

OR: odds ratio

PDA: patent ductus arteriosus

RCTs: randomized clinical trials

1. BACKGROUND

In fetal life, the ductus arteriosus connects the pulmonary artery to the aorta, playing a central role in the regulation of fetal circulation. At birth, when breathing begins, ductus arteriosus starts closing. However, failure to close or reopening can occur. This condition, defined as patent ductus arteriosus (PDA), has been associated in preterm infants with increased mortality and with major complications, including metabolic acidosis, renal failure, intraventricular hemorrhage (IVH), pulmonary hemorrhage, bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), prolonged ventilator dependence, and heart failure[1]. PDA is one of the most common cardiovascular diseases in premature infants. It occurs in up to 33% and 65% in very low birth-weight infants and extremely low birth-weight infants, respectively [2, 3].

Management of PDA is based on conservative treatments (i.e. fluid restriction, diuretics, etc.) while waiting for spontaneous closure [4], pharmacological therapy with cyclooxygenase inhibitors, and surgical closure [5].

A major issue in the management of patients with PDA is the choice of treatment, both in terms of timing and type of treatment. The most common options for pharmacological closure of PDA are indomethacin and ibuprofen. Indomethacin has been historically used as the main first-line therapy, but it has been associated with several adverse events (AEs) (i.e. renal insufficiency, NEC) [6]. As for ibuprofen, a recent meta-analysis demonstrated that it is as effective as indomethacin in closing PDA, with significantly lower gastrointestinal and renal AEs, and recommended it as first-line treatment [7].

More recently, acetaminophen has also been introduced in clinical practice for the management of PDA, mainly in infants with contraindications to cyclooxygenase inhibitors. According to a recent Cochrane systematic review, acetaminophen resulted comparable to ibuprofen in terms of efficacy, with a better safety profile [8]. However, this approach still awaits definitive validation due to a lack of data on long-term follow-up of acetaminophen-treated infants.

In 2018, a network meta-analysis (NMA) comparing the efficacy and safety of these three active principles was published [9] and concluded that high-dose oral ibuprofen represented the most effective pharmacotherapeutic option for PDA closure. However, that NMA included only RCTs. As randomized allocation protects against bias and confounding effects that can undermine the validity of the study, RCTs are the gold standard to evaluate drug efficacy. However, RCT design may have limitations. In particular, due to strict inclusion criteria, RCTs may not provide a representative picture of "real world" management of the disease. Moreover, RCTs, generally with short follow-up and small sample size, are often inadequate to evaluate drug safety because only frequent and acute AEs are usually assessed in these studies, whereas unknown, rare, and/or long-term latency AEs are difficult to detect due to insufficient length of follow up. Thus, observational studies may provide additional information also regarding safety. Another advantage of including non-randomized studies is that network meta-analysis including studies with both designs allow to improve density network and to connect disconnected drugs [10]. All these advantages may offer opportunities to provide more comprehensive evidence about the comparative safety and effectiveness of treatments.

We conducted a systematic review and NMA of both RCTs and observational studies, using a Bayesian approach, for the comparison of the efficacy and safety profiles of the pharmacotherapeutic options available for PDA treatment, namely indomethacin, ibuprofen, and acetaminophen, with the aim of complementing current knowledge on this issue and contributing to evidence-based drug selection.

2. METHODS

The protocol for this systemic review and network meta-analysis has been registered in the PROSPERO database (CRD42016053487).

2.1. Criteria for considering studies

Types of studies: We considered RCTs and observational studies. We considered full-text publications written in English, irrespective of date of publication.

Types of participants: We included studies performed on preterm infants (<37 weeks' gestational age), full term (≥37 weeks' gestational age), low-birth-weight (<2500 g), and normal-weight infants (≥2500 g), with PDA diagnosed either clinically or by echocardiographic (ECHO) criteria in the neonatal period (<28 days).

Types of interventions: We considered studies employing any of the following pharmacological treatments: ibuprofen; indomethacin; acetaminophen; no active intervention. For each intervention, we considered:

i) the active principle;

ii) the route of administration: oral, intravenous (IV), or rectal;

iii) the type of IV infusion: rapid infusion (bolus over 1 min), standard infusion (over 5-30 min), slow infusion (over 30-60 min), continuous infusion (CI, over 4-36 h);

iv) the type of administration: ECHO-guided administration (i.e. PDA status was verified after each administration; if PDA closured occurred, no further dose was administered) vs non-ECHO-guided administration (i.e. the whole course was administered independently of occurrence of PDA closure before the end of the course).

v) cycle of treatment: number of times therapy was repeated, if any.

vi) the following treatment dosage scheme:

- For indomethacin:
    - Low dose (total intake ≤0.30 mg/kg; max duration of treatment: 3 days): 0.1 mg/kg x 3 doses, every 12 or 24 h; 0.15 mg/kg x 2 doses at 12-h interval; 1 dose of 0.2 mg/kg.
    - Intermediate dose (total intake between 0.40 and 0.70 mg/kg; max duration of treatment: 3 days): 0.2 mg/kg x 3 doses every 12 or 24 h; 0.2 mg/kg x 1 dose + 0.1

mg/kg x 2 doses every 12 or 24 h; 0.2 mg/kg x 1 dose + 0.25 mg/kg x 2 doses every 12 or 24 h; 0.2 mg/kg x 2 doses at 24- h interval; 0.25 mg/kg x 2 doses at 24-h interval.

- High dose (total intake >0.70 mg/kg): 0.30 mg/kg x 3 doses at 24-h interval (schedule intervals not further specified).
- Prolonged treatment (total intake of 0.60-0.80 mg/kg; duration of treatment: 6-7 days): 0.1 mg/kg x 6 doses at 24-h interval; 0.1 mg/kg x 7 doses at 24-h interval; 0.15 mg/kg x 2 doses at 12-h interval + 0.1 mg/kg x 5 doses at 24-h interval).

- For ibuprofen:
  - Low dose: 1 dose of ibuprofen 10 mg/kg.
  - Intermediate dose (total intake of 20 mg/kg): 10 mg/kg x 1 dose + 5 mg/kg x 2 doses, every 12 or 24 h.
  - High dose (total intake between 30-40 mg/kg): 20 mg/kg x 1 dose + 10 mg/kg x 2 doses, every 12 or 24 h; 10 mg/kg x 3 doses, at 24-h interval.
- For acetaminophen:
  - Intermediate dose (total intake <200 mg/kg; duration 3-4 days): 15 mg/kg every 6 h for 3 days (tot: 195 mg/kg); 20 mg/kg x 1 dose + maintaining doses of 7.5 mg/kg every 6 h for 4 days (145 mg/kg); 10 mg/kg every 6 h for 3 days (tot: 130 mg/kg).
  - Prolonged treatment (total intake >400 mg/kg; duration 7 days): 15 mg/kg every 6 h for 7 days (tot: 435 mg/kg).

All these parameters were analyzed separately in subgroup analysis.

Types of outcome measures: We assessed benefits and harm of pharmacological interventions by evaluating the following outcomes: failure to close PDA (according to ECHO criteria and/or clinical evaluation) as primary outcome; need for surgical PDA closure, death, and occurrence of selected AEs, as secondary outcomes. AEs were defined as any untoward medical occurrence, or death, not necessarily having a causal relationship with treatment. Based on biological plausibility

and expert clinical consensus, we considered the following AEs: NEC, Intestinal perforation, Gastrointestinal bleeding, BPD, IVH, Periventricular leukomalacia, and Oliguria.

2.2. Search methods for identification of studies

Electronic searches: We searched PubMed and Embase from inception to October 30, 2018 for studies comparing two or more of the above interventions on infants with PDA. To identify additional trials, we also searched ClinicalTrials.gov. Full search strategies are available in ***Appendix 1***. Briefly, two search themes were combined using the Boolean operator "AND": the first theme about drugs (i.e. Non-Steroidal Anti-Inflammatory Drugs - NSAIDs, acetaminophen, ibuprofen, indomethacin), and the second theme about condition (i.e. patent ductus arteriosus).

Papers selection: EndNote Basic software was used to manage the records retrieved from the searches. Two authors (EM, AB) independently identified studies for inclusion by screening titles and abstracts yielded from the search. We retrieved the full-text of all articles that at least one of the review authors had identified for potential inclusion. We selected studies for inclusion on the basis of review of full-text articles. Discrepancies were resolved through consensus.

2.3. Data extraction and management

Two authors (EM, AB) independently extracted the following data:

1. Treatment data: active principle; route of administration; type of IV infusion (when appropriate); ECHO- or non-ECHO-guided administration; cycles of treatment; dosage.
2. Outcome data: number of randomized participants and number of participants included in the analysis (for RCTs); number of participants with events for binary outcomes; definition of outcomes, if appropriate.
3. Data on potential effect modifiers: participants' characteristics, such as age, gender; assessment of bias risk.

4. Other data: study design; year of publication; country in which participants were recruited; follow-up time; funding sources.

Assessment of risk of bias: To assess the risk of bias of RCTs, we followed the *Cochrane Handbook for Systematic Reviews of Interventions [11]*. Specifically, we assessed risk of bias for the following domains: selection (random sequence generation; allocation concealment); performance (blinding of participants and personnel); detection (blinding of outcome); attrition (incomplete outcome data); reporting (selective reporting); other unclear bias. To assess the risk of bias of observational studies, we followed the *Newcastle-Ottawa Quality Assessment Scale* [12]. Specifically, for cohort studies, we assessed risk of bias for the following domains: selection (representativeness of the exposed cohort; selection of the non-exposed cohort; ascertainment of exposure; lack of definition of pre-defined end-point); comparability; outcome (assessment of outcome; appropriate length of follow-up; adequacy of follow-up of cohorts).

2.4. Data analysis

We first estimated proportions of subjects with failure to close the PDA, subjects in whom surgical closure was performed after pharmacological treatment, deaths, and subjects with selected AEs. We defined proportion as number of subjects reporting the selected events divided by total number of subjects. We considered studies comparing two active drugs or one drug with control (placebo or no treatment), and studies comparing the same drugs at different doses, routes or types of administration, and types of infusion.

We conducted a random effect frequentist meta-analysis of arm-specific proportions using the arcsine transformation for arm-specific proportions, the 95% Clopper-Pearson Confidence Interval, CI, for arm-specific CI, the inverse variance method for pooling the overall proportion, and the DerSimonian-Laird method for estimation of the between-study variance. We used the “metaprop” routine within the META R package [13]. Results are presented as pooled proportions with 95% Confidence Interval (CI).

We then compared drugs with each other and with control by meta-analyzing studies that comparing two active drugs or one drug with control (placebo or no treatment) and by considering results reported at the end of the treatment (i.e. last cycle of treatment) regardless of route and type of administration, type of infusion, dose, and study design and quality. Thus, we did not consider studies comparing the same drugs at different doses, routes or types of administration, and types of infusion).

We also considered separately the first, second, and third cycle of treatment for failure to close PDA, and compared route and type of administration, type of infusion, and dose within active principle for failure to close PDA and need of surgical closure. We performed a network meta-analysis with the aim of simultaneously analyzing direct comparisons of interventions within studies (subject of conventional pairwise meta-analysis), and indirect comparisons across studies. If the efficacy of two interventions (A and B) is to be compared but no studies comparing them are available, indirect evidence can be obtained by studying either A or B versus a common comparator. When both direct and indirect evidence were available (mixed comparison), the information was combined. The network maps show which interventions are directly compared with each other and depict how much information is available for each drug and for each comparison. For mixed-treatment comparison, we performed a random-effect NMA within a Bayesian framework using the GeMTC (Generate Mixed Treatment Comparisons) R package (https://CRAN.R-project.org/package=gemtc) [14]. We simultaneously ran four chains with different arbitrarily-chosen initial values, with a variance scaling factor of 2.5. Convergence and lack of autocorrelation were checked and confirmed after 20,000 iterations with thinning interval equal to 1, followed by 50,000 iterations to estimate parameters. We used default noninformative values for priors, and default values for the likelihood and link functions (suitable for the data). Results are presented as Odds Ratios (ORs) and their 95% Credible Intervals (CrIs), the Bayesian equivalent to Confidence Intervals (CIs). For direct comparisons, we performed a random-effects pairwise meta-analysis within the frequentist approach using the Mantel-Haenszel method for

pooling, continuity correction of 0.5 in studies with zero cell frequencies, and the DerSimonian-Laird method for estimation of the between-study variance. We used the routine "metabin" within the META R package (https://CRAN.R- project.org/package=meta) [13]. Results are presented as ORs and their 95% CIs.

We assessed heterogeneity in meta-analyses of arm-specific proportions and in pairwise meta-analyses of direct comparisons with the Cochrane Q test.

We assessed inconsistency in network meta-analysis with node-splitting analysis.

We assessed robustness of results by performing subgroup analysis by study design (RCTs versus observational studies).

We assessed similarity between RCTs and observational studies by comparing pairwise meta-analyses of direct comparisons limited to RCTs with those limited to observational studies.

A p-value < 0.05 was considered statistically significant.

3. RESULTS

The reference flow is summarized in the study flow diagram (***Fig. 1***). We identified 5,395 references through electronic searches of PubMed (n=1760), Embase (n=3590) and ClinicalTrials.gov (n=45). After removing 1592 duplicates, 3803 references were screened. We excluded 3275 irrelevant references by reading titles and abstracts. We retrieved 528 full-text references, of which 437 were excluded as detailed in Figure 1. In total, 88 references met inclusion criteria, 64 were RCTs [15-78] and 24 observational studies [79-102]. All observational studies included had a cohort design. The intervention strategies of the 88 included studies are reported in ***Appendix* 2**.

Data on efficacy outcome, defined as failure to close PDA, were available for 83 studies (63 RCTs, 20 observational studies), and 59 studies (46 RCTs, 13 observational studies) compared two or more interventions (***Appendix 3***). Data about the need for PDA surgical closure were available for 54 studies (36 RCTs, 18 observational studies), and 34 studies (22 RCTs, 12 observational studies)

compared two or more interventions. Data on safety were reported in 71 studies (51 RCTs, 20 observational studies); 42 studies (30 RCTs, 12 observational studies) compared two or more interventions in terms of death; 39 studies (28 RCTs, 11 observational studies) compared two or more interventions in terms of NEC; 14 studies (7 RCTs, 7 observational studies) compared two or more interventions in terms of intestinal perforation; 17 studies (14 RCTs, 3 observational studies) compared two or more interventions in terms of gastrointestinal bleeding; 29 studies (21 RCTs, 8 observational studies) compared two or more interventions in terms of BPD; 34 studies (26 RCTs, 8 observational studies) compared two or more interventions in terms of IVH; 14 studies (11 RCTs, 3 observational studies) compared two or more interventions in terms of periventricular leukomalacia; and 12 studies (9 RCTs, 3 observational studies) compared two or more interventions in terms of oliguria**.**

Overall, 14,568 subjects were investigated (5339 in RCTs and 9229 in observational studies). Median follow-up was 18 (range 0.5-70) months for RCTs, and 53 (11-120) months for observational studies. With respect to intervention, 8292 subjects received indomethacin, 4761 ibuprofen, 574 acetaminophen, and 941 control, including placebo or no intervention.

3.1. Risk of bias

30 RCTs were judged at high risk of performance bias [15-18, 20, 21, 25-28, 30, 31, 35, 39, 42, 44, 45, 47, 48, 53, 57, 59-62, 64, 70, 73, 74, 77], 11 at high risk of attrition bias [15, 22, 23, 31, 35, 44, 54, 56, 60, 62, 69], 12 at high risk of detection bias [18, 21, 26-28, 48, 53, 57, 61, 70, 73, 74], and three at high risk of selection bias (either considering randomization or allocation) [52, 54, 55] (***Appendix 4 and Appendix 5***). Nineteen studies were at high risk of bias in at least two items, 27 were at low/unclear risk of bias in all items, and two studies had low risk of bias in all items. Selective reporting bias was the least reported domain, with no studies judged at high risk.

Considering observational studies, all 24 studies had a cohort design. Based on the *Newcastle-Ottawa Quality Assessment Scale* for this type of study design, 12 studies obtained a score of 9 out

of 9 [79-81, 84, 89, 91, 93-95, 97, 99, 101], nine had a score of 8 [83, 85, 86, 88, 92, 96, 98, 100, 102], two studies a score of 7 [82, 87], and one a score of 6 [90] (***Appendix 6).***

3.2. Efficacy - failure to close PDA

The proportion of subjects with failure to close the PDA was 0.24 (95% CI: 0.20, 0.29) for indomethacin, 0.18 (0.14, 0.22) for ibuprofen, 0.19 (0.09, 0.30) for acetaminophen, and 0.59 (0.48, 0.69) for control (***Table 1***).

Fifty-nine studies compared the efficacy of different active principles to treat PDA (***Fig. 2a***). At last cycle of treatment, we found an inverse association between active principles and failure to close PDA as compared to control (OR was 0.17 [95% CI: 0.11, 0.24] for indomethacin, 0.19 [0.12, 0.28] for ibuprofen, and 0.15 [0.09, 0.26] for acetaminophen), with no differences among them (***Table 2***). All direct evidences contributing to the meta-analyses that showed the above significant ORs came from RCTs: 2 studies for acetaminophen versus control, 6 studies for ibuprofen versus control, and 10 studies for indomethacin versus control (***Appendix 2***). The overall quality of these RCTs was moderate for acetaminophen versus control (1 out of 2 studies was judged at high risk of performance and detection bias, ***Appendix 5***) and indomethacin versus control (6 out of 10 studies were judged at high risk of selection or attrition or performance bias), and high for ibuprofen versus control (1 out of 6 studies was judged at high risk of performance and detection bias).

Regarding cycle of treatment, we observed similar effectiveness of studied drugs for both the first and second pharmacological course (***Table 2***). Data for the third cycle were scanty and the control arm was missing, thus, it was not possible to compare results of this cycle with those of the last cycle of treatment. Direct comparisons confirmed the results of mixed comparisons.

When we limited analysis to RCTs (***Appendix 7***) these results were confirmed, as we found no association between failure to close PDA and different routes of administration, dosages or procedures for indomethacin (***Appendix 8***) and ibuprofen (***Appendix 9***). No study tested different routes of administrations, dosages or procedures for acetaminophen. When we compared results of

direct comparisons from RCTs and observational studies (***Appendix 7***), similarity between study designs was observed.

3.3. Need for surgical closure

The proportion of subjects in whom surgical closure was performed after pharmacological treatment was 0.12 (95% CI: 0.10, 0.15) for indomethacin, 0.09 (0.06, 0.12) for ibuprofen, 0.03 (0.00, 0.15) for acetaminophen, and 0.18 (0.08, 0.31) for control (***Table 1***).

Thirty-four studies compared the proportion of surgical PDA closure for different drugs (***Fig. 2b***). Mixed comparisons showed inverse associations between active principles and need for surgical closure as compared to control (OR was 0.28 [95%CrI: 0.15, 0.50] for indomethacin, 0.30 [0.16, 0.54] for ibuprofen, and 0.19 [0.07, 0.46] for acetaminophen), without significant differences among drugs (***Table 2***).

Direct comparisons confirmed the results of mixed comparisons.

These results were confirmed when we limited analysis to RCTs (***Appendix 7***), and we found no association between surgical PDA closure and different routes of administrations, dosages or procedures of indomethacin (***Appendix 8***) and ibuprofen (***Appendix 9***). No study tested different routes of administration, dosages or procedures of acetaminophen.

When we compared results of direct comparisons from RCTs and observational studies (***Appendix 7***), similarity between study designs was observed.

3.4. Safety

The proportion of deaths ranged between 0.09 and 0.11 for acetaminophen, ibuprofen and indomethacin, and it was 0.13 for control (***Table 1***). Many different AEs were reported in the included studies (***Appendix 3***).

The proportions of subjects with NEC, intestinal perforation, gastrointestinal bleeding, and periventricular leukomalacia were between 0.02 and 0.11 (***Table 1***). High proportions were

observed for BDP in subjects treated with indomethacin (0.39), ibuprofen (0.31), and control (0.29, for IVH in subjects treated with indomethacin (0.17), ibuprofen or acetaminophen (0.12) or control (0.18), and for oliguria in subjects treated with indomethacin (0.20) or control (0.28).

No significant association was found for the above AEs and active principles, with the exception of IVH and oliguria (***Table 3***). Indomethacin was directly associated with IVH (OR=1.27; 95% CrI: 1.00, 1.62) as compared to ibuprofen, and with oliguria as compared to ibuprofen (3.92 [1.69, 9.82]) or acetaminophen (10.8 [1.86, 93.31]).

These results were confirmed when we limited analysis to RCTs (***Appendix 10***). When we compared results of direct comparisons from RCTs and observational studies, similarity between study designs was observed with exception of indomethacin vs ibuprofen (though p-values from heterogeneity test for subgroup differences were not significant) regarding death, intestinal perforation and oliguria where direct RCT evidence produces pooled OR of 1.05 (0.69, 1.59) while observational evidence 0.74 (0.63, 0.86) for death, 1.16 (0.44, 3.04) and 0.47 (0.35, 0.63) for intestinal perforation, 3.75 (1.74, 8.07) and 2.69 (0.79,9.10) for oliguria.

4. DISCUSSION

To the best of our knowledge, this is the first NMA that systematically assesses the efficacy and safety of indomethacin, ibuprofen, and acetaminophen in closing PDA in preterm infants through analysis of both RCTs and observational studies.

In our NMA, indomethacin, ibuprofen and acetaminophen had similar effect on failure to close the PDA closure and decreasing the need for surgical closure, independent from the treatment cycle. We can judge the superiority of ibuprofen over control with high quality of evidence (RCTs with overall high quality), the superiority of indomethacin over control with moderate quality of evidence (RCTs with overall moderate quality), and the superiority of acetaminophen over control with low quality of evidence (only 2 RCTs with overall moderate).

All routes of administration, dosages, and ECHO- or non-ECHO-guided administrations were found to have similar efficacy within the same medication. Occurrence of NEC, intestinal perforation, gastrointestinal bleeding and periventricular leukomalacia was low (below 0.11) among the three treatments. The most frequently reported AEs were BPD for indomethacin (0.39), ibuprofen (0.31), and control (0.29), IVH for indomethacin (0.17), ibuprofen or acetaminophen (0.12) and control (0.18), and oliguria (a proxy of acute renal failure) for indomethacin (0.20) and control (0.28). In the comparison analysis, we found a direct association between indomethacin and IVH compared to ibuprofen, and between indomethacin and oliguria compared to ibuprofen or acetaminophen, confirming its poorest safety profile.

To date, only one NMA compared the efficacy and safety profiles of indomethacin, ibuprofen, and acetaminophen in closing PDA [9]. That NMA was performed only on RCTs, including 4802 infants, and concluded that a high dose of oral ibuprofen was associated with higher rates of PDA closure compared to standard dose of intravenous ibuprofen (OR 3.59; 95%CrI 1.64 -8.17) or indomethacin (2.35; 1.08-5.31). Moreover, no significant differences in the odds of mortality, NEC, IVH, and oliguria were found between pharmacological treatments and control groups. These results seem partly at variance with our findings, but actually they cannot be directly compared as our NMA was based on a much larger number of subjects, included observational studies as well, and evaluated the possible effect of administration route within drug. Furthermore, in the cited NMA, the superiority of a high dose of oral ibuprofen was mostly driven by the results of just three RCTs [22, 62, 103] ; of note, those results cannot be easily translated into clinical practice due to limited availability of oral ibuprofen and, mainly, of limited use of high ibuprofen doses.

On the other hand, our results are in partial agreement with a Cochrane review published in 2018 [7] concluding that ibuprofen is as effective as indomethacin in closing PDA while reducing the risk of NEC and transient renal insufficiency, and with another Cochrane review published in 2018 [104] concluding that paracetamol is as effective as ibuprofen in closing a PDA, with a possibly lower risk of gastrointestinal and renal AEs.

Pharmacological treatment of PDA has changed over recent decades with the introduction of ibuprofen and quite recently of acetaminophen as alternatives to the traditional approach based on indomethacin.

The favorable results of acetaminophen may have a pharmacological explanation as it is now clear that, contrary to a long-held tenet, acetaminophen also inhibits cyclo-oxygenase, thus explaining its efficacy in favoring PDA closure [105]. Our study reinforces the notion that active pharmacological treatment is superior to non-treatment in decreasing the risks of unfavorable clinical conditions associated with PDA, such as an increase of pulmonary blood flow and edema, and a decrease of renal, mesenteric and cerebral perfusion. Similarly, by decreasing the need for surgical closure, effective pharmacological therapy avoids surgical risks and postoperative complications [106]. However, despite the higher rates of failure to close PDA, we observed that controls had similar mortality as well as similar risk of overall AEs in comparison with active treatments. On the other hand, it has been previously reported that the lack of improvement in preterm infants' outcomes in trials on PDA treatment may reflect several possible factors, such as the inaccurate assessment of hemodynamic significance of PDA in studied infants, and the 50-70% cross-over of placebo-assigned infants to the active treatment group [107]. Thus, the "treatment" versus "no treatment" RCTs may not accurately capture the morbidity effects of PDA in preterm infants [108, 109].

The present study has some limitations. First, this NMA was based on the assumption that baseline clinical characteristics were largely similar among different studies comparing different medications. Variations in gestational age, birth weight, timing of treatment, comorbidities and co-treatments may have influenced our results. More important, the inclusion of both preterm and term infants in the review could substantially affect interpretation of results as the physiology, natural history and management of PDA are different in the two populations. Second, the no risk-adjusted estimates from the included observational studies may have influenced our results even if no differences were observed between results from RCTs and those from observational studies. Third,

limited sample size of studies evaluating specific AEs or types of intervention may have resulted in imprecision in estimating proportions, precluding the derivation of meaningful inferences.

5. CONCLUSIONS

In conclusion, our NMA confirms that pharmacological treatment with either indomethacin, ibuprofen or acetaminophen is effective (with moderate, high and low quality of evidence, respectively) in closing PDA and limiting PDA surgical closure in comparison with non-treatment. Ibuprofen limits the risk of IVH and oliguria in comparison to indomethacin; acetaminophen pose less risk of oliguria in comparison to indomethacin. We are confident that ongoing further RCTs, comparing short-term effects on PDA closure and safety and long-term effects on neurodevelopmental outcome, in preterm infants treated with ibuprofen or paracetamol will support evidence-based neonatologists' prescription choices.

Author Contributions

EM and AB contributed equally to the study.

EL had full access to all data and took responsibility for its integrity and the accuracy of its analysis.

Study concept and design: GA, CD, AM, and EL.

Administrative, technical, or material support and acquisition of data: EM and AB.

Statistical analysis: VP and EL.

Drafting of the manuscript: EM, AB, and EL.

Critical revision of the manuscript for important intellectual content: All authors.

Study supervision: EL.

Conflict of Interest Disclosures

EM, AB, VP, AV, ST, and EL have no conflict of interest to declare. GA has served as a consultant to Angelini. CD has served as scientific consultant for Orphan Europe. AM was a member of a Board Meeting by Angelini.

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Figure legends

Figure 1. Study flow diagram, retrieved on October 30, 2018.

Figure 2. Direct comparisons of interventions among included studies evaluating a) failure to close PDA, n=59studies; and b) the need for surgical intervention, n=34 studies).

Node size is proportional to the number of direct treatment comparisons which include that node, edge size is proportional to the number of direct treatment comparisons.

a) Failure to close the PDA (2 studies compared acetaminophen with indomethacin, 10 with ibuprofen, and 2 with control; 31studies compared indomethacin with ibuprofen, and 10 with control; 6 studies compared ibuprofen with control).
b) Need for surgical closure (1 study compared acetaminophen with indomethacin, 3 with ibuprofen; 23 studies compared indomethacin with ibuprofen, and 6 with control; 3 studies compared ibuprofen with control).

834 **Table 1.** Meta-analysis of proportions of failure to close PDA, need for surgical PDA closure and occurrence
835 of selected adverse events stratified according to intervention.

	Number of study-arms	proportion[a] (95% CI)
Failure to close PDA		
Indomethacin	64	0.24 (0.20, 0.29)
Ibuprofen	76	0.18 (0.14, 0.22)
Acetaminophen	13	0.19 (0.09, 0.30)
Control	18	0.59 (0.48, 0.69)
Need of surgical closure		
Indomethacin	45	0.12 (0.10, 0.15)
Ibuprofen	52	0.09 (0.06, 0.12)
Acetaminophen	3	0.03 (0.00, 0.15)
Control	9	0.18 (0.08, 0.31)
Death		
Indomethacin	46	0.11 (0.10, 0.13)
Ibuprofen	50	0.10 (0.08, 0.12)
Acetaminophen	8	0.09 (0.04, 0.17)
Control	12	0.13 (0.09, 0.19)
Necrotizing enterocolitis (NEC)		
Indomethacin	42	0.08 (0.06, 0.11)
Ibuprofen	53	0.06 (0.05, 0.08)
Acetaminophen	10	0.05 (0.01, 0.11)
Control	8	0.03 (0.01, 0.05)
Intestinal perforation		
Indomethacin	16	0.02 (0.01, 0.04)
Ibuprofen	21	0.03 (0.01, 0.04)
Control	3	0.02 (0.00, 0.08)
Gastrointestinal bleeding		
Indomethacin	20	0.11 (0.06, 0.17)
Ibuprofen	27	0.04 (0.02, 0.07)
Acetaminophen	6	0.03 (0.00, 0.09)
Control	4	0.04 (0.00, 0.19)
Bronchopulmonary dysplasia (BPD)		
Indomethacin	23	0.39 (0.32, 0.46)
Ibuprofen	32	0.31 (0.24, 0.39)
Acetaminophen	7	0.08 (0.02, 0.17)
Control	8	0.29 (0.13, 0.48)
Intraventricular haemorrhage (IVH)		
Indomethacin	30	0.17 (0.14, 0.22)
Ibuprofen	40	0.12 (0.10, 0.15)
Acetaminophen	10	0.12 (0.06, 0.19)
Control	6	0.18 (0.07, 0.33)
Periventricular leukomalacia		
Indomethacin	15	0.06 (0.04, 0.09)

Ibuprofen	14	0.06 (0.04, 0.08)
Acetaminophen	4	0.05 (0.00, 0.17)
Control	3	0.04 (0.01, 0.08)
Oliguria		
Indomethacin	17	0.20 (0.14, 0.28)
Ibuprofen	27	0.03 (0.01, 0.06)
Acetaminophen	3	0.08 (0.02, 0.19)
Control	1	0.28 (0.13, 0.47)

[a] Estimates obtained by random effect meta-analysis of arm-specific proportions using the arcsine transformation for arm-specific proportions, the 95% Clopper-Pearson Confidence Interval for arm-specific Confidence Intervals, the inverse variance method for pooling, and the DerSimonian-Laird method for between-study variance.
CI: Confidence Interval

Table 2. Comparison of active principles and controls on **failure to close PDA** and **need for surgical PDA closure**, overall and stratified according to cycle of treatment.

Failure to close PDA			
Last cycle			
Indomethacin	0.88 (0.71, 1.11), 31 studies[1]	1.22 (0.54, 2.74), 2 studies[2]	**0.17 (0.13, 0.24),** 10 studies[3]
0.89 (0.68, 1.17)	Ibuprofen	1.02 (0.72, 1.44), 10 studies[4]	**0.27 (0.11, 0.64)**[a],6 studies[5]
1.09 (0.66, 1.79)	1.22 (0.77, 1.91) [b]	Acetaminophen	0.07 (0.00, 2.18) [c], 2 studies[6]
0.17 (0.11, 0.24)	**0.19 (0.12, 0.28)**	**0.15 (0.09, 0.26)**	Control
1st cycle			
Indomethacin	**0.77 (0.64, 0.93),** 26 studies[7]	1.11 (0.41, 3.06), 2 studies[8]	**0.16 (0.12, 0.22)**, 8 studies[9]
0.78 (0.63, 0.98)	Ibuprofen	1.19 (0.88, 1.60), 10 studies[10]	**0.18 (0.04, 0.72)** [d], 4 studies[11]
0.97 (0.66, 1.41)	1.25 (0.89, 1.73)	Acetaminophen	**1.15 (0.02, 0.88),** 2 studies[12]
0.15 (0.11, 0.21)	**0.19 (0.13, 0.28)**	**0.15 (0.10, 0.25)**	Control
2nd cycle			
Indomethacin	1.15 (0.79, 1.69), 12 studies[13]	1.10 (0.47, 2.53), 1 study[14]	1.14 (0.09, 0.22), 2 studies[15]
1.26 (0.84, 1.99) [d]	Ibuprofen	1.24 (0.81, 1.89), 6 studies[16]	-
1.82 (0.94, 3.81)	1.45 (0.79, 2.72) [e]	Acetaminophen	**0.01 (0.00, 0.06),** 1 study[17]
0.08 (0.03, 0.20) [f]	**0.07 (0.02, 0.17)**	**0.04 (0.01, 0.12)**[g]	Control
3rd cycle			
Indomethacin	1.87 (0.55, 6.36), 3 studies[18]	-	
2.52 (0.51, 25.61)	Ibuprofen	0.44 (0.02, 12.01), 1 study[19]	
1.854e-06 (1.376e-21, 5.77)	6.921e-07 (5.88e-22, 1.71)	Acetaminophen	
Need for surgical PDA ligation			
Indomethacin	0.90 (0.80, 1.00), 23 studies[20]	1.10 (0.47, 2.53), 1 study[21]	**0.35 (0.15, 0.79)**, 6 studies[22]
0.92 (0.79, 1.12)	Ibuprofen	1.66 (0.80, 3.47), 3 studies[23]	0.32 (0.04, 2.26), 3 studies[24]
1.48 (0.76, 3.30)	1.59 (0.81, 3.50)	Acetaminophen	-
0.28 (0.15, 0.50)	**0.30 (0.16, 0.54)**	**0.19 (0.07, 0.46)**	Control

Data are reported as odds ratios (ORs) and 95% credible intervals for mixed comparisons and 95% confidence intervals for direct ones. Mixed ORs are shown in the triangle below the diagonal and direct ORs are shown in the triangle above the diagonal. Significant results are in bold.

[a] p-value for heterogeneity =0.01; [b] p-value for inconsistency=0.02; [c] p-value for heterogeneity =0.001; [d] p-value for inconsistency=0.04; [e] p-value for inconsistency=0.04; [f] p-value for inconsistency=0.03

1[18, 27, 34, 36, 42, 45, 48, 51, 53, 58, 59, 61, 68, 70, 71, 73, 74, 76, 78-81, 84, 86, 88, 91, 93-96, 101]; 2[30, 34]; 3[37, 40, 44, 47, 52, 54-56, 65, 75]; 4[17, 20, 22, 23, 28, 33, 34, 57, 76, 82]; 5[16, 19, 32, 38, 66, 67]; 6[21, 43]; 7[18, 27, 34, 36, 42, 45, 48, 51, 53, 58, 59, 61, 68, 70, 71, 73, 74, 76, 79, 81, 84, 86, 88, 91, 94-96, 101]; 8[30, 34]; 9[37, 47, 52, 54-56, 65, 75]; 10[17, 20, 22, 23, 28, 33, 34, 57, 76, 82]; 11[16, 19, 32, 38, 66]; 12[21, 43]; 13[34, 36, 42, 48, 68, 76, 81, 91, 95, 96, 101]; 14[34]; 15[37, 40]; 16[17, 22, 23, 28, 33, 34]; 17[21]; 18[36, 81, 91]; 19[17]; 20[34, 42, 45, 48, 51, 68, 70, 73, 74, 76, 78, 80, 81, 84, 86-90, 92, 93, 96, 101]; 21[34]; 22[40, 46, 54, 55, 65, 75]; 23[33, 34, 57]; 24[38, 66, 67].

855 **Table 3.** Comparison of different active principles on **occurrence of selected adverse events.**

Death			
Indomethacin	**0.77 (0.67, 0.89)**, 23 studies[1]	0.97 (0.32, 2.91), 1 study[2]	0.55 (0.29, 1.07), 8 studies[3]
0.85 (0.70, 1.10)	Ibuprofen	1.07 (0.62, 1.86), 6 studies[4]	0.62 (0.26, 1.44), 3 studies[5]
0.94 (0.55, 1.68)	1.11 (0.65, 1.88)	Acetaminophen	6.40 (0.75, 54.78), 1 study[6]
0.51 (0.29, 0.85)	**0.60 (0.34, 0.99)**	0.54 (0.25, 1.10)	Control
Necrotizing enterocolitis (NEC)			
Indomethacin	1.08 (0.85, 1.38), 23 studies[7]	2.72 (0.94, 7.89), 2 study[8]	1.43 (0.41, 4.93), 4 studies[9]
1.16 (0.88, 1.62)	Ibuprofen	0.99 (0.57, 1.71), 8 studies[10]	1.45 (0.39, 5.45), 3 studies[11]
1.40 (0.77, 2.76)	1.20 (0.68, 2.22)	Acetaminophen	0.35 (0.01, 8.96), 1 study[12]
1.39 (0.55, 3.55)	1.19 (0.45, 3.05)	1.00 (0.34, 2.93)[a]	Control
Intestinal perforation			
Indomethacin	**0.51 (0.38, 0.68)**, 11 studies[13]		0.98 (0.06, 16.09), 1 study[14]
0.58 (0.36, 1.11)	Ibuprofen		0.51 (0.10, 2.53), 2 studies[15]
0.37 (0.06, 2.26)	0.63 (0.10, 3.61)		Control
Gastrointestinal bleeding			
Indomethacin	1.03 (0.61, 1.76), 8 studies[16]	2.28 (0.12, 43.14) [a], 2 studies[17]	0.77 (0.11, 5.41), 3 studies[18]
0.87 (0.39, 2.07)	Ibuprofen	**3.51 (1.36, 9.08)**, 5 studies[19]	3.01 (0.96, 9.42), 1 studiy[20]
2.56 (0.79, 11.29)	2.94 (0.94, 11.81)	Acetaminophen	-
1.58 (0.22, 9.79)	1.82 (0.25, 10.48)	0.61 (0.05, 4.62)	Control
Bronchopulmonary dysplasia (BPD)			
Indomethacin	**0.89 (0.81, 0.99)**, 15 studies[21]	-	0.67 (0.40, 1.11), 4 studies[22]
0.86 (0.71, 1.02)	Ibuprofen	1.20 (0.56, 2.54), 6 studies[23]	1.05 (0.18, 6.25), 3 studies[24]
1.21 (0.62, 2.46)	1.40 (0.74, 2.82)	Acetaminophen	0.47 (0.15, 1.55), 1 study[25]
0.70 (0.44, 1.08)	0.81 (0.51, 1.28)	0.58 (0.27, 1.17)	Control
Intraventricular haemorrhage (IVH)			
Indomethacin	**1.25 (1.01, 1.56)**, 19 studies[26]	1.32 (0.52, 3.34), 2 studies[27]	0.92 (0.05, 18.05), 2 studies[28]
1.27 (1.00, 1.62)	Ibuprofen	0.98 (0.58, 1.64), 8 studies[29]	0.92 (0.47, 1.82), 3 studies[30]
1.27 (0.78, 2.08)	0.99 (0.63, 1.60)	Acetaminophen	0.53 (0.16 1.81), 1 study[31]
1.00 (0.54, 1.83)	0.79 (0.44, 1.39)	0.80 (0.40, 1.53)	Control
Periventricular leukomalacia			
Indomethacin	0.83 (0.53, 1.30), 7 studies[32]	0.82 (0.27, 2.54), 1 studies[33]	2.58 (0.48, 13.85), 1 study[34]
0.90 (0.53, 1.61)	Ibuprofen	0.88 (0.28, 2.71), 3 studies[35]	1.91 (0.53, 6.82), 2 studies[36]
0.79 (0.27, 2.35)	0.88 (0.29, 2.60)	Acetaminophen	-
2.24 (0.70, 7.99)	2.48 (0.80, 8.53)	2.85 (0.63, 14.18)	Control
Oliguria			

Indomethacin	**3.29 (1.80, 6.00)**, 9 studies[37]	-	-
3.92 (1.69, 9.82)	Ibuprofen	2.45 (0.63, 9.54), 2 studies[38]	-
10.81 (1.86, 93.31)	2.75 (0.57, 18.38)	Acetaminophen	0.71 (0.19, 2.68), 1 study[39]
7.62 (0.42, 188.2)	1.94 (0.12, 40.50)	0.69 (0.07, 7.24)	Control

Data are reported as odds ratios (ORs) and 95% credible intervals for mixed comparisons and 95% confidence intervals for direct ones. Mixed ORs are shown in the columns (i.e. in the triangle below the diagonal with the treatments) and direct ORs are shown in the rows (i.e. in the triangle above the diagonal).
Significant results are in bold.
[a] p-value for heterogeneity=0.01
1[27, 36, 42, 45, 48, 51, 68, 70, 71, 73, 74, 76, 81, 84, 87-90, 92, 93, 95, 96, 101]; 2[30]; 3[40, 44, 46, 47, 54, 55, 65, 75]; 4[17, 23, 28, 33, 57, 82]; 5[38, 66, 67]; 6[43]; 7[27, 34, 36, 42, 45, 48, 51, 68, 70, 71, 73, 74, 76, 81, 84, 87, 89, 91-94, 96, 101]; 8[30, 34]; 9[40, 46, 54, 75]; 10[17, 23, 28, 33, 34, 57, 77, 82]; 11[38, 66, 67]; 12[43]; 13[48, 68, 73, 74, 81, 87, 89, 90, 92, 93, 101]; 14[75]; 15[38, 67]; 16[34, 45, 68, 70, 73, 81, 94, 101]; 17[30, 34]; 18[46, 54, 65]; 19[28, 33, 34, 57, 76]; 20[66]; 21[27, 45, 48, 51, 68, 71, 74, 78, 81, 87, 89, 90, 93, 96, 101]; 22[40, 44, 46, 75]; 23[17, 23, 28, 33, 77, 82]; 24[38, 66, 67]; 25[43]; 26[27, 34, 36, 45, 51, 53, 68, 70, 71, 74, 76, 78, 81, 87, 89, 92, 93, 96, 101]; 27[30, 34]; 28[40, 75]; 29[17, 23, 28, 33, 34, 57, 77, 82]; 30[38, 66, 67]; 31[43]; 32[45, 48, 68, 70, 74, 87, 93]; 33[30]; 34[75]; 35[17, 28, 82]; 36[38, 67]; 37[45, 48, 53, 68, 73, 74, 88, 91, 94]; 38[28, 77]; 39[43].