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

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Research article

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Abstract

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 as intraventricular hemorrhage (IVH), but many studies have reported contraindicated outcomes of its significance. Therefore, we aim to systematically review and meta-analyze the data of prophylactic indomethacin on preterm infants.

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 August 12, 2020.

Results

The final list of our included studies is comprised of 22 randomized trials and cohort studies. Our analysis of observational data showed that intubation in the delivery room/first day (74%), bronchopulmonary dysplasia (BPD) (33.2%), and patent ductus arteriosus (PDA) (32.2%) were the most prevalent outcomes in infants that received prophylactic indomethacin. Among all the studies outcomes, the only significant favorable outcome was lowering the rate of PDA (P< 0.001) while no significance was recorded with BPD, pulmonary hemorrhage, neurodevelopmental delays (IVH), mortality, length of hospital stays, and time spent on ventilators outcomes (P = 0.106, 0.123, 0.460, 0.340, 0.625, and 0.732, respectively). Moreover, necrotizing enterocolitis was significantly increased when applying prophylactic indomethacin in these infants (P< 0.001).

Conclusion

The use of prophylactic indomethacin in preterm infants should be generally discouraged due to its neutral effect on most of the mortality and morbidity outcomes and the significant occurrence of its adverse events despite the positive effect on ductal closure.

Structured Summary

Background

Many authors believe neurologic disabilities have been associated with preterm labor presumed due to either over circulation or under circulation secondary to patent ductus arteriosus.

Objectives

Systemically revied all published RCT and meta-analysis to find if prophylactic indomethacin can decrease CNS complications.

Data sources

Following 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 to 12th August 2020, 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).

Study eligibility criteria, participants, and interventions

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. 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. in vitro or animal studies;
III. data duplication, overlapping or unreliably extracted or incomplete data;
IV. abstract only articles, reviews, thesis, books, conference papers, or articles without available full texts (conferences, editorials, author response, letters, and comments.

Risk of bias

The revised Cochrane quality assessment tool (RoB 2) was used to determine the quality of randomized studies and the risk of bias in non-randomized studies - of interventions (ROBINS-I) tool for non-randomized studies.

Data analysis

All data were analyzed using R software version 4.0.2. Using the “meta” package, odds ratios (OR) and prevalence rates of different 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 considering it significant with I2 value > 50% or P-value < 0.05.

The publication bias was assessed using Egger’s regression test and represented graphically by Begg’s funnel plot when there were ten 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 to add studies that appeared to be missing to enhance the symmetry.

Limitations

Limitations to our study include the significant heterogeneity in the analysis of some outcomes due to the different study designs that were included in this study. However, we estimated the risk of bias in most cases when significant heterogeneity was estimated, and no significant risk was found in these events.

Conclusions

Prophylactic indomethacin in VLBW infants has proven efficient in preventing short-term events as PDA. My analysis, however, showed no significance on IVH despite the many investigations that were published before which showed that indomethacin can reduce the incidence of IVH and other neurodevelopmental abnormalities.

Implications of key findings

I tried to lose the debate in this matter, so the clinician can work on other interventions or quality projects to help in decreasing CNS complications in preterm infants.

Systematic review registration number

We could not obtain because there are a big waiting list and priority for UK researchers.

Background

Many cardiopulmonary and neurologic disabilities have been associated with preterm labor including patent ductus arteriosus (PDA), pulmonary hemorrhage, intracranial hemorrhage, and mental retardation (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 are liable to intraventricular hemorrhage (IVH) which is usually associated with the 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), 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 six hours after birth (14-17). Besides, it helps in the closure of ductus arteriosus and therefore, can prevent the complications of PDA 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 as hypoxia, hypercapnia, and hypotension usually develop after birth in VLBW infants (25). Most cases of preterm infants develop IVH within 6-8 hours 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 measurement (16, 27-29). Although indomethacin administration showed favorable outcomes in reducing IVH incidence, many concerns have aroused concerning 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.

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 to 12th August 2020, 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 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) in vitro or animal studies; iii) data duplication, overlapping or unreliably extracted or incomplete data; iv) 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, outcomes, and risk of bias tool. Two authors extracted the data and reviewed by a third reviewer when necessary. If a disagreement occurs, a senior author was consulted.

Risk of bias

Three independent authors assessed the risk of bias among different included studies using the revised Cochrane quality assessment tool (RoB 2) was used to determine the quality of randomized studies (34) and the risk of bias in non-randomized studies - of interventions (ROBINS-I) tool for non-randomized studies (35). Any discrepancy between the reviewers was solved by discussion or in conjugation with the senior author.

Statistical analysis

All data were analyzed using R software version 4.0.2 (36). Using the "meta" package, odds ratios (OR) and prevalence rates of different outcomes were calculated (37). 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 I^2 test considering it significant with I^2 value > 50% or P-value < 0.05 (38).

The publication bias was assessed using Egger's regression test (39, 40) and represented graphically by Begg's funnel plot (41) when there were ten 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 to add studies that appeared to be missing (42) 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. Two papers were added after performing manual search trials. Finally, we included 22 studies for this systematic review and meta-analysis **(Figure 1)**.

Study characteristics and risk of bias

Out of the 22 included studies; seven were randomized controlled trials and the remaining 15 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 groups was 28 weeks (ranging from 25 to 50 weeks), while it was 27 weeks in control ones (ranging from 26 to 29 weeks). **Table 1** shows the main characteristics of the included studies.

The overall risk of bias in the included RCTs was low in more than 50% of all items. The domains with major problems were deviations from intended interventions, randomization processes, and missing outcome data **(Figure 2)**. For non-randomized trials, the risk of bias was higher with more than 50% of all items showing serious of critical risks of bias. Domains with the biggest issues were deviations from intended interventions, selective reporting, and cofounding of the results **(Figure 3)**.

Cardiopulmonary Outcomes

Eight studies, with a total of 20,708 preterm infants, were included in the analysis of patent ductus arteriosus (PDA) rates. Infants with prophylactic doses of indomethacin showed significantly lower rates of PDA compared to those who did not (OR= 0.33; 95% CI= 0.27-0.39; P-value< 0.001). However, there was significant heterogeneity among the included studies (I^2= 72%; P-value< 0.001) **(Figure 4)**.

In contrast, there was no significant differences among the two groups when compared in terms of BPD (OR= 1.08; 95% CI= 0.98-1.18; P-value= 106) and pulmonary hemorrhage rates (OR= 0.84; 95% CI= 0.67-1.05; P-value= 0.132). There was no significant heterogeneity among the included studies for both BPD (I^2= 48%; P-value= 0.121) and pulmonary hemorrhage (I^2= 0%; P-value= 0.786) outcomes **(Figure 4)**.

Neuro-developmental Outcomes

Nine studies, with 17,949 pre-term infants, and five studies, with 20,116 pre-term infants, were included in the analyses of IVH and cerebral palsy (CP)/neurodevelopmental delay outcomes, respectively. There were no significant differences between prophylactic indomethacin group and the placebo/no treatment group in terms of IVH (OR= 0.90; 95% CI= 0.69-1.18; P-value= 0.460) and CP/neurodevelopmental delay (OR= 1.00; 95% CI= 0.81-1.23; P-value= 0.997). For heterogeneity, there was a significant heterogeneity in both analyses with (I^2= 84%; P-value< 0.001) and (I^2= 76%; P-value= 0.002) for IV and CP/neurodevelopmental delay, respectively **(Figure 5)**.

Necrotizing enterocolitis/Intestinal perforation, and death

Nine studies, with 35,759 preterm infants, were included in the analysis of necrotizing enter colitis (NEC)/Intestinal perforation (IP) rates. There was a significant increase in NEC/IP rates in prophylactic indomethacin group when compared to the placebo/no treatment group (OR= 1.36; 95% CI= 1.24-1.49; P-value< 0.001). Moreover, there was no significant heterogeneity among the included studies (I^2= 44%; P-value= 0.088) **(Figure 6)**.

In the same context, death rates were compared in 47,265 patients of 13 included studies. There were no significant differences in death rates of prophylactic indomethacin group when compared to the placebo/no treatment group (OR= 1.06; 95% CI= 0.94-1.19; P-value= 0.340). However, there was significant heterogeneity among the included studies (I^2= 69%; P-value< 0.001). There was no significant risk of bias when tested using Egger's regression test (P-value= 0.428) **(Figure 7)**.

Hospitalization outcomes

Two studies of 340 patients were included in the analyses of hospitalization days and days spent of ventilation. On comparing these outcomes among the prophylactic indomethacin and placebo/no treatment groups, there was no statistically significant difference for hospitalization days (MD= 3.67; 95%CI= -11.03-18.37; P-value= 0.625) and days spent of ventilation (MD= -1.00; 95%CI= -6.71-4.71; P-value= 0.732). There was a significant heterogeneity in the analysis of hospitalization days (I^2= 56%; P-value= 0.132), while it was not present in the analysis of days spent of ventilation (I^2= 0%; P-value= 1.000) **(Figure 8)**.

Prevalence of different outcomes in indomethacin group

For studies with a single prophylactic indomethacin group (no placebo/no treatment group), they were pooled with all other studies (two-armed) with similar outcomes to get the overall prevalence. The highest prevalence observed in pre-term infants with prophylactic indomethacin was the intubation in delivery room/first day (74%; 95%CI= 52.9-100.0), followed by BPD (33.2%; 95%CI= 25.6-43.1), PDA (32.2%; 95%CI= 27.3-38.0) and IVH (26.1%; 95%CI= 19.1-35.7), respectively **(Figure 9)**. All prevalence analyses showed a significant heterogeneity (I^2> 50%; P-value< 0.001); however, there was no significant risk of bias in all analyses (Egger's P-value > 0.10). **Table 2** details the prevalence of different outcomes in the prophylactic indomethacin group.

Discussion

In this study, we have included 22 studies from the systematic and manual search to be analyzed to study indomethacin as a prophylactic measurement in pre-term infants from many aspects including the cardiopulmonary, neurodevelopmental delays, necrotizing enterocolitis/Intestinal perforation and death, days of hospitalization and the time spent on mechanical ventilation together with the prevalence of these outcomes from eligible study designs. The pooled results of our analysis showed that intubation on the first day at the delivery room was the most prevalent outcome, while pulmonary hemorrhage was the least. In general, these rates are like previously published reports. Laptook e*t al.* (43) reported a prevalence rate of 29.2% for neurodevelopmental delays VLBW infants. PDA was prevalent in 65.57% in neonates at birth and 41% of the patient who received indomethacin did not have favorable outcomes in Koch *et al.* study (44). The quality of the included studies was good in general which is suggestive of valid data included in the analysis. However, analyzed data showed various 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.

As for the cardiopulmonary outcomes, our analysis showed that prophylactic indomethacin administration in infants significantly lowers the rates of PDA formation (P-value< 0.001). Although, significant heterogeneity was estimated (I^2= 72%; P-value< 0.001) due to the different study designs that were included in the analysis, our results were similar to previously published studies (45, 46). On the other hand, the effect of indomethacin on BPD and pulmonary hemorrhage rates was statistically non-significant (P-value =106 and 0.132, respectively). This is consistent with previously published meta-analysis studies of RCTs which found significance in terms of lowering PDA rates, but no difference in terms of BPD (45). Jensen *et al.* (46) 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 of BPD.

In terms of neurodevelopmental outcomes, our analysis showed that indomethacin prophylaxis did not significantly reduce the risk of IVH and CP/neurodevelopmental outcomes in preterm infants when compared to the placebo group (P-value =0.460 and 0.997, respectively). Our results are consistent with the results of Cooke *et al.* (47) which found no significance on the effect of prophylactic indomethacin on IVH and other neurodevelopmental abnormalities as retinopathy of prematurity. On the other hand, Fowlie *et al.* found a significant reduction in IVH incidence in infants that were prophylactically injected with indomethacin. However, significant heterogeneity in this study was estimated due to the inconsistency of treatment efficacy among their included studies (45). None of the studies, however, measured the long-term outcomes, they have only focused on the short ones. Schmidt *et al.* (15) in their big trial on 18-month 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.

Other adverse events of prophylactic indomethacin application include increase incidence rates of necrotizing enter colitis (NEC)/Intestinal perforation (IP). In our study, a significant increase in the rate of these outcomes was estimated (P-value< 0.001). Our study results are inconsistent with the results of other previously published systematic reviews which found no significance on the effect of indomethacin on increasing the incidence of NEC (14, 45, 47). Additionally, other events were discussed by these studies as the effect of indomethacin on renal function. Fowlie e*t al.* (14) found significance in the increased rate of oliguria but not creatinine levels.

Furthermore, we found no significance between the use of prophylactic indomethacin on infants in reducing the time of hospital stay and time spent on mechanical ventilation. Fowlie *et al.* (14) result favored the control groups in terms of time spent in the hospital with no significance (P =0.087), however, the opposite was reported with the time spent on ventilation with reported statistical significance (P =0.33). Besides, the data of 13 included studies showed no significance in reducing the rates of mortality in infants that received prophylactic indomethacin (P =0.34). Despite the heterogeneity in our analysis, the results are consistent with these shown by Fowlie e*t al.* (14, 45). On the other hand, Jensen e*t al.* (46) subgroup analysis showed a low rate of mortality in the infants that received prophylactic indomethacin with no intrauterine growth restriction and with no requirement for subsequent PDA treatment. However, the authors included observational data only.

Limitations to our study include the significant heterogeneity in the analysis of some outcomes due to the different study designs that were included in this study. However, we estimated the risk of bias in most cases when significant heterogeneity was estimated, and no significant risk was found in these events.

Conclusion

Prophylactic indomethacin in VLBW infants has proven efficient in preventing short-term events as PDA. Our analysis, however, showed no significance on IVH despite the many investigations that were published before which showed that indomethacin can reduce the incidence of IVH and other neurodevelopmental abnormalities. Consequently, and based on the findings that higher rates of NEC/IP and the neutral effect on infant mortality, the use of prophylactic indomethacin should be generally discouraged until a proper assessment of the case has been provided.

Abbreviations

Patent ductus arteriosus (PDA); Necrotizing enter colitis (NEC); Intestinal perforation (IP); Intraventricular hemorrhage (IVH); Bronchopulmonary dysplasia (BPD); Very low birth weight (VLBW).

Declarations

This study by analysis of existing publicaions and not involve with patient so consent was not indicated.

Ethical approval

Ethical approval was obtained from the Institutional Review Board in King Fahad Medical City, Riyadh, Saudi Arabia before any study started.

Availability of the data and Materials

Data is available upon request.

Competing interest

The authors have no conflicts of interest to declare

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Author Contributor

N/A

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Tables

Table 1. Characteristics of the included studies

Author Year	Design	Sample Size	Gestational Age						Birth Weight						Male	
			Treatment Group			Control Group			Treatment Group			Control Group			Treatment Group	
			Total	Mean	SD	Total	Mean	SD	Total	Mean	SD	Total	Mean	SD	Event	Total
Alfaleh et al. 2008	RCT	1202	1202	25.91	1.87	-	-	-	-	-	-	-	-	-	615	1202
Bada et al. 1989	RCT	141	71	28	2.2	70	28	2.6	71	1103	253	70	1074	265	37	71
Bandstra et al. 1988	RCT	199	99	29	2.3	100	29.3	2.1	99	970	174	100	970	183	51	99
Bhat et al. 2019	Cohort	1154	912	25.1	1.94	-	-	-	912	687.6	179.39	-	-	-	442	912
Clyman et al. 2007	RCT	1202	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Foglia et al. 2018	RCT	1196	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Jensen et al. 2017	Cohort	7,831	2,587	25.9	1.5	5244	26.7	1.6	2,587	777	197	5244	913	246	1270	2,587
Kelleher et al. 2014	Cohort	15751	-	-	-	-	-	-	-	-	-	-	-	-	2862	5874
Laughon et al. 2007	Cohort	34602	-	-	-	-	-	-	-	-	-	-	-	-	3293	6189
Liebowitz et al. 2016	Cohort	313	215	26.1	1.1	98	26.1	1.1	215	833	203	98	826	205	114	215
Liebowitz et al. 2017	Cohort	397	247	26.1	1.2	150	26	1.2	247	813	197	150	802	200	117	247
Maruyama et al. 2012	RCT	19	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Mirza et al. 2013	Cohort	868	868	26.36	1.97	-	-	-	868	864.82	210.84	-	-	-	431	868
Mirza et al. 2015	Cohort	4255	4,255	50	0.65	-	-	-	4,255	744	147	-	-	-	2,077	4,255
Narayanan et al. 2000	Cohort	300	130	25.5	1.1	170	25.5	1.1	130	798	172	170	803	180	68	130
Nelin et al. 2017	Cohort	671	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Rolnitsky et al. 2015	Cohort	3465	-	-	-	-	-	-	269	749	151	3,189	858	214	135	269

Schmidt et al. 2001	RCT	1202	601	25.9	1.8	601	26	1.9	601	782	131	601	783	130	309	601
Schmidt et al. 2003	Cohort	910	910	26.2	1.8	-	-	-	910	793	127	-	-	-	454	910
Schmidt et al. 2006	Cohort	999	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Schmidt et al. 2011	Cohort	1202	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Stavel et	Cohort	4268	-	-	-	-	-	-	-	-	-	-	-	-	244	498

al. 2017

SD: standard deviation; RCT: randomized controlled trial

Table 2. Prevalence of different outcomes in the prophylactic indomethacin group

Outcome	Prevalence	LCI	UCI	N	Event	Total	Heterogeneity measures		
							I^2	τ^2	P-value
Intubated in delivery room/First day	74.9	52.9	100.0	3	369	445	97%	0.09	< 0.001
Bronchopulmonary dysplasia	33.2	25.6	43.1	6	1772	4801	97%	0.10	< 0.001
Patent Ductus Arteriosus	32.2	27.3	38.0	13	4800	14003	97%	0.08	< 0.001
Intraventricular Hemorrhage	26.1	19.1	35.7	12	3526	14898	99%	0.28	< 0.001
CP/Neurodevelopmental delay	19.1	12.9	28.2	6	1889	9031	99%	0.23	< 0.001
Death	17.8	12.1	26.1	15	4722	23794	100%	0.53	< 0.001
NEC/Intestinal perforation	10.0	6.9	14.4	10	1460	15029	97%	0.29	< 0.001
Pulmonary Hemorrhage	8.3	5.4	12.8	5	212	2284	88%	0.19	< 0.001

LCI: 95% low confidence interval; N: number of the included studies; UCI: 95% upper confidence interval; NEC: necrotizing enterocolitis

Figures

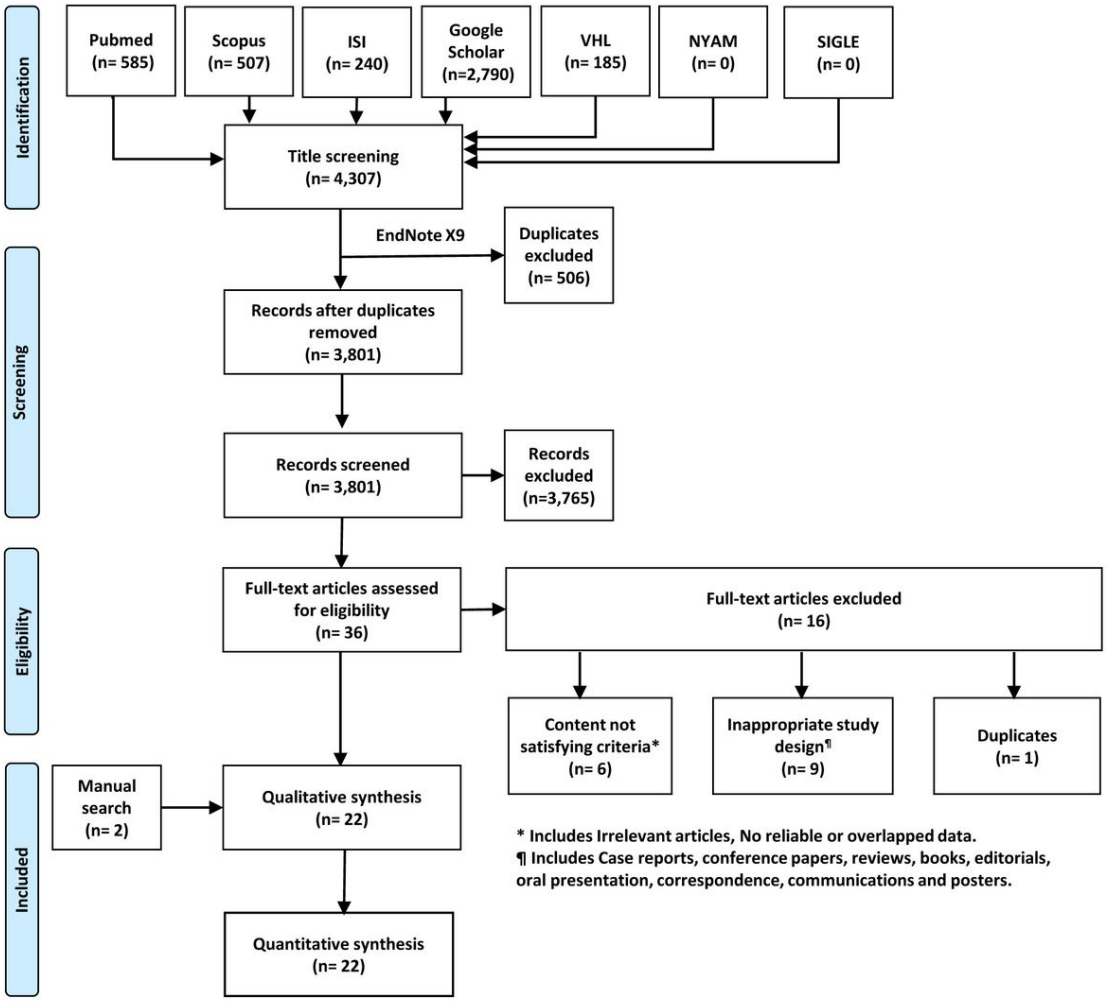

Figure 1

PRISMA flowchart of the search and screening process.

Figure 2

Quality of the included randomized controlled trials. A: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies; B: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

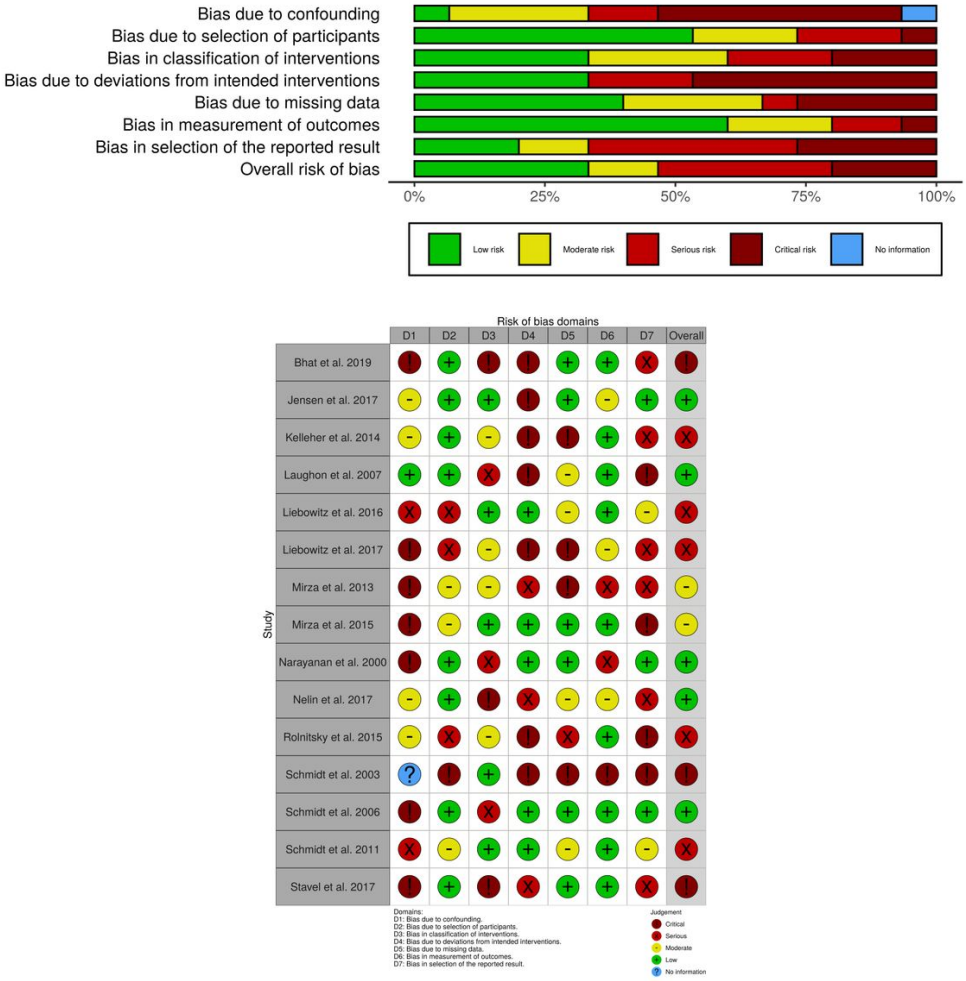

Figure 3

Quality of the included non-randomized controlled trials. A: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies; B: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

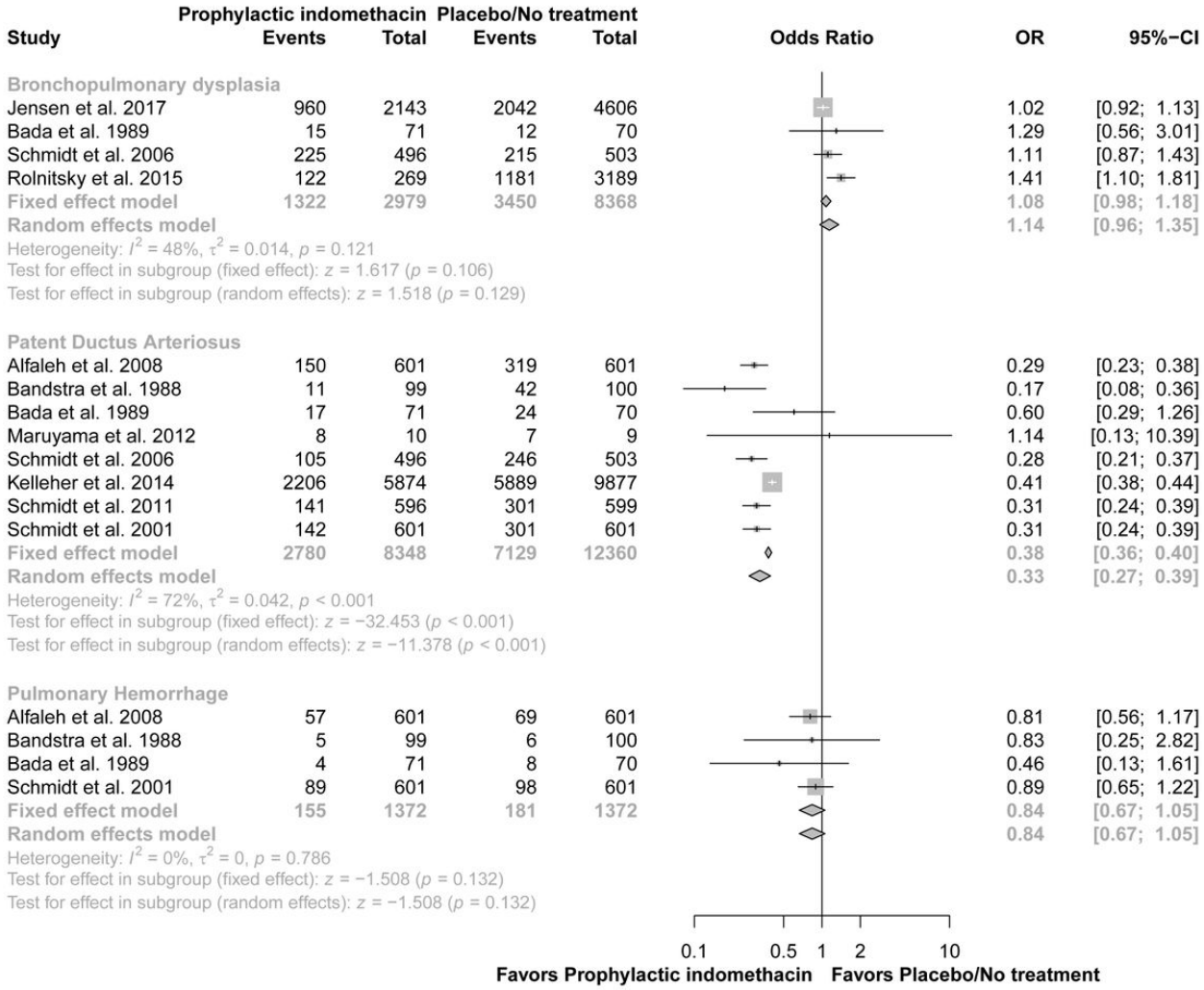

Figure 4

Forest plot for cardiopulmonary outcomes.

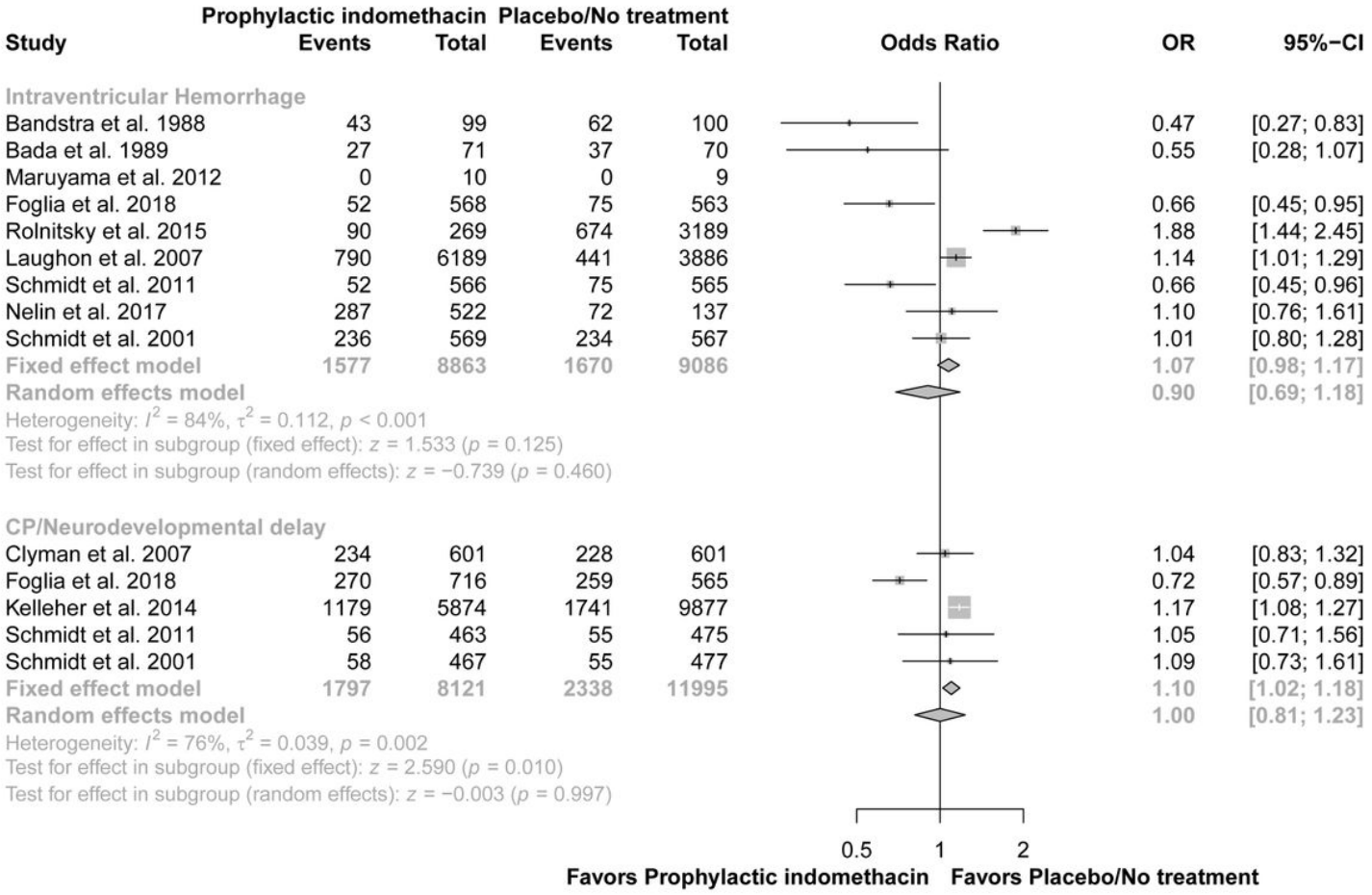

Figure 5

Forest plot for neurodevelopmental outcomes.

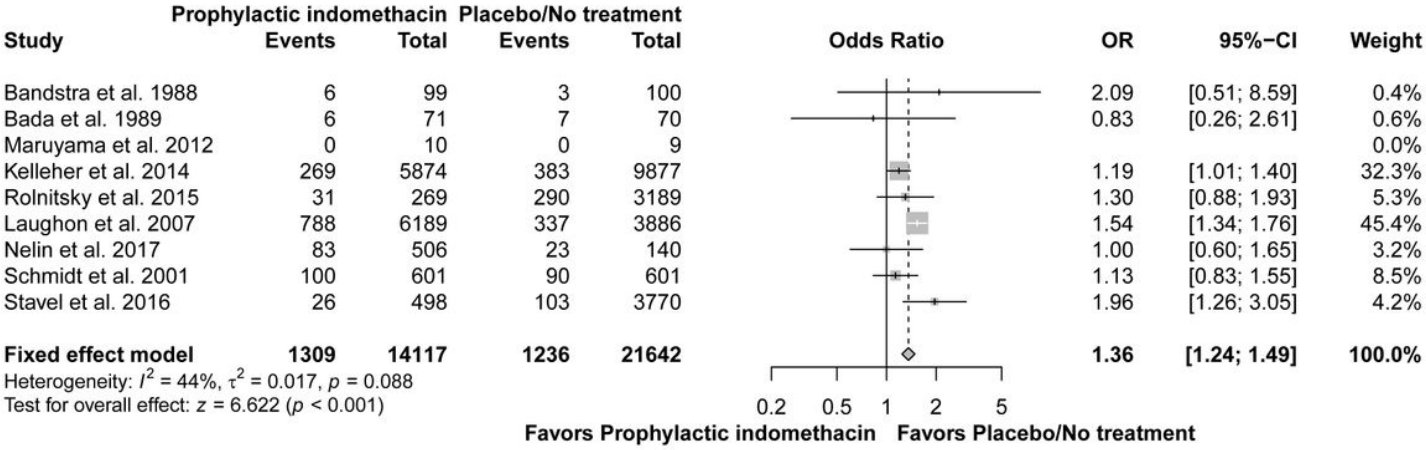

Figure 6

Forest plot for necrotizing enterocolitis/intestinal perforation.

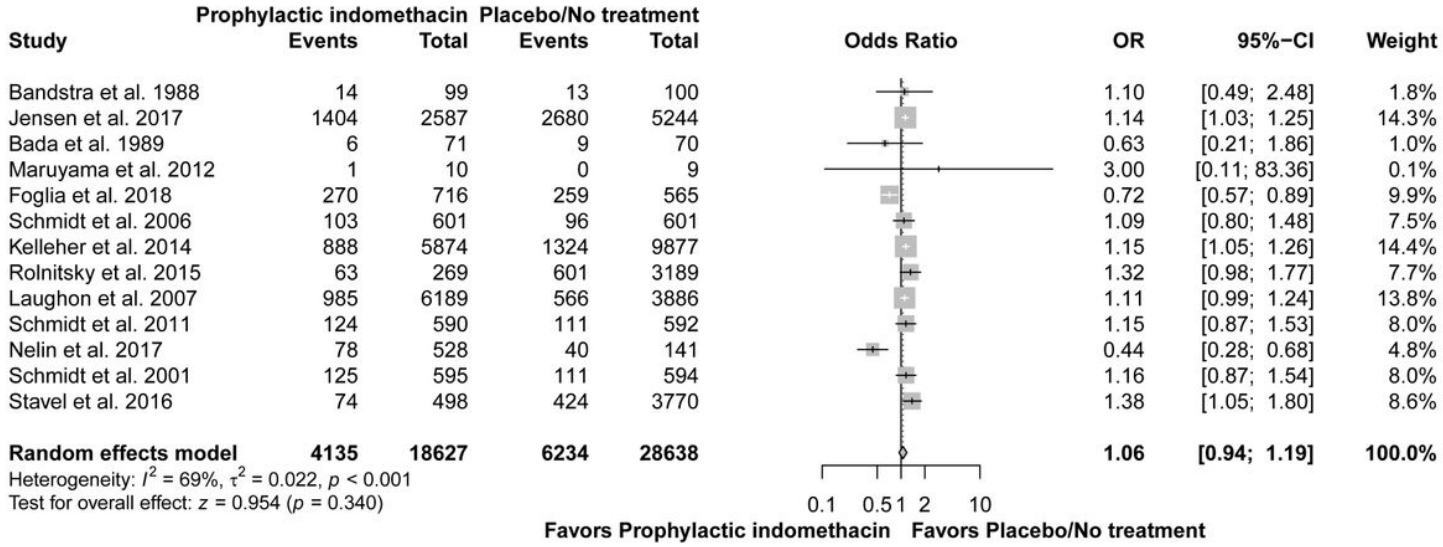

Figure 7

Forest plot for death rates.

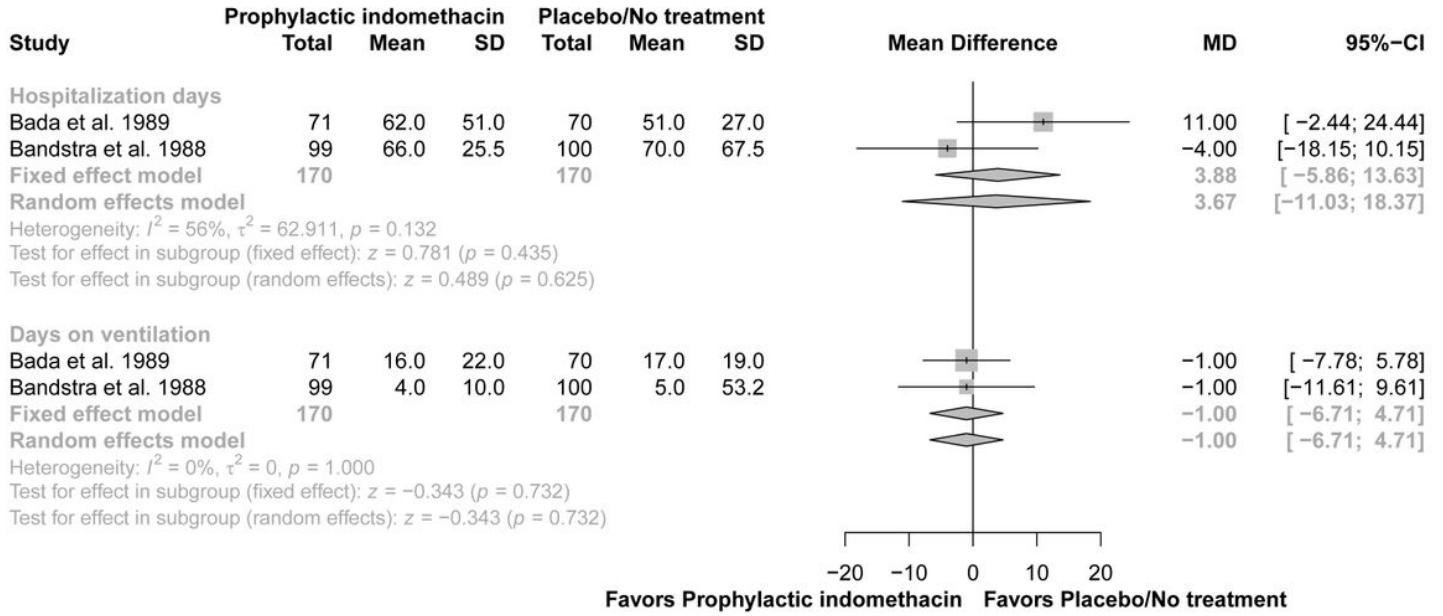

Figure 8

Forest plot for hospitalization outcomes.

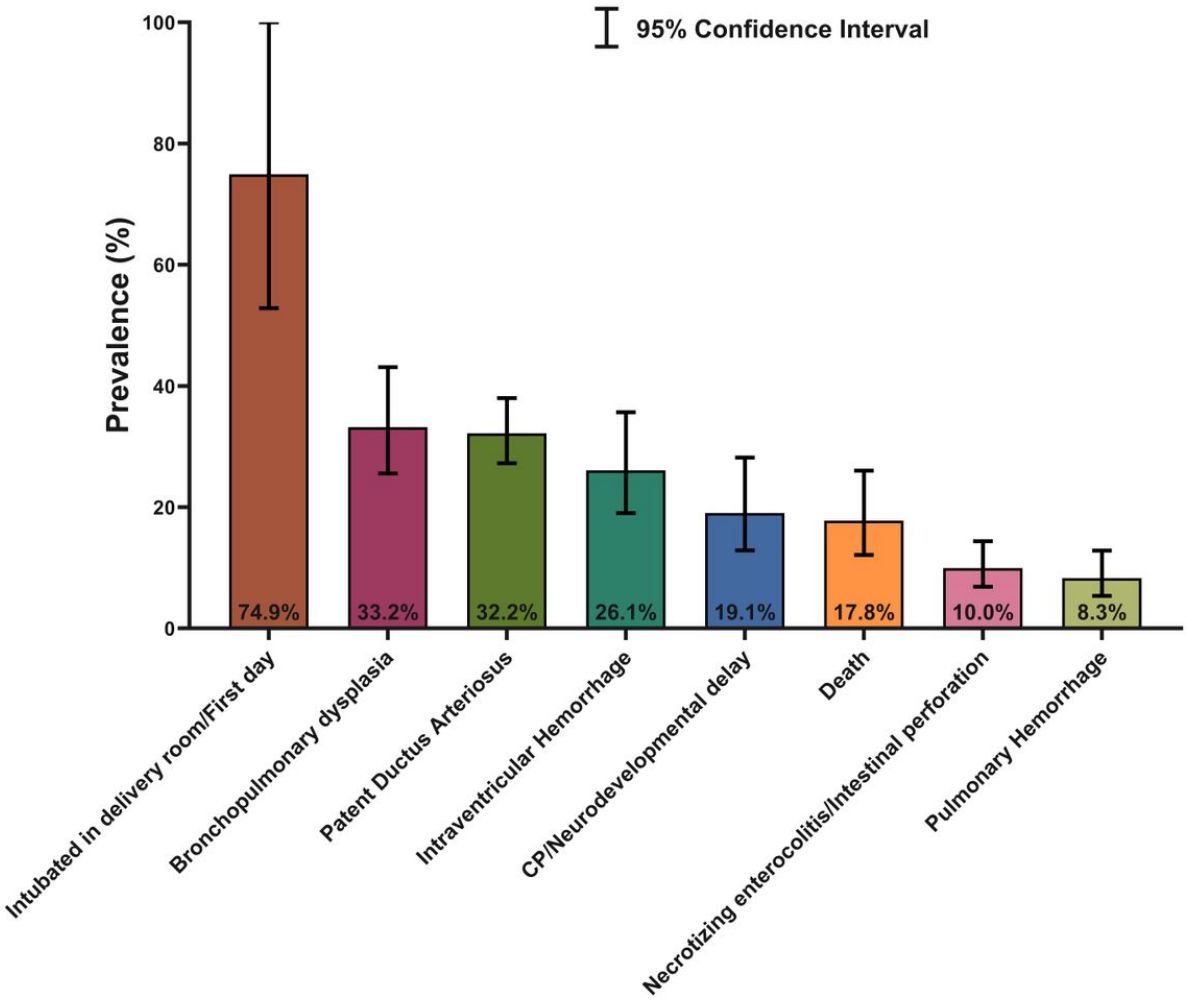

Figure 9

Forest plot for prevalence of different outcomes in prophylactic indomethacin group.

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