EUROMEDITERRANEAN BIOMEDICAL JOURNAL
2021,16 (29) 124-130
(*FORMERLY: CAPSULA EBURNEA*)

Original article

THE EFFICACY, SIDE-EFFECTS, AND MORTALITY COMPARISON BETWEEN PARACETAMOL AND IBUPROFEN IN PATENT DUCTUS ARTERIOSUS TREATMENT FOR PREMATURE INFANTS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ARTICLE INFO

Article history:
Accepted 12 Jun 2021
Revised 03 Sep 2021
Published 04 Oct 2021

Keywords:
Ibuprofen, paracetamol, patent ductus arteriosus, preterm.

ABSTRACT

Nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen, have long been a standard pharmacotherapy for patent ductus arteriosus (PDA). However, recently, paracetamol has also proven to produce the same effect by preventing prostaglandin synthesis. Several studies have compared the efficacy and side-effects of both drugs, but the results are not straightforward. The meta-analysis aims to compare the efficacy, side effects, and mortality of ibuprofen and paracetamol for treatment of PDA in preterm infants. Relevant articles were searched for on PubMed, Clinical Key, EMBASE, Cochrane Database, and Google Scholar before the study's quality was assessed using the Jadad criteria and the data were analyzed using Review Manager. Fifteen clinical studies with 1477 preterm infants as the samples were analyzed using a meta-analysis. No significant statistical difference was found between the efficacy of paracetamol and ibuprofen in the DA closure and mortality cases. Meanwhile, for oliguria, kidney disease, and gastrointestinal bleeding, significant statistical difference was found with a lower risk in paracetamol.

1. Introduction

Congenital heart disease (CHD) is a typical inborn defect found in newborns. CHD's main feature is an abnormality in the anatomical structure of a fetus's heart during pregnancy. The conditions increasing the risk of CHD include genetic disorder, excessive alcohol consumption or drugs during pregnancy, infection during the first period of a trimester, and family health history.[1] There are various types of CHD, such as ventricular septal defect (VSD), atrial septal defect (ASD), or tetralogy of Fallot (ToF), and among those, patent ductus arteriosus (PDA) is worth further analysis.[2]

PDA is a cyanotic CHD, featuring open ductus arteriosus (DA) after birth. The condition occurs due to the insensitivity of the ductus arteriosus to the partial pressure of oxygen increase and high level of prostaglandin.[3,4] PDA is often found in preterm infants, amounting to 5-10% of all CHD cases.[3]

For infants with 30-37 weeks' gestational age, 10% of them experience the failure of the DA closure in the fourth day, while for infants with 25-28 weeks' and 24 weeks' gestational age, the number reaches 80% and 90%, respectively. In Indonesia, recorded PDA incidents are in RSUP (General Public Hospital) Cipto Mangunkusumo, Jakarta, and RSUP Mohammad Hosein, Palembang, making up around 32% and 58,7% of all cases.[3,6]

Among PDA cases, PDA with hemodynamics is one of the most common. PDA with hemodynamics can increase the risk for various complications, such as bronchopulmonary dysplasia, intraventricular hemorrhage, and necrotizing enterocolitis. Typically, the implemented treatments are pharmacotherapy or surgery.[3,7] However, due to its non-invasiveness and ability in preventing many comorbidities that may occur in surgical therapy, such as vocal cord paralysis, pulmonary dysplasia, and neurosensory dysfunction, pharmacotherapy is often recommended as the first-line treatment.[7-9]

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DOI: 10.3269/1970-5492.2021.16.29
 ISSN: 2279-7165 - Available on-line at www.embj.org

The standard pharmacotherapy for this case is administering a nonsteroidal anti-inflammatory drug (NSAIDs), such as indomethacin and ibuprofen, which acts in halting prostaglandin synthesis by blocking the function of the cyclooxygenase.[10] Although ibuprofen and indomethacin are equally effective in triggering the DA closure, ibuprofen is preferred as it has a fewer side-effects,[11-12] Meanwhile, recently, the use of paracetamol as an alternative treatment is also increasing, considering that paracetamol also acts in preventing prostaglandin synthesis through peroxidase enzyme's inhibition.[3,10] The problem is that recent research of paracetamol showed inconclusive results regarding its comparative efficacy to ibuprofen.

For example, some clinical studies, such as Sari et al.[6] and El-Farrash et al.[13] reported that paracetamol has a higher effectiveness than ibuprofen in triggering DA closure for preterm infants; while other studies, such as Lu et al. [14] and Dani et al. [15] reported that ibuprofen is more effective than paracetamol in triggering DA closure. Indeed, other research, such as El-Mashad et al.[16] and Dang et al.[17] found no significant difference between those drugs in starting DA closure, although paracetamol has fewer side effects. Against these findings, this study analyzes the various and sometimes contradictory previous findings with a systematic review and meta-analysis. The study compares the efficacy, side effects, and mortality cases between paracetamol and ibuprofen for PDA pharmacotherapy in preterm infants.

2. Material and methods

The study is a quantitative research performed using a systematic review and meta-analysis as the design. The design followed the guidelines from *the Preferred Reporting Items for Systematic Review and Meta-Analyses* (PRISMA).[18] The study protocol using this approach was not registered in the PROSPERO database. The inclusive criteria of this study were original clinical studies published in the past ten years. The characteristic of each study followed PICO's framework, as illustrated in Table 1.

The literature search was based on PubMed, Clinical Key, EMBASE, Cochrane Database, and Google Scholar publications from October 2020. The chosen literature was limited to free articles in Indonesian or English published in the past ten years (January 1, 2011, to October 32, 2020). Search criteria included the MesH term used with the keyword *"persistent ductus arteriosus" OR "PDA" AND "paracetamol" OR "acetaminophen" AND "ibuprofen" AND "preterm neonates."* The collected literature was compiled in the Mendeley software while disposing of the duplicate articles.

The literature was selected systematically by two reviewers (IAA and LDL) by reading the title and abstract, resulting in ruling out the considered ineligible literature. The data were collected using Microsoft Excel's worksheet. Data collected were author name, publication year, country, research design, the sample number, patient characteristics, primary outcomes (ductus arteriosus closure) and secondary outcomes (side effects and mortality).

The study quality was assessed using the Jadad scale, which assessed the validity of each study investigated. The Jadad scale assesses three aspects of validities: randomization, double-blinding, and drop out. 0 was the minimum score, and 5 was the maximum score.[19] The two reviewers (IAA and LDL) assessed the studies independently using the Jadad scale.

Data analysis in the present meta-analysis used Review Manager software version 5.4.[20]

The effect size to analyze all studies' combined effects was the odds ratio (OR) because the data collected was dichotomous. The established confidence interval was 95%. The heterogeneity of the studies was assessed using Cochran's Q and I^2 tests. If no variation between studies were found [the p-value of the heterogeneity test was >0,05 and I^2 small was (≤50%)], the analysis model used would be the fixed effect model (FEM). If the studies varied [the p-value of the heterogeneity test was <0,05 or I^2 big was (>50%)], the analysis model used would be the random effects model (REM).[21] The combined effect would be significant if the p-value <0,05 and the confidence interval did not reach the vertical line (number 1). For publication bias, a funnel plot was used for a visual assessment, while the egger's test and Begg's test were used for a statistical assessment.

PICO	Inclusion Criteria
Population	Preterm infants (<37 months) diagnosed with PDA and, through doppler echocardiography, hemodynamics disturbance.
Intervention	Oral or intravenous paracetamol.
Comparison	Oral or intravenous ibuprofen.
Outcome	Primary: efficacy (primary closure and complete closure of DA) Secondary: side effects (kidney disease, oliguria, gastrointestinal bleeding, thrombocytopenia, and hyperbilirubinemia) and mortality.

Table 1. Inclusion Criteria

3.Results

As many as 1559 articles were identified from the five databases mentioned, namely PubMed, Google Scholar, Cochrane, Clinical Key, and Embase, of which 236 papers were duplicates and thus excluded. The article filter based on titles and abstracts excluded another 1303 articles. Subsequently, 20 articles left were analyzed thoroughly, resulting in excluding another 5 articles. Among the 5 articles, 2 articles demonstrated different outcomes, 1 article was written in neither Indonesian nor English, and 2 articles were of low quality. The 15 remaining articles were analyzed for this study. Information regarding the literature selection process can be seen in Figure 1.

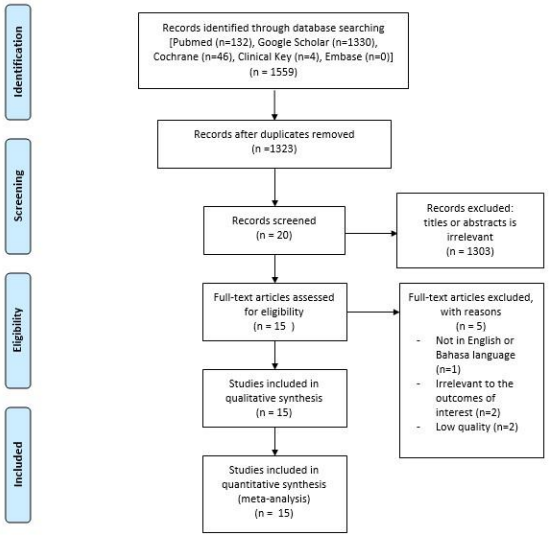

Figure 1. Study flow diagram

Authors	Country, Year	Journal Name	Design, Blinding	Participants	Intervention (route, dosage, duration)	Jadad Scale
Ghaderin et al[26]	Iran, 2019	Journal of Research in Medical Sciences	RCT, SB	Sample size (P/I): 20/20 GA (week): 29 BW (grams): 1281.5 DD (mm): NR	Paracetamol (mg/kg/d): IV, 60-60-60, 3 days Ibuprofen (mg/kg/d): Oral, 10-5-5, 3 days	5
Jafari et al[27]	Iran, 2019	Journal of Medical Council of Islamic Republic of Iran	RCT, SB	Sample size (P/I): 16/14 GA (week): <34 BW (grams): <2500 DD (mm): NR	Paracetamol (mg/kg/d): IV, 60-60-60, 3 days Ibuprofen (mg/kg/d): IV, 10-5-5, 3 days	3
Kumar et al[28]	India, 2020	Journal of Pediatrics	RCT, SB	Sample size (P/I): 81/80 GA (week): 28.7 BW (grams): 1148 DD (mm): 2.2	Paracetamol (mg/kg/d): Oral, 60-60-60, 3 days Ibuprofen (mg/kg/d): Oral, 10-5-5, 3 days	5
Oncel et al[29]	Turkey, 2020	Journal of Pediatrics	RCT, SB	Sample size (P/I): 41/40 GA (week): 27.3 BW (grams): 952.5 DD (mm): 2.28	Paracetamol (mg/kg/d): Oral, 60-60-60, 3 days Ibuprofen (mg/kg/d): Oral, 20-10-10, 3 days	3
Sari et al[6]	Indonesia, 2016	Sari Pediatri	RCT, OL	Sample size (P/I): 36/40 GA (week): 30.57 BW (grams): 1587.4 DD (mm): NR	Paracetamol (mg/kg/d): IV, 60-60-60, 3 days Ibuprofen (mg/kg/d): Oral, 10-5-5, 3 days	3
Sinol et al[30]	India, 2016	Asian Journal of Pediatric Research	RCT, SB	Sample size (P/I): 70/70 GA (week): 29.5 BW (grams): 1135 DD (mm): NR	Paracetamol (mg/kg/d): Oral, 60-60-60, 3 days Ibuprofen (mg/kg/d): Oral, 10-5-5, 3 days	3
Yang et al[31]	China, 2016	Experimental and Therapeutic Medicine	RCT, SB	Sample size (P/I): 44/43 GA (week): 33.5 BW (grams): 2155 DD (mm): NR	Paracetamol (mg/kg/d): Oral, 60-60-60, 3 days Ibuprofen (mg/kg/d): Oral, 10-5-5, 3 days	3
Al-lawama et al[22]	Jordan, 2017	Journal of International Medical Research	RCT, SB	Sample size (P/I): 13/9 GA (week): 28.33 BW (grams): 1125.5 DD (mm): NR	Paracetamol (mg/kg/d): Oral, 40-40-40, 3 days Ibuprofen (mg/kg/d): Oral, 10-10-10, 3 days	3
Asadpour et al[23]	Iran, 2018	Journal of Clinical Neonatology	RCT, SB	Sample size (P/I): 25/25 GA (week): <37 BW (grams): NR DD (mm): NR	Paracetamol (mg/kg/d): Oral, 40-40-40, 3 days Ibuprofen (mg/kg/d): Oral, 10-5-5, 3 days	3
Bagheri et al[24]	Iran, 2016	Iranian Journal of Pediatrics	RCT, SB	Sample size (P/I): 80/80 GA (week): 31.61 BW (grams): 1644.44 DD (mm): NR	Paracetamol (mg/kg/d): Oral, 60-60-60, 3 days Ibuprofen (mg/kg/d): Oral, 20-10-10, 3 days	3
Balachander et al[25]	India, 2018	Journal of Maternal-Fetal and Neonatal Medicine	RCT, SB	Sample size (P/I): 55/55 GA (week): 31.56 BW (grams): 1524.1 DD (mm): 2.39	Paracetamol (mg/kg/d): Oral, 60-60-60, 3 days Ibuprofen (mg/kg/d): Oral, 10-5-5, 3 days	3
Dang et al[17]	China, 2013	PLoS ONE	RCT, SB	Sample size (P/I): 80/80 GA (week): 31.11 BW (grams): 1561.51 DD (mm): 2.85	Paracetamol (mg/kg/d): Oral, 60-60-60, 3 days Ibuprofen (mg/kg/d): Oral, 20-10-10, 3 days	3
Dani et al[18]	Italy, 2020	European Journal of Pediatrics	RCT, SB	Sample size (P/I): 52/49 GA (week): 28.3 BW (grams): 1536 DD (mm): NR	Paracetamol (mg/kg/d): IV, 60-60-60, 3 days Ibuprofen (mg/kg/d): IV, 10-5-5, 3 days	3
El-farrash et al[15]	Egypt, 2018	Journal of Maternal-Fetal and Neonatal Medicine	RCT, SB	Sample size (P/I): 30/30 GA (week): 31.13 BW (grams): 1635 DD (mm): NR	Paracetamol (mg/kg/d): Oral, 60-60-60, 3 days Ibuprofen (mg/kg/d): Oral, 10-5-5, 3 days	3
El-mashad et al[16]	Egypt, 2017	European Journal of Pediatrics	RCT, SB	Sample size (P/I): 100/100 GA (week): 25.5 BW (grams): 1050 DD (mm): 2.75	Paracetamol (mg/kg/d): IV, 60-60-60, 3 days Ibuprofen (mg/kg/d): IV, 10-5-5, 3 days	3

Abbreviation: BM, birth weight; DB, double blind; DD, ductal diameter; GA, gestational age; I, ibuprofen; IV, intravenous; NR, not reported; OL, open label; P, paracetamol; RCT, randomized controlled trial; SB, single blind

Table 2. Characteristics of included study

Characteristics of the Study

The 15 RCT studies were analyzed using a systematic review and meta-analysis.

The characteristic of each study is presented in Table 2. The total sample included 1477 preterm infants (Paracetamol n=742; Ibuprofen n=735). 4 studies were conducted in Iran, 3 studies in India, 2 studies in China and Egypt, and 1 study in Jordan, Italy, and Indonesia. The routes of drug administration were divided into three categories, namely oral-oral (n=10), intravenous-intravenous (n=3), and intravenous-oral (n=2). The dose and duration of paracetamol and ibuprofen for each study were relatively similar; for paracetamol, 15mg/kg BB/6 hour for three days; for ibuprofen, 10mg/kg BB/24 hours for the first day and 5 mg/kg BB/24 hours in the second and third day.

Study Quality Assessment

Based on the Jadad scale, two studies were scored 5 (very good), while the other 13 studies were scored 3 (good). The study quality assessment is presented in Table 2.

Primary Outcomes: Efficacy of DA closure

Figure 2 illustrates the forest plot of the efficacy comparison between paracetamol and ibuprofen in DA primary closure (DA closure after one-time treatment) and DA complete closure (complete closure of DA after one- or two-time treatment). The analysis model used was FEM because all studies were homogenous ($I^2 = 40\%$, $p = 0.06$; $I^2 = 0\%$, $p = 0.75$). The OR combined value for DA primary closure was 1,03 (95% CI: 0.82, 1.29) and DA complete closure was 1.20 (95% CI: 0.90, 1.61). No statistically significant difference was found between the two drugs' efficacy in question, in the DA primary closure ($p = 0.82$) or DA complete closure ($p = 0.21$).

Secondary Outcomes: Side Effects and Mortality

Figure 3 shows the forest plot of the side effect and mortality comparison between paracetamol and ibuprofen. The assessment of oliguria, kidney disease, and gastrointestinal bleeding (Figure 3a-c) showed significant statistical differences between paracetamol and ibuprofen. The combined OR amounted to 0.46 (95% CI: 0.25, 0.85; $p = 0.01$), 0.27 (95% CI: 0.1, 0.77; $p = 0.01$), and 0.32 (95% CI: 0.18, 0.59; $p = 0.0003$), respectively. The analysis model used was FEM with the heterogeneity value of oliguria and kidney disease accounting for 0% and gastrointestinal bleeding 55%.

Assessment of hyperbilirubinemia and thrombocytopenia (Figure 3d-e) showed no statistically significant difference between two drugs. The OR combined value was 0.74 (95% CI: 0.24, 2.3; $p = 0.6$) and 0.27 (95% CI: 0.01, 8.62; $p = 0.46$), respectively. The analysis model used was REM considering variation in the studies ($I2 = 70\%$, $p = 0.04$; $I2 = 82\%$, $p = 0.02$). The assessment of the mortality by using FEM analysis, due to no variation found in the studies ($I2 = 26\%$, $p = 0.21$), showed no statistically significant difference as well as the OR value combined accounting to 0.97 (95% CI: 0.68, 1.37; $p = 0.85$).

Publication Bias Assessment

Statistical publication bias assessment with Eggers's test and Begg's test showed no statistically significant publication bias in the DA primary closure outcomes (Egger's test = 0.97; Begg's test = 0.69) or in DA complete closure outcomes (Egger's test = 0.94; Begg's test = 0.76). Visual assessment using a funnel plot (Figure 4a-b) reflected a relatively symmetric pattern.

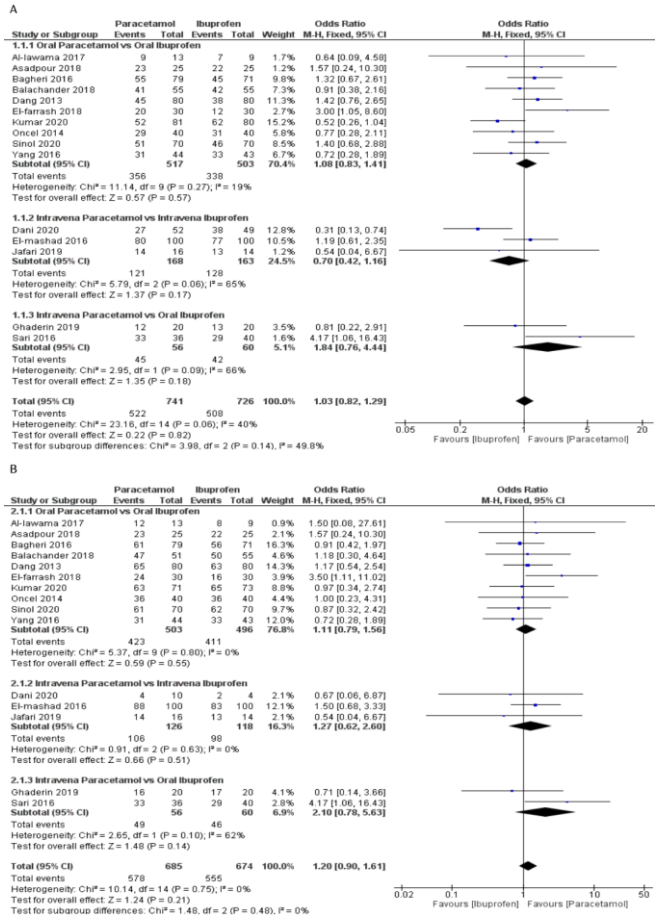

Figure 2. Forest plot comparing the efficacy of paracetamol and ibuprofen in DA closure. (a) Primary DA closure (b) total DA closure.

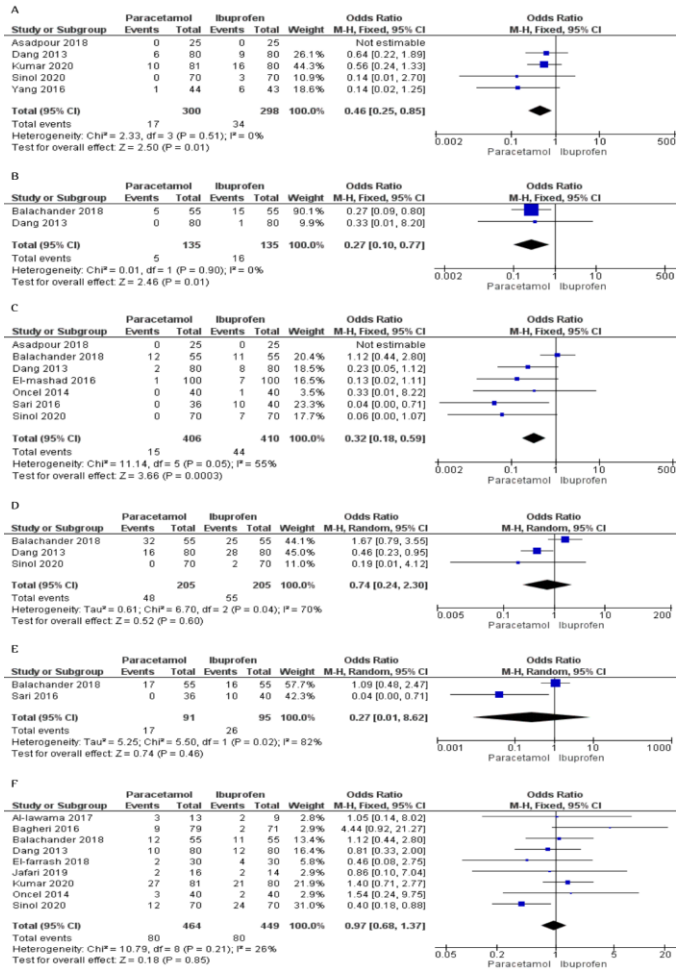

Figure 3 a-f. Forest plot comparing the side effects and the mortality cases of paracetamol and ibuprofen in management of PDA. (a) oliguria, (b) renal failure, (c) gastrointestinal bleeding, (d) hyperbilirubinemia, (e) thrombocytopenia, (f) mortality.

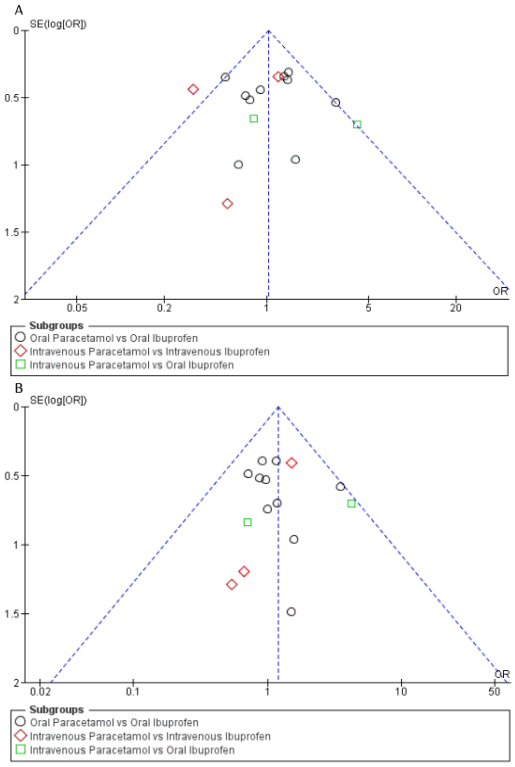

Figure 4 a-b. Publication bias assessment using funnel plot. (a) primary DA closure (b) total DA closure.

4. Discussion

The meta-analysis showed no statistically significant difference between administering paracetamol or ibuprofen for the DA primary closure in the preterm infants after one-time treatment (p = 0.82). Similarly, no significant difference was found in the DA complete closure after two-times treatment (p = 0.21). The previous meta-analysis conducted by Huang et al.[8] and Das et al. [32] synthesizing 5 RCT and 2 RCT with fewer samples also reported no statistically significant difference. The best explanation is that the two drugs had no potential difference in closing DA. Paracetamol prevents peroxidase from postponing prostaglandin G2's transformation to prostaglandin H_2,[6] while ibuprofen prevents COX-1 and COX-2 to form prostaglandin.[10] Prostaglandin maintains DA open, while the drugs induce the DA to close.[3] Furthermore, differences in route (oral-oral, intravenous-intravenous, and intravenous-oral) were statistically significant in inducing DA closure in the preterm infants, indicating that oral and intravenous produce the same effectiveness. Oral treatment is preferable merely due to the lower cost and more straightforward procedure.[6]

However, the meta-analysis also showed that administering paracetamol was statistically significant in reducing the risk of oliguria 0,46 times for preterm infants with PDA instead of ibuprofen. The previous research reported no statistically significant difference.[17,28,30,31] The difference happens arguably due to inadequate samples of the previous research. Interestingly, after the studies were compiled in this meta-analysis, the combined effects were statistically significant.

Administering paracetamol was also significant in reducing the risk of kidney disease 0,27 in preterm infants with PDA. The previous meta-analysis reported no significant difference with the OR combined value (95% CI: 0.04, 1.15; p = 0.7).[8] The difference occurred due to the difference in the number of samples investigated. Ibuprofen had a higher risk of oliguria and kidney disease because ibuprofen prevented prostaglandin synthesis in the kidney, resulting in the kidney blood vessel's vasoconstriction and kidney blood flow disturbance.[33,34]

Furthermore, the meta-analysis showed that administering paracetamol was statistically significant in reducing the risk of gastrointestinal bleeding 0,32 times. The previous research reported a statistically significant difference with the OR combined value at 0,28.[8] Ibuprofen increases the risk of gastrointestinal bleeding as it figures in preventing COX-1, causing the decrease of HCO_3^- production and eventually disturbing the mechanism of gastric mucosa protection. [34,35] Besides, ibuprofen also affects platelet aggregation, increasing the risk of hemorrhage.[8]

Meanwhile, the meta-analysis of the comparison between paracetamol and ibuprofen in the cases of hyperbilirubinemia showed no statistically significant difference. Dang et al. [17] reported a statistically significant difference (p = 0.03). Similar to the previous section, it may be due to a difference in the numbers of samples. Administering ibuprofen is riskier because it may cause hyperbilirubinemia. In a higher concentration, ibuprofen competes with bilirubin to bond with albumin. As a result, bilirubin is bonded with albumin decreases. [17]

The meta-analysis showed no significant difference in the thrombocytopenia for both drugs in the preterm infants with DAP. However, the use of ibuprofen with a high dose may cause thrombocytopenia because ibuprofen can increase platelet destruction and trigger bone-marrow pressure.[36] The mortality cases were not significant between the drugs in question. Sinol et al[30] reported a significant statistical difference (p = 0.003). The difference may also appear due to inadequate samples. The present studies compiled different RCT studies, including Sinol et al.[30] with a more representative sample. The study limitations is that the research only used English or Indonesian online and free articles, excluding unpublished articles and non-Indonesian and non-English research.

5. Conclusions

The systematic review and meta-analysis showed that paracetamol and ibuprofen had the same efficacy in closing patent ductus arteriosus in preterm infants with lower side effects, such as oliguria, kidney disease, and lower gastrointestinal bleeding, in paracetamol. The risk of hyperbilirubinemia, thrombocytopenia, and mortality was also not different. The researchers recommend a further meta-analysis that includes numerous investigated studies and variables.

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