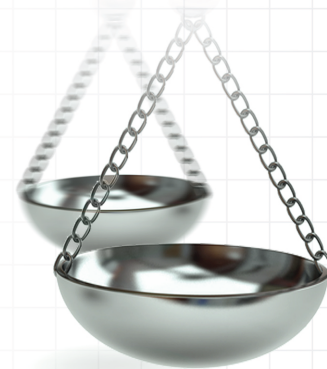




Use of ibuprofen for the closure of patent ductus arteriosus in preterm infants: a systematic review of meta-analyses

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Aim: To systematically review ibuprofen, including versus indomethacin and paracetamol/acetaminophen, for the closure of patent ductus arteriosus (PDA). **Methods:** Pubmed, Embase, Cochrane and gray literature were searched to summarize ibuprofen outcomes in closure of PDA in published meta-analyses (MAs). **Results:** Seven MAs were included. Including high dose (HD) use, ibuprofen is equivalent/superior to indomethacin, and inferior/equivalent to paracetamol. Oral ibuprofen had higher efficacy than IV ibuprofen, including compared with indomethacin and paracetamol. Ibuprofen had safety advantages over indomethacin. Indomethacin and paracetamol had safety advantages over IV ibuprofen. HD of ibuprofen increases efficacy, but not toxicity. **Conclusion:** Evidence on ibuprofen effectiveness and safety, including the dosage forms, is limited by heterogeneity in doses and the levels of methods quality and risk of bias.

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Current management of preterm infants with patent ductus arteriosus (PDA), clinically diagnosed using echocardiographic (ECHO) guidance, can involve fluid restriction and watchful waiting, such as conservative fluid restriction and thiazide diuretics; pharmacologic management such as indomethacin, ibuprofen or paracetamol/acetaminophen; and surgical ligation. Surgery is unlikely to be considered first-line due to adverse events (AEs), and it is usually reserved for infants who cannot be managed pharmacologically [1].

Significant issues in the management of preterm and low birth weight (LBW) newborns with hemodynamically significant PDA (HSPDA) are the timing and type of treatment. Indomethacin, a cyclooxygenase inhibitor, given intravenously (IV), started to be used in the 1970s. It was first trialed for the treatment of infants with symptomatic PDA [2,3]. The first trial that confirmed indomethacin's efficacy for PDA management was published in 1983 [4]. However, it has been associated with several AEs, such as non-intracranial hemorrhage and gastrointestinal (GI) bleeding, weakened platelet aggregation and renal failure. Alternative treatments had been awaited and, by 2003, Ohlsson *et al.* [5] suggested that oral ibuprofen may be as effective in PDA closure as indomethacin, with the potential benefits of fewer GI and renal side effects.

In 2011, Hammerman *et al.* [6] suggested the use of off-label paracetamol at a dose of 15 mg/kg six-hourly as another treatment option in preterm infants with HSPDA, who had failed or had contraindications to indomethacin and ibuprofen, which resulted in ductal closure within 2 days without AEs [6].

Also, an issue is the route of administration. Traditionally treatments have been given IV, but the oral route is now increasingly used. Oral ibuprofen, and now oral paracetamol, have become popular options in many neonatal intensive care units (NICU). One element of the decision is the lower cost of oral compared with IV administration [7].

Our preliminary literature search suggested that there are numerous meta-analyses (MAs) published to provide evidence on the use of oral and IV ibuprofen to treat PDA in preterm infants, including important network MA

(NMA) and Cochrane reviews. The MAs, however, are associated with contrasting results, and with different levels of methods quality and risk of bias. This, therefore, potentially limits the easiness of access to (and interpretation of) evidence. In such instances, the systematic review of MAs is a study design that does not provide new evidence, but it addresses the growing problem of information overload, enables the filtration of large volumes of evidence to enhance access to targeted evidence (where it is being added and where it is being duplicated), and to better inform healthcare decision-making by caregivers [8].

Consequently, the current study sought to perform a systematic review to summarize the evidence provided by published MAs about the primary efficacy and safety aspects of using ibuprofen, compared with paracetamol and indomethacin, for the treatment of PDA in preterm infants. Summaries of evidence will also be matched with the levels of quality of methods and risk of bias in included MAs.

Methods

The current is a systematic review that follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, [Supplementary Material 1](#). PROSPERO registration number CRD42020165457.

Included studies

MAs of randomized controlled trials (RCTs) or quasi-randomized controlled trials (QRCTs) and observational studies, investigating the use of ibuprofen, including versus paracetamol or indomethacin, for the treatment of PDA in preterm infants. Excluded publications included expert opinions, narrative and qualitative reviews, previous versions of current/updated MAs, and ibuprofen's use as prevention against PDA. Also excluded were MAs of studies that were all included in more recent MAs that are included in our analysis. Such older MAs, however, were included in the current analysis if reported pairwise comparisons between interventions that were not included in the more recent MAs.

Participants

Preterm infants (≤ 37 weeks) with HSPDA. There were no inclusion or exclusion criteria on birth weight or postnatal age.

Interventions

Ibuprofen versus indomethacin or paracetamol, via any formulation and dosing regimen, or comparing different formulations or doses of ibuprofen, for PDA treatment.

Outcome measures

Outcomes of interest were efficacy and safety outcomes of ibuprofen as reported in pairwise comparisons included in the MAs. Successful PDA closure was the outcome of interest, and there were no inclusion or exclusion criteria on the reporting of other outcomes. The analysis in this review only included outcomes that are reported in two or more MAs/NMAs. As reported in included studies, the effect measure of ibuprofen as a risk ratio (RR), odds ratio (OR) or mean difference (MD). These were provided at 95% confidence intervals (CI). For NMAs, the SUCRA (surface under the cumulative ranking curve) measures could be included, presented by a mean SUCRA score and a median ranking for the treatment modality.

Search strategy & selection of MAs

We searched Embase, PubMed and the Cochrane Database of Systematic Reviews (CDSR). Search terms used were based on variations of the key terms 'ibuprofen' and 'patent ductus arteriosus' in literature, from inception to June 2020. Detailed search strategies are in [Supplementary Material 2](#). Google Scholar and references of the included studies were manually searched for additional relevant articles in the gray literature over the same search duration. An English language restriction was imposed on the search.

Two reviewers independently screened the identified studies based on the above criteria, including duplicate removal, first by title and abstract for an initial eligibility assessment, before a final full-text screening. Any disagreement was resolved by consensus and referral to a third reviewer. With a similar process, two reviewers independently extracted the main study characteristics and the outcomes of interest.

Table 1. Characteristics of included studies.

Study (year)	Type of study	Comparative interventions	Gestational age	Birth weight	Effects measured	Test of heterogeneity	Ref.
Jones <i>et al.</i> (2011)	NMA	INDO, IBU, PBO	23–34 weeks	≤2500 grams	RR, 95% CI	I ² , χ^2	[24]
Huang <i>et al.</i> (2018)	MA	APAP, IBU	25.5–33.5 weeks	952–2155 grams	RR, 95% CI	I ² , χ^2	[25]
Ohlsson <i>et al.</i> (2020)	MA	APAP, IBU, PBO	28–34 weeks	No criteria on BW (≤1500 grams)	RR, RD, MD, 95% CI	I ²	[21]
Ohlsson <i>et al.</i> (2020)	MA	IBU, INDO, PBO	≤37 weeks	≤2500 grams	RR, RD, MD, 95% CI	I ²	[13]
Mitra <i>et al.</i> (2018)	NMA	APAP, IBU, INDO, PBO	25.5–33.6 weeks	≤2500 grams	OR, Mean SUCRA values, Median rank, 95% CI	I ²	[22]
Marconi <i>et al.</i> (2019)	NMA	APAP, IBU, INDO, PBO	23–33.6 weeks	No criteria on BW	OR, 95% CI	Cochrane Q test	[23]
Loomba <i>et al.</i> (2015)	MA	IBU, INDO	25.3 ± 1.5, and 33.2 ± 3.1 weeks	No criteria on BW (800 ± 100, and 1900 ± 500 grams)	OR, MD, 95% CI	I ² , χ^2	[26]

APAP: Paracetamol/acetaminophen; BW: Birth weight; GA: Gestational age; IBU: Ibuprofen; INDO: Indomethacin; MA: Meta-analysis; MD: Mean difference; NMA: Network meta-analysis; OR: Odds ratio; PBO: Placebo or no treatment; QRCT: Quasi-randomized controlled trial; RCT: Randomized controlled trial; RD: Risk difference; RR: Relative risk or risk ratio; SUCRA: Surface under the cumulative ranking curve; χ^2 : Chi-square test.

Quality of methods assessment

As generally performed in the literature [9], the quality of methods and risk of bias are evaluated for included MAs to enable the interpretation of conclusions identified from the MAs. Two reviewers independently assessed MAs' methodological quality based on AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews-2, https://amstar.ca/Amstar_Checklist.php) [10]. No identified tool has been proposed to especially evaluate the methodological quality of NMAs. Because of its good validity, reliability and responsibility, AMSTAR-2 is currently the most commonly used tool for the assessment of methods quality in MAs and, in the current study, consistent with relevant similar studies in the literature, will also be used to assess the quality in NMAs [11]. The quality of methods was rated as high, moderate, low and critically low. Disagreements were resolved by consensus and referral to a third reviewer.

Risk of bias assessment

The ROBIS (Risk of Bias in Systematic Reviews) tool [12] is most proposed for assessing the risk of bias in MAs, including NMAs. Two reviewers independently evaluated the risk of bias in the studies. The risk of bias was rated 'high risk of bias', 'unclear risk of bias', or 'low risk of bias'. Disagreements were resolved by consensus and referral to a third reviewer.

Results

Out of 1924 studies returning from the literature search, 7 studies were included for analysis. A detailed flow diagram of study inclusion is in [Supplementary Material 3](#). A list of excluded studies based on full-text is in [Supplementary Material 4](#).

The MAs included two Cochrane reviews, by Ohlsson *et al.*, undertaking two Cochrane series of MA updates; one series focused on ibuprofen [5,13–18] and the other on paracetamol [19–21]. The current study included the last update in each [13,21]. Included MAs were recent [13,21–26], published between 2011 and 2020, including four MAs [13,21,25,26] and three NMAs [22–24]. Details of study characteristics are presented in [Table 1](#) and [Table 2](#), including the MAs' reported pairwise comparisons.

As discussed in methods, the analysis in this review includes the outcomes reported in two or more MAs. Here, based on the outcomes reported by included MAs ([Supplementary Material 5](#)), efficacy outcomes of interest in our analysis were PDA closure, need for surgical ligation, retreatment, reopening and duration of hospitalization, while safety outcomes were based on AEs reported, with those deemed of interest being mortality, necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), intraventricular hemorrhage (IVH), intestinal perforation, GI bleeding, periventricular leukomalacia (PVL), oliguria and elevated serum creatinine levels, retinopathy of prematurity (ROP), sepsis, pulmonary hemorrhage, pulmonary hypertension, serum bilirubin, platelet count and duration of ventilator support.

As can be seen in [Table 3](#), all included studies reported the PDA closure outcome. A significant difference

Table 2. Pairwise treatment comparisons within included studies.

Study (year)	Type of study included in the analysis	Drug 1 and formulation ^{†,‡,§}	Drug 2 and formulation ^{†,‡,§}	N of studies (of which RCTs or QRCT)	N of infants	Ref.
Ohlsson <i>et al.</i> (2020)	RCT and QRCT	IBU (oral or IV)	INDO (oral or IV)	24 (24)	1590	[13]
		IV IBU	PBO	2 (2)	206	
		Oral IBU	INDO (oral or IV)	8 (8)	272	
		Oral IBU	IV IBU	5 (5)	406	
		High dose IBU (oral or IV)	IBU (oral or IV)	3 (3)	190	
Ohlsson <i>et al.</i> (2020)	RCT and QRCT	Oral APAP	Oral IBU	5 (5)	559	[21]
		APAP	INDO	2 (2)	273	
Marconi <i>et al.</i> (2019)	RCT and observational studies	IBU	INDO	31 (19)	2843	[23]
		IBU	APAP	10 (9)	1036	
		IBU	PBO	6 (6)	426	
		APAP	INDO	2 (2)	377	
		APAP	PBO	2 (2)	117	
Loomba <i>et al.</i> (2015)	RCT and observational studies	INDO	PBO	10 (10)	1091	[26]
		Oral IBU	Oral APAP	4 (4)	477	
		IV IBU	IV INDO	10 (10)	643	
		IV INDO	PBO	9 (9)	666	
		IV IBU	PBO	1 (1)	28	
Mitra <i>et al.</i> (2018)	RCT	IBU	INDO	22 (14)	1583	[22]
		High dose oral IBU	Oral APAP	1 (1)	129	
		High dose oral IBU	Oral IBU	2 (2)	120	
		High dose IV IBU	INDO, continuous IV infusion	1 (1)	73	
		High dose IV IBU	IV IBU	1 (1)	70	
		Oral APAP	Oral IBU	3 (3)	327	
		Oral IBU	IV INDO	4 (4)	103	
		Oral IBU	INDO, other types	4 (4)	162	
		Oral IBU	IV IBU	4 (4)	304	
		Oral IBU	PBO or no treatment	4 (4)	264	
		IV INDO	INDO, continuous IV infusion	2 (2)	50	
		IV INDO	IV IBU	12 (12)	883	
		INDO	INDO, continuous IV infusion	10 (10)	802	
		INDO	PBO or no treatment	5 (5)	164	
		INDO, continuous IV infusion	IV IBU	1 (1)	63	
		INDO, continuous IV infusion	PBO or no treatment	4 (4)	495	
		IV IBU	IBU, continuous IV infusion	1 (1)	111	
		IV IBU	PBO or no treatment	1 (1)	136	
		INDO	INDO, continuous IV infusion	10 (10)	802	

[†]When the formulation is not reported, this indicated that the study included all formulations (oral, IV or rectal) of a drug with no separation in analysis.

[‡]A formulation of 'oral or IV' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.

[§]Doses are standard unless stated as high doses.

APAP: Paracetamol/acetaminophen; IBU: Ibuprofen; INDO: Indomethacin; IV: Intravenous; MA: Meta-analysis; NMA: Network meta-analysis; PBO: Placebo; QRCT: Quasi-randomized controlled trial; RCT: Randomized controlled trial.

Table 3. Studies for patent ductus arteriosus closure.

Study (year)	Drug 1 and formulation ^{‡,§,¶}	Drug 2 and formulation ^{‡,§,¶}	N of studies and infants	Cycles of treatment for PDA closure	Effect size (95% CI)	Heterogeneity	Statistically significant difference	Ref.
Ohlsson <i>et al.</i> (2020)	IBU (oral or IV)	INDO (oral or IV)	24 studies, 1590 infants	3 doses IBU of 10, 5, 5 mg/kg, 24-h interval. INDO 0.1–0.2 mg/kg, 12- to 24-h interval	RR 1.07 (0.92, 1.24)	I ² = 0%	No	[13]
	Oral IBU	INDO (oral or IV)	8 studies, 272 infants	3 doses IBU of 10, 5, 5 mg/kg, 24-h interval. INDO 0.2 mg/kg, 12- to 24-h interval	RR 0.96 (0.73, 1.27)	I ² = 0%	No	
	Oral IBU	IV IBU	5 studies, 406 infants	3 doses IBU of 10, 5, 5 mg/kg, 24-h interval for 3 days	RR 0.38 (0.26, 0.56)	I ² = 0%	Yes, in favor of oral IBU	
	High-dose IBU (oral or IV)	IBU (oral or IV)	3 studies, 190 infants	3 high doses IBU of 20, 10, 10 mg/kg OR 15, 7.5, 7.5 mg/kg, 24-h interval Standard dose IBU of 10, 5, 5 mg/kg, 24-h interval	RR 0.37 (0.22, 0.61)	I ² = 4%	Yes, in favor of high-dose IBU (oral or IV)	
Jones <i>et al.</i> (2011)	IV IBU	IV INDO	10 studies, 615 infants	3 doses IBU of 10, 5, 5 mg/kg, 24-h interval. INDO 0.2 mg/kg, 12-h interval	RR 1.00 (0.93, 1.08)	χ ² = 3.24, I ² = 0%	No	[24]
Mitra <i>et al.</i> (2018) [†]	High-dose oral IBU	IV INDO	Direct and indirect studies	3 doses IBU of 15, 7.5, 7.5 mg/kg OR 20, 10, 10 mg/kg, 12- to 24-hour interval INDO 0.1–0.3 mg/kg	OR 2.35 (1.08, 5.31)	NA	Yes, in favor of high-dose oral IBU	[22]
	IV IBU	IV INDO	12 studies, 879 infants	3 doses IBU of 10, 5, 5 mg/kg, 12- to 24-h interval INDO 0.1–0.3 mg/kg	OR 0.86 (0.59, 1.24)	NA	No	
	High-dose IV IBU	IV INDO	Direct and indirect studies	3 doses	OR 2.41 (0.68, 9.86)	NA	No	
	Oral IBU	IV INDO	Direct and indirect studies	3 doses	OR 1.45 (0.94, 2.24)	NA	No	
	High-dose oral IBU	Oral IBU	Direct and indirect studies	3 doses	OR 1.63 (0.84, 3.24)	NA	No	
	High-dose IV IBU	IV IBU	Direct and indirect studies	3 doses	OR 3.68 (1.09, 14.59)	NA	Yes, in favor of high-dose IV IBU	
	High-dose oral IBU	IV IBU	Direct and indirect studies	3 doses	OR 3.59 (1.64, 8.17)	NA	Yes, in favor of high-dose oral IBU	
Marconi <i>et al.</i> (2019)	IBU	INDO	31 studies	End of treatment (1–3 course cycles). The course: 3 doses IBU of 10, 5, 5 mg/kg, 24-h interval 3 doses INDO of 0.1–0.25 mg/kg, 12- to 24-h interval, including prolonged treatment with INDO (6 doses)	OR 0.88 (0.71, 1.11)	NA	No	[23]
	IBU	INDO	Direct and indirect studies	End of treatment (1–3 cycles)	OR 0.89 (0.68, 1.17)	NA	No	

[†]In overall, Mitra *et al.* reported for IV IBU in PDA closure a mean SUCRA 0.24, SD ±0.07; median rank 8, 95% CI 7–9, for high dose oral IBU a mean SUCRA 0.89, SD ±0.12; median rank 2, 95% CI 1–5, and for high dose IV IBU a mean SUCRA 0.84, SD ±0.20; median rank 2, 95% CI 1–7.

[‡]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.

[§]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.

[¶]Doses are standard unless stated as high doses.

High dose regimen: 15–20 mg/kg/day followed by ibuprofen 7.5–10 mg/kg/day for two doses.

APAP: Acetaminophen/paracetamol; I²: I-square index; IBU: Ibuprofen; INDO: Indomethacin; IV: Intravenous; NA: not available; OR: Odds ratio; PBO: Placebo; RCT: Randomized controlled trial, including quasi-RCT; RR: Risk ratio; SD: Standard deviation; χ²: Chi-square test.

Table 3. Studies for patent ductus arteriosus closure (cont.).

Study (year)	Drug 1 and formulation ^{‡,§,¶}	Drug 2 and formulation ^{‡,§,¶}	N of studies and infants	Cycles of treatment for PDA closure	Effect size (95% CI)	Heterogeneity	Statistically significant difference	Ref.
Loomba et al. (2015)	IV IBU	IV INDO	14 studies, 1068 infants	(1–2 cycles). 3 doses IBU of 10, 5, 5 mg/kg, 24-h interval INDO 0.1–0.25 mg/kg, 12- to 24-h interval	OR 1.07 (0.81, 1.43)	$\chi^2 = 6.09$, $I^2 = 0\%$	No	[26]
	Oral IBU	IV INDO	6 studies, 412 infants	(1–2 cycles). 3 doses IBU of 10, 5, 5 mg/kg, 24-h interval INDO 0.1–0.25 mg/kg, 12- to 24-h interval	OR 0.76 (0.50, 1.18)	$I^2 = 0\%$	No	
Ohlsson et al. (2020)	IBU (oral or IV)	APAP (oral or IV)	5 studies, 559 infants	(1 course). 3 doses IBU of 10, 5, 5 mg/kg, 24-h interval. APAP 10–15 mg/kg, 6-h interval for 3 days	RR 0.95 (0.75, 1.21)	$I^2 = 0\%$	No	[21]
Huang et al. (2018)	Oral IBU	Oral APAP	4 studies, 477 infants	3 doses IBU of 10, 5, 5 mg/kg, 24-h interval for 3 days APAP 60, 60, 60 mg/day for 3 days	RR 1.02 (0.90, 1.16)	$\chi^2 = 2.46$, $I^2 = 0\%$	No	[25]
Mitra et al. (2018) [†]	High dose oral IBU	Oral APAP	Direct and indirect studies	3 doses	OR 1.23 (0.62, 2.48)	NA	No	[22]
	High dose IV IBU	Oral APAP	Direct and indirect studies	3 doses APAP 15 mg/kg, 6-h interval for 3, 5, 7 days	OR 1.25 (0.31, 5.77)	NA	No	
	Oral IBU	Oral APAP	Direct and indirect studies	3 doses	OR 1.33 (0.81, 2.17)	NA	No	
	IV IBU	Oral APAP	Direct and indirect studies	3 doses	OR 2.93 (1.53, 5.62)	NA	Yes, in favor of oral APAP	
	IBU, continuous IV infusion	Oral APAP	Direct and indirect studies	3 doses	OR 4.08 (1.35, 12.47)	NA	Yes, in favor of oral APAP	
Marconi et al. (2019)	APAP	IBU	10 studies	End of treatment (1–3 cycles). The cycle: 3 doses IBU of 10, 5, 5 mg/kg, 24-h interval APAP 10–15 mg/kg, 6-h interval for 3 days, including prolonged treatment of APAP (7 days)	OR 1.02 (0.72, 1.44)	NA	No	[23]
	APAP	IBU	Direct and indirect studies	End of treatment (1–3 cycles)	OR 1.22 (0.77, 1.91)	NA	No	

[†]In overall, Mitra et al. reported for IV IBU in PDA closure a mean SUCRA 0.24, SD ± 0.07 ; median rank 8, 95% CI 7–9, for high dose oral IBU a mean SUCRA 0.89, SD ± 0.12 ; median rank 2, 95% CI 1–5, and for high dose IV IBU a mean SUCRA 0.84, SD ± 0.20 ; median rank 2, 95% CI 1–7.

[‡]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.

[§]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.

[¶]Doses are standard unless stated as high doses.

High dose regimen: 15–20 mg/kg/day followed by ibuprofen 7.5–10 mg/kg/day for two doses.

APAP: Acetaminophen/paracetamol; I^2 : I-square index; IBU: Ibuprofen; INDO: Indomethacin; IV: Intravenous; NA: not available; OR: Odds ratio; PBO: Placebo; RCT: Randomized controlled trial, including quasi-RCT; RR: Risk ratio; SD: Standard deviation; χ^2 : Chi-square test.

in performance was reported in seven pairwise comparisons, with reported superiority of oral ibuprofen over IV ibuprofen, high dose (HD) of mixed oral/IV ibuprofen formulations over standard-dose ibuprofen, HD oral ibuprofen over standard-dose IV indomethacin/ibuprofen, HD IV ibuprofen over standard-dose IV ibuprofen, oral paracetamol over IV ibuprofen.

Details of the need for surgical ligation pairwise comparisons are in Table 4, where superiority was reported in three comparisons, to the advantage of the HD of ibuprofen against IV indomethacin/ibuprofen or oral ibuprofen.

Table 4. Studies for the need for surgical ligation.

Study (year)	Drug 1 and formulation ^{†,‡,§}	Drug 2 and formulation ^{†,‡,§}	N of studies and infants	Effect size (95% CI)	Heterogeneity	Statistically significant difference	Ref.
Loomba <i>et al.</i> (2015)	IV IBU	IV INDO	9 studies, 835 infants	OR 0.86 (0.58, 1.28)	$\chi^2 = 3.69$, $I^2 = 0\%$	No	[26]
	Oral IBU	IV INDO	4 studies, 342 infants	OR 0.78 (0.45, 1.37)	$\chi^2 = 2.47$, $I^2 = 0\%$	No	
Ohlsson <i>et al.</i> (2020)	IBU (oral or IV)	INDO (oral or IV)	16 studies, 1275 infants	RR 1.06 (0.81, 1.39)	$I^2 = 0\%$	No	[13]
	Oral IBU	INDO (oral or IV)	4 studies, 174 infants	RR 0.93 (0.50, 1.74)	$I^2 = 0\%$	No	
	Oral IBU	IV IBU	5 studies, 406 infants	RR 0.41 (0.41, 1.21)	$I^2 = 0\%$	No	
	High dose IBU (oral or IV)	IBU (oral or IV)	1 studies, 70 infants	RR 1.00 (0.15, 6.71)	NA	No	
Marconi <i>et al.</i> (2019)	IBU	INDO	23 studies	OR 0.9 (0.8, 1.00)	NA	No	[23]
	IBU	INDO	Indirect studies	OR 0.92 (0.79, 1.12)	NA	No	
Mitra <i>et al.</i> (2018)	High dose oral IBU	IV INDO	Indirect studies	OR 0.01 (0, 0.38)	NA	Yes, in favor of high dose oral IBU	[22]
	High dose IV IBU	IV INDO	Indirect studies	OR 1.41 (0.10, 22.80)	NA	No	
	Oral IBU	IV INDO	Direct and indirect studies	OR 0.62 (0.20, 1.76)	NA	No	
	IV IBU	IV INDO	Direct and indirect studies	OR 1.42 (0.79, 3.01)	NA	No	
	High dose oral IBU	IV IBU	Indirect studies	OR 1.01 (0.00, 0.26)	NA	Yes, in favor of high dose oral IBU	
	High dose IV IBU	IV IBU	Direct and indirect studies	OR 0.97 (0.07, 14.2)	NA	No	
	High dose oral IBU	Oral IBU	Indirect studies	OR 0.02 (0.00, 0.50)	NA	Yes, in favor of high dose oral IBU	
	High dose IV IBU	Oral IBU	Direct and indirect studies	OR 2.22 (0.14, 50.00)	NA	No	
	High dose oral IBU	Oral APAP	Indirect studies	OR 0.04 (0, 2.81)	NA	No	
	High dose IV IBU	Oral APAP	Indirect studies	OR 4.0 (0.1, 100)	NA	No	
Ohlsson <i>et al.</i> (2020)	APAP (oral or IV)	IBU (oral or IV)	2 studies, 290 infants	RR 0.68 (0.35, 1.32)	$I^2 = 0\%$	No	[21]

[†]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.
[‡]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.
[§]Doses are standard unless stated as high doses.
 High dose regimen: 15–20 mg/kg/day followed by ibuprofen 7.5–10 mg/kg/day for two doses.
 I²: I-square index; IBU: Ibuprofen; IV: Intravenous; OR: Odds ratio; RR: Risk ratio; χ^2 : Chi-square test.

Only one of the analyzed comparisons for neonatal mortality reported superiority, favoring mixed oral/IV formulations use of indomethacin over ibuprofen, as shown in [Table 5](#).

As summarized in [Table 6](#), superiority for NEC was seen in three comparisons, where oral ibuprofen performed better than IV indomethacin or the mixed oral/IV formulations of indomethacin, and the use of mixed formulations of ibuprofen was superior over the mixed formulations of indomethacin.

The superiority concerning BPD was seen in two comparisons, where IV indomethacin or its use with oral indomethacin outperformed IV ibuprofen or its use with oral ibuprofen, respectively ([Table 7](#)).

For IVH, in two comparisons, the outcome favored mixed oral/IV ibuprofen use over mixed oral/IV indomethacin use ([Table 8](#)). Mixed oral/IV use of paracetamol was associated with reduced GI bleeding in three comparisons ([Table 9](#)) compared with mixed oral/IV ibuprofen use.

The outcome of oliguria was in favor of mixed oral/IV ibuprofen over mixed oral/IV indomethacin in three comparisons, in favor of oral ibuprofen over IV indomethacin in one comparison, and in favor of IV ibuprofen over IV indomethacin in two comparisons, as illustrated in [Table 10](#).

The elevation in serum creatinine levels outcome is reported in [Table 11](#) and, as seen based on five comparisons, was less associated with IV ibuprofen versus IV indomethacin, oral ibuprofen versus oral indomethacin or IV ibuprofen, mixed oral/IV ibuprofen versus mixed oral/IV indomethacin, and with oral paracetamol over oral ibuprofen.

Table 5. Studies for neonatal mortality.

Study (year)	Drug 1 and formulation ^{‡,§,¶}	Drug 2 and formulation ^{‡,§,¶}	N of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference	Ref.
Ohlsson <i>et al.</i> (2020)	IBU (oral or IV)	INDO (oral or IV)	10 studies, 697 infants	RR 0.79 (0.54, 1.17)	$\chi^2 = 7.29$, $I^2 = 0\%$	No	[13]
	IBU PO	INDO (oral or IV)	4 studies, 165 infants	RD -0.1 (-0.2, 0)	$\chi^2 = 0.58$, $I^2 = 0\%$	No	
	IBU PO	IBU IV	1 study, 64 infants	RR 1.13 (0.5, 2.55)	NA	No	
	High dose IBU (oral or IV)	Standard dose IBU (oral or IV)	2 studies, 155 infants	RR 1.02 (0.58, 1.79)	$\chi^2 = 0.36$, $I^2 = 0\%$	No	
Jones <i>et al.</i> (2011)	IV IBU	IV INDO	5 studies, 473 infants	RR 0.99 (0.55, 1.80)	NA	No	[24]
Mitra <i>et al.</i> (2018) [†]	High dose oral IBU	IV INDO	Direct and indirect studies	OR 2.19 (0.15, 72.38)	NA	No	[22]
	High dose IV IBU	IV INDO	Direct and indirect studies	OR 1.07 (0.27, 4.81)	NA	No	
	Oral IBU	IV INDO	Direct and indirect studies	OR 0.84 (0.45, 1.53)	NA	No	
	IV IBU	IV INDO	Direct and indirect studies	OR 0.91 (0.56, 1.44)	NA	No	
Marconi <i>et al.</i> (2019)	IBU	INDO	23 studies	OR 0.77 (0.67, 0.89)	NA	Yes, in favor of INDO	[23]
	IBU	INDO	Direct and indirect studies	OR 0.85 (0.70, 1.10)	NA	No	
Loomba <i>et al.</i> (2015)	IV IBU	IV INDO	9 studies, 944 infants	OR 1.03 (0.67, 1.58)	$\chi^2 = 11.24$, $I^2 = 29\%$	No	[26]
Ohlsson <i>et al.</i> (2020)	APAP (oral or IV)	IBU (oral or IV)	3 studies, 272 infants	RR 0.96 (0.55, 1.67)	$I^2 = 0\%$	No	[21]
Huang <i>et al.</i> (2018)	APAP (oral or IV)	IBU (oral or IV)	3 studies, 390 infants	RR 1.45 (0.55, 3.81)	$\chi^2 = 3.43$, $I^2 = 42\%$	No	[25]
Mitra <i>et al.</i> (2018) [†]	High dose oral IBU	Oral APAP	Direct and indirect studies	OR 2.47 (0.15, 80.63)	NA	No	[22]
	High dose IV IBU	Oral APAP	Direct and indirect studies	OR 1.24 (0.25, 6.83)	NA	No	
	Oral IBU	Oral APAP	Direct and indirect studies	OR 1.03 (0.49, 2.34)	NA	No	
	IV IBU	Oral APAP	Direct and indirect studies	OR 0.95 (0.38, 2.52)	NA	No	
	IBU, continuous IV infusion	Oral APAP	Direct and indirect studies	OR 1.09 (0.04, 45.81)	NA	No	
Marconi <i>et al.</i> (2019)	IBU	APAP	6 studies	OR 1.07 (0.62, 1.86)	NA	No	[23]
	IBU	APAP	Direct and indirect studies	OR 1.11 (0.65, 1.88)	NA	No	

[†]In overall, Mitra *et al.* reported for IV IBU in neonatal mortality a mean SUCRA 0.71, SD ± 0.2 ; median rank 3, 95% CI 1–8.

[‡]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.

[§]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.

[¶]Doses are standard unless stated as high doses.

High dose regimen: 15–20 mg/kg/day followed by ibuprofen 7.5–10 mg/kg/day for two doses.

APAP: Acetaminophen/paracetamol; I^2 : I-square index; IBU: Ibuprofen; INDO: Indomethacin; IV: Intravenous; NA: not available; OR: Odds ratio; PBO: Placebo; RCT: Randomized controlled trial, including quasi-RCT; RR: Risk ratio; SD: Standard deviation; χ^2 : Chi-square test.

As summarized in Tables 12–14, no significant difference was observed between the pairwise comparisons of ROP, sepsis, and PVL. A significant difference with intestinal perforation was reported in 1 pairwise comparison, with a superiority of ibuprofen over indomethacin (Table 15).

Efficacy and safety outcomes reported in only two MAs were combined in Supplementary Material 8. The need for retreatment was observed to be superior in 1 comparison, where IV ibuprofen was favored over oral ibuprofen (Supplementary Material 8). Other reported outcomes, including reopening rates, pulmonary hemorrhage, pulmonary hypertension and duration of hospitalization, had no significant difference. A substantial increase in serum bilirubin post-treatment was observed in mixed oral/IV ibuprofen compared with oral/IV indomethacin or oral/IV paracetamol, where indomethacin or paracetamol performed better than ibuprofen. In two comparisons regarding platelet count, mixed oral/IV ibuprofen outperformed mixed oral/IV indomethacin, and mixed

Table 6. Studies for necrotizing enterocolitis.

Study (year)	Drug 1 and formulation ^{‡,§,¶}	Drug 2 and formulation ^{‡,§,¶}	N of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference	Ref.
Ohlsson <i>et al.</i> (2020)	IBU (oral or IV)	INDO (oral or IV)	18 studies, 1292 infants	RR 0.68 (0.49, 0.94)	$I^2 = 0\%$	Yes, in favor of IBU (oral or IV)	[13]
	Oral IBU	INDO (oral or IV)	7 studies, 249 infants	RR 0.41 (0.23, 0.73)	$I^2 = 0\%$	Yes, in favor of oral IBU	
	High dose IBU (oral or IV)	IBU (oral or IV)	2 studies, 130 infants	RR 1.00 (0.40, 2.50)	$I^2 = 0\%$	No	
Jones <i>et al.</i> (2011)	IV IBU	IV INDO	3 studies, 473 infants	Pooled RR 0.6 (0.27, 1.33)	NA	No	[24]
Mitra <i>et al.</i> (2018) [†]	Oral IBU	IV INDO	Direct and indirect studies	OR 0.41 (0.21, 0.75)	NA	Yes, in favor of oral IBU	[22]
	High dose oral IBU	IV INDO	Direct and indirect studies	OR 0.30 (0.05, 1.72)	NA	No	
	High dose IV IBU	IV INDO	Direct and indirect studies	OR 0.97 (0.17, 6.29)	NA	No	
	IV IBU	IV INDO	Direct and indirect studies	OR 0.67 (0.40, 1.14)	NA	No	
	IBU, continuous IV infusion	IV INDO	Direct and indirect studies	OR 0.25 (0.04, 1.21)	NA	No	
Marconi <i>et al.</i> (2019)	IBU	INDO	23 studies	OR 1.08 (0.85, 1.38)	NA	No	[23]
	IBU	INDO	Direct and indirect studies	OR 1.16 (0.88, 1.62)	NA	No	
Loomba <i>et al.</i> (2015)	IV IBU	IV INDO	8 studies, 825 infants	OR 0.97 (0.63, 1.50)	$\chi^2 = 4.40, I^2 = 0\%$	No	[26]
	Oral IBU	IV INDO	5 studies, 391 infants	OR 0.60 (0.30, 1.24)	$\chi^2 = 3.93, I^2 = 0\%$	No	
Ohlsson <i>et al.</i> (2020)	APAP (oral or IV)	IBU (oral or IV)	5 studies, 559 infants	RR 0.88 (0.46, 1.7)	$I^2 = 0\%$	No	[21]
Huang <i>et al.</i> (2018)	APAP (oral or IV)	IBU (oral or IV)	5 studies	RR 0.86 (0.41, 1.81)	NA	No	[25]
Mitra <i>et al.</i> (2018) [†]	High dose oral IBU	Oral APAP	Direct and indirect studies	OR 0.66 (0.10, 4.24)	NA	No	[22]
	High dose IV IBU	Oral APAP	Direct and indirect studies	OR 2.16 (0.29, 18.21)	NA	No	
	Oral IBU	Oral APAP	Direct and indirect studies	OR 1.12 (0.42, 2.88)	NA	No	
	IV IBU	Oral APAP	Direct and indirect studies	OR 0.68 (0.23, 2.04)	NA	No	
	IBU, continuous IV infusion	Oral APAP	Direct and indirect studies	OR 0.56 (0.07, 3.34)	NA	No	
Marconi <i>et al.</i> (2019)	APAP	IBU	8 studies	OR 0.99 (0.57, 1.71)	NA	No	[23]

[†]In overall, Mitra *et al.* reported for IV IBU in NEC a mean SUCRA 0.42, SD ± 0.14 ; median rank 6, 95% CI 4–8.

[‡]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.

[§]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.

[¶]Doses are standard unless stated as high doses.

High dose regimen: 15–20 mg/kg/day followed by ibuprofen 7.5–10 mg/kg/day for two doses.

APAP: Acetaminophen/paracetamol; I^2 : I-square index; IBU: Ibuprofen; INDO: Indomethacin; IV: Intravenous; NA: Not available; OR: Odds ratio; PBO: Placebo; RCT: Randomized controlled trial, including quasi-RCT; RR: Risk ratio; SD: Standard deviation; χ^2 : Chi-square test.

oral/IV paracetamol outperformed mixed oral/IV ibuprofen. The duration of ventilator support was superior in 1 comparison, where mixed oral/IV ibuprofen performed better than mixed oral/IV indomethacin.

Quality of methods assessment

Based on the AMSTAR-2 assessment of the four studies, the quality of methods was assessed to be low in three MAs [23–25], critically low in one MA [26], moderate in one study [22] and high in the two Cochrane studies [13,21]. Assessment items were studies underperformed can be seen in [Supplementary Material 6](#).

Table 7. Studies for bronchopulmonary dysplasia at 28 days and/or 36 weeks postmenstrual age.

Study (year)	Drug 1 and formulation ^{‡,§,¶}	Drug 2 and formulation ^{‡,§,¶}	N of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference	Ref.
Ohlsson <i>et al.</i> (2020)	IBU (oral or IV)	INDO (oral or IV)	5 studies, 292 infants	RR 1.12 (0.93, 1.55) for CLD at 28 days	$\chi^2 = 2.58, I^2 = 0\%$	No	[13]
	IBU (oral or IV)	INDO (oral or IV)	3 studies, 357 infants	RR 1.12 (0.77, 1.61) for CLD at 36 weeks	$\chi^2 = 1.81, I^2 = 0\%$	No	
	Oral IBU	IV IBU	3 studies, 236 infants	RR 0.82 (0.56, 1.2) at 36 weeks	$\chi^2 = 0.07, I^2 = 0\%$	No	
	High-dose IBU	Standard-dose IBU	1 study, 70 infants	RR 1.6 (0.85, 3.02) at 36 weeks	NA	No	
Jones <i>et al.</i> (2011)	IV IBU	IV INDO	5 studies, 463 infants	RR 1.28 (1.03, 1.60),	NA	Yes, in favor of IV INDO	[24]
Mitra <i>et al.</i> (2018) [†]	High dose IV IBU	IV INDO	Direct and indirect studies	OR 2.37 (0.73, 8.02) at 36 weeks	NA	No	[22]
	Oral IBU	IV INDO	Direct and indirect studies	OR 0.68 (0.40, 1.14) at 36 weeks	NA	No	
	IV IBU	IV INDO	Direct and indirect studies	OR 1.10 (0.78, 1.55) at 36 weeks	NA	No	
	IBU, continuous IV infusion	IV INDO	Direct and indirect studies	OR 1.25 (0.40, 3.76) at 36 weeks	NA	No	
Marconi <i>et al.</i> (2019)	IBU	INDO	15 studies	OR 0.89 (0.81, 0.99)	NA	Yes, in favor of INDO	[23]
	IBU	INDO	Direct and indirect studies	OR 0.86 (0.71, 1.54)	NA	No	
Loomba <i>et al.</i> (2015)	IV IBU	IV INDO	6 studies, 640 infants	OR 1.09 (0.77, 1.54) for BPD at 28 days	$\chi^2 = 5.69, I^2 = 12\%$	No	[26]
	Oral IBU	IV INDO	4 studies, 120 infants	OR 0.80 (0.47, 1.36) for BPD at 28 days	$\chi^2 = 3.35, I^2 = 10\%$	No	
Ohlsson <i>et al.</i> (2020)	APAP (oral or IV)	IBU (oral or IV)	1 study, 90 infants	RR 0.79 (0.46, 1.35) at 28 days	NA	No	[21]
	APAP (oral or IV)	IBU (oral or IV)	1 study, 90 infants	RR 0.71 (0.38, 1.3) at 36 weeks	NA	No	
Huang <i>et al.</i> (2018)	APAP (oral or IV)	IBU (oral or IV)	3 studies, 327 infants	RR 0.69 (0.41, 1.16)	$\chi^2 = 0.22, I^2 = 0\%$	No	[25]
Mitra <i>et al.</i> (2018) [†]	Oral IBU	IV IBU	Direct and indirect studies	OR 0.62 (0.36, 1.03) at 36 weeks	NA	No	[22]
	Oral APAP	IV IBU	Direct and indirect studies	OR 0.57 (0.22, 1.38) at 36 weeks	NA	No	
	High dose IV IBU	IV IBU	Direct and indirect studies	OR 2.14 (0.71, 6.86) at 36 weeks	NA	No	
	Oral APAP	Oral IBU	Direct and indirect studies	OR 0.92 (0.38, 2.15) at 36 weeks	NA	No	
	High dose IV IBU	Oral IBU	Direct and indirect studies	OR 3.49 (1.00, 12.43) at 36 weeks	NA	No	
	IBU	APAP	6 studies	OR 1.20 (0.56, 2.54)	NA	No	
Marconi <i>et al.</i> (2019)	IBU	APAP	Direct and indirect studies	OR 1.40 (0.74, 2.82)	NA	No	[23]
	IBU	APAP	Direct and indirect studies	OR 1.40 (0.74, 2.82)	NA	No	

[†]In overall, Mitra *et al.* reported for oral IBU in BPD a mean SUCRA 0.87 SD ± 0.13 ; median rank 2, 95% CI 1–4.

[‡]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.

[§]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.

[¶]Doses are standard unless stated as high doses.

High dose regimen: 15–20 mg/kg/day followed by ibuprofen 7.5–10 mg/kg/day for two doses.

APAP: acetaminophen/paracetamol; CLD: chronic lung disease; I^2 : I-square index; IBU: ibuprofen; INDO: indomethacin; IV: intravenous; NA: not available; OR: odd ratio; PBO: placebo; RCT: randomized controlled trial, including quasi-RCT; RR: risk ratio; SD: Standard deviation; χ^2 : Chi-square test.

Table 8. Studies for intraventricular hemorrhage.

Study (year)	Drug 1 and formulation ^{†,‡,§}	Drug 2 and formulation ^{†,‡,§}	N of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference	Ref.
Ohlsson <i>et al.</i> (2020)	IBU (oral or IV)	INDO (oral or IV)	7 studies, 524 infants	RR 0.89 (0.61, 1.31)	$\chi^2 = 1.49$, $I^2 = 0\%$	No	[13]
	IBU (oral or IV)	INDO (oral or IV)	10 studies, 798 infants	RR 1.05 (0.68, 1.63) for grade III–IV	$\chi^2 = 3.46$, $I^2 = 0\%$	No	
	Oral IBU	INDO (oral or IV)	3 studies, 77 infants	RD -0.03 (-0.22, 0.16)	$\chi^2 = 0.69$, $I^2 = 0\%$	No	
	Oral IBU	INDO (oral or IV)	2 studies, 124 infants	RD -0.04 (-0.14, 0.05) for grade III–IV	$\chi^2 = 0.34$, $I^2 = 0\%$	No	
	Oral IBU	IV IBU	1 study, 64 infants	RR 1.08 (0.59, 2)	NA	No	
	High dose IBU	Standard dose IBU	1 study, 70 infants	RR 0.67 (0.21, 2.16)	NA	No	
	High dose IBU	Standard dose IBU	1 study, 70 infants	RR 0.5 (0.1, 2.56) grade III–IV	NA	No	
Jones <i>et al.</i> (2011)	IV IBU	IV INDO	6 studies, 496 infants	RR 1.16 (0.61, 2.21)	NA	No	[24]
Mitra <i>et al.</i> (2018)	High dose IV IBU	IV INDO	Direct and indirect studies	OR 0.53 (0.11, 2.50)	NA	No	[22]
	Oral IBU	IV INDO	Direct and indirect studies	OR 0.93 (0.51, 1.66)	NA	No	
	IV IBU	IV INDO	Direct and indirect studies	OR 0.89 (0.49, 1.65)	NA	No	
Marconi <i>et al.</i> (2019)	INDO	IBU	19 studies	OR 1.25 (1.01, 1.56)	NA	Yes, in favor of IBU	[23]
	INDO	IBU	Direct and indirect studies	OR 1.27 (1.00, 1.62)	NA	Yes, in favor of IBU	
Loomba <i>et al.</i> (2015)	IV IBU	IV INDO	7 studies, 785 infants	OR 0.79 (0.47, 1.31) grade III–IV	$\chi^2 = 5.66$, $I^2 = 0\%$	No	[26]
Ohlsson <i>et al.</i> (2020)	APAP (oral or IV)	IBU (oral or IBU)	5 studies, 559 infants	RR 0.97 (0.77, 1.23)	$\chi^2 = 2.59$, $I^2 = 0\%$	No	[21]
	APAP (oral or IV)	IBU (oral or IBU)	3 studies, 272 infants	RR 1 (0.3, 3.37) for grade III–IV	$\chi^2 = 0$, $I^2 = 0\%$	No	
Huang <i>et al.</i> (2018)	APAP (oral or IV)	IBU (oral or IV)	5 studies, 677 infants	RR 0.84 (0.49, 1.46)	$\chi^2 = 0.79$, $I^2 = 0\%$	No	[25]
Mitra <i>et al.</i> (2018)	Oral IBU	IV IBU	Direct and indirect studies	OR 1.04 (0.62, 1.77)	NA	No	[22]
	Oral APAP	IV IBU	Direct and indirect studies	1.14 (0.50, 2.59)	NA	No	
	High dose IV IBU	IV IBU	Direct and indirect studies	0.59 (0.14, 2.45)	NA	No	
	Oral APAP	Oral IBU	Direct and indirect studies	OR 1.09 (0.54, 2.22)	NA	No	
	High dose IV IBU	Oral IBU	Direct and indirect studies	OR 0.57 (0.12, 2.64)	NA	No	
Marconi <i>et al.</i> (2019)	IBU	APAP	9 studies	OR 0.98 (0.58, 1.64)	NA	No	[23]
	IBU	APAP	Direct and indirect studies	OR 0.99 (0.63, 1.60)	NA	No	

[†]When the formulation is not reported, this indicated that the study included all formulations (oral, IV or rectal) of a drug with no separation in analysis.
[‡]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.
[§]Doses are standard unless stated as high doses.
 High dose IBU regimen: 15–20 mg/kg/day followed by ibuprofen 7.5–10 mg/kg/day for two doses.
 APAP: Acetaminophen/paracetamol; I^2 : I-square index; IBU: Ibuprofen; INDO: Indomethacin, IV: Intravenous; NA: Not available; OR: Odds ratio; PBO: Placebo; RCT: Randomized controlled trial, including quasi-RCT; RR: Risk ratio; χ^2 : Chi-square test.

Risk of bias assessment

Based on the ROBIS assessment, the risk of bias was determined to be high in two studies [25,26] and unclear in two studies [23,24] and low in three studies [13,21,22]. Domains of ROBIS where studies underperformed were identifying and selecting studies, data collection and study appraisal, and the synthesis and findings (Supplementary Material 7).

Table 9. Studies for gastrointestinal bleeding.

Study (year)	Drug 1 and formulation ^{†,‡,§}	Drug 2 and formulation ^{†,‡,§}	N of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference	Ref.
Marconi <i>et al.</i> (2019)	IBU	INDO	8 studies	OR 1.03 (0.61, 1.76)	NA	No	[23]
	IBU	INDO	Direct and indirect studies	OR 0.87 (0.39, 2.07)	NA	No	
Loomba <i>et al.</i> (2015)	IV IBU	IV INDO	4 studies, 317 infants	OR 1.40 (0.73, 2.69)	No significant heterogeneity	No	[26]
	Oral IBU	IV INDO	3 studies, 313 infants	OR 0.62 (0.31, 1.27)	$\chi^2 = 2.75$, $I^2 = 27\%$	No	
Ohlsson <i>et al.</i> (2018)	IBU (oral or IV)	INDO (Oral or IV)	7 studies, 514 infants	RR 0.94 (0.55, 1.61)	$\chi^2 = 3.51$, $I^2 = 0\%$	No	[13]
	Oral IBU	INDO (Oral or IV)	3 studies, 85 infants	RD 0.07 (-0.05, 0.18)	$\chi^2 = 0.73$, $I^2 = 0\%$	No	
	Oral IBU	IV IBU	2 studies, 172 infants	RR 2.89 (0.12, 69.24)	NA	No	
	High dose IBU (oral or IV)	Standard IBU (oral or IV)	2 studies, 120 infants	RR 1.5 (0.58, 3.86)	$\chi^2 = 0.07$, $I^2 = 0\%$	No	
Ohlsson <i>et al.</i> (2018)	APAP (oral or IV)	IBU (oral or IV)	4 studies, 537 infants	RR 0.28 (0.12, 0.69)	$I^2 = 0$	Yes, in favor of oral or IV APAP	[21]
Huang <i>et al.</i> (2018)	APAP	IBU	4 studies, 527 infants	RR 0.28 (0.11, 0.73)	$\chi^2 = 0.88$, $I^2 = 0\%$	Yes, in favor of APAP	[25]
Marconi <i>et al.</i> (2019)	IBU	APAP	5 studies	OR 3.51 (1.36, 9.08)	NA	Yes, in favor of APAP	[23]
	IBU	APAP	Direct and indirect studies	OR 2.94 (0.94, 11.81)	NA	No	

[†]When the formulation is not reported, this indicated that the study included all formulations (oral, IV or rectal) of a drug with no separation in analysis.

[‡]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.

[§]Doses are standard unless stated as high doses.

High dose regimen: 15–20 mg/kg/day followed by ibuprofen 7.5–10 mg/kg/day for two doses.

APAP: Acetaminophen/paracetamol; I^2 : I-square index; IBU: Ibuprofen; INDO: Indomethacin; IV: Intravenous; NA: Not available; OR: Odds ratio; PBO: Placebo; RCT: Randomized controlled trial, including quasi-RCT; RR: Risk ratio; χ^2 : Chi-square test.

Discussion

This systematic review of MAs summarizes the comparative evidence about the use of ibuprofen, including versus indomethacin and paracetamol, to treat PDA infants in the NICU, including different formulations. The review included seven MAs published within the last decade, including three NMAs [22–24] and two Cochrane reviews [13,21]. Included patients in all MAs were preterm infants. All MAs were based on RCTs, with two MAs also including observational studies [23,26]. The primary outcome measure in all included MAs was focusing on the closure rate of the PDA upon treatment. Successful PDA closure is generally defined as a transductal diameter of less than 1.5 mm via cardiac ECHO, by 24 h after receiving one course of IBU ibuprofen therapy; whereby, the commonly suggested standard ibuprofen dose is an initial dose of 10 mg/kg ibuprofen, followed by two doses of 5 mg/kg at 24-h intervals of either formulation [7,27–30]. Within this context, the use of HD ibuprofen was also evaluated in two MAs; one against indomethacin and paracetamol [22], and one against ibuprofen's standard dose [13]. Here, we note that doses were not necessarily reported in all included MAs, and were summarized in Table 4 based on how they were reported in included studies. This also applies to the HD of ibuprofen that, based on the reported doses (Table 4), seems to range from 1.5 to two-times the standard doses; 15–20 mg/kg, followed by two doses of 7.5–10 mg/kg at 24-h intervals of either formulation.

Mixed ibuprofen formulations, standard dose

The use of mixed oral and IV of ibuprofen was assessed against mixed oral and IV formulations of indomethacin or paracetamol in several studies. The rate of PDA closure was not statistically different using ibuprofen against indomethacin [13,23]. A no-difference trend was also observed against paracetamol [21,23]. For the need for surgical ligation efficacy outcome, ibuprofen was compared with indomethacin and paracetamol, where no difference was measured [13,21,23].

Regarding adverse events, ibuprofen was inferior to indomethacin when it comes to neonatal mortality [23]. Based on the same MA, however, analyzing ibuprofen versus indomethacin based on direct and indirect comparisons of RCTs and observational studies, ibuprofen did not differ in mortality from indomethacin. Against paracetamol, mortality did not differ with ibuprofen [21,23,25].

Table 10. Studies for oliguria.

Study (year)	Drug 1 and formulation ^{†,§,¶}	Drug 2 and formulation ^{†,§,¶}	N of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference	Ref.
Ohlsson <i>et al.</i> (2020)	IBU (oral or IV)	INDO (oral or IV)	6 studies, 576 infants	RR 0.28 (0.14, 0.54)	I ² = 24%	Yes, in favor of IBU (oral or IV)	[13]
	Oral IBU	IV IBU	4 studies, 304 infants	RR 0.14 (0.01, 2.66)	NA	No	
	High dose IBU (oral or IV)	IBU (oral or IV)	2 studies, 120 infants	RR 1.57 (0.44, 5.63)	I ² = 0%	No	
Mitra <i>et al.</i> (2018)	Oral IBU	IV INDO	Direct and indirect studies	OR 0.20 (0.04, 0.92)	NA	Yes, in favor of oral IBU	[22]
	IV INDO	IV IBU	Direct and indirect studies	OR 0.29 (0.18, 0.46)	NA	Yes, in favor of IV IBU	
	IV INDO	IBU, continuous IV infusion	Direct and indirect studies	OR 0.02 (0.00, 0.52)	NA	Yes, in favor of IBU, continuous IV infusion	
	IV INDO	High dose IV IBU	Direct and indirect studies	OR 0.47 (0.06, 3.88)	NA	no	
Marconi <i>et al.</i> (2019)	INDO	IBU	12 studies	OR 3.29 (1.80, 6.00)	NA	Yes, in favor of IBU	[23]
	INDO	IBU	Direct and indirect studies	OR 3.92 (1.69, 9.82)	NA	Yes, in favor of IBU	
Ohlsson <i>et al.</i> (2020)	APAP (oral or IV)	IBU (oral or IV)	3 studies, 337 infants	RR 0.46 (0.2, 1.1)	I ² = 33.24%	No	[21]
Mitra <i>et al.</i> (2018)	Oral APAP	Oral IBU	Direct and indirect studies	OR 0.55 (0.22, 1.27)	NA	No	[22]
	Oral APAP	IV IBU	Direct and indirect studies	OR 0.35 (0.07, 1.98)	NA	No	
Marconi <i>et al.</i> (2019)	APAP	IBU	2 studies	OR 2.45 (0.63, 9.54)	NA	No	[23]
	IBU	APAP	Direct and indirect studies	OR 2.75 (0.57, 18.38)	NA	No	

[†]In overall, Mitra *et al.* reported for oral IBU in oliguria a mean SUCRA 0.60, SD ±0.19; median rank 4, 95% CI 2–7.

[‡]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.

[§]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.

[¶]Doses are standard unless stated as high doses.

High dose regimen: 15–20 mg/kg/day followed by ibuprofen 7.5–10 mg/kg/day for two doses.

APAP: Acetaminophen/paracetamol; I²: I-square index; IBU: Ibuprofen; INDO: Indomethacin, IV: Intravenous; NA: Not available; OR: Odds ratio; PBO: Placebo; RCT: Randomized controlled trial, including quasi-RCT; RR: Risk ratio; SD: Standard deviation; χ^2 : Chi-square test.

Table 11. Studies for serum creatinine level.

Study (year)	Drug 1 and formulation ^{†,‡,§}	Drug 2 and formulation ^{†,‡,§}	Number of studies and infants	Effect and size (95% CI)	Heterogeneity	Statistically significant difference	Ref.
Loomba <i>et al.</i> (2015)	IV IBU	IV INDO	7 studies, 655 infants	MD -0.08 (-0.16, 0.00)	$\chi^2 = 1244.0$, I ² = 100%	Yes, in favor of IV IBU	[26]
	Oral IBU	IV INDO	5 studies, 272 infants	MD -0.03 (-0.11, 0.05)	$\chi^2 = 4.09$, I ² = 2%	No	
	Oral IBU	Oral INDO	2 studies, 103 infants	MD -0.1 (-0.13, -0.07)	$\chi^2 = 0.22$, I ² = 0%	Yes, in favor of oral IBU	
Ohlsson <i>et al.</i> (2020)	Oral APAP	Oral IBU	4 studies, 537 infants	MD -8.92 (-11.28, -6.55)	I ² = 84%	Yes, in favor of oral APAP	[21]
Ohlsson <i>et al.</i> (2020)	IBU (oral or IV)	INDO (oral or IV)	11 studies, 918 infants	MD -8.12 (-10.81, -5.43)	I ² = 83%	Yes, in favor of IBU	[13]
	Oral IBU	INDO (oral or IV)	5 studies, 190 infants	MD -0.51 (-6.04, 5.01)	I ² = 72%	No	
	Oral IBU	IV IBU	2 studies, 170 infants	MD -22.47 (-32.40, -12.53)	I ² = 81%	Yes in favor of oral IBU	
	High dose IBU (oral or IV)	IBU (oral or IV)	1 study, 60 infants	MD 8.84 (-4.41, 22.09)	Not applicable	No	

[†]When the formulation is not reported, this indicated that the study included all formulations (oral, IV or rectal) of a drug with no separation in analysis.

[‡]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.

[§]Doses are standard unless stated as high doses.

APAP: Acetaminophen/paracetamol; I²: I-square index; IBU: Ibuprofen; INDO: Indomethacin, IV: Intravenous; NA: Not available; OR: Odds ratio; PBO: Placebo; RCT: Randomized controlled trial, including quasi-RCT; RR: Risk ratio; χ^2 : Chi-square test.

Table 12. Studies for retinopathy of prematurity.

Study (year)	Drug 1 and formulation ^{†,‡,§}	Drug 2 and formulation ^{†,‡,§}	N of studies and infants	Outcome effect and size (95% CI)	Heterogeneity	Statistically significant difference	Ref.
Ohlsson <i>et al.</i> (2020)	IBU (oral or IV)	INDO (oral or IV)	7 studies, 581 infants	ROP RR 0.81 (0.6, 1.1)	$\chi^2 = 1.51, I^2 = 0\%$	No	[13]
	Oral IBU	INDO (oral or IV)	2 studies, 71 infants	RD 0 (-0.81, 0.17)	$\chi^2 = 0.38, I^2 = 0\%$	No	
	Oral IBU	IV IBU	2 studies, 172	RR 0.59 (0.26, 1.34) required laser treatment	$\chi^2 = 0.56, I^2 = 0\%$	No	
	High dose IBU	Standard dose IBU	1 study, 70 infants	RR 1 (0.27, 3.69)	NA	No	
	High dose IBU	Standard dose IBU	1 study, 70 infants	RR 2 (0.19, 21.06) stage 3–4	NA	No	
Ohlsson <i>et al.</i> (2020)	APAP (oral or IV)	IBU (oral or IV)	4 studies, 472 infants	ROP RR 0.71 (0.42, 1.23)	$\chi^2 = 0.05, I^2 = 0\%$	No	[21]
	APAP (oral or IV)	IBU (oral or IV)	1 study, 90 infants	RR 0.71 (0.12, 1.55) grade 3–4	NA	No	
Huang <i>et al.</i> (2018)	APAP	IBU	4 studies, 580 infants	ROP RR 0.58 (0.28, 1.21)	$\chi^2 = 1.94, I^2 = 0\%$	No	[25]

[†]When the formulation is not reported, this indicated that the study included all formulations (oral, IV or rectal) of a drug with no separation in analysis.

[‡]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.

[§]Doses are standard unless stated as high doses.

APAP: Acetaminophen/paracetamol; I^2 : I-square index; IBU: Ibuprofen; INDO: Indomethacin, IV: Intravenous; NA: Not available; OR: Odds ratio; PBO: Placebo; RCT: Randomized controlled trial, including quasi-RCT; RR: Risk ratio; χ^2 : Chi-square test.

Table 13. Studies for sepsis.

Study (year)	Drug 1 and formulation ^{†,‡,§}	Drug 2 and formulation ^{†,‡,§}	N of studies and infants	Outcome effect and size (95% CI)	Heterogeneity	Statistically significant difference	Ref.
Ohlsson <i>et al.</i> (2020)	IBU (oral or IV)	INDO (oral or IV)	7 studies, 735 infants	Sepsis RR 1.22 (0.84, 1.76)	$\chi^2 = 1.33, I^2 = 0\%$	No	[13]
	Oral IBU	INDO (oral or IV)	2 studies, 53 infants	RR 0.03 (-0.22, 0.28)	$\chi^2 = 0.08, I^2 = 0\%$	No	
	Oral IBU	IV IBU	3 studies, 236 infants	Sepsis RR 0.82 (0.54, 1.25)	$\chi^2 = 1.68, I^2 = 0\%$	No	
Ohlsson <i>et al.</i> (2020)	APAP (oral or IV)	IBU (oral or IV)	4 studies, 472 infants	Sepsis RR 0.88 (0.64, 1.21)	$\chi^2 = 1.19, I^2 = 0\%$	No	[21]
Huang <i>et al.</i> (2018)	APAP	IBU	4 studies, 590 infants	Sepsis RR 0.88 (0.62, 1.25)	$\chi^2 = 1.50, I^2 = 0\%$	No	[25]

[†]When the formulation is not reported, this indicated that the study included all formulations (oral, IV or rectal) of a drug with no separation in analysis.

[‡]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.

[§]Doses are standard unless stated as high doses.

APAP: Acetaminophen/paracetamol; I^2 : I-square index; IBU: Ibuprofen; INDO: Indomethacin, IV: Intravenous; NA: Not available; OR: Odds ratio; PBO: Placebo; RCT: Randomized controlled trial, including quasi-RCT; RR: Risk ratio; χ^2 : Chi-square test.

Against indomethacin, ibuprofen use was significantly associated with a lower incidence of NEC, IVH, oliguria, increased creatinine level, intestinal perforation, platelet count and days on ventilator support, at high AMSTAR and low ROBIS [13]. As per a low AMSTAR with unclear ROBIS NMA, by Marconi *et al.* [23], however, the NEC advantage with ibuprofen was cancelled, as no difference in GI bleeding was reported, and lower rates of BPD and significantly reduced serum bilirubin levels were associated with indomethacin. Compared with paracetamol, ibuprofen was not differently associated with neonatal mortality, NEC, BPD, IVH and oliguria events [23,25]. However, paracetamol was associated with a lower incidence of GI bleeding [21,23,25], increased serum bilirubin [21], and decreased platelet count post-treatment [21].

IV Ibuprofen, standard dose

Three MAs [22,24,26] reported no difference between IV ibuprofen and IV indomethacin for successful PDA closure. However, against oral paracetamol, IV ibuprofen was reported to be inferior for PDA closure based on one MA, with moderate AMSTAR and low ROBIS [22], including when IV ibuprofen is via continuous infusion. Based on the SUCRA analysis, by Mitra *et al.* [22], the IV ibuprofen had a low median rank of 8 among ten treatment

Table 14. Studies for periventricular leukomalacia.

Study (year)	Drug 1 and formulation ^{†,‡,§}	Drug 2 and formulation ^{†,‡,§}	N of studies and infants	Outcome effect and size (95% CI)	Heterogeneity	Statistically significant difference	Ref.
Ohlsson <i>et al.</i> (2020)	IBU (oral or IV)	INDO (oral or IV)	6 studies, 573 infants	RR 1.24 (0.67, 2.3)	$\chi^2 = 3.18$, $I^2 = 0\%$	No	[13]
	Oral IBU	INDO (oral or IV)	1 study, 41 infants	RR -0.05 (-0.18, 0.08)	NA	No	
	Oral IBU	IV IBU	1 study, 64 infants	RR 1 (0.15, 6.67)	NA	No	
	High dose IBU	Standard dose IBU	1 study, 70 infants	RR 1.5 (0.27, 8.43)	NA	No	
Marconi <i>et al.</i> (2019)	IBU	INDO	7 studies	OR 0.83 (0.53, 1.30)	NA	No	[23]
	IBU	INDO	Direct and indirect studies	OR 0.90 (0.53, 1.61)	NA	No	
Ohlsson <i>et al.</i> (2020)	APAP (oral or IV)	IBU (oral or IV)	3 studies, 272 infants	RR 1 (0.36, 2.76)	$\chi^2 = 0.43$, $I^2 = 0\%$	No	[21]

[†]When the formulation is not reported, this indicated that the study included all formulations (oral, IV or rectal) of a drug with no separation in analysis.
[‡]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.
[§]Doses are standard unless stated as high doses.
 High dose regimen: 15–20 mg/kg/day followed by ibuprofen 7.5–10 mg/kg/day for two doses.
 APAP: Acetaminophen/paracetamol; χ^2 : Chi-square test; I^2 : I-square index; IBU: Ibuprofen; INDO: Indomethacin, IV: Intravenous; NA: Not available; OR: Odds ratio; PBO: Placebo; RCT: Randomized controlled trial, including quasi-RCT; RR: Risk ratio; χ^2 : Chi-square test.

Table 15. Studies for intestinal perforation.

Study (year)	Drug 1 and formulation ^{†,‡,§}	Drug 2 and formulation ^{†,‡,§}	N of studies and infants	Outcome effect and size (95% CI)	Heterogeneity	Statistically significant difference	Ref.
Ohlsson <i>et al.</i> (2020)	IBU (oral or IV)	INDO (oral or IV)	5 studies, 255 infants	RR 0.48 (0.2, 1.14)	$\chi^2 = 2.61$, $I^2 = 0\%$	No	[13]
	Oral IBU	INDO (oral or IV)	2 studies, 62 infants	RR -0.1 (-0.25, 0.04)	$\chi^2 = 1.61$, $I^2 = 37.91\%$	No	
	Oral IBU	IV IBU	2 studies, 134 infants	RR 0.32 (0.01, 7.48)	NA	No	
Marconi <i>et al.</i> (2019)	IBU	INDO	11 studies	OR 0.51 (0.38, 0.68)	NA	Yes, in favor of IBU	[23]
	IBU	INDO	Direct and indirect studies	OR 0.58 (0.36, 1.11)	NA	No	
Loomba <i>et al.</i> (2015)	IV IBU	IV INDO	7 studies, 762 infants	OR 1.09 (0.54, 2.20)	$\chi^2 = 3.09$, $I^2 = 0\%$	No	[26]
Ohlsson <i>et al.</i> (2020)	APAP (oral or IV)	IBU (oral or IV)	1 study, 90 infants	NA	NA	NA	[21]

[†]When the formulation is not reported, this indicated that the study included all formulations (oral, IV, or rectal) of a drug with no separation in analysis.
[‡]A formulation of 'IV or oral' refers to a study that included mixed of both IV and oral formulations of a drug with no separation in analysis.
[§]Doses are standard unless stated as high doses.
 Higher doses regimen: 20 mg/kg/day followed by ibuprofen 10 mg/kg/day for two doses.
 APAP: Acetaminophen/paracetamol; I^2 : I-square index; IBU: Ibuprofen; INDO: Indomethacin, IV: Intravenous; NA: Not available; OR: Odds ratio; PBO: Placebo; RCT: Randomized controlled trial, including quasi-RCT; RR: Risk ratio; χ^2 : Chi-square test.

modalities for PDA closure (Table 5). Regarding the need for surgical ligation, in two studies, the standard dose IV ibuprofen did not differ from the IV indomethacin [22,26].

The neonatal mortality, NEC, IVH, GI bleeding, and intestinal perforation did not differ between IV ibuprofen and IV indomethacin based on three studies [22,24,26]. This included the IV continuous infusion of ibuprofen, for mortality and NEC [22]. No difference in the mortality, NEC, and IVH events rates was also reported against paracetamol in one study [22], including the IV continuous infusion of ibuprofen for NEC [22]. Based on the Mitra *et al.* SUCRA analysis [22], the IV ibuprofen ranked sixth among ten treatment modalities for association with NEC events (Table 7).

One MA reported IV ibuprofen to be inferior to IV indomethacin concerning the BPD events, with low AMSTAR and unclear ROBIS [24]. However, the rate of the BPD event between IV ibuprofen and indomethacin was not found different in two other MAs, at moderate AMSTAR and low ROBIS [22] and critically low AMSTAR and high ROBIS [26], including in the case when the IV ibuprofen was a continuous infusion [22]. The BPD with IV ibuprofen was also not different compared with oral paracetamol [22].

IV ibuprofen had a significantly lesser association with elevated creatinine levels and oliguria than IV indomethacin [22,26]. However, oliguria was not different between IV ibuprofen and oral paracetamol [22].

Oral Ibuprofen, standard dose

For PDA closure, oral ibuprofen was not statistically different from IV indomethacin based on two MAs [22,26], and was also not different compared with both oral and IV indomethacin in a third study [13]. Against oral paracetamol, oral ibuprofen was not different for the PDA closure in two MAs [22,25]. Out of four pooled pairwise analyses that evaluated the need for surgical ligation with oral ibuprofen versus indomethacin, three reported no difference compared with IV indomethacin [13,22,26]. In the remaining study, oral ibuprofen did not perform differently from mixed oral and IV indomethacin administration [13].

Against IV indomethacin, oral ibuprofen was not statistically different in neonatal mortality [22,24], and also not significantly different in BPD [22,26]. Mortality and BPD were not different between oral ibuprofen and oral paracetamol [22]. Based on a SUCRA analysis [22], oral ibuprofen has third and second lowest-risks for mortality and BPD, respectively, among 10 treatment modalities (Table 6 & 7). IVH was not different between oral ibuprofen and IV indomethacin or oral paracetamol [22]. The only GI bleeding study with oral ibuprofen reported a not statistical difference from IV indomethacin [26]. Oral ibuprofen was significantly associated with less NEC compared with mixed oral and IV indomethacin or IV indomethacin [13,22]. In contrast, oral ibuprofen was reported as not different from IV indomethacin for NEC events in one study with critically low AMSTAR and high ROBIS [26]. Oral ibuprofen was also compared against oral paracetamol with no significant difference in the incidence of NEC [22]. Oliguria was statistically less with oral ibuprofen compared with IV indomethacin [22] but was not different compared with oral paracetamol [22]. Oral ibuprofen was ranked fourth in risk for oliguria among ten treatment modalities based on one SUCRA analysis (Table 11) [22]. In one MA, oral ibuprofen was not different in creatinine levels compared with IV indomethacin, but was associated with a significantly reduced increase in creatinine levels compared with oral indomethacin [26]. In another study, against mixed oral and IV formulations use of indomethacin, no difference was reported with oral ibuprofen [13].

Oral Ibuprofen versus IV Ibuprofen, standard dose

Only one study evaluated the effect of ibuprofen formulation on PDA closure [13]; oral ibuprofen had a lower risk of failure to close the PDA than IV ibuprofen. In the same study, however, for the need for surgical ligation, no difference was observed.

For adverse events, BPD and IVH were not different between the two formulations in one study [22]. With a similar trend, but at a higher AMSTAR, oliguria did not differ between the two formulations in another study [13]. Only the serum creatinine level differed between the formulations, where oral ibuprofen was associated with lower increase in levels [13]. One MA reported the need for retreatment with oral versus IV ibuprofen to close the PDA, which was statistically significant with oral ibuprofen [22]. Other efficacy and safety outcomes were not different between the oral and IV formulations.

High dose Ibuprofen, oral & IV formulations

One MA, by Mitra *et al.*, reported the difference between HD ibuprofen and IV indomethacin [22], where HD oral ibuprofen was associated with a significant advantage in relation to PDA closure and the need for surgical ligation. Still, it was not different with neonatal mortality, NEC, and BPD. HD IV ibuprofen performed differently from HD oral ibuprofen against IV indomethacin, where there was no difference for both PDA closure and the need for surgical ligation. HD IV ibuprofen was not different from IV indomethacin concerning neonatal mortality, NEC, BPD, IVH, and oliguria [22].

According to Mitra *et al.*, HD oral and IV ibuprofen performed similarly against oral paracetamol [22]. No difference with HD ibuprofen against the oral paracetamol was observed for PDA closure and the need for surgical ligation. A similar trend was observed for neonatal mortality and NEC.

Regarding the effect with HD versus standard dose of mixed oral and IV ibuprofen use, by Ohlsson *et al.* [13], PDA closure was significantly better achieved when at HD, but not for the need for surgical ligation, based on one RCT. A similar trend of no difference was observed with oliguria and creatinine levels, based on one RCT [13].

Looking at the ibuprofen formulations separately, one MA found no difference between HD oral ibuprofen versus standard-dose oral ibuprofen for PDA closure [22], but reported that HD of either oral or IV ibuprofen was more effective than standard-dose IV ibuprofen for PDA closure. For the need for surgery, this was significantly lesser

with HD oral ibuprofen than standard doses of either oral or IV ibuprofen [22]. In contrast, the HD IV ibuprofen did not perform differently for the same outcome from the standard doses of either oral or IV ibuprofen [22]. Based on the same MA, HD IV ibuprofen did not perform differently from either oral or IV ibuprofen for BPD and IVH events.

This is consistent with the SUCRA analysis performed by Mitra *et al.* in their NMA [22]; whereby, for PDA closure, out of 9 treatment modalities, the two highest-ranked were HD oral ibuprofen and HD IV ibuprofen. Based on the 95% confidence intervals reported, no significant difference could be seen within at least the first five ranked treatments, including oral ibuprofen and oral paracetamol (Table 4).

In the current study, general observations are consistent with recent trends of having ibuprofen as first-line therapy for PDA in neonates, particularly against the older and previous standard treatment, indomethacin, due to reported enhanced efficacy and reduced toxicity in the literature [16,31–34]. Paracetamol is a more recently suggested alternative for PDA, where it demonstrated efficacy and safety, particularly advantageous in patients with clinical contraindications to ibuprofen [6]. Our observation is that paracetamol, overall, performed better than indomethacin compared with ibuprofen. Also consistent with our observations, is the recent trends of increased interest in the off-label oral ibuprofen compared with IV ibuprofen, particularly as IV ibuprofen may not be available in all practices, especially in low-income countries. Oral ibuprofen has the advantage of a lower acquisition cost compared with IV ibuprofen, added to ease of availability and administration [35–41].

The current study's applicability is limited by the lack of information about a consistent administration timing of ibuprofen medication. The medication timing highly depends on the clinical diagnostic criteria used to define the HSPDA. A study by Koehne *et al.* found, however, that it is normal for HSPDA to be clinically silent for the first 2–3 days of life and, hence, accurate and early diagnosis of HSPDA best depends on early ECHO assessment [42]. There is, nonetheless, no evidence in included MAs of overall consistency in how early and how often the ECHO was performed for PDA diagnosis in individual studies. In the Cochrane review, by Ohlsson *et al.* [13], for example, the diagnosis among included RCTs varied from prophylactic (within 24 h) to 2, 3, 7 or 21 days of life, to selective, to not stated.

Several limitations exist in the current systematic review. The analysis only included outcomes reported in two or more MAs. Hence, this did not include all reported efficacy and safety outcomes in the literature, excluding, for example, neurodevelopment impairment. This does not undermine how important such outcomes are. However, given the objective of the current review, which is to simplify access to summaries of outcomes where an information overload exists, a decision was made whereby outcomes that are reported in only one MA are easily accessible and interpretable, noting that, for the interest of care providers, we identified the literature studies where these were reported (Supplementary Material 5). Besides, some studies were included in more than one included MA, which may create double counting of data, which is inherent in systematic reviews of MAs and is challenging to eliminate. However, as already discussed, we looked to minimize this limitation's impact by excluding older versions of more recent MAs' updates. The language-restricted search is another limitation and might have missed relevant non-English published studies. No resources were available to authors, however, to translate non-English studies if found. Furthermore, while we believe that our literature search was comprehensive and included all relevant studies, it is always possible that additional search terms and combinations of them may identify other studies.

Conclusion

Ibuprofen seems to be as effective as indomethacin, with reduced NEC, oliguria, and elevated creatinine levels with its IV, oral and mixed formulations use. Indomethacin is associated with reduced BPD and IVH, but not against oral ibuprofen. The use of HD of ibuprofen gives PDA closure superiority and the reduced need for surgery with the oral ibuprofen, not IV ibuprofen, compared with indomethacin.

Oral and mixed formulations use of ibuprofen is as effective as oral paracetamol, but paracetamol is more effective for PDA closure than IV ibuprofen. Paracetamol is also associated with reduced GI bleeding compared with the mixed use of ibuprofen formulations. The HD of ibuprofen does affect the relative efficacy and safety against paracetamol.

Oral ibuprofen has enhanced PDA closure over IV ibuprofen, while also being associated with less effect on creatinine levels. HD of oral ibuprofen had improved PDA closure compared with standard dose IV ibuprofen, but not oral ibuprofen, and was associated with reduced need for surgery compared with standard doses of either oral or IV ibuprofen. HD of IV ibuprofen was only superior over the standard dose of IV ibuprofen for PDA closure. Higher doses of ibuprofen were not associated with any increased toxicity in all studies.

Results should be considered with caution given the variability in dosing regimens and levels of quality and bias, except in support of enhanced PDA closure with oral versus IV ibuprofen and high versus standard-dose ibuprofen, in other words, high AMSTAR and low ROBIS, where further investigations in future research will be valuable, including the need to assess the impact of the timing of medication on outcomes.

Summary points

- Seven published meta-analyses (MAs), including network MAs, have provided evidence on different pairwise comparisons for ibuprofen for patent ductus arteriosus (PDA) in preterm neonates.
- The use of ibuprofen, including at higher doses, is equivalent to superior compared with indomethacin and equivalent to inferior compared with paracetamol/acetaminophen for PDA closure.
- The efficacy of mixed oral and IV formulations of ibuprofen was equivalent to the use of mixed formulations of indomethacin or paracetamol for PDA closure and surgical ligation.
- Ibuprofen has safety advantages over indomethacin in necrotizing enterocolitis, intraventricular hemorrhage, oliguria, creatinine levels, intestinal perforation and platelet count. Indomethacin has safety advantages over ibuprofen, but not oral ibuprofen alone, concerning mortality, bronchopulmonary dysplasia, and serum bilirubin levels. Regarding ibuprofen versus paracetamol, paracetamol has a safety advantage, with reduced gastrointestinal bleeding, serum bilirubin levels and platelet count.
- Oral ibuprofen was as effective and at least as safe as indomethacin and paracetamol in all relevant analyses, where a significant reduction in NEC and oliguria compared with IV indomethacin, and in creatinine levels compared with oral indomethacin were reported.
- Oral ibuprofen is associated with enhanced PDA closure and a favorable effect on serum creatinine levels against IV ibuprofen, which is further enhanced at higher doses of oral ibuprofen. Higher doses of IV ibuprofen is only more efficacious than IV ibuprofen. Higher doses of ibuprofen are not associated with decreased safety.
- Higher-doses oral ibuprofen performed better than IV indomethacin, but had no difference against oral paracetamol, with similar adverse event occurrence to both. Compared with standard doses of IV or mixed formulation of ibuprofen, the high-dose ibuprofen was associated with enhanced PDA closure when administered via oral or mixed formulation, at no increase in toxicity. This advantage was not seen compared with the standard oral ibuprofen dose.
- Except in support of oral versus IV ibuprofen and of the higher HD doses of ibuprofen (i.e. high quality of methods and low risk of bias), outcomes of pairwise comparisons in MAs are supported by contrasting levels of methods quality and risk of bias.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/er-2020-0235

Author contributions

D Al-Badriyeh conceived and designed the study. All authors contributed equally in data collection and analysis, result interpretation, and revising the manuscript. Al-Shaibi S wrote the first manuscript draft. All authors read and approved the final manuscript.

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