JAMA Network Open

Original Investigation | Pediatrics

Interventions to Reduce Severe Brain Injury Risk in Preterm Neonates
A Systematic Review and Meta-analysis

Abdul Razak, MD; Waseemoddin Patel, MD; Naveed Ur Rehman Durrani, MD; Abdul Kareem Pullattayil, MISt

Abstract

IMPORTANCE Interventions to reduce severe brain injury risk are the prime focus in neonatal clinical trials.

OBJECTIVE To evaluate multiple perinatal interventions across clinical settings for reducing the risk of severe intraventricular hemorrhage (sIVH) and cystic periventricular leukomalacia (cPVL) in preterm neonates.

DATA SOURCES MEDLINE, Embase, CENTRAL (Cochrane Central Register of Controlled Trials), and CINAHL (Cumulative Index to Nursing and Allied Health Literature) databases were searched from inception until September 8, 2022, using prespecified search terms and no language restrictions.

STUDY SELECTION Randomized clinical trials (RCTs) that evaluated perinatal interventions, chosen a priori, and reported 1 or more outcomes (sIVH, cPVL, and severe brain injury) were included.

DATA EXTRACTION AND SYNTHESIS Two co-authors independently extracted the data, assessed the quality of the trials, and evaluated the certainty of the evidence using the Cochrane GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach. Fixed-effects pairwise meta-analysis was used for data synthesis.

MAIN OUTCOMES AND MEASURES The 3 prespecified outcomes were sIVH, cPVL, and severe brain injury.

RESULTS A total of 221 RCTs that assessed 44 perinatal interventions (6 antenatal, 6 delivery room, and 32 neonatal) were included. Meta-analysis showed with moderate certainty that antenatal corticosteroids were associated with small reduction in sIVH risk (risk ratio [RR], 0.54 [95% CI, 0.35-0.82]; absolute risk difference [ARD], −1% [95% CI, −2% to 0%]; number needed to treat [NNT], 80 [95% CI, 48-232]), whereas indomethacin prophylaxis was associated with moderate reduction in sIVH risk (RR, 0.64 [95% CI, 0.52-0.79]; ARD, −5% [95% CI, −8% to −3%]; NNT, 20 [95% CI, 13-39]). Similarly, the meta-analysis showed with low certainty that volume-targeted ventilation was associated with large reduction in risk of sIVH (RR, 0.51 [95% CI, 0.36-0.72]; ARD, −9% [95% CI, −13% to −5%]; NNT, 11 [95% CI, 7-23]). Additionally, early erythropoiesis-stimulating agents (RR, 0.68 [95% CI, 0.57-0.83]; ARD, −3% [95% CI, −4% to −1%]; NNT, 34 [95% CI, 22-67]) and prophylactic ethamsylate (RR, 0.68 [95% CI, 0.48-0.97]; ARD, −4% [95% CI, −7% to 0%]; NNT, 26 [95% CI, 13-372]) were associated with moderate reduction in sIVH risk (low certainty). The meta-analysis also showed with low certainty that compared with delayed cord clamping, umbilical cord milking was associated with a moderate increase in sIVH risk (RR, 1.82 [95% CI, 1.03-3.21]; ARD, 3% [95% CI, 0%-6%]; NNT, −30 [95% CI, −368 to −16]).

(continued)

Key Points

Question Which perinatal interventions associated with reducing the risk of severe intraventricular hemorrhage (sIVH) in neonates born at less than 37 weeks' gestation?

Findings In this systematic review and meta-analysis of 221 randomized clinical trials that assessed 44 perinatal interventions, antenatal corticosteroids for lung maturation (small decrease) and indomethacin prophylaxis (moderate decrease) were found with moderate certainty to be associated with reduced risk of sIVH in preterm neonates. With low certainty, volume-targeted ventilation (large decrease), early erythropoiesis-stimulating agents (moderate decrease), and prophylactic ethamsylate (moderate decrease) were associated with reduced sIVH risk, whereas umbilical cord milking (moderate increase) was associated with increased risk of sIVH in preterm neonates.

Meaning Findings of this study suggest a few interventions were associated with reduced sIVH risk; however, clinicians need to consider all of the critical factors that may affect applicability in these interventions, including certainty of the evidence, before applying them to clinical practice.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Abstract (continued)

CONCLUSIONS AND RELEVANCE Results of this study suggest that a few interventions, including antenatal corticosteroids and indomethacin prophylaxis, were associated with reduction in sIVH risk (moderate certainty), and volume-targeted ventilation, early erythropoiesis-stimulating agents, and prophylactic ethamsylate were associated with reduction in sIVH risk (low certainty) in preterm neonates. However, clinicians should carefully consider all of the critical factors that may affect applicability in these interventions, including certainty of the evidence, before applying them to clinical practice.

JAMA Network Open. 2023;6(4):e237473. doi:10.1001/jamanetworkopen.2023.7473

Introduction

Intraventricular hemorrhage (IVH) and periventricular leukomalacia (PVL) are acquired brain injuries in neonates born before 37 weeks' gestation. Severe IVH (sIVH), often referred to as IVH with ventricular distension or periventricular hemorrhagic infarction, occurs in 7.7% of very preterm infants (gestational age <32 weeks) and 16.2% of extremely preterm infants (gestational age <28 weeks).[1] Cystic PVL (cPVL), a type of brain injury characterized by necrosis of white matter near the lateral ventricles, occurs in 6.1% of extremely preterm infants.[2] Both sIVH and cPVL, which are collectively recognized as severe brain injury, are detrimental to long-term neurodevelopmental outcomes,[3] and interventions to reduce their risk in preterm neonates are of utmost importance in neonatal medicine.

Several perinatal interventions have been tested in clinical trials to reduce the risk of severe brain injury in preterm neonates. Therefore, a summary of literature focusing on the role of potential interventions is needed. To our knowledge, there has been no published systematic review of interventions or a network meta-analysis of the role that the interventions evaluated in clinical trials play in reducing the risk of severe brain injury in preterm neonates. A network meta-analysis may not be appropriate because interventions for reducing the risk of severe brain injury have been studied in diverse clinical settings and at different time points. Although a comprehensive overview of intervention reviews is appropriate for summarizing the literature, evaluating a specific question may not be helpful. In addition, some reviews may be outdated given the ongoing proliferation of newer clinical trials. Hence, rather than an overview format, we used an intervention review format to evaluate multiple perinatal interventions for reducing the risk of sIVH and cPVL in preterm neonates across clinical settings.

Methods

We conducted this systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[4] We registered the study protocol for the systematic review with PROSPERO (registration number CRD42020186590).

Search Strategy and Study Selection

We performed a comprehensive systematic search of the literature using appropriate prespecified search terms in MEDLINE, Embase, CENTRAL (Cochrane Central Register of Controlled Trials), and CINAHL (Cumulative Index to Nursing and Allied Health Literature) from database inception to September 8, 2022, without any language restriction. Details of the search strategy for each database are provided in eAppendix 1 in Supplement 1. To identify relevant reports, we searched the reference lists of systematic and narrative reviews and studies that fulfilled the eligibility criteria of the present study. Additionally, we explored the *Similar articles* feature in PubMed and the *Cited by*

tool in Google Scholar and Web of Science. We identified the trial registration records in CENTRAL and conference abstracts in CENTRAL and Embase.

We included randomized clinical trials (RCTs) that reported 1 or more prespecified outcomes (sIVH, cPVL, and severe brain injury) of this systematic review. We excluded observational reports, reviews, case reports, and case series. We included trials that reported outcomes in preterm neonates (<37 weeks' gestational age) or in term and preterm neonates for whom data could be extracted. We included trials of any interventions that were chosen a priori based on discussion and consensus. One of us (A.R.) prepared a preliminary list of potential interventions after searching PubMed, Cochrane Neonatal, and Cochrane Pregnancy and Childbirth. A final list of 44 interventions was prepared based on discussion and consensus between 3 of us (A.R., W.P., and N.U.R.D.). The registered protocol and eAppendix 2 in Supplement 1 list all of the interventions evaluated in the systematic review.

Study Outcomes and Data Extraction

The 3 prespecified outcomes were (1) sIVH, defined as hemorrhage into the ventricles with ventricular distension, intraparenchymal hemorrhage, or parenchymal hemorrhagic infarct (grade III or IV using the Papile classification), identified on cranial ultrasound any time before discharge[5]; (2) cPVL, defined as white matter injury characterized by the necrosis of white matter near the lateral ventricles (must include cystic changes), identified on cranial ultrasound any time before discharge[6]; and (3) severe brain injury, defined as the presence of either sIVH or cPVL.

One of us (A.K.P.) searched the literature in the databases and compiled a final list using a reference management software (EndNote, version X9.3.3; Thomson Reuters). Two of us (W.P. and N.U.R.D.) independently screened the titles and abstracts using the screening form (eAppendix 3 in Supplement 1) and read the short-listed full-text articles to determine their eligibility. We selected clinical trials and independently examined their population characteristics, inclusion criteria, outcomes, and risk of bias. We contacted the study authors for relevant, missing, or any unclear information. We compared the extracted data for any discrepancies and resolved discrepancies by discussion and consensus with another author (A.R.).

Statistical Analysis

Two of us (W.P. and N.U.R.D.) independently assessed the methodological quality of included trials using the Cochrane Risk-of-Bias Tool for Randomized Trials, version 1 (Cochrane Methods) for the following domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. In addition, we resolved conflicts between us through discussion and consensus with a third author (A.R.).

We examined the treatment effects in the individual trials using Review Manager 5.3 (Cochrane Collaboration) and reported Mantel-Haenszel risk ratios (RRs) with fixed 95% CIs. We performed a fixed-effects model meta-analysis to yield the pooled RR (with 95% CI) and *P* value for each outcome. We also reported the absolute risk difference (ARD) and the number needed to treat (NNT) or the number needed to harm (with 95% CI) for outcomes with significant differences. We considered a $P < .05$ to be statistically significant.

We examined heterogeneity by inspecting the forest plots. Additionally, we determined the *P* value for χ^2 and I^2 tests to detect statistical heterogeneity. We conducted sensitivity and subgroup analyses to explore the causes of substantial heterogeneity (I^2 >50%) if data were available. The subgroup analysis was based on the gestational ages younger than 28 weeks and 28 weeks or older. The sensitivity analysis included only high-quality studies with low risk of bias (low risk of bias in all domains) or probably low (unclear risk of bias in 1 domain and low risk of bias in all other domains).

We assessed the risk of bias due to missing results in a synthesis by using a funnel plot and the Egger test when more than 10 studies were included for any individual meta-analysis. Three of us (A.R., N.U.R.D., and W.P.) independently assessed the certainty of evidence using the Cochrane

Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach, as outlined in the GRADE Handbook,[7] for all 3 outcomes. To communicate the systematic review findings, we used the language for interpretation based on the GRADE informative statements outlined by Santesso et al.[8] We considered the effect size of fewer than 20 per 1000 newborns for small, 20 to 50 per 1000 newborns for moderate, and more than 50 per 1000 newborns for large benefit or harm.

Results

The results of the database search and study selection are provided in eFigure 1 in Supplement 1. After removing 1196 duplicates from 9983 identified records, we screened the titles and abstracts of 8787 records and found 395 articles that were relevant for full-text screening. We further determined the eligibility of 395 short-listed articles and excluded 174 articles for the reasons shown in eAppendix 4 in Supplement 1. A total of 221 RCTs were included in the final sample.[9-229] These trials evaluated 44 interventions, which included 6 antenatal, 6 delivery room, and 32 neonatal interventions. Details of the included trials are included in eTable 1 in Supplement 1.

We summarized the risk-of-bias assessment in eTable 1 in Supplement 1. Bias from the randomization process varied across studies. In a few studies, blinding the participants was not feasible, and the domain was assessed as high risk. Additionally, most trials provided no information on the blinding of outcome assessment and were marked unclear. However, bias in the measurement of the outcome was not an issue in most studies. Other bias domains are reported in eTable 1 in Supplement 1. Overall, some studies were at low risk of bias in all domains; however, most trials had methodological limitations in 1 or more domains.

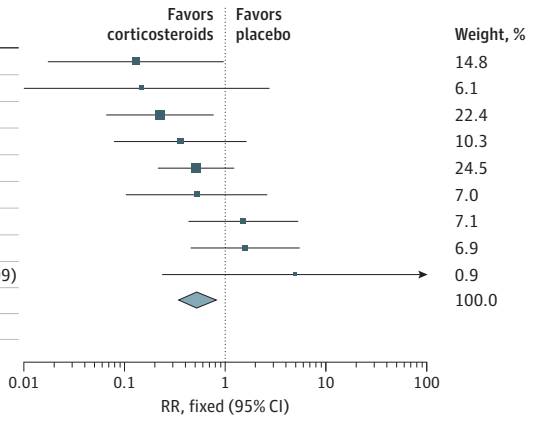
Outcome: sIVH

Meta-analysis of data from 9 trials (4368 participants)[66,75,76,89,133,157,158,175,197] showed a small reduction in sIVH risk (RR, 0.54 [95% CI, 0.35-0.82]; I^2 = 36%; ARD, −1% [95% CI, −2% to −0%]; NNT, 80 [95% CI, 48-232]) (**Table** and **Figure 1**). We assessed the certainty of evidence as moderate, which was a downgrade for serious study design limitations. Meta-analysis of data showed no treatment effect for other antenatal interventions, including betamethasone vs dexamethasone for lung maturity, repeat vs single antenatal corticosteroids, magnesium sulfate for neuroprotection or tocolysis or antibiotics for preterm premature rupture of membranes (Table; eFigures 2-5 in Supplement 1). No data were available for cesarean delivery vs vaginal delivery for preterm birth.

Figure 1. Forest Plot for Antenatal Corticosteroids for Lung Maturity vs Placebo in Preterm Neonates for the Outcome of Severe Intraventricular Hemorrhage

Study or subgroup	Any corticosteroids Events, No.	Any corticosteroids Total, No.	Placebo Events, No.	Placebo Total, No.	RR, fixed (95% CI)	Weight, %
Garite et al,[76] 1992	1	31	9	36	0.13 (0.02-0.96)	14.8
Lewis et al,[133] 1996	0	38	3	39	0.15 (0.01-2.74)	6.1
Morales et al,[157] 1989	3	87	12	78	0.22 (0.07-0.77)	22.4
Silver et al,[197] 1996	2	28	6	30	0.36 (0.08-1.63)	10.3
Morales et al,[158] 1986	7	121	14	124	0.51 (0.21-1.23)	24.5
Eronen et al,[66] 1993	2	28	4	29	0.52 (0.10-2.61)	7.0
Garite et al,[75] 2009	6	272	4	274	1.51 (0.43-5.30)	7.1
Peltoniemi et al,[175] 2007	6	159	4	167	1.58 (0.45-5.48)	6.9
Gyamfi-Bannerman et al,[89] 2016	2	1427	0	1400	4.91 (0.24-102.09)	0.9
Total (95% CI)		2191		2177	0.54 (0.35-0.82)	100.0
Total events	29		56			

Heterogeneity: $\chi^2 = 12.45$, $df = 8$ ($P = .13$); $I^2 = 36\%$
Test for overall effect: $z = 2.84$ ($P = .004$)



Diamond indicates the overall effect estimate from the meta-analysis, and squares indicate a point estimate for the individual study. RR indicates risk ratio.

Table. Summary of Meta-analysis of Interventions on Severe Intraventricular Hemorrhage

Intervention	No. of RCTs	No. of patients	RR (95% CI)	Heterogeneity, I^2, %[a]	GRADE
Antenatal interventions					
Antenatal corticosteroids for lung maturity	9	4368	0.54 (0.35-0.82)[b]	36	Moderate[c]
Betamethasone vs dexamethasone for lung maturity	4	1956	2.17 (0.89-5.25)	0	Moderate[c]
Repeat antenatal corticosteroids vs single-course antenatal corticosteroids	8	5472	1.06 (0.73-1.56)	13	Moderate[c]
Magnesium sulfate for neuroprotection or tocolysis	6	4559	0.80 (0.61-1.06)	10	Moderate[c]
Antibiotics for premature rupture of membranes	4	893	0.73 (0.42-1.26)	0	Low[c,d]
Cesarean delivery vs vaginal delivery for preterm birth	NA	NA	NA	NA	NA
Delivery room interventions					
Lower vs higher FiO_2 for resuscitation	8	918	0.92 (0.61-1.40)	0	Moderate[c]
Sustained inflation vs standard resuscitation	10	1290	0.92 (0.67-1.26)	0	Moderate[c]
Delayed cord clamping vs early cord clamping	15	2501	0.96 (0.65-1.42)	0	Moderate[c]
Umbilical cord milking vs early cord clamping	12	1005	0.91 (0.61-1.37)	0	Moderate[c]
Umbilical cord milking vs delayed cord clamping	6	866	1.82 (1.03-3.21)[b]	27	Low[c,d]
Delayed cord clamping with respiratory support vs without respiratory support	1	150	1.33 (0.31-5.75)	NA	Low[c,d]
Neonatal interventions					
Supine head midline vs supine head rotated	3	290	0.71 (0.37-1.33)	0	Low[c,d]
LISA vs INSURE	6	1227	0.79 (0.52-1.20)	3	Low[c,d]
Volume-targeted vs pressure-limited ventilation	13	878	0.51 (0.36-0.72)[b]	9	Low[c,e]
Elective HFOV vs conventional ventilation	19	4196	1.11 (0.96-1.29)	16	Moderate[c]
Elective HFJV vs conventional ventilation	2	193	1.37 (0.79-2.37)	19	Low[c,d]
Oxygen saturation target after birth: 85%-89% vs 91%-95%	4	3684	0.92 (0.77-1.10)	0	High
Permissive hypercapnia vs normocapnia	5	912	0.92 (0.71-1.21)	0	Low[c,d]
Early extubation vs delayed extubation	1	86	0.32 (0.07-1.49)	NA	Low[c,d]
Caffeine prophylaxis or treatment for apnea or postextubation	3	2106	0.91 (0.72-1.16)	48	Moderate[a]
High-dose vs low-dose caffeine for apnea or postextubation	6	662	1.34 (0.74-2.41)	0	Low[c,d]
Sedation during ventilation: midazolam vs placebo	1	43	1.59 (0.43-5.84)	NA	Low[c,d]
Sedation during ventilation: opioids vs no placebo	5	1106	1.02 (0.73-1.43)	34	Moderate[c]
Sedation during ventilation: phenobarbitone vs placebo	NA	NA	NA	NA	NA
Neuromuscular paralysis during ventilation vs placebo	2	217	0.51 (0.25-1.06)	78	Very low[a,c,d]
Early erythropoiesis-stimulating agents vs placebo	12	5117	0.68 (0.57-0.83)[b]	45	Low[a,c]
Volume expansion vs inotropes (any) for hypotension	1	39	1.47 (0.96-2.25)	NA	Low[c,d]
Dopamine vs dobutamine for hypotension	2	83	0.73 (0.15-3.50)	0	Low[c,d]
Indomethacin prophylaxis for PDA vs placebo	15	2584	0.64 (0.52-0.79)[b]	0	Moderate[c]
Indomethacin presymptomatic treatment for PDA vs placebo	1	92	0.36 (0.08-1.71)	NA	Low[c,d]
Ibuprofen prophylaxis for PDA vs placebo	8	959	0.68 (0.46-1.01)	31	Low[c,d]
Ibuprofen presymptomatic treatment for PDA vs placebo	3	467	1.18 (0.75-1.88)	0	Moderate[d]
Restrictive vs liberal packed red blood cell transfusion for anemia	4	1157	0.97 (0.63-1.47)	0	Moderate[c]
Low vs high threshold for platelet transfusion for thrombocytopenia[f]	NA	NA	NA	NA	NA
Prophylactic plasma administration vs placebo	2	588	0.67 (0.37-1.24)	5	Low[c,d]
Prophylactic factor VII administration vs placebo	NA	NA	NA	NA	NA
Prophylactic antithrombin III administration vs placebo	2	175	0.92 (0.40-2.14)	0	Low[c,d]
Prophylactic ethamsylate administration vs placebo	6	1117	0.68 (0.48-0.97)[b]	2	Low[c,d]
Prophylactic heparin administration vs placebo	1	107	0.87 (0.31-2.43)	NA	Low[c,d]
Stem cell therapy	NA	NA	NA	NA	NA
Vitamin A supplementation vs placebo	7	1384	0.84 (0.65-1.07)	26	Low[c,d]
Vitamin E supplementation vs placebo	7	1095	0.96 (0.68-1.36)	29	Moderate[d]
Vitamin K supplementation vs placebo	NA	NA	NA	NA	NA

Abbreviations: FiO_2, fraction of inspired oxygen; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HFJV, high-frequency jet ventilation; HFOV, high-frequency oscillatory ventilation; INSURE, Intubate-surfactant-extubate; LISA, less-invasive surfactant administration; NA, not available; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; RCT, randomized clinical trial; RR, relative risk.

[a] Heterogeneity.

[b] Significant association.

[c] Risk of bias.

[d] Imprecision.

[e] Publication bias.

[f] Two RCTs[51,129] were available and provided data on IVH, but a meta-analysis was not performed due to heterogeneous comparisons in the trials. No significant differences were found between the groups in all of the trials.

Meta-analysis of data from 6 trials (866 participants)[31,70,112,114,115,181] showed a moderate increase in sIVH risk (RR, 1.82 [95% CI, 1.03-3.21]; I^2 = 27%; ARD, 3% [95% CI, 0%-6%]; NNT, −30 [95% CI, −368 to −16]) with umbilical cord milking (UCM) vs delayed cord clamping (DCC) (Table; eFigure 6 in Supplement 1). We assessed the certainty of evidence as low, which was a downgrade for serious study design limitations and imprecision. Meta-analysis showed no treatment effect for other delivery room interventions, including lower vs higher fraction of inspired oxygen for resuscitation, sustained inflation vs standard resuscitation, DCC vs early cord clamping, UCM vs early cord clamping, or DCC with respiratory support vs without respiratory support (Table; eFigures 7-11 in Supplement 1).

Meta-analysis of data from 15 trials (2584 participants)[23,24,46,57,92,108,127,147-150,159,192,224,228] showed a moderate reduction in sIVH risk (RR, 0.64 [95% CI, 0.52-0.79]; I^2 = 0%; ARD, −5% [95% CI, −8% to −3%]; NNT, 20 [95% CI, 13-39]) with indomethacin prophylaxis for patent ductus arteriosus (PDA) vs placebo (Table and **Figure 2**). We assessed the certainty of evidence as moderate, which was a downgrade for serious study design limitations, and found no statistically significant evidence of publication bias (funnel plot: symmetrical; Egger intercept test: 1-tailed P = .13) (eFigures 12 and 13 in Supplement 1).

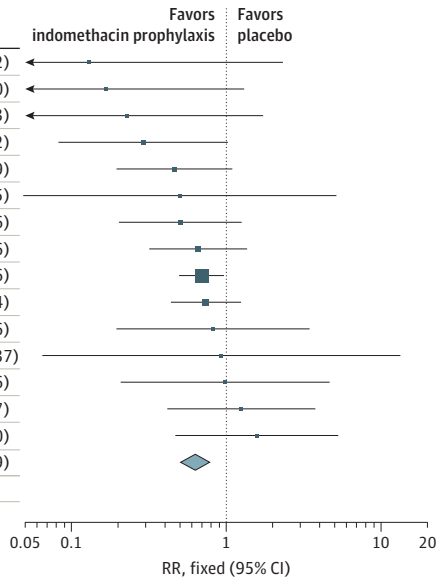
Meta-analysis of data from 13 trials (878 participants)[40,52,60,88,116,126,138,139,163,178,179,199,201] showed a large reduction in sIVH risk (RR, 0.51 [95% CI, 0.36-0.72]; I^2 = 9%; ARD, −9% [95% CI, −13% to −5%]; NNT, 11 [95% CI, 7-23]) with volume-targeted ventilation vs pressure-limited ventilation (Table and **Figure 3**). We assessed the certainty of evidence as low, which was a downgrade for serious study design limitations and serious risk of publication bias (funnel plot: asymmetrical; Egger intercept test: 1-tailed P = .03) (eFigures 14 and 15 in Supplement 1).

Meta-analysis of data from 12 trials (5117 participants)[32,68,69,90,107,142,164,169,170,174,203,212] showed a moderate reduction in sIVH risk (RR, 0.68 [95% CI, 0.57-0.83]; I^2 = 45%; ARD, −3% [95% CI, −4% to −1%]; NNT, 34 [95% CI, 22-67]) with early erythropoiesis-stimulating agents (ESAs) vs placebo (Table; eFigure 16 in Supplement 1). We assessed the certainty of evidence as low, which was a downgrade for serious study design limitations and serious risk of heterogeneity. No statistically

Figure 2. Forest Plot for Indomethacin Prophylaxis for Patent Ductus Arteriosus vs Placebo in Preterm Neonates for the Outcome of Severe Intraventricular Hemorrhage

Study or subgroup	Indomethacin prophylaxis Events, No.	Indomethacin prophylaxis Total, No.	Placebo Events, No.	Placebo Total, No.	RR, fixed (95% CI)	Weight, %
Ment et al,[148] 1988	0	19	3	17	0.13 (0.01-2.32)	2.0
Kalani et al,[108] 2016	1	31	6	31	0.17 (0.02-1.30)	3.3
Krueger et al,[127] 1987	1	15	5	17	0.23 (0.03-1.73)	2.6
Ment et al,[150] 1994	3	209	11	222	0.29 (0.08-1.02)	5.8
Morales-Suarez et al,[159] 1994	6	40	13	40	0.46 (0.19-1.09)	7.1
Ment et al,[147] 1985	1	24	2	24	0.50 (0.05-5.15)	1.1
Domanico et al,[57] 1994	6	52	11	48	0.50 (0.20-1.26)	6.3
Bada et al,[23] 1989	10	71	15	70	0.66 (0.32-1.36)	8.3
Schmidt et al,[192] 2001	52	569	75	567	0.69 (0.49-0.96)	41.1
Bandstra et al,[24] 1988	19	99	26	100	0.74 (0.44-1.24)	14.1
Couser et al,[46] 1996	3	43	4	47	0.82 (0.19-3.46)	2.1
Yaseen et al,[228] 1997	1	14	1	13	0.93 (0.06-13.37)	0.6
Hanigan et al,[92] 1988	3	56	3	55	0.98 (0.21-4.66)	1.7
Vincer et al,[224] 1987	5	15	4	15	1.25 (0.41-3.77)	2.2
Ment et al,[149] 1994	5	27	4	34	1.57 (0.47-5.30)	1.9
Total (95% CI)		1284		1300	0.64 (0.52-0.79)	100.0
Total events	116		183			

Heterogeneity: χ^2 = 10.71, df = 14 (P = .71); I^2 = 0%
Test for overall effect: z = 4.07 (P < .001)



Diamond indicates the overall effect estimate from the meta-analysis, and squares indicate a point estimate for the individual study. RR indicates risk ratio.

significant evidence of publication bias was found (funnel plot: symmetrical; Egger intercept test: 1-tailed P = .18) (eFigure 17 in Supplement 1).

Meta-analysis of data from 6 trials (1117 participants)[16,28,39,85,160,189] showed a moderate reduction in sIVH risk (RR, 0.68 [95% CI, 0.48-0.97]; I^2 = 2%; ARD, −4% [95% CI, −7% to 0%]; NNT, 26 [95% CI, 13-372]) with prophylactic ethamsylate administration vs placebo (Table; eFigure 18 in Supplement 1). We assessed the certainty of evidence as low, which was a downgrade for serious study design limitations and serious risk of imprecision. The other neonatal interventions that the meta-analysis showed as not having treatment effects are listed in the Table and eFigures 19 to 41 in Supplement 1.

Outcome: cPVL

Meta-analysis of data from 3 trials (1551 participants)[68,164,203] showed a moderate reduction in cPVL risk (RR, 0.59 [95% CI, 0.42-0.83]; I^2 = 0%; ARD, −4% [95% CI, −7% to −1%]; NNT, 22 [95% CI, 14-57]) with early ESAs vs placebo (eTable 2 and eFigure 42 in Supplement 1). We assessed the certainty of evidence as low, which was a downgrade for serious study design limitations.

The data from 1 trial,[221] including 64 participants, showed an increased risk of cPVL with elective high-frequency jet ventilation vs placebo (RR, 5.00; 95% CI, 1.19-21.04) (eTable 2 and eFigure 43 in Supplement 1). We assessed the certainty of evidence as low, which was a downgrade for serious study design limitation and serious risk of imprecision. The remaining interventions that the meta-analysis showed as not being associated with cPVL are provided in eTable 2 and eFigures 44 to 64 in Supplement 1.

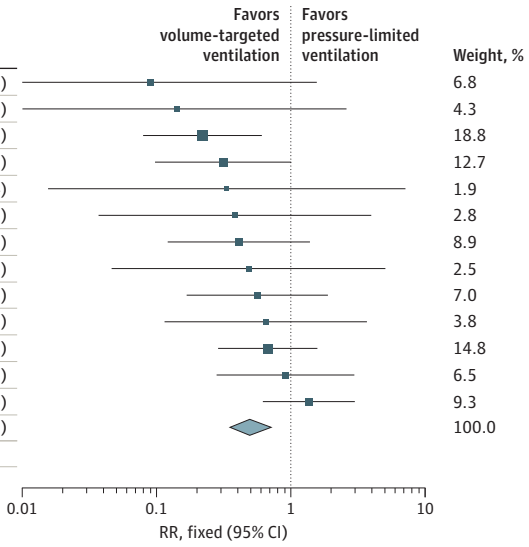
Outcome: Severe Brain Injury

Only a limited number of trials[27,43,45,46,61,93,105,120,121,165,180,190-192,208,213] provided data on severe brain injury associated with various interventions (eTable 2 in Supplement 1). Meta-analysis of trials showed no significant differences in implications of various interventions, except for elective high-frequency oscillatory ventilation (HFOV) vs conventional ventilation. Specifically, the meta-analysis of data from 4 trials (1769 participants)[45,61,105,180] showed a reduced risk of severe brain injury with elective HFOV vs placebo, and the evidence certainty was assessed as low (RR, 0.79 [95% CI, 0.63-0.99]; ARD, −4% [95% CI, −8% to −0%]; NNT, 23 [95% CI, 12-501]) (eTable 2 and eFigure 65 in

Figure 3. Forest Plot for Volume-Targeted vs Pressure-Limited Ventilation in Preterm Neonates for the Outcome of Severe Intraventricular Hemorrhage

Study or subgroup	Volume-targeted ventilation Events, No.	Volume-targeted ventilation Total, No.	Pressure-limited ventilation Events, No.	Pressure-limited ventilation Total, No.	RR, fixed (95% CI)	Weight, %
Sinha et al,[201] 1997	0	25	5	25	0.09 (0.01-1.56)	6.8
Chowdhury et al,[40] 2013	0	20	3	20	0.14 (0.01-2.60)	4.3
Guven et al,[88] 2013	4	42	13	30	0.22 (0.08-0.61)	18.8
Piotrowski et al,[179] 1997	3	27	11	31	0.31 (0.10-1.01)	12.7
Keszler et al,[116] 2004	0	8	1	8	0.33 (0.02-7.14)	1.9
Lista et al,[138] 2004	1	30	2	23	0.38 (0.04-3.97)	2.8
Duman et al,[60] 2012	3	23	7	22	0.41 (0.12-1.39)	8.9
Liu et al,[139] 2011	1	31	2	30	0.48 (0.05-5.06)	2.5
Nafday et al,[163] 2005	3	16	6	18	0.56 (0.17-1.89)	7.0
Krishna et al,[126] 2019	2	41	3	40	0.65 (0.11-3.69)	3.8
D'Angio et al,[52] 2005	8	101	12	102	0.67 (0.29-1.58)	14.8
Singh et al,[199] 2006	5	57	5	52	0.91 (0.28-2.97)	6.5
Piotrowski et al,[178] 2007	11	30	7	26	1.36 (0.62-3.00)	9.3
Total (95% CI)		451		427	0.51 (0.36-0.72)	100.0
Total events	41		77			

Heterogeneity: χ^2 = 13.13, df = 12 (P = .36); I^2 = 9%
Test for overall effect: z = 3.86 (P = .001)



Diamond indicates the overall effect estimate from the meta-analysis, and squares indicate a point estimate for the individual study. RR indicates risk ratio.

Supplement 1). The interventions that the meta-analysis showed no treatment effect for severe brain injury are provided in eTable 2 and eFigures 66 to 71 in Supplement 1.

Subgroup and sensitivity analyses are provided in eTable 3 in Supplement 1. For most of the interventions, the analyses were not conducted due to a lack of subgroup data, high-quality studies, and the absence of substantial heterogeneity (I^2 >50%).

Discussion

In this systematic review and meta-analysis of 221 trials[9-229] that assessed 44 perinatal interventions, we found with moderate certainty that antenatal corticosteroids for lung maturation (small decrease) and indomethacin prophylaxis (moderate decrease) were associated with reduced risk of sIVH in preterm neonates. We also found low certainty evidence that volume-targeted ventilation (large decrease), early ESAs (moderate decrease), and prophylactic ethamsylate (moderate decrease) were associated with lower risk of sIVH, whereas UCM (moderate increase) were associated with higher risk of sIVH in preterm neonates.

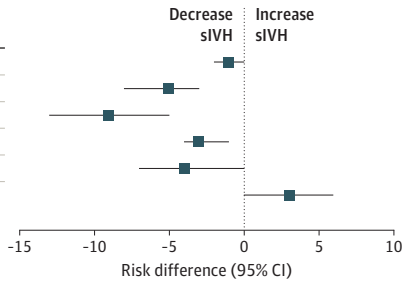
Severe IVH and cPVL have detrimental roles in childhood neurodevelopmental outcomes.[3] Therefore, it is essential for clinicians to be aware of the evidence-based interventions available for reducing the risk of severe brain injury in preterm neonates. To our knowledge, this systematic review and meta-analysis was the first to collate and summarize the breadth of evidence for such potential interventions, albeit not all. By outlining the evidence and its certainty using the GRADE approach, we believe that this study helps clinicians and decision-makers to understand the role of these interventions in reducing the risk of sIVH and cPVL in preterm neonates.

In this systematic review and meta-analysis, we found only a few perinatal interventions (antenatal corticosteroids,[66,75,76,89,133,157,158,175,197] indomethacin prophylaxis,[23, 24, 46, 57, 92, 108, 127, 147-150, 159, 192, 224, 228] volume-targeted ventilation,[40, 52, 60, 88, 116, 126, 138, 139, 163, 178, 179, 199, 201] early ESAs,[32, 68, 69, 90, 107, 142, 164, 169, 170, 174, 203, 212] and prophylactic ethamsylate[16,28,39,85,160,189]) that were associated with decreased risk of sIVH in preterm neonates (**Figure 4**). The certainty of the evidence for these interventions was low to moderate. We studied 6 antenatal interventions but found that only antenatal corticosteroid for lung maturity was beneficial in reducing sIVH risk in this preterm population. For this intervention, the certainty of the evidence was moderate and the effect size was small. Nonetheless, the small treatment effect of antenatal corticosteroids in sIVH is important. Additionally, several other benefits of antenatal corticosteroids, such as reduced perinatal and neonatal mortality, respiratory distress syndrome, need for mechanical ventilation, and necrotizing enterocolitis, compel their use in pregnant individuals who are at risk of preterm delivery.

We found no significant decrease in the risk of sIVH associated with the delivery room interventions assessed in this systematic review and meta-analysis. On the other hand, compared with DCC, UCM was associated with a moderate increase in the risk of sIVH in preterm neonates (low certainty). This finding is consistent with a finding from the PREMOD-2 (Premature Infants Receiving

Figure 4. Summary Estimates of Meta-analyses of Clinical Trials Comparing Interventions for the Prevention of Severe Intraventricular Hemorrhage (sIVH) in Preterm Neonates

Intervention	Certainty of evidence	Risk difference (95% CI)
Antenatal corticosteroids	Moderate	-1 (0 to -2)
Indomethacin prophylaxis	Moderate	-5 (-3 to -8)
Volume-targeted ventilation	Low	-9 (-5 to -13)
Early erythropoiesis-stimulating agents	Low	-3 (-1 to -4)
Prophylactic ethamsylate	Low	-4 (0 to -7)
Umbilical cord milking	Low	3 (0 to 6)



Squares indicate the overall effect estimate from the meta-analysis for that intervention.

Cord Milking) trial,[112] which was prematurely terminated due to a higher rate of sIVH occurring with UCM than with DCC in neonates born at less than 32 weeks' gestation. In contrast, a recent network meta-analysis comparing DCC with UCM showed no difference in sIVH risk associated with UCM.[230] It is important to note that the network meta-analysis used a random-effects model, which weighed the studies relatively more equally than would a fixed-effects meta-analysis in the presence of heterogeneity. On the other hand, we used a fixed-effects model, which offered more weight to the large trials (therefore, the analysis was affected by the largest-conducted PREMOD-2 trial[112]), and there was no significant between-studies heterogeneity. Nevertheless, the overall sample size from all of the included trials contributing to the meta-analysis was insufficient; hence, more data for this intervention are required.

Among the neonatal interventions, indomethacin prophylaxis was associated with a moderate decrease in sIVH risk in preterm neonates (moderate certainty). The use of indomethacin prophylaxis for reducing sIVH risk is a better option compared with its use for reducing the incidence of PDA and PDA requiring surgical ligation, which is now becoming obsolete given the uncertainties of the management of PDA. However, the lack of a long-term neurodevelopment benefit may prevent clinicians from using indomethacin prophylaxis for the short-term benefit. Nonetheless, clinicians should consider the baseline risks; given that the risk of sIVH for a particular newborn may be higher, prophylaxis may be beneficial for some preterm neonates.

The meta-analysis found a large reduction in sIVH risk associated with volume-targeted ventilation compared with pressure-limited ventilation for preterm neonates with respiratory distress syndrome; however, the evidence had low certainty. Nevertheless, volume-targeted ventilation offers several benefits, such as reduction in pneumothorax, chronic lung disease, hypocarbia, and ventilation duration, which may support its use in preterm infants.[231] Despite these benefits, the uptake of volume-targeted ventilation has been slow, and efforts are ongoing to improve the understanding of volume-targeted ventilation and bridge the knowledge gap.[231]

The meta-analysis found a moderate reduction in sIVH and cPVL risk associated with early ESA (low certainty). However, the reduction in sIVH risk with early ESA was inconsistent across the studies, as evident by significant between-studies heterogeneity. Of the 3 large RCTs affecting the meta-analysis,[107,203,212] 2 multicenter trials[203,212] with substantial limitations in study design showed a large reduction in sIVH risk with erythropoietin. A recent multicenter RCT with no methodological concerns that included more fragile preterm infants (28 weeks' vs <32 weeks' gestation) and used a higher initial dose (1000 U/kg vs 500 U/kg) and prolonged duration (5-9 weeks vs 2 weeks) showed no reduction in sIVH risk with erythropoietin.[107] Similarly, the reduction in cPVL risk was inconsistent, and the studies had substantial methodological limitations. We also found a moderate decrease in sIVH risk with prophylactic ethamsylate administration and in severe brain injury risk with elective HFOV; however, the confidence in the estimate was low, and the trials assessed in the meta-analysis were older and may not reflect current practice.

Limitations

This systematic review and meta-analysis has several limitations. First, we did not study the treatment effects of the interventions for mortality, other short-term neonatal morbidities, and long-term neurodevelopmental outcomes, given that the study focused on comprehensively reviewing the interventions relevant to severe brain injury. Some of the interventions studied may not play a role in sIVH or severe brain injury but may be a considerable factor in other important outcomes; hence, to ensure the intervention is meaningful for a preterm newborn, clinicians should consider all of the critical outcomes in individual trials and their reviews. However, in the present study, we provided a balanced approach and conclusion for the potential interventions. Second, we evaluated interventions as decided a priori, which included an exhaustive list, but it may not be complete. Some interventions for preventing sIVH or severe brain injury, such as minimal handling of a preterm neonate, in utero transport for a premature neonate, hypothermia prevention, avoidance of boluses and bicarbonate therapy, and avoidance of fluctuation in carbon dioxide and blood pressure, have

not been studied, as it may not be feasible to evaluate them in RCTs. Third, we did not examine the treatment effects of the interventions in milder forms of brain injury, such as any IVH or any PVL, which may still have considerable implications for long-term neurodevelopmental outcomes. Fourth, we had limited data for several intervention comparisons and sparse data for the cPVL outcome.

Conclusions

In this systematic review and meta-analysis, a few interventions that were assessed in trials, including antenatal corticosteroids and indomethacin prophylaxis, were associated with reduction in sIVH risk with moderate certainty in preterm newborns; interventions such as volume-targeted ventilation, early ESAs, and prophylactic ethamsylate were associated with reduced risk with low certainty. However, clinicians should carefully consider all of the critical factors in such interventions, such as certainty of the evidence, effect size, clinical context, and methodological limitations and size of the studies included in the meta-analysis, before applying the interventions to clinical practice. This study offered a transparent and structured summary of the evidence using the GRADE approach, which may help readers understand the role of potential interventions in reducing the risk of severe brain injury in preterm neonates. Further studies are required to identify more interventions for reducing severe brain injury risk in preterm neonates. These studies should assess the implications of interventions for childhood neurodevelopmental outcomes.

ARTICLE INFORMATION

Accepted for Publication: February 23, 2023.

Published: April 13, 2023. doi:10.1001/jamanetworkopen.2023.7473

Corresponding Author: Abdul Razak, MD, Department of Pediatrics, Monash University, Melbourne, Victoria 3186, Australia (abdul.razak@monash.edu); Naveed Ur Rehman Durrani, MD, Department of Pediatrics, Sidra Medicine, Al Gharrafa St, Ar-Rayyan, Doha, Qatar (ndurrani@sidra.org).

Author Affiliations: Department of Pediatrics, Monash University, Melbourne, Victoria, Australia (Razak); Monash Newborn, Monash Children's Hospital, Melbourne, Victoria, Australia (Razak); Ritchie Centre, Hudson Institute of Medical Research, Melbourne, Victoria, Australia (Razak); Division of Neonatology, Department of Pediatrics, Sidra Medicine, Doha, Qatar (Patel, Durrani); Department of Pediatrics, Weill Cornell Medicine–Qatar, Doha, Qatar (Durrani); Health Sciences Library, Queen's University, Kingston, Ontario, Canada (Pullattayil).

Author Contributions: Drs Patel and Durrani had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Razak, Patel, and Durrani have contributed equally and are joint first authors.

Concept and design: Razak, Pullattayil.

Acquisition, analysis, or interpretation of data: Razak, Patel, Durrani.

Drafting of the manuscript: Razak, Patel, Pullattayil.

Critical revision of the manuscript for important intellectual content: Razak, Patel, Durrani.

Statistical analysis: Razak.

Administrative, technical, or material support: Razak, Patel, Durrani.

Supervision: Razak.

Conflict of Interest Disclosures: Dr. Razak reported receiving a doctoral scholarship from Monash University and the Lions Cord Blood Foundation.

Funding/Support: Open access funding was provided by Qatar National Library.

Role of the Funder/Sponsor: The funder had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Data Sharing Statement: See Supplement 2.

REFERENCES

1. Handley SC, Passarella M, Lee HC, Lorch SA. Incidence trends and risk factor variation in severe intraventricular hemorrhage across a population based cohort. *J Pediatr*. 2018;200:24-29.e3. doi:10.1016/j.jpeds.2018.04.020

2. Sarkar S, Shankaran S, Barks J, et al; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Outcome of preterm infants with transient cystic periventricular leukomalacia on serial cranial imaging up to term equivalent age. *J Pediatr*. 2018;195:59-65.e3. doi:10.1016/j.jpeds.2017.12.010

3. Gotardo JW, Volkmer NDFV, Stangler GP, Dornelles AD, Bohrer BBDA, Carvalho CG. Impact of peri-intraventricular haemorrhage and periventricular leukomalacia in the neurodevelopment of preterms: a systematic review and meta-analysis. *PLoS One*. 2019;14(10):e0223427. doi:10.1371/journal.pone.0223427

4. Welch V, Petticrew M, Petkovic J, et al; PRISMA-Equity Bellagio group. Extending the PRISMA statement to equity-focused systematic reviews (PRISMA-E 2012): explanation and elaboration. *Int J Equity Health*. 2015;14(1):92. doi:10.1186/s12939-015-0219-2

5. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. *J Pediatr*. 1978;92(4):529-534. doi:10.1016/S0022-3476(78)80282-0

6. de Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. *Behav Brain Res*. 1992;49(1):1-6. doi:10.1016/S0166-4328(05)80189-5

7. Schünemann H, Brożek J, Guyatt G, Oxman A, eds. *The GRADE Handbook for Grading Quality of Evidence and Strength of Recommendations*. Cochrane Collaboration; 2013.

8. Santesso N, Glenton C, Dahm P, et al; GRADE Working Group. GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions. *J Clin Epidemiol*. 2020;119:126-135. doi:10.1016/j.jclinepi.2019.10.014

9. Abuel Hamd WA, El Sherbiny DE, El Houchi SZ, Iskandar IF, Akmal DM. Sustained lung inflation in pre-term infants at birth: a randomized controlled trial. *J Trop Pediatr*. 2021;67(1):fmaa097. doi:10.1093/tropej/fmaa097

10. Aghajafari F, Murphy K, Ohlsson A, Amankwah K, Matthews S, Hannah ME. Multiple versus single courses of antenatal corticosteroids for preterm birth: a pilot study. *J Obstet Gynaecol Can*. 2002;24(4):321-329. doi:10.1016/S1701-2163(16)30625-9

11. Aguar M, Brugada M, Escobar J, et al. Resuscitation of ELBW infants with initial FiO2 of 30% vs. 60%, a randomized, controlled, blinded study: the REOX trial. Presented at: Pediatric Academic Societies Annual Meeting; May 4-7, 2013; Washington, DC.

12. Al-Abdi S, Alallah J, Al Omran A, Al Alwan Q, Al Hashimi H, Haidar S. The risk of intraventricular hemorrhage with flat midline versus flat right lateral head positions: a prematurely terminated multicenter randomized clinical trial. Presented at: Pediatric Academic Societies Annual Meeting; April 25-28 2015; San Diego, CA.

13. Al-Abdi SY, Nojoom MS, Alshaalan HM, Al-Aamri MA. Pilot-randomized study on intraventricular hemorrhage with midline versus lateral head positions. *Saudi Med J*. 2011;32(4):420-421.

14. Alan S, Arsan S, Okulu E, et al. Effects of umbilical cord milking on the need for packed red blood cell transfusions and early neonatal hemodynamic adaptation in preterm infants born ≤1500 g: a prospective, randomized, controlled trial. *J Pediatr Hematol Oncol*. 2014;36(8):e493-e498. doi:10.1097/MPH.0000000000000143

15. Amaro CM, Bello JA, Jain D, et al. Early caffeine and weaning from mechanical ventilation in preterm infants: a randomized, placebo-controlled trial. *J Pediatr*. 2018;196:52-57. doi:10.1016/j.jpeds.2018.01.010

16. Amato M, Hüppi P, Markus D. Prevention of symptomatic patent ductus arteriosus with ethamsylate in babies treated with exogenous surfactant. *J Perinatol*. 1993;13(1):2-7.

17. Anand KJ, Barton BA, McIntosh N, et al. Analgesia and sedation in preterm neonates who require ventilatory support: results from the NOPAIN trial—Neonatal Outcome and Prolonged Analgesia in Neonates. *Arch Pediatr Adolesc Med*. 1999;153(4):331-338. doi:10.1001/archpedi.153.4.331

18. Anand KJS, Hall RW, Desai N, et al; NEOPAIN Trial Investigators Group. Effects of morphine analgesia in ventilated preterm neonates: primary outcomes from the NEOPAIN randomised trial. *Lancet*. 2004;363(9422):1673-1682. doi:10.1016/S0140-6736(04)16251-X

19. Aranda JV, Clyman R, Cox B, et al. A randomized, double-blind, placebo-controlled trial on intravenous ibuprofen L-lysine for the early closure of nonsymptomatic patent ductus arteriosus within 72 hours of birth in extremely low-birth-weight infants. *Am J Perinatol*. 2009;26(3):235-245. doi:10.1055/s-0028-1103515

20. Armanian A, Ghasemi Tehrani H, Ansari M, Ghaemi S. Is "delayed umbilical cord clamping" beneficial for premature newborns? *Int J Pediatr*. 2017;5(5):4909-4918. doi:10.22038/ijp.2016.7909

21. August Fuhr N, Becker C, van Baalen A, Bauer K, Hopp H. Antibiotic therapy for preterm premature rupture of membranes—results of a multicenter study. *J Perinat Med*. 2006;34(3):203-206. doi:10.1515/JPM.2006.035

22. Backes CH, Huang H, Iams JD, Bauer JA, Giannone PJ. Timing of umbilical cord clamping among infants born at 22 through 27 weeks' gestation. *J Perinatol*. 2016;36(1):35-40. doi:10.1038/jp.2015.117

23. Bada HS, Green RS, Pourcyrous M, et al. Indomethacin reduces the risks of severe intraventricular hemorrhage. *J Pediatr*. 1989;115(4):631-637. doi:10.1016/S0022-3476(89)80300-2

24. Bandstra ES, Montalvo BM, Goldberg RN, et al. Prophylactic indomethacin for prevention of intraventricular hemorrhage in premature infants. *Pediatrics*. 1988;82(4):533-542. doi:10.1542/peds.82.4.533

25. Bao Y, Zhang G, Wu M, Ma L, Zhu J. A pilot study of less invasive surfactant administration in very preterm infants in a Chinese tertiary center. *BMC Pediatr*. 2015;15(1):21. doi:10.1186/s12887-015-0342-7

26. Barekatain B, Saraeian S, Farghadani M, et al. Effect of vitamin E in prevention of intraventricular hemorrhage in preterm neonates. *Int J Prev Med*. 2018;9(97):97. doi:10.4103/ijpvm.IJPVM_296_17

27. Bell EF Sr, Strauss RG, Widness JA, et al. Randomized trial of liberal versus restrictive guidelines for red blood cell transfusion in preterm infants. *Pediatrics*. 2005;115(6):1685-1691. doi:10.1542/peds.2004-1884

28. Benson JW, Drayton MR, Hayward C, et al. Multicentre trial of ethamsylate for prevention of periventricular haemorrhage in very low birthweight infants. *Lancet*. 1986;2(8519):1297-1300. doi:10.1016/S0140-6736(86)91432-7

29. Bental RY, Cooper PA, Cummins RR, Sandler DL, Wainer S, Rotschild A. Vitamin A therapy—effects on the incidence of bronchopulmonary dysplasia. *South African Journal of Food Science and Nutrition*. 1994;6(4):141-145.

30. Beverley DW, Pitts-Tucker TJ, Congdon PJ, Arthur RJ, Tate G. Prevention of intraventricular haemorrhage by fresh frozen plasma. *Arch Dis Child*. 1985;60(8):710-713. doi:10.1136/adc.60.8.710

31. Bichkar VV, Mondkar J, Manerkar S, Bhisikar S. Umbilical cord milking reduces duration of inotrope support in preterm infants less than 32 weeks of gestation, born with caesarean section in comparison to delayed cord clamping. *Int J Sci Stud*. 2019;7(7):38-43.

32. Bierer R, Peceny MC, Hartenberger CH, Ohls RK. Erythropoietin concentrations and neurodevelopmental outcome in preterm infants. *Pediatrics*. 2006;118(3):e635-e640. doi:10.1542/peds.2005-3186

33. Boronat N, Aguar M, Rook D, et al. Survival and neurodevelopmental outcomes of preterms resuscitated with different oxygen fractions. *Pediatrics*. 2016;138(6):e20161405. doi:10.1542/peds.2016-1405

34. Carlo WA, Stark AR, Bauer C, et al. Effects of minimal ventilation in a multicenter randomized controlled trial of ventilator support and early corticosteroid therapy in extremely low birth weight infants. *Pediatrics*. 1999;104(suppl):738.

35. Carlo WA, Stark AR, Wright LL, et al. Minimal ventilation to prevent bronchopulmonary dysplasia in extremely-low-birth-weight infants. *J Pediatr*. 2002;141(3):370-374. doi:10.1067/mpd.2002.127507

36. Chang GY, Lueder FL, DiMichele DM, Radkowski MA, McWilliams LJ, Jansen RD. Heparin and the risk of intraventricular hemorrhage in premature infants. *J Pediatr*. 1997;131(3):362-366. doi:10.1016/S0022-3476(97)80059-5

37. Chen CY, Wang KG, Chang TY, Chen CP, Loo JH. Effects of antenatal betamethasone and dexamethasone in preterm neonates. *Taiwan J Obstet Gynecol*. 2005;44(3):247-251. doi:10.1016/S1028-4559(09)60147-9

38. Chen HL, Tseng HI, Lu CC, Yang SN, Fan HC, Yang RC. Effect of blood transfusions on the outcome of very low body weight preterm infants under two different transfusion criteria. *Pediatr Neonatol*. 2009;50(3):110-116. doi:10.1016/S1875-9572(09)60045-0

39. Chen JY. Ethamsylate in the prevention of periventricular-intraventricular hemorrhage in premature infants. *J Formos Med Assoc*. 1993;92(10):889-893. doi:10.1016/j.jfma.2016.06.004

40. Chowdhury O, Patel DS, Hannam S, et al. Randomised trial of volume-targeted ventilation versus pressure-limited ventilation in acute respiratory failure in prematurely born infants. *Neonatology*. 2013;104(4):290-294. doi:10.1159/000353956

41. Chu KS, Shah PS, Whittle WL, Windrim R, Murphy KE. The "DUC" trial: a pilot randomized controlled trial of immediate versus delayed cord clamping in preterm infants born between 24 and 32 weeks gestation. *J Matern Fetal Neonatal Med*. 2021;34(24):4049-4052. doi:10.1080/14767058.2019.1702959

42. Clark RH, Gerstmann DR, Null DM Jr, deLemos RA. Prospective randomized comparison of high-frequency oscillatory and conventional ventilation in respiratory distress syndrome. *Pediatrics*. 1992;89(1):5-12. doi:10.1542/peds.89.1.5

43. Oladapo OT, Vogel JP, Piaggio G, et al; WHO ACTION Trials Collaborators. Antenatal dexamethasone for early preterm birth in low-resource countries. *N Engl J Med*. 2020;383(26):2514-2525. doi:10.1056/NEJMoa2022398

44. Connelly RJ, Stone SH, Whyte RK. Early vs. late red cell transfusion in low birth weight infants 986. *Pediatr Res*. 1998;43(suppl 4):170. doi:10.1203/00006450-199804001-01007

45. Courtney SE, Durand DJ, Asselin JM, Hudak ML, Aschner JL, Shoemaker CT; Neonatal Ventilation Study Group. High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. *N Engl J Med*. 2002;347(9):643-652. doi:10.1056/NEJMoa012750

46. Couser RJ, Ferrara TB, Wright GB, et al. Prophylactic indomethacin therapy in the first twenty-four hours of life for the prevention of patent ductus arteriosus in preterm infants treated prophylactically with surfactant in the delivery room. *J Pediatr*. 1996;128(5 pt 1):631-637. doi:10.1016/S0022-3476(96)80127-2

47. Craft AP, Bhandari V, Finer NN. The sy-fi study: a randomized prospective trial of synchronized intermittent mandatory ventilation versus a high-frequency flow interrupter in infants less than 1000 g. *J Perinatol*. 2003;23 (1):14-19. doi:10.1038/sj.jp.7210849

48. Crowther CA, Ashwood P, Andersen CC, et al; ASTEROID Study Group. Maternal intramuscular dexamethasone versus betamethasone before preterm birth (ASTEROID): a multicentre, double-blind, randomised controlled trial. *Lancet Child Adolesc Health*. 2019;3(11):769-780. doi:10.1016/S2352-4642(19) 30292-5

49. Crowther CA, Haslam RR, Hiller JE, Doyle LW, Robinson JS; Australasian Collaborative Trial of Repeat Doses of Steroids (ACTORDS) Study Group. Neonatal respiratory distress syndrome after repeat exposure to antenatal corticosteroids: a randomised controlled trial. *Lancet*. 2006;367(9526):1913-1919. doi:10.1016/S0140-6736(06) 68846-6

50. Crowther CA, Hiller JE, Doyle LW, Haslam RR; Australasian Collaborative Trial of Magnesium Sulphate (ACTOMg SO4) Collaborative Group. Effect of magnesium sulfate given for neuroprotection before preterm birth: a randomized controlled trial. *JAMA*. 2003;290(20):2669-2676. doi:10.1001/jama.290.20.2669

51. Curley A, Stanworth SJ, Willoughby K, et al; PlaNeT2 MATISSE Collaborators. Randomized trial of platelet-transfusion thresholds in neonates. *N Engl J Med*. 2019;380(3):242-251. doi:10.1056/NEJMoa1807320

52. D'Angio CT, Chess PR, Kovacs SJ, et al. Pressure-regulated volume control ventilation vs synchronized intermittent mandatory ventilation for very low-birth-weight infants: a randomized controlled trial. *Arch Pediatr Adolesc Med*. 2005;159(9):868-875. doi:10.1001/archpedi.159.9.868

53. Danan C, Durrmeyer X, Brochard L, Decobert F, Benani M, Dassieu G. A randomized trial of delayed extubation for the reduction of reintubation in extremely preterm infants. *Pediatr Pulmonol*. 2008;43(2):117-124. doi:10. 1002/ppul.20726

54. Dani C, Bertini G, Pezzati M, et al; IntraVentricular Ibuprofen Study Group. Prophylactic ibuprofen for the prevention of intraventricular hemorrhage among preterm infants: a multicenter, randomized study. *Pediatrics*. 2005;115(6):1529-1535. doi:10.1542/peds.2004-1178

55. Dani C, Bertini G, Reali MF, et al. Prophylaxis of patent ductus arteriosus with ibuprofen in preterm infants. *Acta Paediatr*. 2000;89(11):1369-1374. doi:10.1111/j.1651-2227.2000.tb00767.x

56. De Carolis MP, Romagnoli C, Polimeni V, et al. Prophylactic ibuprofen therapy of patent ductus arteriosus in preterm infants. *Eur J Pediatr*. 2000;159(5):364-368. doi:10.1007/s004310051288

57. Domanico RS, Waldman JD, Lester LA, McPhillips HA, Catrambone JE, Covert RF. Prophylactic indomethacin reduces the incidence of pulmonary hemorrhage and patent ductus arteriosus in surfactant treated <1250 g. *Pediatr Res*. 1994;35:331A.

58. Dong X-Y, Sun X-F, Li M-M, Yu Z-B, Han S-P. Influence of delayed cord clamping on preterm infants with a gestational age of <32 weeks. Article in Chinese. *Zhongguo Dang Dai Er Ke Za Zhi*. 2016;18(7):635-638.

59. Duley L, Dorling J, Pushpa-Rajah A, et al; Cord Pilot Trial Collaborative Group. Randomised trial of cord clamping and initial stabilisation at very preterm birth. *Arch Dis Child Fetal Neonatal Ed*. 2018;103(1):F6-F14. doi: 10.1136/archdischild-2016-312567

60. Duman N, Tuzun F, Sutcuoglu S, Yesilirmak CD, Kumral A, Ozkan H. Impact of volume guarantee on synchronized ventilation in preterm infants: a randomized controlled trial. *Intensive Care Med*. 2012;38(8): 1358-1364. doi:10.1007/s00134-012-2601-5

61. Durand DJ, Asselin JM, Hudak ML, et al. Early high-frequency oscillatory ventilation versus synchronized intermittent mandatory ventilation in very low birth weight infants: a pilot study of two ventilation protocols. *J Perinatol*. 2001;21(4):221-229. doi:10.1038/sj.jp.7210527

62. El-Fattah NA, Nasef N, Al-Harrass MF, Khashaba M. Sustained lung inflation at birth for preterm infants at risk of respiratory distress syndrome: the proper pressure and duration. *J Neonatal Perinatal Med*. 2017;10(4): 409-417. doi:10.3233/NPM-171760

63. El-Naggar W, McMillan D, Hussain A, et al. The effect of umbilical cord milking on cerebral blood flow in very preterm infants: a randomized controlled study. *J Perinatol*. 2021;41(2):263-268. doi:10.1038/s41372-020-00780-2

64. Elimian A, Garry D, Figueroa R, Spitzer A, Wiencek V, Quirk JG. Antenatal betamethasone compared with dexamethasone (Betacode Trial): a randomized controlled trial. *Obstet Gynecol*. 2007;110(1):26-30. doi:10.1097/01.AOG.0000268281.36788.81

65. Elimian A, Goodman J, Escobedo M, Nightingale L, Knudtson E, Williams M. Immediate compared with delayed cord clamping in the preterm neonate: a randomized controlled trial. *Obstet Gynecol*. 2014;124(6):1075-1079. doi:10.1097/AOG.0000000000000556

66. Eronen M, Kari A, Pesonen E, Hallman M. The effect of antenatal dexamethasone administration on the fetal and neonatal ductus arteriosus: a randomized double-blind study. *AJDC*. 1993;147(2):187-192.

67. Escrig R, Arruza L, Izquierdo I, et al. Achievement of targeted saturation values in extremely low gestational age neonates resuscitated with low or high oxygen concentrations: a prospective, randomized trial. *Pediatrics*. 2008;121(5):875-881. doi:10.1542/peds.2007-1984

68. Fauchère JC, Koller BM, Tschopp A, Dame C, Ruegger C, Bucher HU; Swiss Erythropoietin Neuroprotection Trial Group. Safety of early high-dose recombinant erythropoietin for neuroprotection in very preterm infants. *J Pediatr*. 2015;167(1):52-57.e1-e3. doi:10.1016/j.jpeds.2015.02.052

69. Fauchère JC, Dame C, Vonthein R, et al. An approach to using recombinant erythropoietin for neuroprotection in very preterm infants. *Pediatrics*. 2008;122(2):375-382. doi:10.1542/peds.2007-2591

70. Finn D, Ryan DH, Pavel A, et al. Clamping the Umbilical Cord in Premature Deliveries (CUPiD): neuromonitoring in the immediate newborn period in a randomized, controlled trial of preterm infants born at <32 weeks of gestation. *J Pediatr*. 2019;208:121-126.e2. doi:10.1016/j.jpeds.2018.12.039

71. Fish WH, Cohen M, Franzek D, Williams JM, Lemons JA. Effect of intramuscular vitamin E on mortality and intracranial hemorrhage in neonates of 1000 grams or less. *Pediatrics*. 1990;85(4):578-584. doi:10.1542/peds.85.4.578

72. Fox MD, Allbert JR, McCaul JF, Martin RW, McLaughlin BN, Morrison JC. Neonatal morbidity between 34 and 37 weeks' gestation. *J Perinatol*. 1993;13(5):349-353.

73. Franz AR, Engel C, Bassler D, et al; ETTNO Investigators. Effects of liberal vs restrictive transfusion thresholds on survival and neurocognitive outcomes in extremely low-birth-weight infants: the ETTNO randomized clinical trial. *JAMA*. 2020;324(6):560-570. doi:10.1001/jama.2020.10690

74. Fulia F, Cordaro S, Meo P, et al. Can the administration of antithrombin III decrease the risk of cerebral hemorrhage in premature infants? *Biol Neonate*. 2003;83(1):1-5. doi:10.1159/000067005

75. Garite TJ, Kurtzman J, Maurel K, Clark R; Obstetrix Collaborative Research Network. Impact of a 'rescue course' of antenatal corticosteroids: a multicenter randomized placebo-controlled trial. *Am J Obstet Gynecol*. 2009;200(3):248.e1-248.e9. doi:10.1016/j.ajog.2009.01.021

76. Garite TJ, Rumney PJ, Briggs GG, et al. A randomized, placebo-controlled trial of betamethasone for the prevention of respiratory distress syndrome at 24 to 28 weeks' gestation. *Am J Obstet Gynecol*. 1992;166(2):646-651. doi:10.1016/0002-9378(92)91691-3

77. Gerstmann DR, Minton SD, Stoddard RA, et al. The Provo multicenter early high-frequency oscillatory ventilation trial: improved pulmonary and clinical outcome in respiratory distress syndrome. *Pediatrics*. 1996;98(6 pt 1):1044-1057. doi:10.1542/peds.98.6.1044

78. Gill AB, Weindling AM. Randomised controlled trial of plasma protein fraction versus dopamine in hypotensive very low birthweight infants. *Arch Dis Child*. 1993;69(3 Spec No):284-287. doi:10.1136/adc.69.3_Spec_No.284

79. Göpel W, Kribs A, Ziegler A, et al; German Neonatal Network. Avoidance of mechanical ventilation by surfactant treatment of spontaneously breathing preterm infants (AMV): an open-label, randomised, controlled trial. *Lancet*. 2011;378(9803):1627-1634. doi:10.1016/S0140-6736(11)60986-0

80. Gournay V, Roze JC, Kuster A, et al. Prophylactic ibuprofen versus placebo in very premature infants: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364(9449):1939-1944. doi:10.1016/S0140-6736(04)17476-X

81. Grable IA, Garcia PM, Perry D, Socol ML. Group B Streptococcus and preterm premature rupture of membranes: a randomized, double-blind clinical trial of antepartum ampicillin. *Am J Obstet Gynecol*. 1996;175(4 pt 1):1036-1042. doi:10.1016/S0002-9378(96)80049-4

82. Gray PH, Flenady VJ, Charles BG, Steer PA; Caffeine Collaborative Study Group. Caffeine citrate for very preterm infants: effects on development, temperament and behaviour. *J Paediatr Child Health*. 2011;47(4):167-172. doi:10.1111/j.1440-1754.2010.01943.x

83. HIFI Study Group. High-frequency oscillatory ventilation compared with conventional mechanical ventilation in the treatment of respiratory failure in preterm infants. *N Engl J Med*. 1989;320(2):88-93. doi:10.1056/NEJM198901123200204

84. A randomized trial comparing the effect of prophylactic intravenous fresh frozen plasma, gelatin or glucose on early mortality and morbidity in preterm babies. The Northern Neonatal Nursing Initiative [NNNI] Trial Group. *Eur J Pediatr*. 1996;155(7):580-588. doi:10.1007/BF01957909

85. The EC Ethamsylate Trial Group. The EC randomised controlled trial of prophylactic ethamsylate for very preterm neonates: early mortality and morbidity. *Arch Dis Child Fetal Neonatal Ed*. 1994;70(3):F201-F205. doi:10.1136/fn.70.3.F201

86. Guinn DA, Atkinson MW, Sullivan L, et al. Single vs weekly courses of antenatal corticosteroids for women at risk of preterm delivery: a randomized controlled trial. *JAMA*. 2001;286(13):1581-1587. doi:10.1001/jama.286.13.1581

87. Gupta BK, Saha AK, Mukherjee S, Saha B. Minimally invasive surfactant therapy versus InSurE in preterm neonates of 28 to 34 weeks with respiratory distress syndrome on non-invasive positive pressure ventilation—a randomized controlled trial. *Eur J Pediatr*. 2020;179(8):1287-1293. doi:10.1007/s00431-020-03682-9

88. Guven S, Bozdag S, Saner H, Cetinkaya M, Yazar AS, Erguven M. Early neonatal outcomes of volume guaranteed ventilation in preterm infants with respiratory distress syndrome. *J Matern Fetal Neonatal Med*. 2013;26(4):396-401. doi:10.3109/14767058.2012.733778

89. Gyamfi-Bannerman C, Thom EA, Blackwell SC, et al; NICHD Maternal–Fetal Medicine Units Network. Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med*. 2016;374(14):1311-1320. doi:10.1056/NEJMoa1516783

90. Haiden N, Cardona F, Schwindt J, et al. Changes in thrombopoiesis and platelet reactivity in extremely low birth weight infants undergoing erythropoietin therapy for treatment of anaemia of prematurity. *Thromb Haemost*. 2005;93(1):118-123. doi:10.1160/TH04-02-0093

91. Han T, Liu H, Zhang H, et al. Minimally invasive surfactant administration for the treatment of neonatal respiratory distress syndrome: a multicenter randomized study in China. *Front Pediatr*. 2020;8:182. doi:10.3389/fped.2020.00182

92. Hanigan WC, Kennedy G, Roemisch F, Anderson R, Cusack T, Powers W. Administration of indomethacin for the prevention of periventricular-intraventricular hemorrhage in high-risk neonates. *J Pediatr*. 1988;112(6):941-947. doi:10.1016/S0022-3476(88)80224-5

93. Hemmati F, Sharma D, Namavar Jahromi B, Salarian L, Farahbakhsh N. Delayed cord clamping for prevention of intraventricular hemorrhage in preterm neonates: a randomized control trial. *J Matern Fetal Neonatal Med*. 2022;35(19):3633-3639. doi:10.1080/14767058.2020.1836148

94. Hentschel R, Hensel D, Brune T, Rabe H, Jorch G. Impact on blood pressure and intestinal perfusion of dobutamine or dopamine in hypotensive preterm infants. *Biol Neonate*. 1995;68(5):318-324. doi:10.1159/000244252

95. Randomized study of high-frequency oscillatory ventilation in infants with severe respiratory distress syndrome: HiFO Study Group. *J Pediatr*. 1993;122(4):609-619. doi:10.1016/S0022-3476(05)83548-6

96. Hittner HM, Godio LB, Rudolph AJ, et al. Retrolental fibroplasia: efficacy of vitamin E in a double-blind clinical study of preterm infants. *N Engl J Med*. 1981;305(23):1365-1371. doi:10.1056/NEJM198112033052301

97. Hittner HM, Speer ME, Rudolph AJ, et al. Retrolental fibroplasia and vitamin E in the preterm infant-comparison of oral versus intramuscular:oral administration. *Pediatrics*. 1984;73(2):238-249. doi:10.1542/peds.73.2.238

98. Hofmeyr GJ, Bolton KD, Bowen DC, Govan JJ. Periventricular/intraventricular haemorrhage and umbilical cord clamping. Findings and hypothesis. *S Afr Med J*. 1988;73(2):104-106.

99. Hofmeyr GJ, Gobetz L, Bex PJ, et al. Periventricular/intraventricular hemorrhage following early and delayed umbilical cord clamping. A randomized controlled trial. *Online J Curr Clin Trials*. 1993;Doc No 110.

100. Hosono S, Mugishima H, Fujita H, et al. Umbilical cord milking reduces the need for red cell transfusions and improves neonatal adaptation in infants born at less than 29 weeks' gestation: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed*. 2008;93(1):F14-F19. doi:10.1136/adc.2006.108902

101. How HY, Cook CR, Cook VD, Miles DE, Spinnato JA. Preterm premature rupture of membranes: aggressive tocolysis versus expectant management. *J Matern Fetal Med*. 1998;7(1):8-12. doi:10.1002/(SICI)1520-6661(199801/02)7:1<8::AID-MFM2>3.0.CO;2-S

102. Iranpour R, Armanian AM, Miladi N, Feizi A. Effect of prophylactic caffeine on noninvasive respiratory support in preterm neonates weighing 1250-2000 g: a randomized controlled trial. *Arch Iran Med*. 2022;25(2):98-104. doi:10.34172/aim.2022.16

103. Jena SR, Bains HS, Pandita A, et al; on behalf of Sure Group. Surfactant therapy in premature babies: SurE or InSurE. *Pediatr Pulmonol*. 2019;54(11):1747-1752. doi:10.1002/ppul.24479

104. Jiravisitkul P, Rattanasiri S, Nuntnarumit P. Randomised controlled trial of sustained lung inflation for resuscitation of preterm infants in the delivery room. *Resuscitation*. 2017;111:68-73. doi:10.1016/j.resuscitation.2016.12.003

105. Johnson AH, Peacock JL, Greenough A, et al; United Kingdom Oscillation Study Group. High-frequency oscillatory ventilation for the prevention of chronic lung disease of prematurity. *N Engl J Med*. 2002;347(9):633-642. doi:10.1056/NEJMoa020432

106. Josephsen JB, Potter S, Armbrecht ES, Al-Hosni M. Umbilical cord milking in extremely preterm infants: a randomized controlled trial comparing cord milking with immediate cord clamping. *Am J Perinatol*. 2022;39(4):436-443. doi:10.1055/s-0040-1716484

107. Juul SE, Comstock BA, Wadhawan R, et al; PENUT Trial Consortium. A randomized trial of erythropoietin for neuroprotection in preterm infants. *N Engl J Med*. 2020;382(3):233-243. doi:10.1056/NEJMoa1907423

108. Kalani M, Shariat M, Khalesi N, Farahani Z, Ahmadi S. A comparison of early ibuprofen and indomethacin administration to prevent intraventricular hemorrhage among preterm infants. *Acta Med Iran*. 2016;54(12):788-792.

109. Kanmaz G, Erdeve O, Canpolat FE, et al. Serum ibuprofen levels of extremely preterm infants treated prophylactically with oral ibuprofen to prevent patent ductus arteriosus. *Eur J Clin Pharmacol*. 2013;69(5):1075-1081. doi:10.1007/s00228-012-1438-8

110. Kapadia VS, Chalak LF, Sparks JE, Allen JR, Savani RC, Wyckoff MH. Resuscitation of preterm neonates with limited versus high oxygen strategy. *Pediatrics*. 2013;132(6):e1488-e1496. doi:10.1542/peds.2013-0978

111. Katheria A, Poeltler D, Durham J, et al. Neonatal resuscitation with an intact cord: a randomized clinical trial. *J Pediatr*. 2016;178:75-80.e3. doi:10.1016/j.jpeds.2016.07.053

112. Katheria A, Reister F, Essers J, et al. Association of umbilical cord milking vs delayed umbilical cord clamping with death or severe intraventricular hemorrhage among preterm infants. *JAMA*. 2019;322(19):1877-1886. doi:10.1001/jama.2019.16004

113. Katheria AC, Leone TA, Woelkers D, Garey DM, Rich W, Finer NN. The effects of umbilical cord milking on hemodynamics and neonatal outcomes in premature neonates. *J Pediatr*. 2014;164(5):1045-1050.e1. doi:10.1016/j.jpeds.2014.01.024

114. Katheria AC, Szychowski JM, Essers J, et al. Early cardiac and cerebral hemodynamics with umbilical cord milking compared with delayed cord clamping in infants born preterm. *J Pediatr*. 2020;223:51-56.e1. doi:10.1016/j.jpeds.2020.04.010

115. Katheria AC, Truong G, Cousins L, Oshiro B, Finer NN. Umbilical cord milking versus delayed cord clamping in preterm infants. *Pediatrics*. 2015;136(1):61-69. doi:10.1542/peds.2015-0368

116. Keszler M, Abubakar K. Volume guarantee: stability of tidal volume and incidence of hypocarbia. *Pediatr Pulmonol*. 2004;38(3):240-245. doi:10.1002/ppul.20063

117. Keszler M, Modanlou HD, Brudno DS, et al. Multicenter controlled clinical trial of high-frequency jet ventilation in preterm infants with uncomplicated respiratory distress syndrome. *Pediatrics*. 1997;100(4):593-599. doi:10.1542/peds.100.4.593

118. Kiatchoosakun P, Jirapradittha J, Panthongviriyakul MC, Khampitak T, Yongvanit P, Boonsiri P. Vitamin A supplementation for prevention of bronchopulmonary dysplasia in very-low-birth-weight premature Thai infants: a randomized trial. *J Med Assoc Thai*. 2014;97(suppl 10):S82-S88.

119. Kirpalani H, Ratcliffe SJ, Keszler M, et al; SAIL Site Investigators. Effect of sustained inflations vs intermittent positive pressure ventilation on bronchopulmonary dysplasia or death among extremely preterm infants: the SAIL randomized clinical trial. *JAMA*. 2019;321(12):1165-1175. doi:10.1001/jama.2019.1660

120. Kirpalani H, Bell EF, Hintz SR, et al; Eunice Kennedy Shriver NICHD Neonatal Research Network. Higher or lower hemoglobin transfusion thresholds for preterm infants. *N Engl J Med*. 2020;383(27):2639-2651. doi:10.1056/NEJMoa2020248

121. Kirpalani H, Whyte RK, Andersen C, et al. The Premature Infants in Need of Transfusion (PINT) study: a randomized, controlled trial of a restrictive (low) versus liberal (high) transfusion threshold for extremely low birth weight infants. *J Pediatr*. 2006;149(3):301-307. doi:10.1016/j.jpeds.2006.05.011

122. Klarr JM, Faix RG, Pryce CJ, Bhatt-Mehta V. Randomized, blind trial of dopamine versus dobutamine for treatment of hypotension in preterm infants with respiratory distress syndrome. *J Pediatr*. 1994;125(1):117-122. doi:10.1016/S0022-3476(94)70137-7

123. Kluckow M, Jeffery M, Gill A, Evans N. A randomised placebo-controlled trial of early treatment of the patent ductus arteriosus. *Arch Dis Child Fetal Neonatal Ed*. 2014;99(2):F99-F104. doi:10.1136/archdischild-2013-304695

124. Kochan M, Leonardi B, Firestine A, et al. Elevated midline head positioning of extremely low birth weight infants: effects on cardiopulmonary function and the incidence of periventricular-intraventricular hemorrhage. *J Perinatol*. 2019;39(1):54-62. doi:10.1038/s41372-018-0261-1

125. Kribs A, Roll C, Göpel W, et al; NINSAPP Trial Investigators. Nonintubated surfactant application vs conventional therapy in extremely preterm infants: a randomized clinical trial. *JAMA Pediatr*. 2015;169(8):723-730. doi:10.1001/jamapediatrics.2015.0504

126. Krishna G, Skariah TA, Edward LL. Volume-guaranteed ventilation versus pressure-controlled ventilation in preterm infants with respiratory distress syndrome: a randomized controlled trial. *IJN Iranian Journal of Neonatology*. 2019;10(2):42-46. doi:10.22038/ijn.2018.33533.1490

127. Krueger E, Mellander M, Bratton D, Cotton R. Prevention of symptomatic patent ductus arteriosus with a single dose of indomethacin. *J Pediatr*. 1987;111(5):749-754. doi:10.1016/S0022-3476(87)80262-7

128. Kugelman A, Borenstein-Levin L, Riskin A, et al. Immediate versus delayed umbilical cord clamping in premature neonates born < 35 weeks: a prospective, randomized, controlled study. *Am J Perinatol*. 2007;24(5):307-315. doi:10.1055/s-2007-981434

129. Kumar J, Dutta S, Sundaram V, Saini SS, Sharma RR, Varma N. Platelet transfusion for PDA closure in preterm infants: a randomized controlled trial. *Pediatrics*. 2019;143(5):e2018-e2045. doi:10.1542/peds.2018-2565

130. La Verde A, Franchini S, Lapergola G, et al. Effects of sustained inflation or positive pressure ventilation on the release of adrenomedullin in preterm infants with respiratory failure at birth. *Am J Perinatol*. 2019;36(S 02):S110-S114. doi:10.1055/s-0039-1692133

131. Lago P, Benini F, Agosto C, Zacchello F. Randomised controlled trial of low dose fentanyl infusion in preterm infants with hyaline membrane disease. *Arch Dis Child Fetal Neonatal Ed*. 1998;79(3):F194-F197. doi:10.1136/fn.79.3.F194

132. Lee MJ, Davies J, Guinn D, et al. Single versus weekly courses of antenatal corticosteroids in preterm premature rupture of membranes. *Obstet Gynecol*. 2004;103(2):274-281. doi:10.1097/01.AOG.0000110249.84858.90

133. Lewis DF, Brody K, Edwards MS, Brouillette RM, Burlison S, London SN. Preterm premature ruptured membranes: a randomized trial of steroids after treatment with antibiotics. *Obstet Gynecol*. 1996;88(5):801-805. doi:10.1016/0029-7844(96)00319-5

134. Li J, Yu B, Wang W, Luo D, Dai QL, Gan XQ. Does intact umbilical cord milking increase infection rates in preterm infants with premature prolonged rupture of membranes? *J Matern Fetal Neonatal Med*. 2020;33(2):184-190. doi:10.1080/14767058.2018.1487947

135. Lindner W, Högel J, Pohlandt F. Sustained pressure-controlled inflation or intermittent mandatory ventilation in preterm infants in the delivery room? a randomized, controlled trial on initial respiratory support via nasopharyngeal tube. *Acta Paediatr*. 2005;94(3):303-309.

136. Lista G, Boni L, Scopesi F, et al; SLI Trial Investigators. Sustained lung inflation at birth for preterm infants: a randomized clinical trial. *Pediatrics*. 2015;135(2):e457-e464. doi:10.1542/peds.2014-1692

137. Lista G, Castoldi F, Bianchi S, Battaglioli M, Cavigioli F, Bosoni MA. Volume guarantee versus high-frequency ventilation: lung inflammation in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 2008;93(4):F252-F256. doi:10.1136/adc.2006.112102

138. Lista G, Colnaghi M, Castoldi F, et al. Impact of targeted-volume ventilation on lung inflammatory response in preterm infants with Respiratory Distress Syndrome (RDS). *Pediatr Pulmonol*. 2004;37(6):510-514. doi:10.1002/ppul.10458

139. Liu CQ, Cui Z, Xia YF, Ma L, Fan LL. Randomized controlled study of targeted tidal volume ventilation for treatment of severe neonatal respiratory distress syndrome. Article in Chinese. *Zhongguo Dang Dai Er Ke Za Zhi*. 2011;13(9):696-699.

140. Lundstrøm KE, Pryds O, Greisen G. Oxygen at birth and prolonged cerebral vasoconstriction in preterm infants. *Arch Dis Child Fetal Neonatal Ed*. 1995;73(2):F81-F86. doi:10.1136/fn.73.2.F81

141. Mactier H, McCulloch DL, Hamilton R, et al. Vitamin A supplementation improves retinal function in infants at risk of retinopathy of prematurity. *J Pediatr*. 2012;160(6):954-959.e1. doi:10.1016/j.jpeds.2011.12.013

142. Maier RF, Obladen M, Scigalla P, et al; European Multicentre Erythropoietin Study Group. The effect of epoetin beta (recombinant human erythropoietin) on the need for transfusion in very-low-birth-weight infants. *N Engl J Med*. 1994;330(17):1173-1178. doi:10.1056/NEJM199404283301701

143. March MI, Hacker MR, Parson AW, Modest AM, de Veciana M. The effects of umbilical cord milking in extremely preterm infants: a randomized controlled trial. *J Perinatol*. 2013;33(10):763-767. doi:10.1038/jp.2013.70

144. Mariani G, Cifuentes J, Carlo WA. Randomized trial of permissive hypercapnia in preterm infants. *Pediatrics*. 1999;104(5 pt 1):1082-1088. doi:10.1542/peds.104.5.1082

145. Marret S, Marpeau L, Zupan-Simunek V, et al; PREMAG trial group. Magnesium sulphate given before very-preterm birth to protect infant brain: the randomised controlled PREMAG trial. *BJOG*. 2007;114(3):310-318. doi:10.1111/j.1471-0528.2006.01162.x

146. McPherson C, Neil JJ, Tjoeng TH, Pineda R, Inder TE. A pilot randomized trial of high-dose caffeine therapy in preterm infants. *Pediatr Res*. 2015;78(2):198-204. doi:10.1038/pr.2015.72

147. Ment LR, Duncan CC, Ehrenkranz RA, et al. Randomized indomethacin trial for prevention of intraventricular hemorrhage in very low birth weight infants. *J Pediatr*. 1985;107(6):937-943. doi:10.1016/S0022-3476(85)80197-9

148. Ment LR, Duncan CC, Ehrenkranz RA, et al. Randomized low-dose indomethacin trial for prevention of intraventricular hemorrhage in very low birth weight neonates. *J Pediatr*. 1988;112(6):948-955. doi:10.1016/S0022-3476(88)80225-7

149. Ment LR, Oh W, Ehrenkranz RA, et al. Low-dose indomethacin therapy and extension of intraventricular hemorrhage: a multicenter randomized trial. *J Pediatr*. 1994;124(6):951-955. doi:10.1016/S0022-3476(05)83191-9

150. Ment LR, Oh W, Ehrenkranz RA, et al. Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. *Pediatrics*. 1994;93(4):543-550. doi:10.1542/peds.93.4.543

151. Mercer BM, Miodovnik M, Thurnau GR, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. Antibiotic therapy for reduction of infant morbidity after preterm premature rupture of the membranes: a randomized controlled trial. *JAMA*. 1997;278(12):989-995. doi:10.1001/jama.1997.03550120049032

152. Mercer JS, Erickson-Owens DA, Vohr BR, et al. Effects of placental transfusion on neonatal and 18 month outcomes in preterm infants: a randomized controlled trial. *J Pediatr*. 2016;168:50-55.e1. doi:10.1016/j.jpeds.2015.09.068

153. Mercer JS, McGrath MM, Hensman A, Silver H, Oh W. Immediate and delayed cord clamping in infants born between 24 and 32 weeks: a pilot randomized controlled trial. *J Perinatol*. 2003;23(6):466-472. doi:10.1038/sj.jp.7210970

154. Mercer JS, Vohr BR, McGrath MM, Padbury JF, Wallach M, Oh W. Delayed cord clamping in very preterm infants reduces the incidence of intraventricular hemorrhage and late-onset sepsis: a randomized, controlled trial. *Pediatrics*. 2006;117(4):1235-1242. doi:10.1542/peds.2005-1706

155. Mohammed S, Nour I, Shabaan AE, Shouman B, Abdel-Hady H, Nasef N. High versus low-dose caffeine for apnea of prematurity: a randomized controlled trial. *Eur J Pediatr*. 2015;174(7):949-956. doi:10.1007/s00431-015-2494-8

156. Mohd Kori AM, Van Rostenberghe H, Ibrahim NR, Yaacob NM, Nasir A. A randomized controlled trial comparing two doses of caffeine for apnoea in prematurity. *Int J Environ Res Public Health*. 2021;18(9):4509-4514. doi:10.3390/ijerph18094509

157. Morales WJ, Angel JL, O'Brien WF, Knuppel RA. Use of ampicillin and corticosteroids in premature rupture of membranes: a randomized study. *Obstet Gynecol*. 1989;73(5 Pt 1):721-726.

158. Morales WJ, Diebel ND, Lazar AJ, Zadrozny D. The effect of antenatal dexamethasone administration on the prevention of respiratory distress syndrome in preterm gestations with premature rupture of membranes. *Am J Obstet Gynecol*. 1986;154(3):591-595. doi:10.1016/0002-9378(86)90607-1

159. Morales-Suarez M, De Jesus Sanchez-Gil T, Lemus-Varela L, Udaeta-Mora E. Low doses indomethacin for prevention of intraventricular hemorrhage in the preterm newborn baby with mechanical ventilation: final report of a randomized study. *Boletín Médico del Hospital Infantil de México*. 1994;51(6):389-394.

160. Morgan ME, Benson JW, Cooke RW. Ethamsylate reduces the incidence of periventricular haemorrhage in very low birth-weight babies. *Lancet*. 1981;2(8251):830-831. doi:10.1016/S0140-6736(81)91103-X

161. Moriette G, Paris-Llado J, Walti H, et al. Prospective randomized multicenter comparison of high-frequency oscillatory ventilation and conventional ventilation in preterm infants of less than 30 weeks with respiratory distress syndrome. *Pediatrics*. 2001;107(2):363-372. doi:10.1542/peds.107.2.363

162. Murphy KE, Hannah ME, Willan AR, et al; MACS Collaborative Group. Multiple Courses of Antenatal Corticosteroids for Preterm Birth (MACS): a randomised controlled trial. *Lancet*. 2008;372(9656):2143-2151. doi:10.1016/S0140-6736(08)61929-7

163. Nafday SM, Green RS, Lin J, Brion LP, Ochshorn I, Holzman IR. Is there an advantage of using pressure support ventilation with volume guarantee in the initial management of premature infants with respiratory distress syndrome? a pilot study. *J Perinatol*. 2005;25(3):193-197. doi:10.1038/sj.jp.7211233

164. Natalucci G, Latal B, Koller B, et al; Swiss EPO Neuroprotection Trial Group. Effect of early prophylactic high-dose recombinant human erythropoietin in very preterm infants on neurodevelopmental outcome at 2 years: a randomized clinical trial. *JAMA*. 2016;315(19):2079-2085. doi:10.1001/jama.2016.5504

165. Carlo WA, Finer NN, Walsh MC, et al; SUPPORT Study Group of the Eunice Kennedy Shriver NICHD Neonatal Research Network. Target ranges of oxygen saturation in extremely preterm infants. *N Engl J Med*. 2010;362(21):1959-1969. doi:10.1056/NEJMoa0911781

166. Ngan AY, Cheung P-Y, Hudson-Mason A, et al. Using exhaled CO_2 to guide initial respiratory support at birth: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed*. 2017;102(6):F525-F531. doi:10.1136/archdischild-2016-312286

167. Oei JL, Saugstad OD, Lui K, et al. Targeted oxygen in the resuscitation of preterm infants, a randomized clinical trial. *Pediatrics*. 2017;139(1):e20161452. doi:10.1542/peds.2016-1452

168. Ogawa Y, Miyasaka K, Kawano T, et al. A multicenter randomized trial of high frequency oscillatory ventilation as compared with conventional mechanical ventilation in preterm infants with respiratory failure. *Early Hum Dev*. 1993;32(1):1-10. doi:10.1016/0378-3782(93)90088-C

169. Ohls RK, Christensen RD, Kamath-Rayne BD, et al. A randomized, masked, placebo-controlled study of darbepoetin alfa in preterm infants. *Pediatrics*. 2013;132(1):e119-e127. doi:10.1542/peds.2013-0143

170. Ohls RK, Ehrenkranz RA, Wright LL, et al. Effects of early erythropoietin therapy on the transfusion requirements of preterm infants below 1250 grams birth weight: a multicenter, randomized, controlled trial. *Pediatrics*. 2001;108(4):934-942. doi:10.1542/peds.108.4.934

171. Owen J, Groome LJ, Hauth JC. Randomized trial of prophylactic antibiotic therapy after preterm amnion rupture. *Am J Obstet Gynecol*. 1993;169(4):976-981. doi:10.1016/0002-9378(93)90038-K

172. Papagaroufalis C, Megreli C, Hagjigeorgi C, Xanthou M. A trial of vitamin A supplementation for the prevention of intraventricular hemorrhage in very low birth weight neonates. *J Perinat Med*. 1991;19(suppl 1):382-387.

173. Parashi S, Bordbar A, Mahmoodi Y, Rezaei Jafari M. The survey of magnesium sulfate in prevention of intraventricular hemorrhage in premature infants: a randomized clinical trial. *Shiraz E-Medical Journal*. 2017;18(11):e55094. doi:10.5812/semj.55094

174. Peltoniemi OM, Anttila E, Kaukola T, Buonocore G, Hallman M. Randomized trial of early erythropoietin supplementation after preterm birth: iron metabolism and outcome. *Early Hum Dev*. 2017;109:44-49. doi:10.1016/j.earlhumdev.2017.04.001

175. Peltoniemi OM, Kari MA, Tammela O, et al; Repeat Antenatal Betamethasone Study Group. Randomized trial of a single repeat dose of prenatal betamethasone treatment in imminent preterm birth. *Pediatrics*. 2007;119(2):290-298. doi:10.1542/peds.2006-1549

176. Perlman JM, Goodman S, Kreusser KL, Volpe JJ. Reduction in intraventricular hemorrhage by elimination of fluctuating cerebral blood-flow velocity in preterm infants with respiratory distress syndrome. *N Engl J Med*. 1985;312(21):1353-1357. doi:10.1056/NEJM198505233122104

177. Phelps DL, Rosenbaum AL, Isenberg SJ, Leake RD, Dorey FJ. Tocopherol efficacy and safety for preventing retinopathy of prematurity: a randomized, controlled, double-masked trial. *Pediatrics*. 1987;79(4):489-500. doi:10.1542/peds.79.4.489

178. Piotrowski A, Bernas S, Fendler W. A randomised trial comparing two synchronised ventilation modes in neonates with respiratory distress syndrome. *Anestezjol Intens Ter*. 2007;39(2):58-63.

179. Piotrowski A, Sobala W, Kawczyński P. Patient-initiated, pressure-regulated, volume-controlled ventilation compared with intermittent mandatory ventilation in neonates: a prospective, randomised study. *Intensive Care Med*. 1997;23(9):975-981. doi:10.1007/s001340050441

180. Plavka R, Kopecký P, Sebroň V, Švihovec P, Zlatohlávková B, Januš V. A prospective randomized comparison of conventional mechanical ventilation and very early high frequency oscillatory ventilation in extremely premature newborns with respiratory distress syndrome. *Intensive Care Med*. 1999;25(1):68-75. doi:10.1007/s001340050789

181. Rabe H, Jewison A, Fernandez Alvarez R, et al; Brighton Perinatal Study Group. Milking compared with delayed cord clamping to increase placental transfusion in preterm neonates: a randomized controlled trial. *Obstet Gynecol*. 2011;117(2 pt 1):205-211. doi:10.1097/AOG.0b013e3181fe46ff

182. Rabe H, Wacker A, Hülskamp G, et al. A randomised controlled trial of delayed cord clamping in very low birth weight preterm infants. *Eur J Pediatr*. 2000;159(10):775-777. doi:10.1007/PL00008345

183. Ram Mohan G, Shashidhar A, Chandrakala BS, Nesargi S, Suman Rao PN. Umbilical cord milking in preterm neonates requiring resuscitation: a randomized controlled trial. *Resuscitation*. 2018;130:88-91. doi:10.1016/j.resuscitation.2018.07.003

184. Ravishankar C, Nafday S, Green RS, et al. A trial of vitamin A therapy to facilitate ductal closure in premature infants. *J Pediatr*. 2003;143(5):644-648. doi:10.1067/S0022-3476(03)00501-8

185. Rettwitz-Volk W, Veldman A, Roth B, et al. A prospective, randomized, multicenter trial of high-frequency oscillatory ventilation compared with conventional ventilation in preterm infants with respiratory distress syndrome receiving surfactant. *J Pediatr*. 1998;132(2):249-254. doi:10.1016/S0022-3476(98)70440-8

186. Rouse DJ, Hirtz DG, Thom E, et al; Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network. A randomized, controlled trial of magnesium sulfate for the prevention of cerebral palsy. *N Engl J Med*. 2008;359(9):895-905. doi:10.1056/NEJMoa0801187

187. Rozé J-C, Cambonie G, Le Thuaut A, et al. Effect of early targeted treatment of ductus arteriosus with ibuprofen on survival without cerebral palsy at 2 years in infants with extreme prematurity: a randomized clinical trial. *J Pediatr*. 2021;233:33-42.e2. doi:10.1016/j.jpeds.2020.12.008

188. Salvo V, Zimmermann LJ, Gavilanes AW, et al. First intention high-frequency oscillatory and conventional mechanical ventilation in premature infants without antenatal glucocorticoid prophylaxis. *Pediatr Crit Care Med*. 2012;13(1):72-79. doi:10.1097/PCC.0b013e318219673e

189. Sanghvi KP, Merchant RH, Karnik A, Kulkarni A. Role of ethamsylate in preventing periventricular-intraventricular hemorrhage in premature infants below 34 weeks of gestation. *Indian Pediatr*. 1999;36(7):653-658.

190. Schmidt B, Roberts RS, Davis P, et al; Caffeine for Apnea of Prematurity Trial Group. Caffeine therapy for apnea of prematurity. *N Engl J Med*. 2006;354(20):2112-2121. doi:10.1056/NEJMoa054065

191. Schmidt B, Whyte RK, Asztalos EV, et al; Canadian Oxygen Trial (COT) Group. Effects of targeting higher vs lower arterial oxygen saturations on death or disability in extremely preterm infants: a randomized clinical trial. *JAMA*. 2013;309(20):2111-2120. doi:10.1001/jama.2013.5555

192. Schmidt B, Davis P, Moddemann D, et al; Trial of Indomethacin Prophylaxis in Preterms Investigators. Long-term effects of indomethacin prophylaxis in extremely-low-birth-weight infants. *N Engl J Med*. 2001;344(26):1966-1972. doi:10.1056/NEJM200106283442602

193. Schmidt B, Gillie P, Mitchell L, Andrew M, Caco C, Roberts R. A placebo-controlled randomized trial of antithrombin therapy in neonatal respiratory distress syndrome. *Am J Respir Crit Care Med*. 1998;158(2):470-476. doi:10.1164/ajrccm.158.2.9712116

194. Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled nitric oxide in premature infants with the respiratory distress syndrome. *N Engl J Med*. 2003;349(22):2099-2107. doi:10.1056/NEJMoa031154

195. Schwaberger B, Pichler G, Avian A, Binder-Heschl C, Baik N, Urlesberger B. Do sustained lung inflations during neonatal resuscitation affect cerebral blood volume in preterm infants? a randomized controlled pilot study. *PLoS One*. 2015;10(9):e0138964. doi:10.1371/journal.pone.0138964

196. Shaw NJ, Cooke RW, Gill AB, Shaw NJ, Saeed M. Randomised trial of routine versus selective paralysis during ventilation for neonatal respiratory distress syndrome. *Arch Dis Child*. 1993;69(5 Spec No):479-482. doi:10.1136/adc.69.5_Spec_No.479

197. Silver RK, Vyskocil C, Solomon SL, Ragin A, Neerhof MG, Farrell EE. Randomized trial of antenatal dexamethasone in surfactant-treated infants delivered before 30 weeks' gestation. *Obstet Gynecol*. 1996;87(5 pt 1):683-691. doi:10.1016/0029-7844(96)00033-6

198. Simons SH, van Dijk M, van Lingen RA, et al. Routine morphine infusion in preterm newborns who received ventilatory support: a randomized controlled trial. *JAMA*. 2003;290(18):2419-2427. doi:10.1001/jama.290.18.2419

199. Singh J, Sinha SK, Clarke P, Byrne S, Donn SM. Mechanical ventilation of very low birth weight infants: is volume or pressure a better target variable? *J Pediatr*. 2006;149(3):308-313. doi:10.1016/j.jpeds.2006.01.044

200. Sinha S, Davies J, Toner N, Bogle S, Chiswick M. Vitamin E supplementation reduces frequency of periventricular haemorrhage in very preterm babies. *Lancet*. 1987;1(8531):466-471. doi:10.1016/S0140-6736(87)92087-3

201. Sinha SK, Donn SM, Gavey J, McCarty M. Randomised trial of volume controlled versus time cycled, pressure limited ventilation in preterm infants with respiratory distress syndrome. *Arch Dis Child Fetal Neonatal Ed*. 1997; 77(3):F202-F205. doi:10.1136/fn.77.3.F202

202. Siwiec J, Porzucek I, Gadzinowski J, Bhat R, Vidyasagar D. Effect of short term morphine infusion on Premature Infant Pain Profile (PIPP) and hemodynamics. *Pediatr Res*. 1999;45(7):69. doi:10.1203/00006450-199904020-00416

203. Song J, Sun H, Xu F, et al. Recombinant human erythropoietin improves neurological outcomes in very preterm infants. *Ann Neurol*. 2016;80(1):24-34. doi:10.1002/ana.24677

204. Song S-Y, Kim Y, Kang B-H, Yoo H-J, Lee M. Safety of umbilical cord milking in very preterm neonates: a randomized controlled study. *Obstet Gynecol Sci*. 2017;60(6):527-534. doi:10.5468/ogs.2017.60.6.527

205. Sosenko IRS, Fajardo MF, Claure N, Bancalari E. Timing of patent ductus arteriosus treatment and respiratory outcome in premature infants: a double-blind randomized controlled trial. *J Pediatr*. 2012;160(6):929-935.e1. doi: 10.1016/j.jpeds.2011.12.031

206. Speer ME, Blifeld C, Rudolph AJ, Chadda P, Holbein ME, Hittner HM. Intraventricular hemorrhage and vitamin E in the very low-birth-weight infant: evidence for efficacy of early intramuscular vitamin E administration. *Pediatrics*. 1984;74(6):1107-1112. doi:10.1542/peds.74.6.1107

207. Steer PA, Flenady VJ, Shearman A, Lee TC, Tudehope DI, Charles BG. Periextubation caffeine in preterm neonates: a randomized dose response trial. *J Paediatr Child Health*. 2003;39(7):511-515. doi:10.1046/j.1440-1754.2003.00207.x

208. Stenson BJ, Tarnow-Mordi WO, Darlow BA, et al; BOOST II United Kingdom Collaborative Group; BOOST II Australia Collaborative Group; BOOST II New Zealand Collaborative Group. Oxygen saturation and outcomes in preterm infants. *N Engl J Med*. 2013;368(22):2094-2104. doi:10.1056/NEJMoa1302298

209. Subtil D, Tiberghien P, Devos P, et al. Immediate and delayed effects of antenatal corticosteroids on fetal heart rate: a randomized trial that compares betamethasone acetate and phosphate, betamethasone phosphate, and dexamethasone. *Am J Obstet Gynecol*. 2003;188(2):524-531. doi:10.1067/mob.2003.136

210. Sun H, Cheng R, Kang W, et al. High-frequency oscillatory ventilation versus synchronized intermittent mandatory ventilation plus pressure support in preterm infants with severe respiratory distress syndrome. *Respir Care*. 2014;59(2):159-169. doi:10.4187/respcare.02382

211. Sun H, Cheng R, Wang Z. Early vitamin A supplementation improves the outcome of retinopathy of prematurity in extremely preterm infants. *Retina*. 2020;40(6):1176-1184. doi:10.1097/IAE.0000000000002543

212. Sun H, Song J, Kang W, et al. Effect of early prophylactic low-dose recombinant human erythropoietin on retinopathy of prematurity in very preterm infants. *J Transl Med*. 2020;18(1):397-403. doi:10.1186/s12967-020-02562-y

213. Tarnow-Mordi W, Morris J, Kirby A, et al; Australian Placental Transfusion Study Collaborative Group. Delayed versus immediate cord clamping in preterm infants. *N Engl J Med*. 2017;377(25):2445-2455. doi:10.1056/NEJMoa1711281

214. Thome U, Kössel H, Lipowsky G, et al. Randomized comparison of high-frequency ventilation with high-rate intermittent positive pressure ventilation in preterm infants with respiratory failure. *J Pediatr*. 1999;135 (1):39-46. doi:10.1016/S0022-3476(99)70325-2

215. Thome UH, Carroll W, Wu T-J, et al. Outcome of extremely preterm infants randomized at birth to different PaCO2 targets during the first seven days of life. *Biol Neonate*. 2006;90(4):218-225. doi:10.1159/000092723

216. Thome UH, Genzel-Boroviczeny O, Bohnhorst B, et al; PHELBI Study Group. Permissive Hypercapnia in Extremely Low Birthweight Infants (PHELBI): a randomised controlled multicentre trial. *Lancet Respir Med*. 2015;3 (7):534-543. doi:10.1016/S2213-2600(15)00204-0

217. Tyson JE, Wright LL, Oh W, et al. Vitamin A supplementation for extremely-low-birth-weight infants: National Institute of Child Health and Human Development Neonatal Research Network. *N Engl J Med*. 1999;340(25): 1962-1968. doi:10.1056/NEJM199906243402505

218. Van Overmeire B, Allegaert K, Casaer A, et al. Prophylactic ibuprofen in premature infants: a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364(9449):1945-1949. doi:10.1016/S0140-6736(04)17477-1

219. Van Reempts P, Borstlap C, Laroche S, Van der Auwera J-C. Early use of high frequency ventilation in the premature neonate. *Eur J Pediatr*. 2003;162(4):219-226. doi:10.1007/s00431-002-1145-z

220. Varvarigou A, Bardin CL, Beharry K, Chemtob S, Papageorgiou A, Aranda JV. Early ibuprofen administration to prevent patent ductus arteriosus in premature newborn infants. *JAMA*. 1996;275(7):539-544. doi:10.1001/jama.1996.03530310045031

221. Vento G, Matassa PG, Ameglio F, et al. HFOV in premature neonates: effects on pulmonary mechanics and epithelial lining fluid cytokines: a randomized controlled trial. *Intensive Care Med*. 2005;31(3):463-470. doi:10.1007/s00134-005-2556-x

222. Vento M, Moro M, Escrig R, et al. Preterm resuscitation with low oxygen causes less oxidative stress, inflammation, and chronic lung disease. *Pediatrics*. 2009;124(3):e439-e449. doi:10.1542/peds.2009-0434

223. Vesoulis ZA, McPherson C, Neil JJ, Mathur AM, Inder TE. Early high-dose caffeine increases seizure burden in extremely preterm neonates: a preliminary study. *J Caffeine Res*. 2016;6(3):101-107. doi:10.1089/jcr.2016.0012

224. Vincer M, Allen A, Evans J, et al. Early intravenous indomethacin prolongs respiratory support in very low birth weight infants. *Acta Paediatr Scand*. 1987;76(6):894-897. doi:10.1111/j.1651-2227.1987.tb17260.x

225. Wang CL, Anderson C, Leone TA, Rich W, Govindaswami B, Finer NN. Resuscitation of preterm neonates by using room air or 100% oxygen. *Pediatrics*. 2008;121(6):1083-1089. doi:10.1542/peds.2007-1460

226. Wapner RJ, Sorokin Y, Thom EA, et al; National Institute of Child Health and Human Development Maternal Fetal Medicine Units Network. Single versus weekly courses of antenatal corticosteroids: evaluation of safety and efficacy. *Am J Obstet Gynecol*. 2006;195(3):633-642. doi:10.1016/j.ajog.2006.03.087

227. Wiswell TE, Graziani LJ, Kornhauser MS, et al. High-frequency jet ventilation in the early management of respiratory distress syndrome is associated with a greater risk for adverse outcomes. *Pediatrics*. 1996;98(6 pt 1):1035-1043. doi:10.1542/peds.98.6.1035

228. Yaseen H, al Umran K, Ali H, Rustum M, Darwich M, al-Faraidy A. Effects of early indomethacin administration on oxygenation and surfactant requirement in low birth weight infants. *J Trop Pediatr*. 1997;43(1):42-46. doi:10.1093/tropej/43.1.42

229. Yunis M, Nour I, Gibreel A, et al. Effect of delayed cord clamping on stem cell transfusion and hematological parameters in preterm infants with placental insufficiency: a pilot randomized trial. *Eur J Pediatr*. 2021;180(1):157-166. doi:10.1007/s00431-020-03730-4

230. Jasani B, Torgalkar R, Ye XY, Syed S, Shah PS. Association of umbilical cord management strategies with outcomes of preterm infants: a systematic review and network meta-analysis. *JAMA Pediatr*. 2021;175(4):e210102. doi:10.1001/jamapediatrics.2021.0102

231. Keszler M. Volume-targeted ventilation: one size does not fit all: evidence-based recommendations for successful use. *Arch Dis Child Fetal Neonatal Ed*. 2019;104(1):F108-F112. doi:10.1136/archdischild-2017-314734

SUPPLEMENT 1.

eAppendix 1. Search Strategy
eAppendix 2. Interventions Considered in the Systematic Review
eAppendix 3. Screening Form
eAppendix 4. Excluded Articles and Their Citations
eTable 1. Characteristics of Studies Studying Interventions on Severe Brain Injury in Preterm Infants
eTable 2. Summary of Meta-analysis of Interventions on Cystic Periventricular Leukomalacia (cPVL) and Severe Brain Injury
eTable 3. Summary of Sensitivity and Subgroup Analysis of Interventions on Severe Intraventricular Hemorrhage (IVH) and cPVL
eFigure 1. Study Flow Diagram Outlining Stages of Search Results and Filtering Process [as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines]
eFigure 2. Forest Plot for Comparison—Betamethasone for Lung Maturity vs. Dexamethasone for Lung Maturity for Outcome Severe IVH
eFigure 3. Forest Plot for Comparison—Antenatal Steroid for Lung Maturity: Repeat Course vs. Single Course for Outcome Severe IVH
eFigure 4. Forest Plot for Comparison—Antenatal MgSO4 Therapy for Neuroprotection or Tocolysis vs. Placebo for the Outcome Severe IVH
eFigure 5. Forest Plot for Comparison—Antibiotics for PPROM vs. Placebo for the Outcome Severe IVH
eFigure 6. Forest Plot for Umbilical Cord Milking vs. Delayed Cord Clamping in Preterm Infants for the Outcome Severe IVH
eFigure 7. Forest Plot for Comparison—Lower FiO2 for Resuscitation vs. Higher FiO2 at Resuscitation for the Outcome Severe IVH
eFigure 8. Forest Plot for Comparison—Sustained Inflation During Resuscitation vs. Standard Resuscitation for the Outcome Severe IVH
eFigure 9. Forest Plot for Comparison—Delayed Cord Clamping vs. Early Cord Clamping for the Outcome Severe IVH

SUPPLEMENT 2.
Data Sharing Statement