ARTICLE

Dual medication therapy (acetaminophen and ibuprofen) for the management of patent ductus arteriosus in preterm infants: a systematic review and meta-analysis

Sanket D. Shah, Kartikeya Makker, Mingyu Zhang, Susan Harnett, Khyzer B. Aziz and Mark L. Hudak

© The Author(s), under exclusive licence to Springer Nature America, Inc. 2022

OBJECTIVE: To examine the efficacy of dual medication therapy (intervention) (DMT: acetaminophen and ibuprofen) vs. single medication therapy (control) (SMT: ibuprofen) for medical management of PDA (outcomes) in preterm infants (population).

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 0.89–1.70] for NRS and RR = 1.18 [95% CI 0.66–2.10] for RCTs), nor were there significant differences in secondary outcomes and adverse events including PDA ligation, bronchopulmonary dysplasia, and necrotizing enterocolitis etc. Markers of hepatic/renal function did not change significantly during treatment.

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

Journal of Perinatology (2022) 42:1654–1661; https://doi.org/10.1038/s41372-022-01500-8

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 hemorhage, 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 indomethacin inhibit the cyclooxygenase while acetaminophen inhibits the peroxidase steps of prostaglandin synthesis, 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...
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 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 (SH) and extensive terminology used to identify all possible articles from electronic database (Table S1). We also searched the following gray 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 Gray. 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 (SH) 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 relevant articles (both RCTs and NRS) that compared DMT with acetaminophen and ibuprofen with ibuprofen monotherapy to assess ductal closure after the first treatment course.

Data extraction and assessment

Two investigators (SS and KM) 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 (SS and KM); there were no discrepancies in data extraction. 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 data analysis.

Study selection

We included all 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. We identified no cross-sectional studies. 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 [30]), bronchopulmonary dysplasia (BPD; oxygen requirement at 36 weeks’ postmenstrual age [31]), severe intraventricular hemorrhage (SIVH; grade III or grade IV per Papile classification [32]), late-onset sepsis (positive blood culture obtained after three days of age [33]), 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).

| 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 1. Changes between initial protocol and manuscript.
Studies determined not to be relevant (n = 462)

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 [22–24, 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 [22–24] 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.

Figures S1–S4 depict risk of bias plots (graph and summary) 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 S2 shows a summary of findings for each outcome for a comparison of DMT and SMT treatment. 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 Fig. 2 and secondary outcomes and adverse events in Fig. 3 (A-F). Here, we briefly describe the results for each outcome.

Successful PDA closure (Fig. 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 = 1.18 [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.
## 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 |
|--------------------------------|------------------|--------------|------------------|--------------------------------------|-----------------|-------------------------------|-----------------------------|-------------------------------|--------------------------------|
| Aikio 2020                    | Finland          | Single center retrospective study | January 2002–December 2018 | 18 103 I BU + ACE: 940 (300)² IBU: 860 (280)² | IBU + ACE: 26.6 (1.9)² IBU: 26.2 (2.1)² | IBU + ACE: 5 (4, 8)² IBU: 4 (1, 27)² | 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)² IBU: 790 (642, 980)² | IBU + ACE: 26.1 (25.2, 26.8)² IBU: 25.7 (24.9, 27.6)² | IBU + ACE: 7 (4, 10)² IBU: 6.5 (3, 12.5)² | Oral IBU mg/kg/dose (10-5-5), oral ACE 15 mg/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)² IBU: 812 (181)² | IBU + ACE: 25.9 (1.1)² IBU: 25.6 (1.2)² | IBU + ACE: 8.5 (2.6)² IBU: 7.5 (1.6)² | IV/oral IBU mg/kg/dose (10-5-5-5), 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)² IBU: 739 (140)² | IBU + ACE: 25.08 (1.2)² IBU: 25.38 (1.46)² | IBU + ACE: 9.8 (2.8)² IBU: 8.6 (3.2)² | Oral IBU mg/kg/dose (10-5-5), oral ACE 15 mg/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. |
| 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 |
|-------------------------------|------------------|-------------|------------------|----------------------------------------|----------------|-----------------------------|-------------------------------|-------------------------------|-------------------------------|
| Hochwald 2018 Israel | Single-center, double-blind, randomized controlled pilot study | 2014–2016 | 12 | 12 | IBU: 1120 (171)<sup>a</sup> IBU: 951 (157)<sup>a</sup> | IBU: 27.7 (1.3)<sup>a</sup> IBU: 27.2 (1.4)<sup>a</sup> | IBU: 6.6 (1.8)<sup>a</sup> IBU: 6.3 (1)<sup>a</sup> | 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 trans ductal 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: 1264.7 (510)<sup>a</sup> IBU: 1353.6 (333.1)<sup>a</sup> | IBU: 30.36 (2.39)<sup>a</sup> IBU: 31.14 (2.35)<sup>a</sup> | IBU: 8.52 (5.9)<sup>a</sup> IBU: 5.44 (2.37)<sup>a</sup> | Oral IBU mg/kg/dose (10-5-5), IV ACE 15 mg/kg/dose every 6 hours for 3 days | LA:Ao ≥1.5, retrograde diastolic flow in the superior mesenteric artery or in the anterior cerebral artery, PDA diameter ≥1.5 mm, and an unrestricted pulsatile trans ductal flow |

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.

*Mean (SD).  
**Median (IQR).
PDA ligation (Fig. 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 0.38–1.62], 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) (Fig. 5S): 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%). Alkio 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) (Fig. 5S): 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 risk 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 (Fig. S5): 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 (Fig. S8): 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 risk 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 (Fig. S9): 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 0.85–1.66] for NRS and RR = 1.15 [95% CI 0.86–1.52] 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 (Fig. 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 Bouazz 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 (M2) 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 therelative 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 of 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) may also shed light on the conundrum of PDA medical management.

Low-certainty evidence shows no superiority of DMT in closing a hemodynamically significant PDA over SMT in preterm infants. Due to a lack of consensus on clinical and echocardiographic criteria to define a hemodynamically significant PDA, we recommend that future studies use the definition recommended by Hamrick et al. [46] that includes both clinical and echocardiographic criteria to achieve consistency in any future study.

DATA AVAILABILITY

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

REFERENCES

1. Dice JE, Bhatia J. Patent ductus arteriosus: an overview. J Pediatr Pharm Ther. 2007;12:138–46.
2. Schneider DJ, Moore JW. Patent ductus arteriosus. Circulation. 2006;114:1873–82.
3. Mehta S, Younoszai A, Pietz J, Achanti B. Pharmacological closure of the patent ductus arteriosus. Images Paediatr Cardiol. 2003;5:1–15.
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;12:1123–36.
5. Benitez WE. Treatment of persistent patent ductus arteriosus in preterm infants: time to accept the null hypothesis? J Perinatol. 2010;30:241–52.
6. Parkinson 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. Pericutaneous patent ductus arteriosus (PDA) closure during infancy: a meta-analysis. Pediatrics. 2017;139:e20162927.
8. Anderson BJ. Paracetamol (Acetaminophen): mechanisms of action. Paediatr Anaesth. 2008;18:915–21.
9. Green K, Drvota V, Vesterqvist O. Pronounced reduction of in vivo prostacyclin synthesis in humans by acetaminophen (paracetamol). Prostaglandins. 1989;37:311–5.
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;40:21.
11. Rostaas SE, McPherson CR. Pharmacotherapy for patent ductus arteriosus: current options and outstanding questions. Curr Pediatr Rev. 2016;12:110–9.
12. El-Mashad AE, El-Mahdy H, El Amrousy D, Eldengy 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;176:233–40.
13. Liebowitz M, Kaempf J, Erdeve O, Bulbul A, Håkansson 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;39:599–607.
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 Wied Rzecz. 2005;9:335–54. 3 Pt 1
