

Dual Medication Therapy (Acetaminophen and Ibuprofen) for the Management of Patent Ductus Arteriosus in Preterm Infants: A Systematic Review and Meta-analysis

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Article

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Abstract

Objective: To examine the efficacy of dual medication therapy (DMT: acetaminophen and ibuprofen) vs. single medication therapy (SMT: ibuprofen) for medical management of PDA.

Study Design: We systematically searched multiple sources to identify randomized controlled trials (RCT) and non-randomized studies (NRS) that compared DMT to SMT for management of hemodynamically significant PDA.

Results: We identified two RCTs and four NRS. There were no differences in the rates of successful PDA closure following the first treatment course between DMT and SMT (RR = 1.23 [95% CI 0.89 to 1.70] for NRS and RR = 1.18 [95% CI 0.66 to 2.10] for RCTs), nor were there significant differences in secondary outcomes and adverse events including PDA ligation, bronchopulmonary dysplasia, severe intraventricular hemorrhage, and necrotizing enterocolitis. etc. Markers of hepatic or renal function did not change significantly during PDA treatment.

Conclusion: We found no evidence for superiority of DMT over SMT in PDA management.

Introduction

In fetal life, the ductus arteriosus allows oxygenated blood that returns from the placenta to bypass the lungs and supply the fetal systemic circulation, thereby preventing right ventricular hypertrophy/failure. [1, 2] Several factors, including fluid overload, sepsis [3], and respiratory distress [4], influence ductal closure. Several co-morbidities have been associated with prolonged patency of the ductus in preterm infants (e.g., prolonged ventilator support, pulmonary hemorrhage, bronchopulmonary dysplasia, and impaired renal function). [5] The optimal medical management of patent ductus arteriosus (PDA) is still debatable, including the choice of medications and timing of PDA treatment. A 2018 survey found great variability among cardiologists and neonatologists regarding PDA management protocols, with some advocating conservative management as an alternative. [6] Currently, three medications: indomethacin, ibuprofen, and acetaminophen, have demonstrated efficacy in the closure of a hemodynamically significant PDA. For those infants who fail medical therapy, surgical ligation or insertion of a coil device via cardiac catheterization are management alternatives. [7]

The Food and Drug Administration has approved both intravenous ibuprofen and intravenous indomethacin for closure of the PDA as a single medication therapy (SMT); however, there is still no consensus on which medication is optimal. Ibuprofen and acetaminophen inhibit the cyclooxygenase and peroxidases region of prostaglandin synthase, respectively, thus reducing local prostaglandins levels. [8–10] Both medications are metabolized in the liver via different pathways [11], and acetaminophen [12] has a more favorable safety profile than ibuprofen and indomethacin, especially related to markers of renal function and platelet counts. Liebowitz et al. reported constriction rates for indomethacin, ibuprofen, and acetaminophen to be 62%, 48%, and 27%, respectively in infants < 28 weeks' gestational age. [13] In a double-blind, multicenter study, the efficacy of ibuprofen appeared similar to indomethacin (69% vs. 80%) for treatment of a PDA. [14] In a meta-analysis of 39 studies involving 2843 infants, Ohlsson A et al. [15] also reported that the efficacy of oral ibuprofen was similar to either intravenous ibuprofen or indomethacin but decreased the risk of renal insufficiency and necrotizing enterocolitis. Acetaminophen has been used more widely for PDA management since Hammerman et al. [16] demonstrated ductal closure after treatment with acetaminophen in five preterm infants. After initial reports of acetaminophen use in PDA management, subsequent studies have also demonstrated that oral acetaminophen and oral ibuprofen have similar efficacies in closing the PDA. [17–20]

Various routes of administration (intravenous and oral) and doses of medications have been used in clinical practice due to the lack of pharmacokinetics and pharmacodynamics data pertinent to all three medications. In 2018, Mitra et al. [21] reviewed available clinical trials on single medical therapy (SMT) comparison for PDA treatment. These authors identified 14 different variations of treatment choices and reported that a higher dose of oral ibuprofen was more effective in closing hemodynamically significant PDA than standard doses of intravenous ibuprofen or intravenous indomethacin. In 2018, Hochwald et al. [22] reported the first use of dual medication therapy (DMT) of ibuprofen and acetaminophen for PDA management in preterm infants. After their initial report, a few more studies have reported experience with DMT for PDA management in preterm infants. [13, 23–26] Each DMT study has used ibuprofen as the SMT and enrolled small number of infants. In order to synthesize the best available evidence for DMT for PDA management, we conducted the first systematic review and meta-analysis of all published articles (both RCTs and NRS) that compared DMT with acetaminophen and ibuprofen with ibuprofen monotherapy to assess ductal closure after the first treatment course.

Methods

Our study protocol was registered in the international Prospective Register of Systematic Reviews database on January 17, 2021 (No. CRD42021226528) [27] prior to the conduct of the systematic review. The reporting of this systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. [28]

Study selection

We included RCTs and NRS (prospective or retrospective cohort studies, case-control studies) that compared the effect of DMT (i.e., the combination of ibuprofen and acetaminophen) to SMT (i.e., ibuprofen) for the management of hemodynamically significant PDA among infants born less than 37 weeks' gestation. We included NRS in this review because few RCTs were available and did not report all secondary outcomes of interest. Furthermore, the findings of a review that includes NRS may also inform the design and conduct of future RCTs on this effect.

The primary outcome was ductal closure after completing a first treatment course of DMT vs. SMT. Pre-defined secondary outcomes included the following conditions: 1) surgical ligation, 2) the need for additional medical treatment, 3) ductal reopening rate, and 4) hepatic toxicity. We also evaluated the following adverse events: 1) necrotizing enterocolitis (NEC; stage II or greater using modified Bell criteria [29]), bronchopulmonary dysplasia (BPD; oxygen requirement at 36 weeks' postmenstrual age [30]), severe intraventricular hemorrhage (SIVH; grade III or grade IV per Papile classification [31]), late-onset sepsis (positive blood culture obtained after three days of age [32]), and death (mortality before hospital discharge). Other outcomes, including ductal reopening rate, need for second treatment, and hepatic toxicity, were initially included in our protocol but could not be included in this review due to lack of data. (Table 1)

Study screening

We systematically searched Pubmed, Embase, Web of Science, and the Cochrane Central Register for Controlled Trials. A detailed search strategy developed by an experienced librarian (S.H.) and extensive terminology used to identify all possible articles from electronic database. (Table S1) We also searched the following grey literature sources: 1) National Institutes of Health Research Portfolio Online Reporting Tools (RePORT), 2) International Standard Randomized Controlled Trial Number Register, 3) CenterWatch, 4) Australia New Zealand Clinical Trials Registry, 5) European Union Clinical Trials, 6) MedNar, 7) Open Grey. We also reviewed and included relevant abstracts and conference proceedings archives (i.e., Pediatric Academic Societies and European Society for Paediatric Research). To identify any ongoing studies on this topic, we also searched for registered trials on *ClinicalTrials.gov*. The librarian (S.H.) conducted the search in January 2021 and updated the search in September 2021. We searched for literature published after 2010 because acetaminophen was first reported to be effective for PDA management in 2011. We retrieved all literature without language restriction.

Initial results from the literature search were exported into the Covidence program [33]. Results unable to be imported into Covidence were reviewed manually. Two investigators (S.S. and K.M.) independently screened all studies, including abstracts and full texts, to assess their eligibility. Any discrepancies in study screening were resolved by involving a third investigator (K.A.).

Data extraction and assessment

Two investigators (S.S. and K.M.) independently and in duplicate performed data extraction using prespecified data extraction forms. Data were collected regarding the study design; number of total subjects in the study; neonatal characteristics such as birth weight and gestational age; eligibility criteria including echocardiogram findings; age (day of life) at PDA treatment; dose and route of medications administration; and adverse outcomes such as BPD, SIVH, NEC, mortality, late-onset sepsis. Data were independently entered in Microsoft Excel and were cross-checked by the two investigators (S.S. and K.M.); there were no discrepancies in data extractions. We contacted the corresponding author of each study through email and asked for any missing data or any clarification on published data. All results obtained via author correspondence were incorporated in the meta-analysis.

Two investigators (S.S. and K.M.) independently and in duplicate assessed the risk of bias for each study using the Cochrane risk-of-bias (RoB-2) tool [34] for RCTs and the Risk of Bias in Non-Randomized Studies - of Interventions (ROBINS-I) [35] for NRS. We created a "risk of bias" table for each domain to conclude the possible risk of bias. Discrepancies in risk of bias assessment were resolved in consultation with a third investigator (M.Z.). We also assessed the funding sources and potential conflicts of interest of each study. We had planned to assess reporting bias using funnel plots, but we did not have enough power due to the insufficient number of the eligible studies. [36]

Data synthesis and analysis

We conducted meta-analyses separately for RCTs and for NRS that compared DMT and SMT in relation to all outcomes and adverse events using Cochrane RevMan 5.4.1. [37] *Results were pooled separately by study design (RCTs vs. NRS), and the estimates were analyzed using a random-effects approach with the expectation that the intervention effects were unlikely to be identical across studies.* [38] We additionally conducted a sensitivity analysis using the fixed-effects approach, assuming that the intervention effects were fixed across studies. Two-sided statistical tests were used with a significance level of $P < 0.05$.

We chose to use the risk ratio (RR) with a 95% confidence interval (CI) to assess treatment effects for all outcomes and adverse events analyzed in the study. The Mantel-Haenszel method was used to calculate 95% CI. We planned to calculate RR using the formula provided in the Cochrane Handbook [39] for studies that reported odds ratios (OR), but no relevant case-control studies were identified. Heterogeneity across studies was quantified by calculating I^2 statistics (percentage of variations). [40] I^2 values of 25%, 50%, and 75% were considered low, moderate, and high heterogeneity.

Results

Characteristics of included studies

We identified a total of 816 citations from a comprehensive literature search, which yielded 472 studies after the removal of duplicates ($n = 344$). Nine studies were considered to be relevant after initial screening. As described in the PRISMA flow diagram, three studies were excluded, leaving six (4 NRS [13, 23, 25, 26] and 2 RCTs [22, 24]) for inclusion in this systematic review. (Figure 1) We found one ongoing trial in a clinical trials registry (Clinical Trials # NCT03648437). We included all six studies for meta-analysis for the primary outcome, but both RCTs were excluded from the meta-analyses of most secondary outcomes due to insufficient data. All four NRS were cohort (either prospective or retrospective) studies, and no case-control or cross-sectional

studies were included. We considered the study by Liebowitz et al. [13] to be an NRS because medication allocation was not randomized, and data were analyzed retrospectively in a secondary analysis.

Table 2 shows the characteristics of the 6 included studies. A total of 352 unique infants were reported in these six studies, among whom 99 received DMT and 253 received SMT. All studies except one [18] included infants less than 32 weeks' gestational age. There was heterogeneity in defining hemodynamically significant PDA by echocardiogram criteria; investigators prospectively defined echocardiogram criteria in 4 studies and did not define any criteria in 2 studies. There was also no uniformity in characteristics in echocardiograms among 4 studies that prospectively determined eligibility criteria. The mean and median day of life at which the first dose of medication was administered were both < 14 days of life in all six studies.

There was variability in the dose and route of administration of medications and in the duration of the treatment course among all six studies. The dose and duration of ibuprofen were similar among five studies; in one study, the duration of ibuprofen treatment was five days. There was a wide variation in the dose of acetaminophen in all included studies. Acetaminophen was administered for more than three days in 4 studies and more than five days in 2 studies. Both medications were given enterally (n = 3) or intravenously (n = 3) for PDA management. Both medications were administered simultaneously in all studies.

Four studies [22, 23, 24, 26] reported no differences in liver function tests pre- and post-treatment with acetaminophen. Only two studies [13, 23] reported acetaminophen levels; the mean/median value of acetaminophen level on day 3 of medication administration was less than 25 mcg/ml. Three studies [22, 23, 24] reported no difference in serum creatinine levels during PDA treatment period and one study [26] showed no change in urine output. These outcomes were not included in the meta-analysis due to insufficient data. None of the studies reported long-term neurodevelopmental outcome data following acetaminophen exposure in preterm infants.

Table S2 shows the assessments of risk of bias for each included study. Three out of the four (75%) NRS [13, 23, 25] were classified as low risk of bias, and one [26] was classified as moderate risk of bias due to concerns about confounding bias. One RCT [22] was classified as low risk of bias, and the other [24] introduced potential bias due to the randomization process and/or deviations from the intended intervention. **Table S3** shows summary of findings for each outcome for a comparison of DMT and SMT treatment. The each outcome was assessed using the GRADE approach and described as high, moderate, low and very low.

Outcomes

The associations of DMT vs. SMT on the primary outcome are provided in Figure 2 and secondary outcomes and adverse events in Figures 3 (A-F). Here, we briefly describe the results for each outcome.

Successful PDA closure (Figure 2): all six studies [13, 22-26] (n = 352 infants) reported on this outcome. There was no significant difference between DMT and SMT groups for successful PDA closure following the first treatment course (RR = 1.23 [95% CI 0.89 to 1.70] for NRS and RR = 1.18 [95% CI 0.66 to 2.10] for RCTs). There was no significant heterogeneity (I² = 0% in NRS and I² = 34% in RCTs) in the analysis. However, the results were imprecise because confidence intervals were wide. Overall, the quality of the evidence was very low for NRS and low for RCTs.

PDA ligation (Figure 3): five studies [13, 22, 23, 25, 26] (n = 241 infants) reported this outcome. Pooled analysis of four NRS showed no significant difference in the rate of PDA ligation between the two groups (RR = 0.78 [95% CI 0.38 to 1.62], I² = 0%). The results were imprecise because there were few events and confidence intervals were wide. Overall, the quality of the evidence was moderate for NRS and low for RCTs.

NEC (stage ≥ 2) (Figure S1): all six studies [13, 22-26] (n = 355 infants) reported on this outcome. The meta-analysis of three NRS showed no significant difference between DMT and SMT groups in the risk of NEC (RR = 1.27 [95% CI 0.51 to 3.16], I² = 0%). Aikio et al [25] reported only stage 3 NEC, hence we excluded this study from the meta-analysis for NEC. The quality of the evidence was very low for NRS and low for RCTs.

SIVH (Grade 3 and 4) (Figure S2): four studies [12, 22, 23, 25] (n = 229 infants) reported on this outcome. The meta-analysis of three NRS showed no significant difference between DMT and SMT groups in the risks of SIVH (RR = 1.10 [95% CI 0.53 to 2.29], I² = 0%). Kimani et al [26] reported all grades of IVH, hence we excluded this study from the meta-analysis for SIVH. The quality of the evidence was low for NRS and very low for RCTs.

BPD (Figure S3): all six studies [13, 22-26] (n = 342 infants) reported on this outcome. Pooled analysis of four NRS and two RCTs found no difference in the risk of BPD (RR = 0.97 [95% CI 0.76 to 1.24], I² = 9% and RR = 0.80 [95% CI 0.28 to 2.27], I² = 0% respectively). However, the results were imprecise because there were few events in both RCTs and confidence intervals were wide. Overall, the quality of the evidence was moderate for all studies.

Late-onset sepsis (Figure S4): four studies [13, 22, 23, 26] (n = 147 infants) reported on this outcome. The meta-analysis of four NRS showed no significant difference between DMT and SMT groups in the risks of late-onset sepsis (RR = 0.58 [95% CI 0.32 to 1.08], I² = 0%). The overall quality of evidence was moderate for NRS.

All-cause mortality (Figure S5): five studies [13, 22, 23, 25, 26] (n = 268 infants) reported on this outcome. The meta-analysis of four NRS showed no significant difference between DMT and SMT groups in the risk of death (RR = 0.66 [95% CI 0.29 to 1.50], I² = 0%). The overall quality of evidence was moderate for NRS.

In our sensitivity analysis, we applied a fixed-effect approach to analyze the estimates. Pooled analysis of four NRS and two RCTs found no difference in the rate of PDA closure following the first treatment course (RR = 1.19 [95% CI 0.85 to 1.66] for NRS and RR = 1.15 [95% CI 0.86 to 1.52] for RCTs). Results

for all other secondary outcomes did not change in a fixed-effect approach.

Discussion

Summary of main results

Effect of DMT vs. SMT on PDA management

To our knowledge, this is the first systematic review and meta-analysis to compare the relatively newer approach of DMT versus conventional SMT for PDA management in preterm infants. We did not observe statistically significant differences of DMT vs. SMT treatment on the successful PDA closure after first treatment in both RCTs and NRS. Similarly, no difference was observed with DMT treatment with respect to the outcome of PDA ligation.

Adverse effects of DMT vs. SMT

We evaluated several adverse events in the course of PDA treatment. There was no difference in NEC, severe IVH, BPD, and mortality with the use of DMT compared to SMT. On the other hand, the incidence of late-onset sepsis was lower with DMT compared to SMT. The forest plot (Figure 3E) demonstrates that most of the 95% CI is on the side that favors DMT. Although these data derive from 4 NRS [13, 23, 25, 26] the one RCT [22] that evaluated this outcome and did not find a difference in late-onset sepsis. We are unable to provide a rationale for why DMT should decrease the incidence of late-onset sepsis compared to SMT.

We also evaluated hepatic and renal function tests as reported in all studies and found inconsistent reporting of the values in the included studies. None of the studies reported derangement of hepatic and renal function after DMT compared to SMT. Liebowitz et al. [13] found no difference in acetaminophen levels as a function of ductal constriction. Similarly, a retrospective study of 36 extremely premature infants found no correlation between acetaminophen concentration and ductal response. [41] Data regarding pharmacokinetics and pharmacodynamics of acetaminophen in preterm infants is lacking. A population pharmacokinetics model by Bouazza et al [42] showed lower effect of acetaminophen on PDA closure in infants less than 27 weeks GA.

Overall completeness and applicability of evidence

To date, only 99 infants enrolled in clinical trials received DMT, compared to 253 infants who received SMT in all six studies. Larger trials may be warranted. Different dosing regimens of acetaminophen have been used in studies for PDA management without any robust pharmacokinetic data. Additionally, few studies have reported a potential association of autism or autism spectrum disorder with the prenatal use of acetaminophen. [43-45] Thus, long-term follow-up should be planned to identify any possible adverse association with acetaminophen.

Potential biases in the review process

We are not aware of any biases in the review process; however, the authors were involved in a study [23] included in this meta-analysis. To eliminate potential bias, a third reviewer (MZ) was assigned to review the RoB 2 independently for each study and resolved conflicts. We also utilized the RoB 2 and ROBINS-I tools to assess biases for both NRS and RCTs. When assessing publication bias, we did not find sources (e.g., sources of funding, conflicts of interest) that may have affected the reporting of the studies or the validity of the study findings.

This systematic review and meta-analysis has multiple strengths. To our knowledge, this is the first study to systematically review and analyze the data comparing the use of combination medication therapy for closure of PDA. Our findings provide important information for clinicians faced with the dilemma of PDA management. Additionally, we have identified a significant gap in the knowledge regarding these strategies to aid in conducting future, more targeted studies. At present, there is one additional RCT underway, which will compare the efficacy of two different DMT strategies: ibuprofen and acetaminophen versus indomethacin and acetaminophen (# NCT03648437).

Our study has limitations. First, only six studies (four NRS and two RCTs) examined the differential effects of DMT versus SMT on PDA management, and only one trial reported data on the secondary outcomes we chose to analyze. The sample size for each study was also relatively small. However, this makes it even more paramount to conduct a systematic review and meta-analysis to answer this key question and aid in PDA management. Second, some of the relevant secondary outcomes like grading of IVH or NEC were not available for all the studies. The authors made several attempts to obtain missing data by reaching out to the corresponding author but were only successful in obtaining relevant information from one [13]. Third, all studies except one did not report liver function tests. These data would have been beneficial to augment the analysis of the safety profile of DMT in addition to its therapeutic efficacy. Lastly, we did not separate studies based on different routes of medication use (intravenous or enteral) due to the small number of included studies. With the likelihood of more and similar studies in the future, an analysis of the efficacy with different administration routes is warranted.

Authors' conclusion

Implication for practice: The limited available evidence does not support the preferential use of DMT over SMT in PDA management. Additionally, data are too limited to provide robust assurance about the hepatic safety of DMT with ibuprofen and acetaminophen.

Implication for research: Larger multicenter RCTs with greater power are needed to better assess the relative efficacy and safety of DMT compared to SMT. If SMT were to achieve a 50% rate and DMT at 65% rate of PDA closure in infants less than 28 weeks' GA, 170 patients would be required per group to detect this improvement with 80% power at a two-sided 5% significance level. Further studies should also evaluate the efficacy with different routes of

administration and investigate the potential hepatic side effects associated with acetaminophen and ibuprofen usage, especially with the dual usage. Results from the ongoing trial (# NCT03648437) could also shed light on the conundrum of PDA medical management.

Abbreviations

BPD
bronchopulmonary dysplasia
DMT
dual medication therapy
IVH
intraventricular hemorrhage
NEC
necrotizing enterocolitis
NRS
non-randomized studies
PDA
patent ductus arteriosus
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT
randomized controlled trials
RR
risk ratio
SMT
single medication therapy

Declarations

Conflict of Interest

The authors declare no conflict of interest.

References

1. Dice JE, Bhatia J. Patent ductus arteriosus: an overview. *J Pediatr Pharmacol Ther* 2007, **12**(3): 138–146.
2. Schneider DJ, Moore JW. Patent ductus arteriosus. *Circulation* 2006, **114**(17): 1873–1882.
3. Mehta S, Younoszai A, Pietz J, Achanti B. Pharmacological closure of the patent ductus arteriosus. *Images Paediatr Cardiol* 2003, **5**(1): 1–15.
4. Silver MM, Freedom RM, Silver MD, Olley PM. The morphology of the human newborn ductus arteriosus: a reappraisal of its structure and closure with special reference to prostaglandin E1 therapy. *Hum Pathol* 1981, **12**(12): 1123–1136.
5. Benitz WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? *J Perinatol* 2010, **30**(4): 241–252.
6. Parkerson S, Philip R, Talati A, Sathanandam S. Management of Patent Ductus Arteriosus in Premature Infants in 2020. *Front Pediatr* 2020, **8**: 590578.
7. Backes CH, Rivera BK, Bridge JA, Armstrong AK, Boe BA, Berman DP, *et al.* Percutaneous Patent Ductus Arteriosus (PDA) Closure During Infancy: A Meta-analysis. *Pediatrics* 2017, **139**(2).
8. Anderson BJ. Paracetamol (Acetaminophen): mechanisms of action. *Paediatr Anaesth* 2008, **18**(10): 915–921.
9. Gr  n K, Drvota V, Vesterqvist O. Pronounced reduction of in vivo prostacyclin synthesis in humans by acetaminophen (paracetamol). *Prostaglandins* 1989, **37**(3): 311–315.
10. Terrin G, Conte F, Scipione A, Bacchio E, Conti MG, Ferro R, *et al.* Efficacy of paracetamol for the treatment of patent ductus arteriosus in preterm neonates. *Ital J Pediatr* 2014, **40**(1): 21.
11. Rostas SE, McPherson CC. Pharmacotherapy for Patent Ductus Arteriosus: Current Options and Outstanding Questions. *Curr Pediatr Rev* 2016, **12**(2): 110–119.
12. El-Mashad AE, El-Mahdy H, El Amrousy D, Elgendy M. Comparative study of the efficacy and safety of paracetamol, ibuprofen, and indomethacin in closure of patent ductus arteriosus in preterm neonates. *Eur J Pediatr* 2017, **176**(2): 233–240.
13. Liebowitz M, Kaempf J, Erdev   O, Bulbul A, H  kansson S, Lindqvist J, *et al.* Comparative effectiveness of drugs used to constrict the patent ductus arteriosus: a secondary analysis of the PDA-TOLERATE trial (NCT01958320). *J Perinatol* 2019, **39**(5): 599–607.
14. Adamska E, Helwich E, Rutkowska M, Zacharska E, Piotrowska A. [Comparison of the efficacy of ibuprofen and indomethacin in the treatment of patent ductus arteriosus in prematurely born infants]. *Med Wieku Rozwoj* 2005, **9**(3 Pt 1): 335–354.
15. Ohlsson A, Walia R, Shah SS. Ibuprofen for the treatment of patent ductus arteriosus in preterm or low birth weight (or both) infants. *Cochrane Database Syst Rev* 2020, **2**: CD003481.

16. Hammerman C, Bin-Nun A, Markovitch E, Schimmel MS, Kaplan M, Fink D. Ductal closure with paracetamol: a surprising new approach to patent ductus arteriosus treatment. *Pediatrics* 2011, **128**(6): e1618-1621.
17. Dang D, Wang D, Zhang C, Zhou W, Zhou Q, Wu H. Comparison of oral paracetamol versus ibuprofen in premature infants with patent ductus arteriosus: a randomized controlled trial. *PLoS One* 2013, **8**(11): e77888.
18. Oncel MY, Yurttutan S, Erdevi O, Uras N, Altug N, Oguz SS, *et al.* Oral paracetamol versus oral ibuprofen in the management of patent ductus arteriosus in preterm infants: a randomized controlled trial. *J Pediatr* 2014, **164**(3): 510–514.e511
19. Bagheri MM, Niknafs P, Sabsevari F, Torabi MH, Bahman Bijari B, Noroozi E, *et al.* Comparison of Oral Acetaminophen Versus Ibuprofen in Premature Infants With Patent Ductus Arteriosus. *Iran J Pediatr* 2016, **26**(4): e3975.
20. Yang B, Gao X, Ren Y, Wang Y, Zhang Q. Oral paracetamol vs. oral ibuprofen in the treatment of symptomatic patent ductus arteriosus in premature infants: A randomized controlled trial. *Exp Ther Med* 2016, **12**(4): 2531–2536.
21. Mitra S, Florez ID, Tamayo ME, Mbuagbaw L, Vanniyasingam T, Veroniki AA, *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* 2018, **319**(12): 1221–1238.
22. Hochwald O, Mainzer G, Borenstein-Levin L, Jubran H, Dinur G, Zucker M, *et al.* Adding Paracetamol to Ibuprofen for the Treatment of Patent Ductus Arteriosus in Preterm Infants: A Double-Blind, Randomized, Placebo-Controlled Pilot Study. *Am J Perinatol* 2018, **35**(13): 1319–1325.
23. Shah SD, Makker K, Nandula P, Smotherman C, Kropf A, Hudak ML. Effectiveness of Dual Medication Therapy (Oral Acetaminophen and Oral Ibuprofen) for the Management of Patent Ductus Arteriosus in Extremely Premature Infants: A Feasibility Trial. *Am J Perinatol* 2021.
24. Oboodi R, Najib KS, Amoozgar H, Pourarian S, Moghtaderi M, Mehdizadegan N, *et al.* Positive tendency toward synchronous use of acetaminophen and ibuprofen in treating patients with patent ductus arteriosus. *Turk Kardiyol Dern Ars* 2020, **48**(6): 605–612.
25. Aikio O, Juujärvi S, Saarela T, Hallman M. Simultaneous paracetamol may promote ibuprofen-induced closure of ductus arteriosus. *Eur J Clin Pharmacol* 2020, **76**(8): 1193–1195.
26. Kimani S, Surak A, Miller M, Bhattacharya S. Use of combination therapy with acetaminophen and ibuprofen for closure of the patent ductus arteriosus in preterm neonates. *Paediatr Child Health* 2021, **26**(4): e177-e183.
27. Shah S, Makker K, Sanchez L. Efficacy and safety of dual medication therapy (ibuprofen and acetaminophen) for the management of patent ductus arteriosus in preterm
28. infants - a network meta-analysis of randomized controlled trials and
29. observation studies. PROSPERO 2021 CRD42021226528
30. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021, **372**: n71.
31. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatr Clin North Am* 1986, **33**(1): 179–201.
32. Stevenson DK, Wright LL, Lemons JA, Oh W, Korones SB, Papile LA, *et al.* Very low birth weight outcomes of the National Institute of Child Health and Human Development Neonatal Research Network, January 1993 through December 1994. *Am J Obstet Gynecol* 1998, **179**(6 Pt 1): 1632–1639.
33. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr* 1978, **92**(4): 529–534.
34. Boghossian NS, Page GP, Bell EF, Stoll BJ, Murray JC, Cotten CM, *et al.* Late-onset sepsis in very low birth weight infants from singleton and multiple-gestation births. *J Pediatr* 2013, **162**(6): 1120–1124, 1124.e1121.
35. Covidence systematic review software, Veritas Health Innovation. Melbourne, Australia. p. Available at .
36. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, *et al.* RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019, **366**: l4898.
37. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016, **355**: i4919.
38. Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. *Stat Med* 2001, **20**(4): 641–654.
39. *Review Manager (RevMan)*. 5.4 ed: *The Cochrane Collaboration*, 2020.
40. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986, **7**(3): 177–188.
41. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, *et al.* Interpreting results and drawing conclusions. *Cochrane Handbook for Systematic Reviews of Interventions*: Cochrane; 2021. p. 15.14.14.14.
42. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003, **327**(7414): 557–560.
43. McPherson C, Luecke CM, Liviskie CJ, Zeller BN, Vesoulis ZA. Acetaminophen Serum Concentrations in Infants Treated Intravenously for Patent Ductus Arteriosus. *J Pediatr Pharmacol Ther* 2019, **24**(2): 134–137.
44. Bouazza N, Treluyer JM, Foissac F, Urien S, Aikio O, Roze JC, *et al.* Pharmacokinetics of Intravenous Paracetamol (Acetaminophen) and Ductus Arteriosus Closure After Premature Birth. *Clin Pharmacol Ther* 2021, **110**(4): 1087–1095.
45. Bauer AZ, Kriebel D, Herbert MR, Bornehag CG, Swan SH. Prenatal paracetamol exposure and child neurodevelopment: A review. *Horm Behav*. 2018;101:125–47.

46. Alemany S, Avella-García C, Liew Z, García-Esteban R, Inoue K, Cadman T, *et al.* Prenatal and postnatal exposure to acetaminophen in relation to autism spectrum and attention-deficit and hyperactivity symptoms in childhood: Meta-analysis in six European population-based cohorts. *Eur J Epidemiol* 2021, **36**(10): 993–1004.
47. Bühner C, Endesfelder S, Scheuer T, Schmitz T. Paracetamol (Acetaminophen) and the Developing Brain. *Int J Mol Sci* 2021, **22**(20).

Tables

Table 1: Changes between initial protocol and manuscript

Sections	Initial Protocol	Final Manuscript	Reason for the changes
Eligibility Criteria	Less than 32 weeks' gestational age	Less than 37 weeks' gestational age	We found one more article outside our initial eligibility criteria.
Literature Search	Search from the inception of the databases to current	Limited the search to citations published after December 2010	Acetaminophen was first reported to be used as an alternative treatment for patent ductus arteriosus management in January 2011.
Secondary Outcomes	1 efficacy and 5 adverse outcomes were initially planned for analysis	1. These 6 outcomes in the initial protocol were not included. 2. Additional outcomes including bronchopulmonary dysplasia, severe intraventricular hemorrhage, late-onset sepsis, and death were included.	1. Paucity of data for these 6 outcomes in the included studies. 2. Additional outcomes were identified during the search process, and they were added to make this review more comprehensive.

Table 2: Characteristics of included studies

Author and year of publication	Location of study	Study Design	Enrollment years	Number of infants enrolled in each arm		Birth weight (g)	Gestational age at birth (wk)	Age at start of treatment (d)	Dose and route of administration	Criteria for hsPDA diagnosis
				DMT	SMT					
Aikio 2020	Finland	single center retrospective study	January 2002 - December 2018	18	103	IBU + ACE: 940 (300) ^a IBU: 860 (280) ^a	IBU + ACE: 26.6 (1.9) ^a IBU: 26.2 (2.1) ^a	IBU + ACE: 5 (4, 8) ^b IBU: 4 (1, 27) ^b	IV IBU mg/kg/dose (10-5-5), IV ACE 20 mg/kg loading dose and 7.5 mg/kg every 6 hours	PDA treated medically, criteria not specified
Kimani 2020	Canada	single center retrospective study	January 2012 - December 2017	17	22	IBU + ACE: 800 (685, 1025) ^b IBU: 790 (642, 980) ^b	IBU + ACE: 26.1 (25.2, 26.8) ^b IBU: 25.7 (24.9, 27.6) ^b	IBU + ACE: 7 (4, 10) ^b IBU: 6.5 (3, 12.5) ^b	Oral IBU mg/kg/dose (10-5-5), oral ACE 15mg/kg/dose every 6 hours for 7 days	Presence of hsPDA on echo; criteria not specified
Liebowitz 2019	USA	Multicenter, randomized controlled study	January 2014 - June 2017	11	27	IBU + ACE: 824 (144) ^a IBU: 812 (181) ^a	IBU + ACE: 25.9 (1.1) ^a IBU: 25.6 (1.2) ^a	IBU + ACE: 8.5 (2.6) ^a IBU: 7.5 (1.6) ^a	IV/oral IBU mg/kg/dose (10-5-5-5-5), IV/oral ACE 20 mg/kg loading dose and 12.5 mg/kg every 6 hours x 5 days	PDA diameter ≥ 1.5 mm or PDA:LPA ratio ≥ 0.5 and one or more of other echo criteria 1) LA: Ao ≥ 1.6 b) ductus flow velocity ≤ 2.5 m/s or mean pressure gradient across the ductus ≤ 8 mm/hg c) reverse diastolic flow in the descending aorta d) LPA diastolic flow velocity > 0.2 m/s
Shah 2021	USA	non-randomized multi-center prospective	July 2017 - May 2019	20	11	IBU + ACE: 764 (135) ^a IBU: 739 (140) ^a	IBU + ACE: 25.08 (1.2) ^a IBU: 25.38 (1.46) ^a	IBU + ACE: 9.8 (2.8) ^a IBU: 8.6 (3.2) ^a	Oral IBU mg/kg/dose (10-5-5), oral ACE 15mg/kg/dose every 6 hours for 3 days	hsPDA as defined by any of the following criteria: increased ventilator or oxygen support attributed by the clinician to the PDA, hypotension and/or widening pulse pressure requiring vasopressors, or signs of congestive heart failure and ratio of PDA to LPA >0.5 on echocardiogram.
Hochwald 2018	Israel	single-center, double-blind, randomized controlled pilot study	2014 - 2016	12	12	IBU + ACE: 1120 (171) ^a IBU: 951 (157) ^a	IBU + ACE: 27.7 (1.3) ^a IBU: 27.2 (1.4) ^a	IBU + ACE: 6.6 (1.8) ^a IBU: 6.3 (1) ^a	IV IBU mg/kg/dose (10-5-5), IV ACE 20 mg/kg loading dose and 10 mg/kg every 6 hours x 3 days	The need for respiratory support with duct diameter >1.5 mm and at least one of the following echocardiographic criteria: LA: Ao >1.5, unrestrictive pulsatile transductal flow (Vmax < 2.0 m/s) and end diastolic reversal blood flow in the descending aorta.
Oboodi 2020	Iran	multicenter randomized controlled study	March 2016- March 2017	19	68	IBU + ACE: 1264.7 (510) ^a IBU:	IBU + ACE: 30.36 (2.39) ^a IBU: 31.14 (2.35) ^a	IBU + ACE: 8.52 (5.9) ^a IBU: 5.44 (2.37) ^a	Oral IBU mg/kg/dose (10-5-5), IV ACE 15mg/kg/dose	LA: Ao ≥ 1.5, retrograde diastolic flow in the superior mesenteric artery or in the anterior

1353.6
(333.1)^a

every 6 hours
for 3 days

cerebral artery,
PDA diameter
≥1.5 mm, and an
unrestrictive
pulsatile
transductal flow

a: mean (SD)

b: median (IQR)

Abbreviations: ACE indicates acetaminophen; DMT, dual medication therapy; hsPDA, hemodynamically significant patent ductus arteriosus; IBU, Ibuprofen; LA:Ao, left atrial aortic root ratio; LPA, left pulmonary artery; PDA, patent ductus arteriosus; SMT, single medication therapy.

Figures

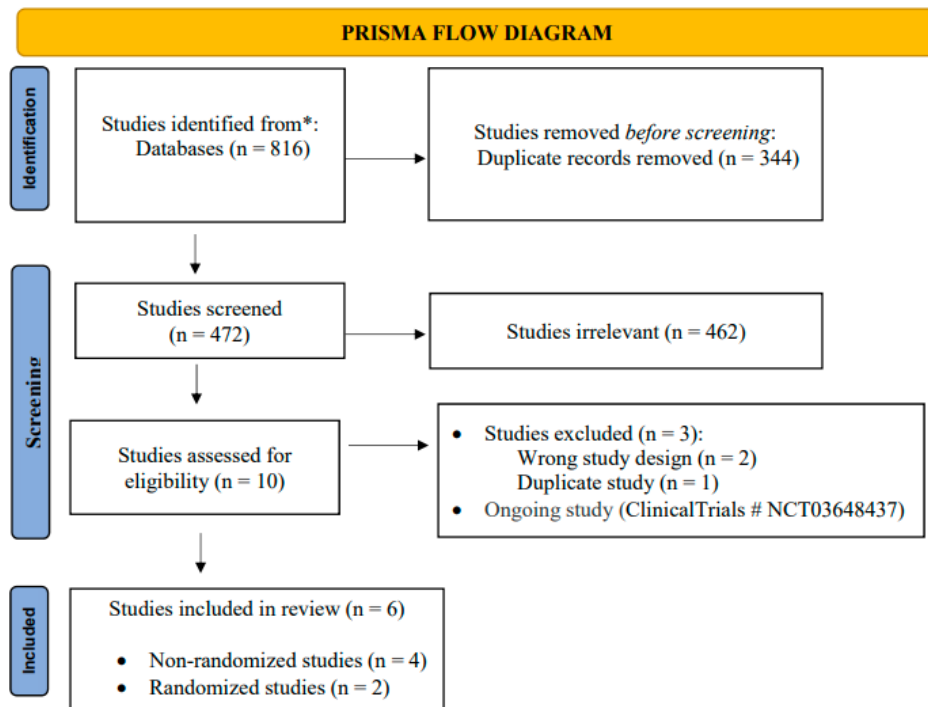


Figure 1

Flow diagram of study selection process

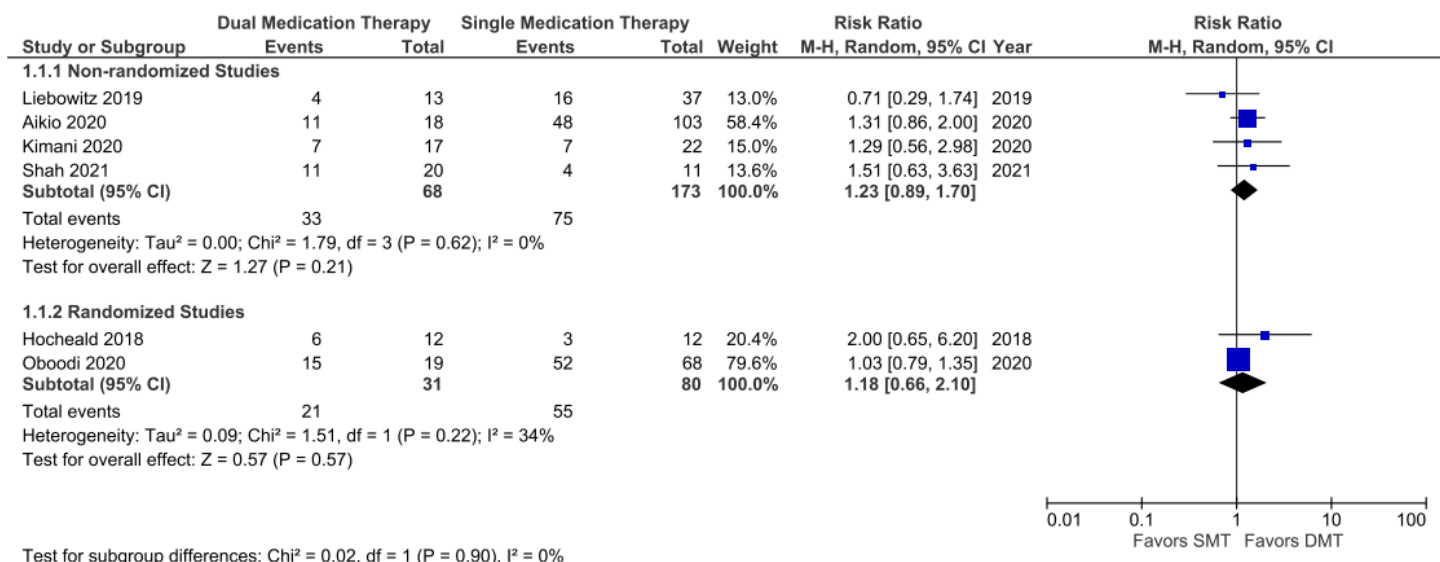


Figure 2

Forest Plot of pooled effect estimates for successful PDA closure with DMT and SMT treatment

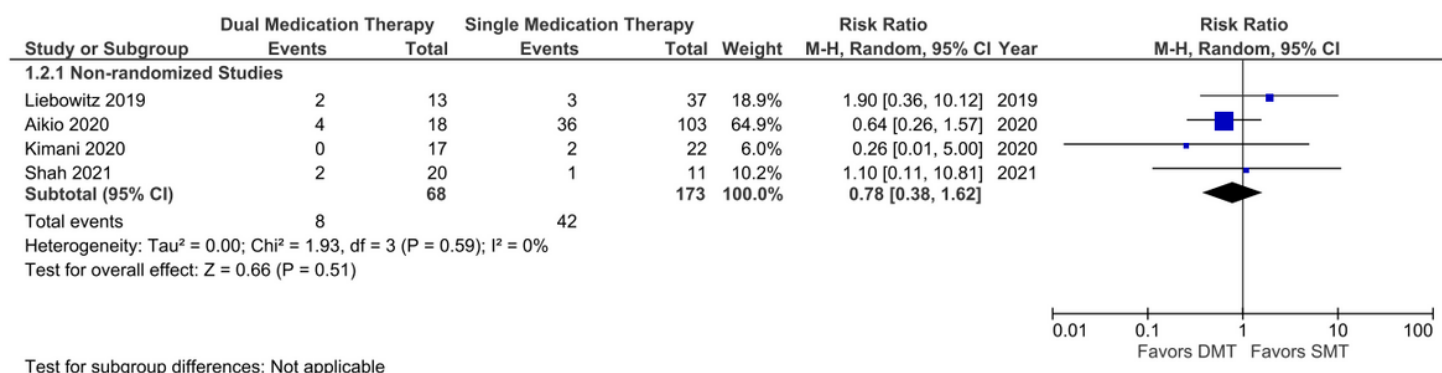


Figure 3

Forest Plot of pooled effect estimates for PDA ligation with DMT and SMT treatment

Supplementary Files

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