

Use of Prophylactic Indomethacin in Preterm Infants: A Systematic Review and Meta-Analysis

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Background: Prophylactic indomethacin has been widely used as an effective intervention for reducing mortalities and morbidities in preterm infants including the cardiopulmonary and neurodevelopmental morbidities such as intraventricular hemorrhage (IVH), but many studies have reported contradictory outcomes regarding its significance. Therefore, we aim to systematically review and meta-analyze the data of prophylactic indomethacin on preterm infants.

OPEN ACCESS

Edited by:

Giovanni Vento, Catholic University of the Sacred Heart, Italy

Reviewed by:

Yogen Singh, Cambridge University Hospitals NHS Foundation Trust, United Kingdom Christoph Bührer, Charité Universitätsmedizin Berlin, Germany

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Specialty section:

This article was submitted to Neonatology, a section of the journal Frontiers in Pediatrics

Received: 17 August 2021 Accepted: 23 February 2022 Published: 07 April 2022

Citation:

Al-matary A, Abu Shaheen A and Abozaid S (2022) Use of Prophylactic Indomethacin in Preterm Infants: A Systematic Review and Meta-Analysis. Front. Pediatr. 10:760029. doi: 10.3389/fped.2022.760029 **Methods:** Our systematic search included the following databases: Pubmed, Google Scholar, Scopus, Web of Science, The New York Academy of Medicine (NYAM), Virtual health library (VHL), and the System for Information on Grey Literature in Europe (SIGLE) to include studies that assessed the use of prophylactic indomethacin in preterm infants until 12 August 2021.

Results: The final list of our included studies is comprised of 23 randomized trials and cohort studies. Among all the studies outcomes, significant favorable outcome was lowering the rate of PDA, surgical PDA ligation (P < 0.001) and severe IVH (P = 0.008) while no significance was recorded with BPD, pulmonary hemorrhage, intraventricular hemorrhage, necrotizing enterocolitis, intestinal perforation, mortality, and length of hospital stay.

Conclusion: Since the meta-analysis results regarding effectiveness of prophylactic indomethacin varied based on the study design particularly with regard to outcomes such as surgical PDA ligation and severe IVH, this warrants the need for more evidence regarding the effectiveness of prophylactic indomethacin in very low birth weight infants.

Keywords: patent ductus arteriosus, intraventricular hemorrhage, prophylactic indomethacin, preterm infants, neonatal outcome

INTRODUCTION

Many cardiopulmonary and neurologic disabilities have been associated with preterm labor including patent ductus arteriosus (PDA), pulmonary hemorrhage, intracranial hemorrhage, and developmental delay (1–4). Although advances in modern medicine have improved the survival rates of very low birth weight (VLBW) infants, many neurodevelopmental complications are still present due to preterm birth such as blindness, deafness, and cerebral palsy. VLBW infants

1

are at risk of developing intraventricular hemorrhage (IVH) which is usually associated with neurodevelopmental decays when related to the brain parenchyma. IVH grade 3–4 is a major risk factor for the occurrence of these complications in preterm infants (5–8). Although the incidence rate of IVH has been markedly reduced since the 1980s (9, 10), as no or minimal reductions have been recorded recently (11, 12).

Many pre- and postnatal interventions have been reported to effectively treat IVH and reduce its incidence in preterm infants (13). One of these is indomethacin prophylaxis which is better administered within the first 6 h after birth (14-17). Besides, it helps in the closure of ductus arteriosus and therefore, can prevent the complications of PDA such as pulmonary hypertension (14, 15, 18). Its mechanisms of action include prostaglandin synthesis inhibition by inhibiting the cyclooxygenase pathways, reduction of hyperemic responses resulting from cerebrovascular hypoxia and hypercapnia, increasing the blood-brain barrier permeability, and prevention of cerebral perfusion-induced ischemia (19-23). Moreover, it enhances microvascular development in the germinal matrix (24). Perfusion-related factors such as hypoxia, hypercapnia, and hypotension usually develop after birth in VLBW infants (25). Most cases of preterm infants develop IVH within 6-8 h after birth regardless of the gestational age (26). It happens probably due to the increased levels of angiopoietin 2 and vascular endothelial growth factor in the germinal matrix that normally decreases within hours after birth (13).

The results of previously published randomized controlled trials (RCTs) have shown that early administration of indomethacin after birth lowers the incidence of symptomatic PDA and severe IVH as a prophylactic measure (16, 27-29). Although indomethacin administration showed favorable outcomes in reducing IVH incidence, many concerns have arised regarding its effect on cerebral perfusion (30, 31). The rates of mortalities, bronchopulmonary dysplasia (BPD), or long-term neurodevelopmental decays reportedly seem to have been not affected. A previously published large RCT advised against using indomethacin as a prophylactic agent (15). Although the study showed favorable outcomes in terms of reducing incidence rates of PDA, PDA ligation, IVH, and pulmonary hemorrhage, no improvement regarding the incidence of death and neurodevelopmental disorders rates has been found. Therefore, in this systematic review, we aim to analyze the data of previously published investigations on the use of prophylactic indomethacin in preterm infants.

MATERIALS AND METHODS

Search Strategy and Study Selection

In accordance with the Preferred Reporting Items for Systematic Review and Meta-analyses statement (PRISMA) recommendations, we performed this systematic review and meta-analysis (32). A systematic electronic database search was conducted for relevant studies published, from inception until 12 August 2021, in seven databases: Pubmed, Google Scholar, Scopus, Web of Science, The New York Academy of Medicine (NYAM), Virtual health library (VHL), and the System for Information on Grey Literature in Europe (SIGLE). The search process was conducted using keywords, medical subject (MeSH) terms, and publication types based on the PICO framework (participants, comparison, intervention, and outcomes). Participants were any preterm infants, the intervention was the prophylactic indomethacin, the comparison was placebo or no treatment groups, and all possible outcomes were included. The systematic search was followed by a manual search in references of the included papers to include missed papers (33).

We included all original studies that assessed the use of prophylactic indomethacin in preterm infants. Papers were excluded if there were one of the following exclusion criteria: (i) non-original studies; (ii) articles in non-English language; (iii) *in vitro* or animal studies; (iv) data duplication, overlapping or unreliably extracted or incomplete data; and (v) abstract only articles, reviews, thesis, books, conference papers, or articles without available full texts (conferences, editorials, author response, letters, and comments). The title and abstract screening were performed by four independent reviewers. Furthermore, three independent reviewers performed full-text screening to ensure the inclusion of relevant papers in our systematic review. Any disagreement was done by discussion and consulting the senior member when necessary.

Data Extraction

Two authors made the pilot extraction of a few papers for building the data extraction sheet. The data extraction sheet included: patient's characteristics, and outcomes. Two authors extracted the data and was reviewed by a third reviewer when necessary. If a disagreement occurred, a senior author was consulted.

Statistical Analysis

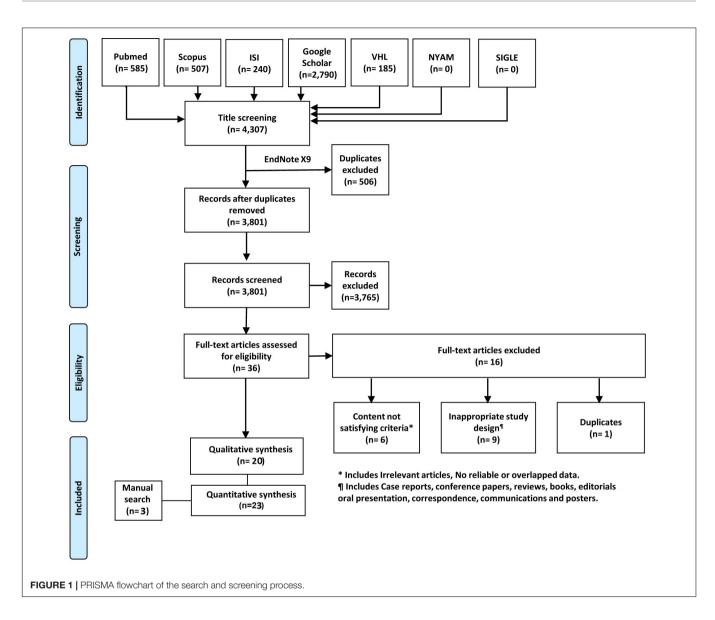
All data were analyzed using Comprehensive Meta-analysis Software Version 3.0, odds ratios (OR) and Standardized mean difference (SDM) outcomes were calculated. The corresponding 95% confidence intervals (CI) of pooled effect size were calculated using a fixed-effects or random-effects, according to heterogeneity level. Heterogeneity was assessed with Q statistics and I² test.

The publication bias was assessed using Egger's regression test (34, 35) and represented graphically by Begg's funnel plot (36). when there were 10 or more studies/effect sizes. Egger's regression test *P*-value <0.10 was considered significant. Whenever publication bias was found, the trim and fill method of Duvall and Tweedie was applied (37) to add studies that appeared to be missing to enhance the symmetry.

RESULTS

Search Results

We identified 3,801 records after excluding of 506 duplicates by using Endnote software version X9. Title and abstract screening resulted in 36 records for further full-text screening. The later



yielded 20 eligible papers for inclusion in our study. Three papers were added after performing manual search trials. Finally, we included 23 studies for this systematic review and meta-analysis (**Figure 1**).

Study Characteristics

Out of the 23 included studies; 15 were randomized controlled trials and the remaining eight were cohort in design. The sample size of the included studies was highly variable ranging from 19 and as high as 34,602 pre-term infants. The average mean age in all reported treatment group and control group was 27 weeks (ranging from 26 to 28 weeks). **Table 1** shows the main characteristics of the included studies (15, 17, 27–29, 38–55).

Publication Bias

With regard to articles with a cohort study design, no publication bias was found in the studies relating to the outcome of death (P = 0.852) using Begg's adjusted rank correlation test. Publication bias related to bronchopulmonary dysplasia, severe intraventricular hemorrhage, necrotizing enterocolitis and surgical PDA ligation was not assessed owing to few number of studies.

Regarding publication bias among RCT studies, overall no publication bias was found in the studies. Regarding PDA, no publication bias was found in the studies (P = 0.524) using Egger's test (**Figure 2A**). No publication bias was found in studies (P = 0.458) using Begg's adjusted rank correlation test with regard to severe interventricular hemorrhage. Regarding necrotizing enterocolitis, no publication bias was found in studies (P = 0.652) using Begg's adjusted rank correlation test. With regard to death, no publication bias was found in the studies (P = 0.394) using Egger's test (**Figure 2B**). Publication bias related to bronchopulmonary dysplasia, intraventricular hemorrhage, pulmonary hemorrhage, intestinal perforation, surgical PDA ligation and hospitalization days were not assessed owing to few studies.

TABLE 1 | Characteristics of the included studies.

RCT

Design Sample size

141

Gestational age

Total

70

Control group

28

Mean SD

2.6 71

Treatment group

28

Mean SD

2.2

Total

71

Author Year

Bada et al. (28)

																			indomethacin in preventing periventricular- intraventricular hemorrhage (PV-IVH)	reduced the relative risk of grades 2 to 4 PV-IVH and severe PV-IVH, but other perinatal variables contributed significantly to the overall risk of PV-IVH
Bandstra et al. (27)	RCT	199	99	29	2.3	100	29.3	2.1	99	970	174	100	970	183	51	99	43	100	To assess the impact of early prophylactic use of intravenous indomethacin on the incidence and severity of periventricular- intraventricular hemorrhage and patent ductus arteriosus in 199 oxygen-requiring premature infants	Early prophylactic indomethacm initiated within 12 h of delivery is effective in reducing the incidence of intraventricular hemorrhage as well as clinically significant patent ductus arteniosus in very low birth weight premature infants
Jensen et al. (38)	Cohort	7,831	2,587	25.9	1.5	5,244	26.7	1.6	2,587	777	197	5,244	913	246	1,270	2,587	2,744	5,244	To assess the association between prophylactic indomethacin and bronchopulmonary dysplasia (BPD) in a recent, large cohort of extremely preterm infants	Prophylactic indomethacin was not associated with either reduced or increased risk for BPD or death
Laughon et al. (39)	Cohort	34,602	_	_	_	_	_	_	-	_	_	-	_	_	3,293	6,189	15,406	28,413	To describe the current use of treatments to prevent or treat patent ductus arteriosus (PDA) in preterm infants, examine the association between different treatment strategies and neonatal outcomes and review the variation in these practices between centers	Indomethacin use for intraventricular hemorrhage prevention and/or treatment of a PDA is common, but the selection of infants for treatment, and the decision of when and how to treat vary widely between centers. Our findings suggest the need for randomized, placebo-controlled trials of the effect of treatment of the PDA in preterm infants
Liebowitz et al. (40)	Cohort	397	247	26.1	1.2	150	26	1.2	247	813	197	150	802	200	117	247	90	150	To determine whether prophylactic indomethacin (prophylactic indomethacin treatment) has more or less morbidity than delayed conservative management of the moderate-to-large patent ductus arteriosus (PDA)	
Maruyama et al. (41)	RCT	19	_	-	-	-	_	_	_	-	-	-	_	_	_	-	_	_	To investigate the effects of prophylactic low-dose indomethacin on renal and intestinal blood flow	Prophylactic low-dose indomethacin increases the diastolic blood flow in the RAand SMAvia a reduction in the ductal shunt volume, with no change in the regional vascular resistance

Birth weight

253

Total

70

Control group

1,074 265

Mean SD

Event

37

Treatment group

Mean SD

1,103

Total

Male

Treatment group Control group

Event

26

Total

70

Total

71

Aim

Main conclusion(s)

To determine the efficacy of indomethacin prophylaxis

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Use of Prophylactic Indomethacin in Preterm Infants

TABLE 1 | (Continued)

Author Year	Design	Sample size		G	iestatio	onal age					Birth we	ight				Ma	e		Aim	Main conclusion(s)
			Trea	tment gr	roup	Cor	ntrol grou	ıp	Tre	atment g	roup	Cor	ntrol gro	up	Treatme	ent group	Control	group		
			Total	Mean	SD	Total	Mean	SD	Total	Mean	SD	Total	Mean	SD	Event	Total	Event	Total		
Virza et al. (42)	Cohort	868	868	26.36	1.97	_	_	_	868	864.82	210.84	_	_	_	431	868	-	_	To test the hypothesis that administration of indomethacin prophylaxis before 6 hours of life results in a lower incidence of intraventricular hemorrhage (IVH) compared with administration after 6 h of life, and that the effects of early prophylaxis depend on gestational age (GA) and sex in very low birth weight infants (birth weight <1,250 g)	Prophylactic indometha administered before 6 h life is not associated wit lower incidence of IVH
Narayanan et al. (43)	Cohort	300	130	25.5	1.1	170	25.5	1.1	130	798	172	170	803	180	68	130	87	170	To examine the role of prophylactic indomethacin in producing permanent DA closure and the mechanism by which this occurs	Prophylactic indometha improved the rate of permanent ductus closs by increasing the degre initial constriction. Prophylactic indometha did not affect the remodeling process, no did it alter the inverse relationship between int maturity and subseque reopening. Even when managed with prophyla indomethacin, the rate - ductus reopening rema unacceptably high in th most immature infants
Nelin et al. (44)	Cohort	671	_	-	_	-	-	-	-	-	-	-	-	_	-	-	-	-	To determine whether PI use in a contemporary cohort of EP infants admitted to an all-referral NICU continues to be associated with beneficial outcomes	PI administration was associated with improv survival in EP infants referred to a level IV Children's Hospital NIC
Schmidt et al. (15)	RCT	1,202	601	25.9	1.8	601	26	1.9	601	782	131	601	783	130	309	601	306	601	To determine whether the prophylactic administration of indomethacin improves survival without neurosensory impairment in extremely-low-birth-weight infants (those with birth weights below 1,000 g)	In extremely-low-birth-we infants, prophylaxis with indomethacin does not improve the rate of sun without neurosensory impairment at 18 montt despite the fact that it reduces the frequency patent ductus arteriosu and severe periventricu and intraventricular hemorrhage

TABLE 1 | (Continued)

Author Year	Design	Sample size			Gestati	onal ag	e				Birth	weight				Ма	le		Aim	Main conclusion(s)
			Trea	atment g	Iroup	Co	ontrol gro	oup	т	reatmen	t group		Control	group	Treatme	ent group	Contro	l group		
			Total	Mean	SD	Total	Mean	SD	Total	Mean	SD	Total	Mean	SD	Event	Total	Event	Total		
Stavel et al. (45)	Cohort	4,268	_	_	-	-	_	_	-	_	-	_	-	-	244	498	1,855	3,770	To determine the effect of concomitant administration of prophylactic indomethacin and early enteral feeds on the risk of spontaneous intestinal perforation (SIP) in extremely low-birth-weight (ELBW) infants, and to describe the variation in prophylactic indomethacin use in Canada	Prophylactic indomethaci was associated with increased odds of SIP independently from early feeding in this cohort; however, early enteral feeding was not associat with SIP. Marked variatior in the use of prophylactic indomethacin was identifi
Couser et al. (46)	RCT	99	43	26.4	1.6	47	26.4	1.8	43	915	209	47	879	202	25	43	22	47	To determine whether a course of low-dose indomethacin therapy, when initiated within 24 h of birth, would decrease ductal shunting in premature infants who received prophylactic surfactant in the delivery room	The prophylactic use of lo doses of indomethacin, when initiated in the first 24 h of life in low birth weight infants who receiv prophylactic surfactart in the delivery room, decreases the incidence left-to-right shunting at th level of the ductus arteriosus
Hanigan et al. (47)	RCT	122	56	30.00	0.3	55	29.7	0.3	56	1,138	31.7	1,153	32.1		30	56	29	55	To test the null hypothesis that the prophylactic administration of indomethacin would not be associated with a significant reduction in the incidence of PVH-IVH	Prophylactic administratic of intravenous indomethacin for the prevention of PVH-IVH cannot be recommended for infants <1,000 g. In preterm infants between 1000 and 1,500 g birth weight, indomethacin significantly reduced the incidence of PVH-IVH
Krueger et al. (48)	RCT	32	15	29.4	0.4	17	28.9	0.4	15	1,126	52	17	1,111	47	10	15	8	17	To determine the efficacy of indomethacin to prevent the occurrence of symptomatic patent ductus arteriosus (PDA)	Results indicate that the use of prophylactic indomethacin is beneficia in prevention of symptomatic PDA
Yaseen et al. (49)	RCT	27	14	30.3	2.5	13	29.1	3.1	14	1,320	350	13	1,230	360	8	14	7	13	To evaluate the oxygenation, and surfactant requirements in preterm low birth weight infants receiving early indomethacin administration	Early indomethacin administration increases oxygen and surfactant requirement
Vincer et al. (50)	RCT	30	15	28.0	25-34	15	29.0	26-36	15	940	700–1,480	15	970	520-1,480	8	15	8	15	To test the efficacy of early intravenous indomethacin therapy in preventing chronic pulmonary disease of prematurity	Data suggests that caution must be exercised with early use of indomethacin

Use of Prophylactic Indomethacin in Preterm Infants

TABLE 1 | (Continued)

Design Sample size

Author Year

Gestational age

Control group

Treatment group

Use of Prophylactic Indomethacin in Preterm Infants

Main conclusion(s)

			Total	Mean	SD	Total	Mean	SD	Total	Mean	SD	Total	Mean	SD	Event	Total	Event	Total		
Vent et al. (51)	RCT	48	24	28.7	1.92	24	28.5	2.20	24	1,010	172	24	1,015	156	-	_	-	_	To examine the use of indomethacin to prevent GMH/IVH in very low birth weight neonates.	Indomethacin should only be used investigationally fo the prevention of GMH/IVH with particular attention to long-term neurodevelopmental outcome and the incidence of severe IVH
<i>M</i> ent et al. (52)	RCT	36	19	28.2	1.9	17	2,813	2.0	19	950	152	17	927	175	10	19	10	17	To determine whether a low dose of indomethacin would prevent germinal matrix or intraventricular hemorrhage and permit adequate urinary output	Ductal status appeared unrelated to the development of germinal matrix or intraventricular hemorrhage
Ment et al. (16)	RCT	61	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	_	To test if indomethacin (0.1 mg/kg given intravenously at 6–12 postnatal hours and every 24 h for two more doses) would prevent extension of intraventricular hemorrhage	In very low birth weight infants with low grade intraventricular hemorrhage within the first 6 postnatal hours, prophylactic indomethacin promotes closure of the patent ductus arteriosus and is no associated with adverse events, but does not affect the events leading to parenchymal involvement of intracranial hemorrhage
Vair et al. (53)	RCT	115	56	27.8	1.2	59	27.9	1.4	56	989.5	93.5	59	995	83.6	-	-	-	-	To study the efficacy and complications of low dose indomethacin in the reduction of major intraventricular hemorrhage (IVH) in very low birth weight (VLBW) babies.	Indomethacin prophylaxis did not confer protection against IVH in very low birth weight babies. Instead it showed an increase in the risk of IVH, other bleeding episodes and chronic lung disease
Rennie et al. (54)	RCT	50	24	28	2.3	26	29	2.0	24	1,214	323	26	1,330	326	13	24	18	26	To temporally relate plasma 6-ketoprostaglandin Fla, indomethacin concentrations, and clinical response in a group of low birthweight infants receiving intensive care	There was no significant difference in the incidence of intraventricular hemorrhage, days of treatment with oxygen or ventilation, or mortality between the two groups
Mahony et al. (55)	RCT	104	51	28.0	1.5	53	28.0	1.6	51	1,020.0	158.0	53	989.0	162.0	21	51	32	53	To investigate the optimal timing for treatment of small premature infants using indomethacin therapy on the first day of life	Although treatment with indomethacin on the first day of life appears to be safe, there is little advantage to its use in centers where the incidence of large shunts through a patent ductus arteriosus is relatively low

Birth weight

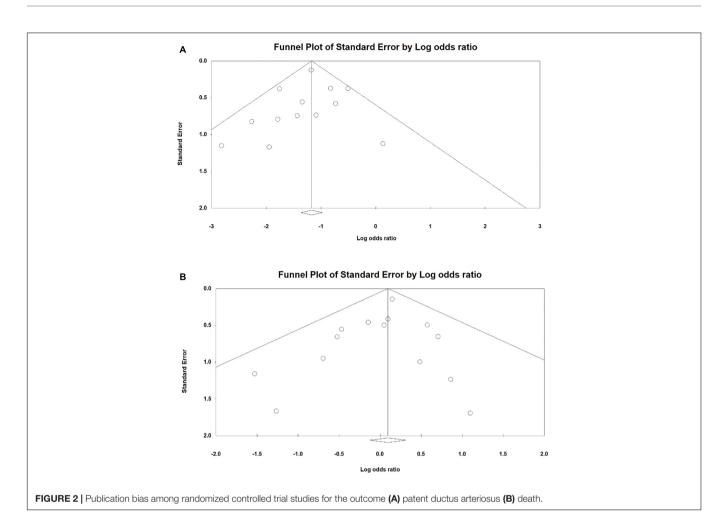
Control group

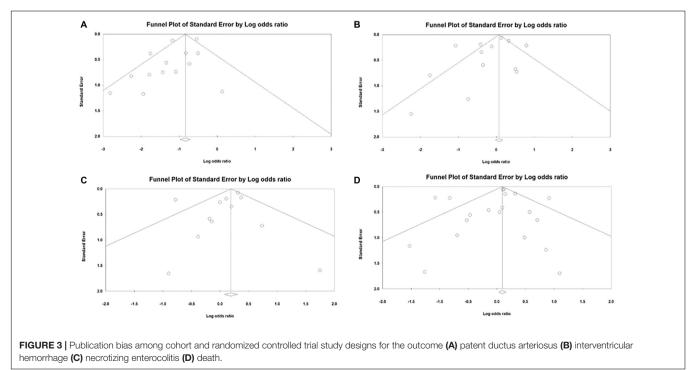
Treatment group

Male

Treatment group Control group

Aim

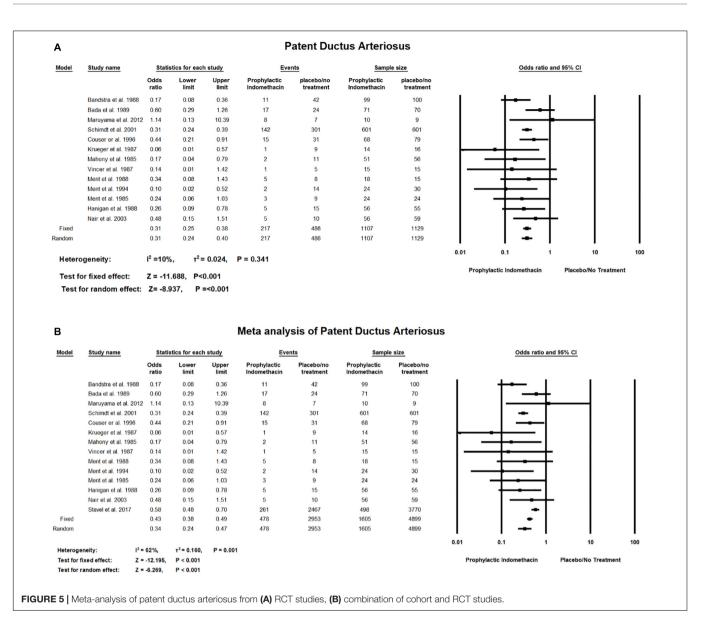




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Model Study name Statistics for each study Events Sample size Odds ratio and 95% Cl	Model Study name Statistics for each study Events Sample size Odds ratio and 95% Cl	Test for rando	lom effect Z= 1.153	9, P = 0.2	49						Prophylactic Indomethacin Placebo/No Treatment
Model Study name Statistics for each study Events Sample size Odds ratio and 95% Cl	Model Study name Statistics for each study Events Sample size Odds ratio and 95% Cl	_				M	leta analysis	of Bronch	opulmonary	Dvsplasia	
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Heterogeneity: 1² = 79%, τ² = 0.170, P < 0.001	Heterogeneity: 1² = 79%, τ² = 0.170, P < 0.001	Rer									+
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Test for fixed effect: Z = 0.386, P = 0.627 Prophylactic Indomethacin Placebo/No Treatment	Test for fixed effect: Z = 0.386, P = 0.627 Prophylactic Indomethacin Placebo/No Treatment	Rer Fixed									
rest for random effect: ∠ = 0.213, P = 0.831	rest for random effect: $z = 0.213$, $P = 0.831$	Rer Fixed Random	l ² = 79%,		, P<0.0	001					
		Rer Fixed Random Heterogeneity: Test for fixed effe	fect: Z = 0.386,	τ ² = 0.170 P = 0.627	, P<0.(001					Prophylactic Indomethacin Placebo/No Treatment

With regard to the publication bias in both cohort and RCT studies, in general no publication bias was seen with the exception of patent ductus arteriosus where publication bias was found in the studies (P = 0.083) using Egger's test (**Figure 3A**). No publication bias was found related to bronchopulmonary dysplasia in studies (P = 0.543) using Begg's adjusted rank correlation test. With regard to intraventricular hemorrhage,

no publication bias was found in studies (P = 0.348) using Begg's adjusted rank correlation test. For severe interventricular hemorrhage as well, no publication bias was found in studies (P = 0.217) using Egger's test (**Figure 3B**). Regarding necrotizing enterocolitis, no publication bias was found in studies (P = 0.364) using Egger's test (**Figure 3C**). With regard to death, no publication bias was found in studies (P = 0.449) using Egger's



test (**Figure 3D**). Using Begg's adjusted rank correlation test, no publication bias was found in studies (P = 0.176) with regard to surgical PDA ligation. Publication bias related to pulmonary hemorrhage, intestinal perforation and hospitalization days was not assessed owing to few studies.

Meta-Analysis of Outcomes

Bronchopulmonary Dysplasia

In the meta-analysis of cohort studies, no significant difference was seen between the group of infants given prophylactic doses of indomethacin and the placebo or no treatment group with regard to the rates of bronchopulmonary dysplasia (OR = 0.88; 95% CI = 0.53–1.46; *P*-value = 0.628). There was high significant heterogeneity among the included studies ($I^2 = 91\%$; *P*-value < 0.001) (**Figure 4A**).

Meta-analysis of RCT studies shows there was no significant difference between the group of infants with prophylactic doses

of indomethacin and the group of placebo or no treatment with regard to the rates of bronchopulmonary dysplasia (OR = 1.64; 95% CI = 0.99–2.71; *P*-value = 0.053). There was no significant heterogeneity among the included studies ($I^2 = 30\%$; *P*-value = 0.234) (**Figure 4B**).

In the combined meta-analysis of cohort and RCT studies, there was no significant difference between the prophylactic indomethacin group and the placebo or no treatment group regarding the rates of bronchopulmonary dysplasia (OR = 1.04; 95% CI = 0.70–1.57; *P*-value = 0.831). There was high significant heterogeneity among the included studies (I² = 79%; *P*-value < 0.001) (**Figure 4C**).

Patent Ductus Arteriosus

Meta-analysis of RCT studies shows infants given prophylactic doses of indomethacin have significantly lower rates of PDA compared to those who did not (OR = 0.31; 95% CI = 0.25-0.38;

Α					meta	analysis of S	groui i	2. Ligati							
Model	Study name		Statist	tics for each	n study	Even	ts	Sampl	e size		Od	lds ratio a	nd 95% C	<u>:</u>	
			Odds ratio	Lower limit	Upper limit	Prophylactic I Indomethacin									
	Laughon et al.	2007	792.17	49.47	12684.06	572	0	6189	3886						>
	Nelin et al. 201	7	1.92	1.25	2.96	191	32	530	141			1 1	-	-	
	Stavel et al. 20	17	0.65	0.47	0.90	45	498	498	3770			+			
Fixed	d		1.01	0.78	1.31	808	530	7217	7797			∔	-		
Randon	n		3.38	0.78	14.67	808	530	7217	7797			+	-+	•	-
	Heterogeneity:		l ² = 95%,	τ ² = 1.3	11, P < 0.00	1				0.1	0.2	0.5 1	2	5	10
	Test for fixed e	ffect:	Z = 0.103	, P = 0.9	18										
	Test for random	n effect:	Z= 1.628,	P = 0.1	04					Prop	hylactic Indo	omethacin	Placebo/N	lo Treatme	ent
в					Meta	analysis of s	Surgical I	PDA Ligati	ion						
Model	Study name		Statistics	for each stu	dy	Events		Sample si	ze		c	odds ratio a	nd 95% Cl		
			Odds I ratio		pper Prophy mit Indome				Placebo/no treatment						
	Couser et al.	1996	0.53	0.21 1	.32 8	16		68	79			+			
	Mahony et al.	1985	0.16	0.02 1	.35 1	6		51	53	- I ·					
	Maruyama et		3.00		3.36 1			10	9				-	+	-1
	Schmidt et al.	2001	0.01		.76 40			601	601						
Fixed			0.50		.72 50			730	742						
Random			0.50	0.35 0	.72 50	96		730	742		1	1		1	1
	fixed effect:	l ² = 0%, Z = -3.713, Z = -3.713,	τ ² = 0, P <0.001 P <0.001	P = 0.523						0.01 P	0.1 rophylactic Indo	1 methacin	Placebo/	10 No Treatment	100 t
с					Meta	analysis of S	Surgical F	PDA Ligati	on						
Mode	Study name		Sta	tistics for eac	h study	Eve	nts	Sam	ple size		Odd	ls ratio and	95% CI		
			Odds ratio	Lower limit	Upper limit	Prophylactic Indomethacin	Placebo/no treatment	Prophylactic Indomethaci	n treatmen						
	Couser et al.		0.53	0.21	1.32	8	16	68	79	1	-	+	I		1
	Laughon et al.		792.17	49.47	12684.06	572	0	6189	3886					_	1
	Mahony et al.		0.16 3.00	0.02	1.35 83.36	1	6 0	51 10	53 9	-					_
	Maruyama et a Nelin et al. 20		3.00	0.11	2.96	1 191	32	530	9 141			_			1
	Schmidt et al.		0.51	0.34	0.76	40	74	601	601						1
	Stavel et al. 2		0.65	0.47	0.90	45	498	498	3770						
Fixe	d		0.80	0.65	0.99	858	626	7947	8539			-			1
Rando	m		1.08	0.49	2.38	858	626	7947	8539	1	I	+	- 1		1
Hete	rogeneity:	l ² = 88%,	T ² = 0.02	7, P<0.001						0.01	0.1	1	10)	100
Test	for fixed effect: for random effect:	Z = -2.064 Z = 0.200,	P = 0.03	9						Prop	hylactic Indome	thacin	Placebo/No	Treatment	

P-value < 0.001). There was no significant heterogeneity among the included studies (I² = 10%; *P*-value = 0.341) (Figure 5A).

Combined meta-analysis of cohort and RCT studies shows infants given prophylactic doses of indomethacin have significantly lower rates of Patent Ductus Arteriosus compared to those who did not (OR = 0.34; 95% CI = 0.24–0.47; *P*-value < 0.001). However, there was medium significant heterogeneity among the included studies ($I^2 = 62\%$; *P*-value = 0.001) (**Figure 5B**).

Surgical PDA Ligation

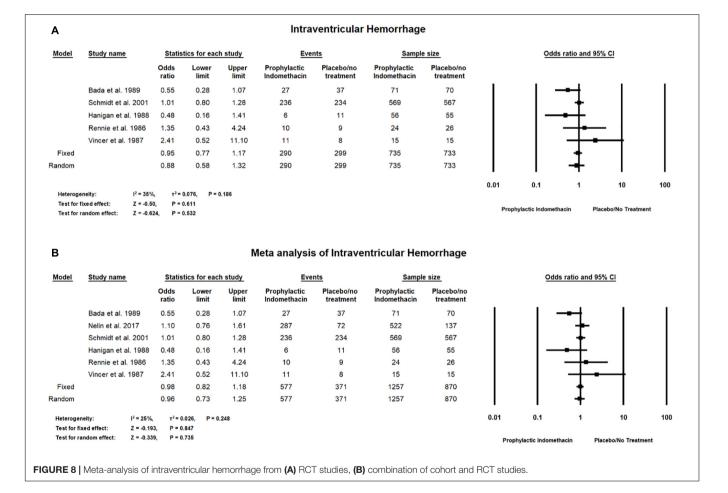
In the meta-analysis of cohort studies, there was no significant differences between the group of infants given prophylactic

doses of indomethacin and placebo or no treatment group with regard to the rates of surgical PDA ligation (OR = 3.84; 95% CI = 0.78–14.67; *P*-value = 0.104). There was high significant heterogeneity among the included studies ($I^2 = 95\%$; *P*-value < 0.001) (**Figure 6A**).

Meta-analysis of RCT studies shows infants with prophylactic doses of indomethacin have significantly lower rates of surgical PDA ligation compared to those who did not (OR = 0.50; 95% CI = 0.35–0.72; *P*-value < 0.001). There was no significant heterogeneity among the included studies ($I^2 = 0\%$; *P*-value = 0.523) (**Figure 6B**).

Combined meta-analysis of cohort and RCT studies shows there was no significant differences between the group of infants

Model	Study name	Statis	tics for each	n study	Ever	nts	Sample	e size			Odds ra	tio and	95% CI		
		Odds ratio	Lower limit	Upper limit	Prophylactic Indomethacin	placebo/no treatment	Prophylactic Indomethacin	placebo/no treatment							
	Bandstra et al. 1988	0.83	0.25	2.82	5	6	99	100	1	1-	_	•	+		1
	Bada et al. 1989	0.46	0.13	1.61	4	8	71	70	·	_		_	- 1		
	Schimdt et al. 2001	0.89	0.65	1.22	89	98	601	601			- 1	╼┼╴			
Fixed		0.86	0.64	1.15	98	112	771	771			- I -	╺┼╴			
Random		0.86	0.64	1.15	98	112	771	771			-	╺┼			
Heterog	reneity: 1 ² = 0%	т ² =	0. P=	0.606					0.1	0.2	0.5	1	2	5	10
	fixed effect: Z = -1.0		0.303												
Test for	random effect: Z = -1.0	29, P =	0.303						Р	rophylactic	Indomethaci	n	Placebo/No	Treatment	e.



given prophylactic doses of indomethacin and the infants in the placebo or no treatment group with regard to the rates of necrotizing enterocolitis (OR = 1.10; 95% CI = 0.79-1.52; *P*-value = 0.571). There was no significant heterogeneity among the included studies (I2 = 0%; *P*-value = 0.825) (**Figure 6C**).

Pulmonary Hemorrhage

Meta-analysis of RCT studies shows there was no significant differences between the group of infants given prophylactic

doses of indomethacin and placebo or no treatment group regarding the rates of pulmonary hemorrhage (OR = 0.86; 95% CI = 0.64–1.15; *P*-value = 0.303). There was no significant heterogeneity among the included studies ($I^2 = 0\%$; *P*-value = 0.606) (**Figure 7**).

Intraventricular Hemorrhage

Meta-analysis of RCT studies shows there was no significant differences between the group of infants given prophylactic

					Severe l	ntraventri	cular Hemo	rrhage								
Model	Study name	Statis	tics for ea	ch study	Ever	its	Sample	size			Odds rat	tio and s	95% CI			
		Odds ratio	Lower limit	Upper limit	Prophylactic Indomethacin	Placebo/no treatment	Prophylactic Indomethacin	Placebo/no treatment								
	Abdi et al. 2021	2.20	1.46	3.33	38	93	200	967	1	1		1	-+	- 1		
	Liebowitz et al. 201	0.34	0.22	0.52	95	97	247	150		1-						
	Nelin et al. 2017	0.88	0.56	1.39	107	31	522	137			<u> </u>	•				
	Stavel et al. 2017	1.39	1.09	1.76	98	566	498	3770					-			
	Laughon et al. 200	7 1.14	1.01	1.29	790	441	6189	3886				+				
Fixed		1.13	1.03	1.25	1128	1228	7656	8910				+				
Random		1.03	0.67	1.57	1128	1228	7656	8910	I.	I	I -	+	- 1		I	
Hetero	geneity:	² =91%,	τ ² = 0.	204, P <	0.001				0.1	0.2	0.5	1	2	5	10	
Test fo	or fixed effect:	Z = 2.448	, P = 0.	014					Pro	phylactic	Indomethacin		Placebo/I	lo Treatm	ent	
Test fo	or random effect:	Z= 0.116,	P = 0.	607												
3					Severe	Intraventri	icular Hemor	rhage								
Model	Study name	Statis	stics for eac	ch study	Ev	ents	Sam	ple size			Odd	ls ratio a	and 95%	CI		
		Odds ratio	Lower limit	Upper limit	Prophylactic Indomethacin	Placebo/no treatment										
	Schimdt et al. 2001	0.66	0.45	0.96	52	75	569	567		1						
	Nair et al. 2003	1.65	0.44	6.19	6	4	56	59				-		-		
	Ment et al. 1988	0.11	0.01	2.22	0	3	19	17				_				
	Ment et al. 1985 Ment et al. 1994	0.48 1.70	0.04 0.41	5.66 7.09	1 5	2 4	24 27	24 34		·			_	_		
	Couser et al. 1996	0.70	0.22	2.26	5	8	68	79				_	_			
	Bada et al. 1989	0.17	0.04	0.83	2	10	71	70		.	_ -					
	Bandstra et al. 1988	0.68	0.35	1.32	19	26	99	100					-			
Fixed		0.68	0.51	0.90	90	132	933	950								
andom		0.68	0.48	0.97	90	132	933	950		I	1			1		
Unterror				0.350					0	01	0.1	1		10		
Heterogene																
Test for fixe		36, P=0	0.008							Prophy	lactic Indomet	thacin	Place	bo/No Tre	atment	
Test for fixe Test for ran	ed effect: Z = -2.6	36, P=0	0.008	Meta	analysis of	Severe lı	ntraventricu	ılar Hemo	rrhag		lactic Indomet	thacin	Place	bo/No Tre	atment	
Test for fixe Test for ran	ed effect: Z = -2.6	36, P=0 35, P=0	0.008		analysis of Event		ntraventricu Sample s		rrhag			thacin ratio and			atment	
Test for fixe Test for ran	ted effect: Z = -2.6 ndom effect: Z = -2.1 Study name	36, P=0 35, P=0	0.008 0.033		-				rrhag						atment	
Test for fixe Test for ran	ted effect: Z = -2.6 ndom effect: Z = -2.1 Study name	36, P = (35, P = (<u>Statistic</u> Odds	0.008 0.033 cs for each s Lower	tudy Upper	<u>Event</u> Prophylactic	<u>s</u> Placebo/no	<u>Sample s</u> Prophylactic	ize Placebo/no	rrhag						atment	
Test for fixe Test for ran	ed effect: Z = -2.6 ndom effect: Z = -2.1 <u>Study name</u> Abdi et al. 2021 Liebowitz et al. 2017	36, P = 0 35, P = 0 <u>Statistic</u> Odds ratio 2.20 0.34	0.008 0.033 25 for each s Lower limit 1.46 0.22	tudy Upper limit 3.33 0.52	Event: Prophylactic Indomethacin 38 95	Placebo/no treatment 93 97	Sample a Prophylactic Indomethacin 200 247	ize Placebo/no treatment 967 150	rrhag						atment	
Test for fixe Test for ran	ed effect: Z = 2.6 ndom effect: Z = 2.1 <u>Study name</u> Abdi et al. 2021 Liebowitz et al. 2017 Nelin et al. 2017	36, P = 0 35, P = 0 <u>Statistic</u> Odds ratio 2.20 0.34 0.88	0.008 0.033 25 for each s Lower limit 1.46 0.22 0.56	tudy Upper limit 3.33 0.52 1.39	Event: Prophylactic Indomethacin 38 95 107	Placebo/no treatment 93 97 31	Sample s Prophylactic Indomethacin 200 247 522	ize Placebo/no treatment 967 150 137	rrhag						atment	
Test for fixe Test for ran	ed effect: Z = -2.6 ndom effect: Z = -2.1 <u>Study name</u> Abdi et al. 2021 Liebowitz et al. 2017	36, P = 0 35, P = 0 <u>Statistic</u> Odds ratio 2.20 0.34	0.008 0.033 25 for each s Lower limit 1.46 0.22	tudy Upper limit 3.33 0.52	Event: Prophylactic Indomethacin 38 95	Placebo/no treatment 93 97	Sample a Prophylactic Indomethacin 200 247	ize Placebo/no treatment 967 150	rrhag						atment	
Test for fixe Test for ran	ed effect: Z = 2.6 ndom effect: Z = 2.1 Study name Abdi et al. 2021 Liebowitz et al. 2017 Nelin et al. 2017 Schimdt et al. 2017 Nair et al. 2003	36, P = 0 35, P = 0 Statistic Odds ratio 2.20 0.34 0.88 0.66	2.008 2.033 2.5 for each s Lower limit 1.46 0.22 0.56 0.45 1.09 0.44	tudy Upper limit 3.33 0.52 1.39 0.96 1.76 6.19	Event: Prophylactic Indomethacin 38 95 107 52 98 6	Placebo/no treatment 93 97 31 75	Sample s Prophylactic Indomethacin 200 247 522 569 498 56	ize Placebo/no treatment 967 150 137 567 3770 59	rrhag						atment	
Test for fixe Test for ran	ed effect: Z = 2.6 ndom effect: Z = 2.1 Study name Abdi et al. 2021 Liebowitz et al. 2017 Nelin et al. 2017 Schimdt et al. 2001 Stavel et al. 2003 Ment et al. 1988	36, P = 0 35, P = 0 Statistic Odds ratio 2.20 0.34 0.88 0.66 1.39 1.65 0.11	2.008 2.033 25 for each s Lower limit 1.46 0.22 0.56 0.45 1.09 0.44 0.01	tudy Upper limit 3.33 0.52 1.39 0.96 1.76 6.19 2.22	Event: Prophylactic Indomethacin 38 95 107 52 98 6 6 0	Placebo/no treatment 93 97 31 75 566 4 3	Sample s Prodyslactic Indomethacin 200 247 522 569 498 56 56 19	ize Placebo/no treatment 967 150 137 567 3770 59 17	rrhag						atment	
Test for fixe Test for ran	Abdi et al. 2021 Liebowitz et al. 2017 Nelin et al. 2017 Schimdt et al. 2017 Stavel et al. 2017 Nair et al. 2017 Nair et al. 2017 Nair et al. 2018 Stavel et al. 2017	36, P = 0 35, P = 0 Odds ratio 2.20 0.34 0.88 0.88 0.88 1.39 1.65 0.11 0.48	2.008 2.033 25 for each s Lower limit 1.46 0.22 0.56 0.45 1.09 0.44 0.01 0.04	tudy Upper limit 3.33 0.52 1.39 0.96 1.76 6.19 2.22 5.66	Event: Prophylactic Indomethacin 38 95 107 52 98 6 0 0 1	Placebo/no treatment 93 97 31 75 566 4 3 2	Sample s Prodomethacitc Indomethacit 200 247 522 569 498 56 19 24	ize Placebo/no treatment 967 150 137 567 3770 59 17 24	rrhag						atment	
Test for fixe Test for ran	ed effect: Z = 2.6 ndom effect: Z = 2.1 Study name Abdi et al. 2021 Liebowitz et al. 2017 Nelin et al. 2017 Schimdt et al. 2001 Stavel et al. 2003 Ment et al. 1988	36, P = 0 35, P = 0 Statistic Odds ratio 2.20 0.34 0.88 0.66 1.39 1.65 0.11	2.008 2.033 25 for each s Lower limit 1.46 0.22 0.56 0.45 1.09 0.44 0.01	tudy Upper limit 3.33 0.52 1.39 0.96 1.76 6.19 2.22	Event: Prophylactic Indomethacin 38 95 107 52 98 6 6 0	Placebo/no treatment 93 97 31 75 566 4 3	Sample s Prodyslactic Indomethacin 200 247 522 569 498 56 56 19	ize Placebo/no treatment 967 150 137 567 3770 59 17	rrhag						atment	
Test for fixe Test for ran	ed effect: Z = 2.6 ndom effect: Z = 2.1 Study name Abdi et al. 2021 Liebowitz et al. 2017 Nelin et al. 2017 Schimdt et al. 2007 Stavel et al. 2017 Nair et al. 2003 Ment et al. 1988 Ment et al. 1985 Laughon et al. 2007 Ment et al. 1994 Couser et al. 1996	36, P = 0 35, P = 0 Statistic 0 Odds 7 7 7 0.34 0.88 0.88 0.66 1.39 1.65 0.11 0.48 1.14 1.70 0.70 7	2.008 2.033 2.5 for each s Lower limit 1.46 0.22 0.56 0.45 1.09 0.44 0.04 0.04 1.01 0.04 1.01 0.041 0.041 0.22	tudy Upper Jimit 3.33 0.52 1.39 0.96 1.76 6.19 2.22 5.66 1.29 7.09 2.26	Event: Prophylactic Indomethacin 38 95 107 52 98 6 0 1 1 790 5 5 5	Placebo/no treatment 93 97 31 75 566 4 3 2 44 3 2 441 4 8	Sample a Prodomethacin 200 247 522 569 498 56 19 24 6189 27 68	ize Placebo/no treatment 150 137 567 3770 59 17 24 3806 34 79	rrhag						atment	
Test for fixe Test for ran	Abdi et al. 2021 Liebowitz et al. 2017 Nelin et al. 2017 Schimid et al. 2017 Schimid et al. 2017 Nair et al. 2017 Nair et al. 2017 Nair et al. 2003 Ment et al. 1988 Ment et al. 1985 Laughon et al. 2007 Ment et al. 1989 Bada et al. 1989	36, P = 0 35, P = 0 Statistic 2 Odds 2 0.34 0.34 0.88 0.66 1.39 1.65 0.11 0.48 1.41 1.70 0.70 0.17	2.008 2.033 2.5 for each s Lower limit 1.46 0.22 0.56 0.45 1.09 0.44 0.04 0.04 1.01 0.04 1.01 0.04 1.01 0.04 1.01 0.22 0.04	tudy Upper Jimit 3.33 0.52 1.39 0.96 1.76 6.19 2.22 5.66 1.29 7.09 2.26 0.83	Event: Prophylactic Indomethacin 388 95 107 52 98 6 0 1 790 5 5 5 2	Placebo/no treatment 93 97 31 75 566 4 3 2 441 41 4 8 10	Sample a Prodomethacin 200 247 522 569 498 56 19 24 6189 27 68 71	ize Placebo/no treatment 150 137 567 3770 59 17 24 3886 34 79 70	rrhag						atment	
Test for fixe Test for ran	ed effect: Z = 2.6 ndom effect: Z = 2.1 Study name Abdi et al. 2021 Liebowitz et al. 2017 Nelin et al. 2017 Schimdt et al. 2007 Stavel et al. 2017 Nair et al. 2003 Ment et al. 1988 Ment et al. 1985 Laughon et al. 2007 Ment et al. 1994 Couser et al. 1996	36, P = 0 35, P = 0 Statistic Odds Codds Codds <td cols<="" td=""><td>2.008 2.033 2.5 for each s 2.6 wer 1.46 0.22 0.56 0.45 1.09 0.45 1.09 0.44 0.01 0.04 1.01 0.04 1.01 0.22 0.04 0.04 0.22 0.04 0.035</td><td>tudy Upper limit 3.33 0.52 1.39 0.96 6.19 2.22 5.66 1.29 7.09 2.26 0.83 1.32</td><td>Event: Prophylactic Indomethacin 38 95 107 52 98 6 0 1 790 5 5 2 2 19</td><td>Placebo/no treatment 93 97 31 75 566 4 3 2 441 4 8 10 26</td><td>Sample s Prodomethacin 200 247 522 569 498 56 19 24 6189 27 68 71 99</td><td>ize Placebo/no treatment 967 150 137 567 3770 59 17 24 3886 34 79 70 70 100</td><td>orrhag</td><td></td><td></td><td></td><td></td><td></td><td>atment</td></td>	<td>2.008 2.033 2.5 for each s 2.6 wer 1.46 0.22 0.56 0.45 1.09 0.45 1.09 0.44 0.01 0.04 1.01 0.04 1.01 0.22 0.04 0.04 0.22 0.04 0.035</td> <td>tudy Upper limit 3.33 0.52 1.39 0.96 6.19 2.22 5.66 1.29 7.09 2.26 0.83 1.32</td> <td>Event: Prophylactic Indomethacin 38 95 107 52 98 6 0 1 790 5 5 2 2 19</td> <td>Placebo/no treatment 93 97 31 75 566 4 3 2 441 4 8 10 26</td> <td>Sample s Prodomethacin 200 247 522 569 498 56 19 24 6189 27 68 71 99</td> <td>ize Placebo/no treatment 967 150 137 567 3770 59 17 24 3886 34 79 70 70 100</td> <td>orrhag</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td>atment</td>	2.008 2.033 2.5 for each s 2.6 wer 1.46 0.22 0.56 0.45 1.09 0.45 1.09 0.44 0.01 0.04 1.01 0.04 1.01 0.22 0.04 0.04 0.22 0.04 0.035	tudy Upper limit 3.33 0.52 1.39 0.96 6.19 2.22 5.66 1.29 7.09 2.26 0.83 1.32	Event: Prophylactic Indomethacin 38 95 107 52 98 6 0 1 790 5 5 2 2 19	Placebo/no treatment 93 97 31 75 566 4 3 2 441 4 8 10 26	Sample s Prodomethacin 200 247 522 569 498 56 19 24 6189 27 68 71 99	ize Placebo/no treatment 967 150 137 567 3770 59 17 24 3886 34 79 70 70 100	orrhag						atment
Test for fixed	Abdi et al. 2021 Liebowitz et al. 2017 Nelin et al. 2017 Schimid et al. 2017 Schimid et al. 2017 Nair et al. 2017 Nair et al. 2017 Nair et al. 2003 Ment et al. 1988 Ment et al. 1985 Laughon et al. 2007 Ment et al. 1989 Bada et al. 1989	36, P = 0 35, P = 0 Statistic 2 Odds 2 0.34 0.34 0.88 0.66 1.39 1.65 0.11 0.48 1.41 1.70 0.70 0.17	2.008 2.033 2.5 for each s Lower limit 1.46 0.22 0.56 0.45 1.09 0.44 0.04 0.04 1.01 0.04 1.01 0.04 1.01 0.04 1.01 0.22 0.04	tudy Upper Jimit 3.33 0.52 1.39 0.96 1.76 6.19 2.22 5.66 1.29 7.09 2.26 0.83	Event: Prophylactic Indomethacin 388 95 107 52 98 6 0 1 790 5 5 5 2	Placebo/no treatment 93 97 31 75 566 4 3 2 441 41 4 8 10	Sample a Prodomethacin 200 247 522 569 498 56 19 24 6189 27 68 71	ize Placebo/no treatment 150 137 567 3770 59 17 24 3886 34 79 70	rrhag						atment	
Test for fixe Test for ran Model Fixed	ed effect: Z = 2.6 ndom effect: Z = 2.1 Study name Abdi et al. 2021 Liebowitz et al. 2017 Nelin et al. 2017 Schimdt et al. 2007 Stavel et al. 2017 Nair et al. 2003 Ment et al. 1988 Ment et al. 1988 Ment et al. 1994 Couser et al. 1998 Bandstra et al. 1988	36, P = 0 35, P = 0 Statistic Odds 2.20 0.34 0.88 0.66 1.39 1.65 0.11 0.48 1.14 1.70 0.70 0.77 0.68 1.07	2.008 2.033 2.5 for each s Lower 1.46 0.22 0.56 0.45 1.09 0.44 0.01 0.04 0.04 0.01 0.04 0.01 0.22 0.04 0.03 0.35 0.98	tudy Upper limit 3.33 0.52 1.39 0.96 1.76 6.19 2.22 5.66 1.29 7.09 2.26 0.83 1.32 1.32 1.32	Event: Prophylactic Indomethacin 38 95 107 52 98 6 0 1 1 790 5 5 5 2 2 19 1218 1218	Placebo/no treatment 93 97 31 75 566 4 3 2 441 4 8 10 26 1360	Sample of Prodomethadis 200 247 522 569 498 56 19 24 6189 27 68 71 99 8589	ize Placebo/no treatment 967 150 137 567 3770 59 17 24 3886 34 79 70 100 9860	0.01						atment	
Test for fixed Test for ran Model Fixed Random Heterogy Test for	acd effect: Z = 2.6 indom effect: Z = 2.1 Study name Abdi et al. 2021 Liebowitz et al. 2017 Nein et al. 2021 Stavel et al. 2017 Schimdt et al. 2017 Schimdt et al. 2017 Stavel et al. 2017 Ment et al. 1985 Laughon et al. 1985 Bandstra et al. 1989 Bandstra et al. 1998 Bandstra et al. 1988 Renelty: I ² fixed effect: Z	36, P = 0 35, P = 0 35, P = 0 23, P = 0 24, 0.0 2,20 0.34 0.88 0.66 1.39 1.39 1.45 0.11 0.48 1.14 1.70 0.70 0.17 0.68 1.07 0.87	2.008 2.033 2.5 for each s Lower limit 1.46 0.22 0.56 0.45 1.09 0.44 0.01 0.44 0.01 0.44 1.01 0.41 0.41	tudy Upper limit 3.33 0.52 1.39 0.96 6.19 2.22 5.66 1.29 7.09 2.26 0.83 1.32 1.18 1.21	Event: Prophylactic Indomethacin 38 95 107 52 98 6 0 1 1 790 5 5 5 2 2 19 1218 1218	Placebo/no treatment 93 97 31 75 566 4 3 2 441 4 8 10 26 1360	Sample of Prodomethadis 200 247 522 569 498 56 19 24 6189 27 68 71 99 8589	ize Placebo/no treatment 967 150 137 567 3770 59 17 24 3886 34 79 70 100 9860	0.01	je 				-		

doses of indomethacin and the placebo or no treatment group with regard to the rates of intraventricular hemorrhage (OR = 0.88; 95% CI = 0.58–1.32; *P*-value = 0.532). There was low heterogeneity among the included studies ($I^2 = 35\%$; *P*-value = 0.186) (**Figure 8A**).

Combined meta-analysis of cohort and RCT studies shows there was no significant differences between the group with infants given prophylactic doses of indomethacin and placebo or no treatment group with regard to the rates of intraventricular hemorrhage (OR = 0.96; 95% CI = 0.73-1.25; *P*-value = 0.735).

A				I	Meta analysi	s of Necro	otizing ente	rocolitis	
Model	Study name				Eve	nts	Sample	e size	Odds ratio and 95% Cl
				ower Upper imit limit	Prophylactic Indomethacin		Prophylactic Indomethacin	Placebo/no treatment	
	Laughon et al.	2007	1.37	1.18 1.59	576	271	6189	3886	+
	Nelin et al. 207	17	1.00 (0.60 1.65	83	23	506	140	
	Stavel et al. 20	017	1.45	.04 2.01	46	248	498	3770	
	Abdi et al. 202	1	1.22 (.62 2.41	11	44	200	967	│ │
	Liebowitz et al	. 2017	0.46	0.30 0.69	85	80	247	150	
Fixed	d		1.22	.08 1.38	801	666	7640	8913	+
Random	n		1.03 ().69 1.54	801	666	7640	8913	+
Hetero	ogeneity:	1 ² = 1	84%,	τ ² = 0.166,	P < 0.001			0.4	1 0.2 0.5 1 2 5 10
Test f	or fixed effect:	Z =	3.196,	P = 0.001					
	or random effect		0.148,	P = 0.884					Prophylactic Indomethacin Placebo/No Treatment
в					Meta analys	sis of Necı	otizing enter	rocolitis	
Model	Study name	S	statistics for	each study	Eve	nts	Samp	le size	Odds ratio and 95% CI
		Od rat			Prophylactic Indomethacin	Placebo/no treatment	Prophylactic Indomethacin	Placebo/no treatment	
	Bandstra et al. 198	88 2.0	0.5	1 8.59	6	3	99	100	
	Bada et al. 1989	0.8			6	7	71	70	
	Schmidt et al. 200				64	58	601	601	
	Ment et al. 1994	0.4			0	1	27	34	
	Mahony et al. 198 Nair et al. 2003	5 0.6 0.8			2 5	3 6	51 56	53 59	
	Vincer et al. 1987	5.1			2	0	15	15	
Fixed		1.			85	78	920	932	
Random		1.1	10 0.7	9 1.52	85	78	920	932	+
Heterogen Test for fix Test for rai		.566,	T ² = 0, P = 0.571 P = 0.571	P = 0.825					0.01 0.1 1 10 100 Prophylactic Indomethacin Placebo/No Treatment
с				Ν	/leta analysi	is of Necr	otizing ente	erocolitis	
Model	Study name	Statis	tics for each	study	Events		Sample size		Odds ratio and 95% Cl
		Odds ratio	Lower limit					cebo/no eatment	
	Bandstra et al. 1988	2.09	0.51	8.59	6	3	99	100	+
	Bada et al. 1989 Laughon et al. 2007	0.83 1.37	0.26	2.61 1.59	6 576	7 271	71 6189	70 3886	
	Laughon et al. 2007 Nelin et al. 2017	1.37	1.18 0.60	1.59	83	271 23	506	3886	
		1.12	0.77	1.62	64	58	601	601	
		0.41	0.02	10.37	0	1	27	34	╽──┼╺┼──┤ │
	Mahony et al. 1985	0.68	0.11	4.25	2	3	51	53	
	Stavel et al. 2017 Abdi et al. 2021	1.45	1.04 0.62	2.01 2.41	46 11	248 44	498 200	3770 967	
	Liebowitz et al. 2017		0.02	0.69	85	80	247	150	
		0.87	0.25	3.02	5	6	56	59	
	Vincer et al. 1987	5.74	0.25	130.37	2	0	15	15	
Fixed Random		1.21 1.05	1.08 0.80	1.35 1.39	886 886	744 744	8560 8560	9845 9845	
	naitu: 12								01 0.1 1 10 100
Heteroger Test for fi		= 61%, = 3.188,	$T^2 = 0.099$ P = 0.007						
			. 0.00						Prophylactic Indomethacin Placebo/No Treatment

FIGURE 10 | Meta-analysis of necrotizing enterocolitis from (A) cohort studies (B) RCT studies (C) combination of cohort and RCT studies.

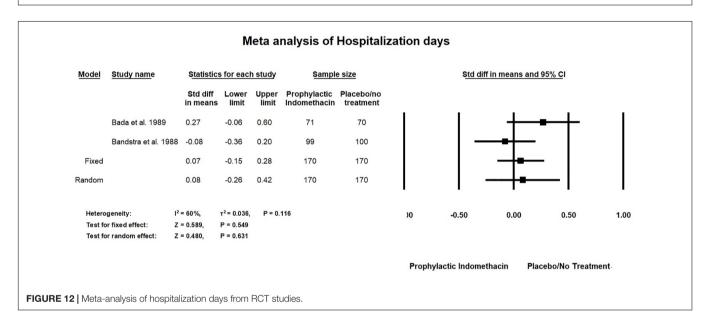
There was low heterogeneity among the included studies ($I^2 = 25\%$; *P*-value = 0.248) (**Figure 8B**).

Severe Intraventricular Hemorrhage

In the meta-analysis of cohort studies, no significant difference was found between the group of infants given prophylactic doses of indomethacin and the placebo or no treatment group regarding the rates of severe intraventricular hemorrhage (OR = 1.03; 95% CI = 0.67–1.57; *P*-value = 0.607). There was high significant heterogeneity among the included studies ($I^2 = 91\%$; *P*-value < 0.001) (**Figure 9A**).

For meta-analysis of RCT studies, as seen in **Figure 9B**, infants with prophylactic doses of indomethacin have significantly lower rates of severe intraventricular hemorrhage compared to those

Model	Study name	Statis	tics for each	study	Ever	nts	Sample	size			Odds ra	tio and	95% CI		
		Odds ratio	Lower limit	Upper limit	Prophylactic Indomethacin	Placebo/no treatment	Prophylactic Indomethacin	Placebo/no treatment							
	Laughon et al. 2007	2.05	1.55	2.71	212	66	6189	3886					+		
	Schimdt et al. 2001	1.13	0.69	1.85	36	32	601	601			-		-1		
Fixed		1.77	1.39	2.26	248	98	6790	4487				- I -	╺╋		
Random		1.58	0.89	2.82	248	98	6790	4487				+	•+-		
Heteroge	and the second second second second		0.135, P = 0.	039					0.1	0.2	0.5	1	2	5	10
	fixed effect: Z = 4.63 random effect: Z = 1.55		0.001 0.121												
									P	rophylactic I	Indomethaci	n I	Placebo/No	Treatment	



who did not (OR = 0.68; 95% CI = 0.51–0.90; *P*-value = 0.008). There was no significant heterogeneity among the included studies ($I^2 = 10\%$; *P*-value = 0.350).

In the combined meta-analysis of cohort and RCT studies, no significant differences between the group of infants given prophylactic doses of indomethacin and the placebo or no treatment group regarding the rates of severe intraventricular hemorrhage (OR = 0.87; 95% CI = 0.63–1.21; *P*-value = 0.408). However, there was high significant heterogeneity among the included studies (I² = 81%; *P*-value < 0.001) (**Figure 9C**).

Necrotizing Enterocolitis

In the meta-analysis of cohort studies, regarding the rate of necrotizing enterocolitis, there was no significant differences between the group of infants with prophylactic doses of indomethacin and the infants in the placebo or no treatment group (OR = 1.03; 95% CI = 0.69–1.54; *P*-value = 0.884). There was high significant heterogeneity among the included studies ($I^2 = 84\%$; *P*-value < 0.001) (**Figure 10A**).

Meta-analysis of RCTs shows there was no significant difference between the group of infants given prophylactic doses

of indomethacin and the infants in the placebo or no treatment group with regard to the rates of necrotizing enterocolitis (OR = 1.10; 95% CI = 0.79-1.52; *P*-value = 0.571). There was no significant heterogeneity among the included studies (I2 = 0%; *P*-value = 0.825) (**Figure 10B**).

Combined meta-analysis of cohort and RCT studies shows there was no significant differences between the group of infants with prophylactic doses of indomethacin and the infants in the placebo or no treatment group regarding the rates of necrotizing enterocolitis (OR = 1.05; 95% CI = 0.80-1.39; *P*-value = 0.711). However, there was medium significant heterogeneity among the included studies (I² = 61%; *P*-value = 0.003) (**Figure 10C**).

Intestinal Perforation

Combined meta-analysis of cohort and RCT studies, shows there was no significant differences between the group of infants given prophylactic doses of indomethacin and the infants in the placebo or no treatment group with regard to the rates of intestinal perforation (OR = 1.58; 95% CI = 0.89–2.82; *P*-value = 0.121). However, there was high significant heterogeneity among the included studies ($I^2 = 77\%$; *P*-value = 0.039) (**Figure 11**).

Α						Meta ar	alysis of [Jeath	
Model	Study name	Statist	ics for eac	ch study	Ever	nts	Sample	size	Odds ratio and 95% Cl
		Odds ratio	Lower limit		Prophylactic Indomethacin	Placebo/no treatment	Prophylactic Indomethacin	Placebo/no treatment	
	Jensen et al. 2017	1.14	1.03	1.25	1404	2680	2587	5244	
	Laughon et al. 200	7 1.11	0.99	1.24	985	566	6189	3886	
	Nelin et al. 2017	0.44	0.28	0.68	78	40	528	141	
	Stavel et al. 2017	1.38	1.05	1.80	74	424	498	3770	
	Abdi et al. 2021	2.49	1.60	3.89	33	71	200	967	
	Liebowitz et al. 20	7 0.34	0.22	0.52	100	100	247	150	
Fixed		1.10	1.03	1.18	2674	3881	10249	14158	
Random		0.96	0.71	1.29	2674	3881	10249	14158	+
Hatava		12 -	0.2%	-2-04					0.1 0.2 0.5 1 2 5 10
	ogeneity: or fixed effect:		92%, 2.814,	$\tau^2 = 0.11$ P = 0.00					
	or random effect		0.277,	P = 0.88					Prophylactic Indomethacin Placebo/No Treatment
в		-	0.277,	1 - 0.00	~	Meta a	nalysis of	Death	
Model	Study name	Stat	istics for ea	ch studv		Events		Sample size	Odds ratio and 95% CI
		Odds	Lower	Upper	Prophylactic	Placebo/	no Prophylad	tic Placebo/r	
		ratio	limit	limit	Indomethaci	n treatme	nt Indometha	icin treatmen	
	Bandstra et al. 1988 Bada et al. 1989	1.10 0.63	0.49	2.48 1.86	14 6	13 9	99 71	100 70	
	Maruyama et al. 201:		0.11	83.36	1	0	10	9	
	Schmidt et al. 2001	1.16	0.87	1.54	125	111	595	594	
	Mahony et al. 1985	1.05	0.40	2.78	10	10	51	53	
	Vincer et al. 1987 Couser et al. 1996	1.63 2.36	0.23	11.46 26.65	3	2	15 68	15 79	
	Hanigan et al. 1988	1.78	0.67	4.70	13	8	56	55	
	Ment et al. 1985	0.22	0.02	2.11	1	4	24	24	
	Ment et al. 1988 Krueger et al. 1987	0.28 0.50	0.01	7.40 3.22	0	1	19 15	17 17	
	Ment et al. 1994	2.03	0.56	7.31	7	5	27	34	
	Rennie et al. 1986	0.59	0.16	2.15	5	8	24	26	
Fixed	Nair et al. 2003	0.86	0.35 0.88	2.13 1.37	11 200	13 189	56 1130	59 1152	
Random		1.10	0.88	1.37	200	189	1130	1152	
Heterogen	neity: I ² :	0%,	τ ² = 0,	P = 0.8	21				0.01 0.1 1 10 100
Test for fix Test for ra		0.827, 0.827,	P = 0.408 P = 0.408						Prophylactic Indomethacin Placebo/No Treatment
						Meta	analysis of I	Death	
С	Model Study na	me	Statistic	s for each stu	Jdy	Events	-	ample size	Odds ratio and 95% Cl
		_	Odds ratio	Lower I limit	Jpper Prophyla limit Indomet	actic Placebo hacin treatm		ic Placebo/no cin treatment	
	Bandstra Jensen e	et al. 1988 al. 2017	1.10	0.49	2.48 14 1.25 140	13 4 268		100 5244	
	Bada et a	. 1989	1.14 0.63	1.03 0.21	1.86 6	9	71	70	
		a et al. 2012 et al. 2007	2 3.00	0.11 0.99	83.36 1 1.24 985	0 566	10 6189	9 3886	
	Nelin et a		0.44	0.28	0.68 78	40	528	141 594	
	Stavel et	l. 2017	1.38	1.05	1.80 74	424	498	3770	
	Mahony e Vincer et		1.05 1.63	0.40 0.23	2.78 10 11.46 3	10 2	51 15	53 15	
	Couser e	al. 1996	2.36	0.21	26.65 2	1	68	79	
	Hanigan Ment et a	t al. 1988 1985	1.78 0.22	0.67 0.02	4.70 13 2.11 1	8	56 24	55 24	
	Ment et a Krueger (0.28	0.01	7.40 0 3.22 2	1	19 15	17 17	
	Ment et a	1994	2.03	0.56	7.31 7	5	27	34	
	Rennie el Abdi et al		0.59 2.49	0.16	2.15 5 3.89 33	8 71	24 200	26 967	
	Liebowitz	et al. 2017	0.34	0.22	0.52 100	100	247	150	
	Nair et al	2003	0.86	0.35	2.13 11 1.17 287-	4 407	0 11379	59 15310	
	Random		1.00	0.81	1.23 287	4 407	0 11379	15310	Ⅰ Ⅰ ┿ Ⅰ Ⅰ 0.01 0.1 1 10 100
	Heterogeneity: Test for fixed eff		l ² = 73%, Z = 2.933,	τ ² = 0.084, P = 0.003	P < 0.001				Prophylactic Indomethacin Placebo/No Treatment
	Test for random	effect:	Z = - 0.041,	P = 0.967					

Hospitalization Days

Meta-analysis of RCT studies shows that two studies with 340 patients were included in the analyses of hospitalization days. On comparing this outcome among the prophylactic indomethacin and placebo/no treatment groups, there was no statistically significant difference for hospitalization days (SMD = 0.08; 95% CI = -0.26: 42; *P*-value = 0.631). There was a medium significant heterogeneity in the analysis of hospitalization days (I² = 60%; *P*-value = 0.116) (**Figure 12**).

Death

In the meta-analysis of cohort studies, **Figure 13A** shows there was no significant differences between the group of infants given prophylactic doses of indomethacin and the placebo or no treatment group with regard to the rates of death (OR = 0.96; 95% CI = 0.71-1.29; *P*-value = 0.884). There was high significant heterogeneity among the included studies (I² = 92%; *P*-value < 0.001).

Meta-analysis of RCT studies shows there was no significant differences between the group of infants given prophylactic doses of indomethacin and the placebo or no treatment group regarding the rates of death (OR = 1.10; 95% CI = 0.88-1.37; *P*-value = 0.408). There was no significant heterogeneity among the included studies (I² = 0%; *P*-value = 0.821) (**Figure 13B**).

Combined meta-analysis cohort and RCT studies shows there was no significant differences between the group of infants given prophylactic doses of indomethacin and the group of placebo or no treatment regarding the rates of death (OR = 1.00; 95% CI = 0.81-1.23; *P*-value = 0.967). However, there was high significant heterogeneity among the included studies (I² = 73%; *P*-value < 0.001) (**Figure 13C**).

DISCUSSION

In this study, we have included 23 studies from the systematic and manual search to be analyzed to study indomethacin as a prophylactic measure in pre-term infants from many aspects including bronchopulmonary dysplasia, patent ductus arteriosus, pulmonary hemorrhage, intraventricular hemorrhage, severe intraventricular hemorrhage, necrotizing enterocolitis, intestinal perforation, death, hospitalization days, and surgical ligation of PDA.

The analyzed data showed a varied heterogeneity in some outcomes which is probably due to the difference in study designs, the different dosages of indomethacin injection, and outcome definition between studies. Moreover, it is important to note that this meta-analysis is fundamentally different from prior ones, in that data from both randomized trials and retrospective cohort studies are included in the present analyses and is likely to be the dominant factor for differences in results.

As for the cardiopulmonary outcomes, our meta-analysis of RCT studies and combined meta-analysis of RCT and cohort studies showed that prophylactic indomethacin administration in infants significantly lowers the rates of PDA formation (*P*-value < 0.001) and no significant heterogeneity was estimated ($I^2 = 10\%$; *P*-value = 0.341) in case of the included RCT studies while medium significant heterogeneity was found in

the combined analysis of RCT and cohort studies. (I2 = 62%; *P*-value = 0.001) which could be due to the different study designs that were included in the analysis similar to previously published studies (56, 57). Regarding the outcome of PDA surgical ligation, meta-anaylsis of RCT studies revealed significantly lower rates of surgical PDA ligation among the infants given prophylactic doses of indomethacin (*P*-value < 0.001) which is similar to the findings of Fowlie et al. who reported a significant lower incidence of surgical PDA ligation among the indomethacin prophylactic group (typical RR 0.51, 95% CI 0.37,0.71) (14).

On the other hand, in the present study, no significant difference was reported between indomethacin prophylactic group and the placebo/no treatment group with regard to the outcome of BPD and pulmonary hemorrhage rates in the metaanalysis of cohort and RCT studies and combined analysis. Jensen et al. (57) in their analysis of observational data found that prophylactic indomethacin did not increase or decrease the risk of developing BPD. Moreover, the authors compared these results with another analysis of RCTs, however, the analysis indicated the same information that prophylactic indomethacin had no beneficial effects on BPD.

With regard to the risk of intraventricular hemorrhage, our analysis showed no significant difference between the group of infants given prophylactic indomethacin when compared to the placebo group. However, with regard to severe IVH, metaanalysis of RCT studies showed significantly lower rates of severe IVH in the prophylactic indomethacin group (P-value = 0.008). Similarly, Fowlie et al. found a significant reduction in severe IVH incidence in infants that were prophylactically injected with indomethacin (typical RR 0.66, 95% CI 0.53-0.82) (14). However, significant heterogeneity in this study was estimated due to the inconsistency of treatment efficacy among their included studies (56). None of the studies, however, measured the long-term outcomes, they have only focused on the short ones. Schmidt et al. (15) in their large trial on 18month infants reported statistical insignificance on long term neurodevelopmental outcomes although IVH grade 3 and 4 were significantly reduced. Therefore, concerns should be made to assess the overall quality of the effect of indomethacin on the long-term neurodevelopmental outcomes and the rate of adverse events incidence due to the vasoconstrictive nature of the drug which may alter the cerebral blood flow.

Furthermore, we found no significance between the use of prophylactic indomethacin on infants in reducing the time of hospital stay. The findings reported by Fowlie et al. favored the control groups in terms of time spent in the hospital with no significance (P = 0.087) (14). With regard to the outcome of death, no significant effect of prophylactic indomethacin was reported in the current study in both cohort and RCT studies. Jensen et al. reported a weak association between indomethacin prophylaxis and decreased risk-adjusted odds of mortality (0.81, 95% CI 0.66–0.98), however, the authors included observational data only (57).

Limitations to our study include variable heterogeneity in the analysis of some outcomes due to the different study designs that were included in this study. However, we estimated the publication bias in most cases no publication bias was found.

CONCLUSION

Prophylactic indomethacin in VLBW infants has proven efficient in preventing short-term events such as PDA, surgical PDA ligation, and severe IVH. On the other hand, it showed no significance with regard to outcomes such as IVH, BPD, pulmonary hemorrhage, necrotizing enterocolitis, intestinal performation, death and hospital stays. Since the meta-analysis results regarding effectiveness of prophylactic indomethacin varied based on the study design particularly with regard to outcomes such as surgical PDA ligation and severe IVH, this warrants the need for long term studies with larger sample size to determine the effectiveness of prophylactic indomethacin.

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DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

AAl proposed, conceptualized, and designed the study and wrote the manuscript. SA and AAS helped in the pilot extraction of a few manuscript for building the data extraction sheet and assessed the risk of bias among different included studies. All authors read and approved the final manuscript.

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