Initial Oxygen Use for Preterm Newborn Resuscitation: A Systematic Review With Meta-analysis

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abstract

CONTEXT: The International Liaison Committee on Resuscitation prioritized to review the initial fraction of inspired oxygen (Fio_2) during the resuscitation of preterm newborns.

OBJECTIVES: This systematic review and meta-analysis provides the scientific summary of initial Fio_2 in preterm newborns (<35 weeks' gestation) who receive respiratory support at birth.

DATA SOURCES: Medline, Embase, Evidence-Based Medicine Reviews, and Cumulative Index to Nursing and Allied Health Literature were searched between January 1, 1980 and August 10, 2018.

STUDY SELECTION: Studies were selected by pairs of independent reviewers in 2 stages with a Cohen's κ of 0.8 and 1.0.

DATA EXTRACTION: Pairs of independent reviewers extracted data, appraised the risk of bias (RoB), and assessed Grading of Recommendations Assessment, Development and Evaluation certainty.

RESULTS: Ten randomized controlled studies and 4 cohort studies included 5697 patients. There are no statistically significant benefits of or harms from starting with lower compared with higher Fio_2 in short-term mortality (n = 968; risk ratio = 0.83 [95% confidence interval 0.50 to 1.37]), long-term mortality, neurodevelopmental impairment, or other key preterm morbidities. A sensitivity analysis in which 1 study with a high RoB was excluded failed to reveal a reduction in mortality with initial low Fio_2 (n = 681; risk ratio = 0.63 [95% confidence interval 0.38 to 1.03]).

LIMITATIONS: The Grading of Recommendations Assessment, Development and Evaluation certainty of evidence was very low for all outcomes due to RoB, inconsistency, and imprecision.

CONCLUSIONS: The ideal initial Fio_2 for preterm newborns is still unknown, although the majority of newborns ≤32 weeks' gestation will require oxygen supplementation.

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The International Liaison Committee on Resuscitation (ILCOR) seeks to evaluate and promote the best available evidence on resuscitation by using a transparent and rigorous evaluation process conducted by a team of multidisciplinary experts culminating in a consensus on science with treatment recommendations (CoSTR).[1] In 2015, on the basis of the ILCOR's recommendations, guidelines from the American Heart Association and several other neonatal societies worldwide were updated to initiate the resuscitation of preterm newborns with a fraction of inspired oxygen (F_{IO_2}) between 0.21 and 0.30.[2–4]

These recommendations were based on evidence from randomized controlled trials (RCTs) that included relatively small numbers of preterm newborns. The ILCOR 2015 meta-analysis revealed no difference in outcomes when resuscitation was started with higher compared with lower F_{IO_2}. The final recommendation of lower F_{IO_2} reflected a stated preference to avoid exposing preterm newborns to additional oxygen without evidence of benefit. After the ILCOR 2015 analysis was completed, the authors of the Targeted Oxygen in the Resuscitation of Preterm Infants and Their Developmental Outcomes (To2rpido) multinational RCT reported on a comparison of mortality of 292 preterm newborns who were resuscitated starting with either room air (F_{IO_2} 0.21) or pure oxygen (F_{IO_2} 1.0).[5] The researchers in a nonprespecified subgroup analysis suggested that resuscitation with a starting F_{IO_2} of 0.21 was associated with an increased risk of death in newborns <28 weeks' gestation. However, the study was nonblinded and was stopped prematurely because of recruitment difficulty and a lack of equipoise. Recently, the ILCOR has moved from a 5-yearly review cycle to a continuous evaluation process, and this allowed for an opportunity to perform an updated analysis on this topic in which this newest study is incorporated.

Preterm newborns appear to be particularly at risk for the toxic effects of oxygen, perhaps related to reduced antioxidant defenses. The administration of high F_{IO_2} leads to free radical formation and is toxic to the newborn lungs, eyes, brain, and other organs.[6,7] Given preterm newborns' incomplete lung, cardiac, and neurological development and immature oxidative defenses, the ideal F_{IO_2} for initial resuscitation remains uncertain.[8]

The World Health Organization defines preterm newborns as infants who are born alive before 37 completed weeks' gestation (up to 36 weeks and 6 days). Extremely preterm is defined as <28 completed weeks' gestation, very preterm is 28 to <32 completed weeks' gestation, moderate preterm is 32 to <35 completed weeks' gestation, and late preterm is 35 to <37 completed weeks' gestation.[9] Late-preterm newborns were grouped together with term newborns (37–42 weeks' gestation) in a separate systematic review and meta-analysis (≥35 weeks' gestation). Preterm newborns <35 weeks' gestation are included in this current meta-analysis.

This systematic review and meta-analysis is the core that serves as the consensus on science for the ILCOR CoSTR. It was completed in parallel and in collaboration with the ILCOR and is published separately from the ILCOR CoSTR, which will be published in the fall of 2019 and will be focused on the treatment recommendations. In cooperation with the ILCOR Neonatal Life Support (NLS) Task Force, in this meta-analysis, we investigate starting resuscitation with lower F_{IO_2} (≤0.5) compared with higher F_{IO_2} (>0.5) on mortality and morbidity among preterm newborns (<35 weeks' gestation) who receive respiratory support at birth. The primary outcome is short-term mortality (STM). Secondary outcomes include long-term mortality, neurologic outcomes, and important preterm morbidity.

METHODS

Protocol

This systematic review and meta-analysis was conducted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* and reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for meta-analysis in health care interventions.[10,11] The protocol was registered in advance of article selection with the Prospective Register of Systematic Reviews (CRD42018084902, registered January 8, 2018; Supplemental Information). The protocol includes term and preterm newborns as predetermined subgroups, and these were separated into individual analyses after initial article selection. Studies were included in this systematic review if >75% of the newborns were <35 weeks' gestation.

Outcomes

The selection and importance rating of patient-oriented outcomes for preterm newborns were determined in advance through discussion and consensus with the ILCOR NLS Task Force.[12] The outcomes were centered on all-cause mortality at 2 time intervals, short-term (primary outcome, in the hospital, or up to 30 days postnatal) and long-term (1–3 years), as well as long-term neurodevelopmental impairment (NDI) (at 1–3 years). NDI is commonly defined as having at least 1 of the following and is categorized by severity: cerebral palsy, cognitive impairment, visual impairment, or hearing impairment. When available, we extracted data

for moderate-to-severe NDI at 1 to 3 years on the basis of the Gross Motor Function Classification System and the Bayley Scales of Infant Development, Third Edition.[13,14]

Additional preterm morbidities were captured: major intraventricular hemorrhage (IVH) (grade III or IV), according to the criteria of Papile et al[15]; severe retinopathy of prematurity (ROP) (stages III–V), defined in the *International Classification of Retinopathy of Prematurity* or on the basis of whether the infant received intravitreal or surgical treatment; necrotizing enterocolitis (NEC) (stage II or III), defined as modified Bell's stage II (pneumatosis) or III (surgical); and bronchopulmonary dysplasia (BPD) (moderate to severe), defined by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (2001) or on the basis of receiving supplemental oxygen at 36 weeks' corrected gestational age.[16–19] The important outcome of time to heart rate (HR) >100 beats per minute was preplanned, but when this was not available, HR (expressed as mean [SD] or median [interquartile range (IQR)]) at 1, 5, and 10 minutes was extracted. If this was not available, then a summary of the HR data provided was extracted.

Search Strategy

Ovid Medline, Embase, all Evidence-Based Medicine (EBM) Reviews (including the Cochrane Controlled Register of Trials and others), and EBSCOhost Cumulative Index to Nursing and Allied Health Literature (CINAHL) were searched for relevant neonatal literature between January 1, 1980, and December 11, 2017 (Supplemental Tables 13 and 14) without language restrictions. The search was updated from December 1, 2017, to August 10, 2018, before publication. The searches were limited to the last 4 decades because no pertinent studies were expected before this. An iterative approach was used to ensure that key articles (identified by content experts and in previous systematic review articles) were found. Additionally, we searched the first 200 hits on Google Scholar, references of systematic reviews on the topic, references of the ILCOR 2015 CoSTR, and trial registries (the US National Library of Medicine [clinicaltrials.gov], the International Standard Randomized Controlled Trial Number registry [isrctn.com], and the European Union Clinical Trials Register [clinicaltrialsregister.eu]; last searched August 10, 2018).

Study Selection and Data Extraction

Covidence software was used for study selection in 2 steps (Covidence systematic review software; Veritas Health Innovation, Melbourne, Australia). Studies were included in this systematic review of F_{IO_2} management of preterm newborns if all subjects were born at <35 completed weeks' gestation. Pairs of independent reviewers screened titles and abstracts. In the event of a disagreement during the abstract screening, the full text was reviewed. Independent reviewers subsequently completed full-text review for eligibility in duplicate. A third reviewer was involved for disagreements at the full-text stage, and final decisions were determined by consensus. The first reason for exclusion was captured according to a predetermined, ordered list of exclusions. Interrater agreement for article selection was assessed by using Cohen's κ coefficient at the abstract and full-text stages.

RCTs, quasi-RCTs, and nonrandomized (observational) studies were eligible if they included a comparison of low and high initial oxygen concentration for respiratory support at birth. Review articles, editorials, comments, case reports, and small case series (≤10 patients) were excluded. Studies that focused on oxygen use beyond the initial stabilization in the delivery room or studies that were focused on oxygen saturation targeting and not initial oxygen concentration were also excluded. To avoid publication bias, the protocol was amended to include data from conference abstracts (not otherwise published) in a sensitivity analysis if the authors provided enough information to confirm the methods, key patient characteristics, and outcomes.

Data Collection, Risk of Bias, and Certainty of Evidence Assessment

For each study, pairs of authors independently extracted predetermined study characteristics and outcomes and then achieved consensus. Pairs of independent authors evaluated the risk of bias (RoB) in individual studies using the Cochrane Risk of Bias Tool for RCTs and the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) Tool for observational studies.[20,21] Similarly, 2 authors assessed the certainty of evidence (confidence in the estimate of effect) for each outcome on the basis of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, including the calculation of the optimal information size to assess imprecision (GRADEpro Guideline Development Tool; McMaster University, Hamilton, Canada).[22] The RoB and GRADE assessments were then reviewed by ILCOR content experts, who are also authors, to achieve consistency and consensus.

Data Analysis

Covidence, GRADEpro, and Review Manager software 5.3 (The Nordic Cochrane Centre, Copenhagen, Denmark) were used to abstract, summarize, and analyze the data, respectively.

Meta-analyses were performed if ≥2 studies were available. Heterogeneity was measured by using the I^2 statistic.[23] Because multiple small studies (<250 patients) were anticipated, a random effects model was used for analysis. We report pooled unadjusted risk ratios (RRs) and corresponding 95% confidence intervals (CIs) using the Mantel-Haenszel (MH) method for dichotomous variables. Forest plots were used for the graphical representation of RRs. To assess for publication bias, we visually inspected funnel plots when >8 studies were available. The absolute risk difference and number needed to treat were calculated when the pooled estimate from RCTs revealed a statistically significant benefit when using the method recommended by the Cochrane Collaboration.[10]

Sensitivity analyses were completed when the inclusion of 1 or more studies was of a concern because of high RoB, incongruent allocation, a mixture of adjusted and nonadjusted analyses, or significant heterogeneity.

Prespecified subgroup analysis was planned if >2 studies were available with relevant outcome information related to gestational age groupings, initial F_{IO_2} groupings, or oxygen saturation targeting as a cointervention. Because extremely preterm newborns were categorized differently in the studies as being either up to 27 weeks and 6/7 days or up to 28 weeks and 6/7 days, we incorporated both and defined the following subgroups by gestational ages: ≤28, ≤32, or <35 weeks. In a post hoc exploratory analysis of the STM outcome for the ≤28 weeks' gestation subgroup, the addition of a hypothetical large study to determine if it would change the statistical significance of the primary outcome was considered.

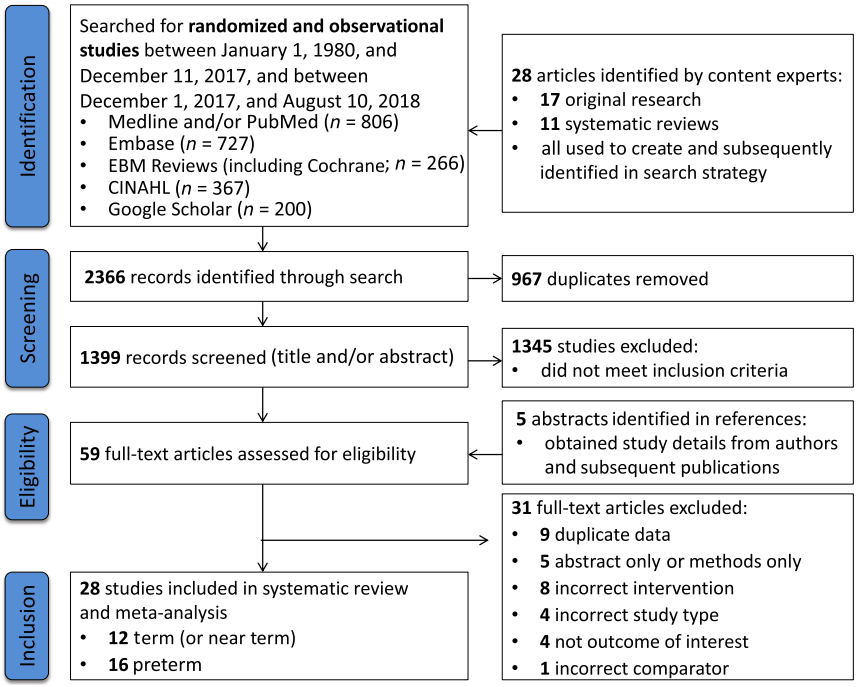

FIGURE 1
PRISMA flow diagram of study selection.

RESULTS

Literature Search and Study Selection

A total of 2366 records were identified with the search strategy, and after removing 967 duplicates, 1399 records were screened by title and abstract. Five additional studies (abstracts) were found via reference searches and added to full-text screening. A total of 59 full-text articles were assessed for eligibility, and 16 publications on preterm newborns were included.[5,24–38] Cohen's κ was 0.81 (excellent) at the abstract stage and 1.0 (full agreement) at the full-text stage. See Fig 1 for the PRISMA study selection diagram, including the reasons for article exclusion.

Of the additional studies considered via reference searches, 1 was a study of preterm newborns that was initially excluded but ultimately included: the study was published as a conference abstract only; however, the authors of a subsequent peer-review publication reported its methods and outcomes.[32] The senior author provided the abstract, conference poster, and additional data (including detailed methods, patient characteristics, and outcomes), and these were all consistent with the original abstract and the published data.[32,34]

One potentially eligible RCT was excluded from this review.[39] The researchers reported preliminary outcomes from the first 18 months of feasibility testing for a larger study that is included in this review.[28] To ensure duplicate data were not used, this was confirmed with the first author, and the preliminary report was excluded.

Lastly, a search of clinical trial registries (ClinicalTrials.gov, the International Standard RCT Number registry, and the European Union Clinical Trials Register) revealed no additional published studies, and 1 additional unpublished study, registered in 2012. The researchers in the Study of Room Air Versus 60% Oxygen for Resuscitation of Premature Infants aimed to

randomly assign newborns ≤28 weeks' gestation to initial respiratory support with room air compared with F_{IO_2} 0.60. Recruitment began in 2013, and 1 of the primary investigators indicated that the study was stopped early because of funding, and no analyses have been published.[40]

Study Characteristics

Tables 1 and 2 include a summary of the characteristics of the included studies. Of the 16 included articles, 10 were RCTs, 2 were long-term follow-ups of included RCTs, and 4 were observational cohort studies.[5,24–38] Only 3 were fully randomized with fully blinded allocation and intervention.[29,32,37]

A total of 1007 preterm newborn patients were included in RCTs, ranging from 32 to 287 patients. Most of the studies were from Europe and North America; they were published between 1995 and 2017 with patient recruitment from 1991 to 2014. Three of the randomized trials were performed by a group of investigators using similar protocols.[28,32,37] Researchers in the 2 oldest RCTs did not monitor oxygen saturation during resuscitation and adjusted the inspired concentration on the basis of the newborn's HR.[24,25] One of the RCTs included 3 groups: a static concentration of F_{IO_2} 1.0 without titration and 2 with oxygen saturation targeting starting at either F_{IO_2} 1.0 or room air. For the analyses, the latter 2 groups were used because they were closely matched comparisons and were similar to the remaining 7 other RCTs in which oxygen saturation targeting was used.[29]

Outcomes were extracted by using the definitions in the methods section with the following exceptions: Severe IVH (grades III–IV) was extracted as grades ≥II from 2 studies.[32,37] Severe ROP (stages III–V) was extracted as grades ≥2 from 3 studies and as treated or blinded from 1 study.[25,28,32,37] NEC (stages II–III) was extracted as all NEC in 1 study and as surgical (stage III) in 2 others.[24–26] The BPD definition has been updated over time, and thus, there were some minor differences.

In addition to the RCTs, a total of 4437 patients were included in 4 observational cohort studies ranging from 125 to 2326 patients.[27,33,35,36] The studies were from Australia, Canada (n = 2), and the United States and were published between 2009 and 2017 with patient recruitment from 2004 to 2012. Oxygen saturation targeting was included as a cointervention in all of these observational studies. Researchers in each of these studies described outcomes observed before and after the delivery room practice for oxygen administration was changed. Researchers in 2 studies compared initiating resuscitation with F_{IO_2} 1.0 (before) to resuscitation with F_{IO_2} 0.21 (after).[27,35] Researchers in the other 2 studies compared initiating resuscitation with F_{IO_2} 1.0 (before) to 2 "after" cohorts: either F_{IO_2} 0.21 or an intermediate oxygen concentration of F_{IO_2} 0.22 to 0.99.[33,36] For these latter 2 studies, only the room air and F_{IO_2} 1.0 groups were used because the intermediate groups had a range of starting oxygen levels and could not be classified as low or high.

Patient Characteristics

In Tables 3 and 4, we outline the patient characteristics of included studies. The intervention and comparator groups were similar in key prognostic variables. The definition of prematurity for this review (<35 weeks' gestation) included a wide range of gestational ages with the potential for different oxygen requirements after birth. Despite the potential for significant heterogeneity in subject enrollment, the studies included subjects with similar postmenstrual ages and birth weights. Although most of the studies enrolled newborns ≤32 weeks' gestation, 7 RCTs included 467 extremely preterm newborns (≤28 weeks' gestation), and researchers either reported separate data for this subgroup or they provided additional data for subgroup analyses.[5,26,28,29,31,32,37]

RoB

The RoB assessment for each study is summarized in Tables 5 and 6. Researchers in only 3 RCTs provided evidence that they were able to fully blind personnel to the F_{IO_2} used.[29,32,37] Many of the studies were determined to have an unclear RoB due to uncertainty regarding the blinding of outcome assessors and bias due to potential deviations from intended interventions.

One study (2 publications) was determined to have a high RoB due to a lack of blinding of personnel, a low recruitment rate, and the early termination of the study due to poor recruitment.[5,38] Researchers in the To2rpido trial intended to include ∼2000 newborns <32 weeks' gestation and screened >6000 newborns, but they stopped after 6.5 years, having recruited only 292 newborns, partly because of a lack of clinical equipoise of using F_{IO_2} 1.0 for initial resuscitation.

Outcome Analysis

Results of the meta-analysis are summarized in Tables 7 through 11, reviewed below, and key analyses are shown in the Figs 2 and 3 forest plots. Additional material is located in the forest plots of Supplemental Figs 4 and 5.

All Preterm Newborns <35 Weeks' Gestation

For the primary outcome, researchers in 10 RCTs involving 968 preterm newborns reported on STM (at hospital discharge or 30 days).[5,24–26,28–32,37] The pooled estimate revealed no statistically significant STM difference in starting

TABLE 1 Study Characteristics in Preterm (<35 Weeks) RCTs and Quasi-RCTs

Study	Study Characteristics					Total Patients	Gestational Age, wk	Patients by Oxygen Levels, *n*		Oxygen Level Definition, %	O_2 Sat Target	Preterm Subgroup, wk			Outcome			
	Years of Recruitment	Country of Recruitment	Multi- or Single Center	Study Design	Blinded to Gas			Low	High			≤28	≤32	<35	STM	LTM	NDI	Other
Lundstrøm et al[24]	1991–1992	Denmark	Single	RCT (convenience)	No	70	<33	34	36	Low 21; high 80	N/A	—	—	Yes	Yes	—	—	Yes
Harling et al[25]	N/A	United Kingdom	Single	RCT	No	52	<31	26	26	Low 50; high 100	N/A	—	Yes	Yes	Yes	—	—	Yes
Wang et al[26]	2005–2007	United States	Multi	RCT	No	41	<32	18	23	Low 21; high 100	80%–85% at 5 min, maintain after 7 min	Yes	Yes	Yes	Yes	—	—	Yes
Vento et al[28]	2005–2008	Spain	Single	RCT	Partial	78	≤28	37	41	Low 30; high 90	Titrated to attain oxygen saturation	Yes	Yes	Yes	Yes	—	—	Yes
Rabi et al[29]	2005–2007	Canada	Single	RCT	Yes	106	≤32	34	34	Low 21; high 100	85%–92%	Yes	Yes	Yes	Yes	—	—	Yes
Armanian and Badiee[30]	2009–2010	Iran	Single	RCT	No	32	<35 (29–34)	16	16	Low 30; high 100	Titrated to HR >100 beats per min and oxygen saturation >85%	—	—	Yes	Yes	—	—	—
Kapadia et al[31]	2010–2011	United States	Single	RCT	No	88	<35	44	44	Low 21; high 100	88%–94%	Yes	Yes	Yes	Yes	—	—	Yes
Aguar et al[32]	2008–2012	Spain	Single	RCT	Yes	60	≤28	34	26	Low 30; high 60	88%–94% at 10 min after birth	Yes	Yes	Yes	Yes	—	—	Yes
Rook et al[37]	2008–2012	Netherlands	Single	RCT	Yes	193	<32	99	94	Low 30; high 65	88%–94% at 10 min after birth	Yes	Yes	Yes	Yes	—	—	Yes
Boronat et al[34]	2008–2012	Spain, Netherlands	Multi	RCT	Yes	253	<32	133	120	Low 30; high 60 or 65	88%–94% at 10 min after birth	—	Yes	Yes	—	Yes	Yes	—
Oei et al[5] (To2rpido)	2008–2014	Australia, Malaysia, Qatar	Multi	RCT	No	287	<32	144	143	Low 21; high 100	80%–95% at 5–10 min	Yes	Yes	Yes	Yes	—	—	Yes
Thamrin et al[38] (To2rpido)	2008–2014	Australia, Malaysia, Qatar	Multi	RCT	No	238	<32	117	121	Low 21; high 100	80%–95% at 5–10 min	Yes	—	—	—	Yes	Yes	—

LTM, long-term mortality; N/A, not available; —, not applicable.

TABLE 2 Study Characteristics in Preterm (<35 Weeks) Retrospective Observational Cohort Studies

Study	Study Characteristics					Total Patients	Gestational Age, wk	Patients by Oxygen Levels, *n*		Oxygen Level Definition, %	O_2 Sat Target	Preterm Subgroup, wk			Outcome			
	Years of Recruitment	Country of Recruitment	Multi- or Single Center	Design	Blinded			Low	High			≤28	≤32	<35	STM	LTM	NDI	Other
Dawson et al[27]	2006–2007	Australia	Single	Prospective before and after	No	125	<30	105	20	Low 21; high 100	90%	—	Yes	Yes	Yes	—	—	—
Rabi et al[33]	2004–2009	Canada	Multi	Retrospective cohort	No	2326	<28	1244	1082	Low 21; high 100	Various	Yes	Yes	Yes	Yes	—	—	Yes
Soraisham et al[36]	2010–2011	Canada	Multi	Retrospective cohort	No	1825	≤28	445	581	Low 21; high 100	Various	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kapadia et al[35]	2009–2012	United States	Single	Retrospective before and after	No	161	≤28	89	110	Low 21; high 100	85%–94%	Yes	Yes	Yes	Yes	Yes	Yes	Yes

LTM, long-term mortality; N/A, not available; —, not applicable.

respiratory support with lower compared with higher oxygen concentration (RR = 0.83 [95% CI 0.50 to 1.37]; I^2 = 18%). The forest plot is presented in Fig 2A, and the RRs are reported in Table 7. The funnel plot (Supplemental Fig 4) revealed reasonable study distribution, although unpublished small studies with negative or neutral results are possible. Clinical heterogeneity was low to moderate, and statistical heterogeneity was low (I^2 = 18%).

Sensitivity analysis was conducted for STM to determine the effect of including or excluding the To2rpido study given its high RoB.[5] The point estimate for STM for this study is contradictory to the majority of studies (Fig 2A). Excluding the To2rpido study would change the point estimate and CIs to RR 0.63 (95% CI 0.38 to 1.03; I^2 = 0%). However, because the RoB was high but not critical, we included this study in all other outcomes and subgroups. To further explore the reasons for heterogeneity, a sensitivity analysis was conducted for STM to compare the blinded and unblinded studies (Fig 2B). The point estimate for STM for the blinded studies is RR 0.51 (95% CI 0.25 to 1.02; I^2 = 0%).

Long-term mortality was reported in 3 RCTs (2 were combined in 1 publication) at 2 years' follow-up involving 491 preterm newborns. Pooled estimates revealed no statistically significant difference in starting with lower compared with higher F_{IO_2} (RR = 1.05 [95% CI 0.32 to 3.39]; I^2 = 79%).[5,34] This outcome revealed high heterogeneity, as evidenced by a visual inspection of the forest plot and statistical heterogeneity (I^2 = 79%; Supplemental Fig 5A). Because RCT data for long-term mortality at 2 years were found in only 2 publications of 3 studies and had high heterogeneity, data from observational cohort studies were

TABLE 3 Patient Characteristics in Preterm RCTs and Quasi-RCTs

Study	Oxygen Level	Gestational Age, wk	Male Sex, %	Birth Wt, g	Antenatal Steroid Administration, %	Cesarean Delivery, %	Intubation and Mechanical Ventilation, %	Chest Compressions, %
Lundstrøm et al[24]								
	Low	29 (25–32)[a]	71	1043 (610–2590)[a]	88	68	0	N/A
	High	29 (24–32)[a]	61	1113 (550–1870)[a]	86	81	0	N/A
Harling et al[25]								
	Low	27 (23–31)[a]	42	1010 (518–1528)[a]	100	39	N/A	N/A
	High	28 (24–30)[a]	50	973 (560–1562)[a]	100	50	N/A	N/A
Wang et al[26]								
	Low	28.1 (2.2)[b]	39	1066 (368)[b]	62	50	55	0
	High	27.6 (2.1)[b]	39	1013 (444)[b]	74	70	43	13
Vento et al[28]								
	Low	26.0 (1.5)[b]	38	854.7 (170.1)[b]	97	51	57	N/A
	High	26.3 (1.3)[b]	44	901.7 (195.4)[b]	93	59	61	N/A
Rabi et al[29]								
	Low	29 (28–30)[a]	53	1242 (1092–1391)[a]	85	N/A	29	N/A
	High	29 (28–30)[a]	35	1231 (1091–1371)[a]	85	N/A	26	N/A
Armanian and Badiee[30]								
	Low	Mean 32	N/A	Mean 1700	N/A	N/A	N/A	N/A
	High	Mean 30.8	N/A	Mean 1600	N/A	N/A	N/A	N/A
Kapadia et al[31]								
	Low	30 (24–34)[a]	48	1678 (634)[b]	55	63	20	0
	High	30 (24–34)[a]	55	1463 (6606)[b]	48	73	39	0
Aguar et al[32]								
	Low	27.1 (1.6)[b]	74	1013 (306)[b]	100	65	N/A	N/A
	High	26.7 (1.5)[b]	60	925 (174)[b]	100	60	N/A	N/A
Rook et al[37]								
	Low	29 (27–30)[a]	44	1013 (820–1280)[a]	100	70	31	N/A
	High	29 (26–31)[a]	46	1123 (790–1368)[a]	100	65	30	N/A
Boronat et al[34]								
	Low	28 (24–32)[a]	48	944 (720–1280)[a]	100	68	N/A	N/A
	High	27 (23–31)[a]	52	1040 (755–1368)[a]	100	63	N/A	N/A
Oei et al[5] (To2rpido)								
	Low	28 (2)[b]	55	1147 (363)[b]	97	66	30	1
	High	28 (2)[b]	50	1136 (321)[b]	97	76	29	0
Thamrin et al[38] (To2rpido)								
	Low	28 (2)[b]	55	1147 (363)[b]	97	66	30	1
	High	28 (2)[b]	50	1136 (321)[b]	97	76	29	0

N/A, not available (not collected in original study).
[a] Reported as median (IQR).
[b] Reported as mean (SD).

also considered. Two observational cohort studies involving 1225 preterm newborns receiving respiratory support at birth revealed a statistically significant benefit of starting with lower compared with higher F_{IO_2} (RR = 0.77 [95% CI 0.59 to 0.99]; I^2 = 6%; Supplemental Fig 5B).

Long-term NDI (1–3 years) was reported in 3 RCTs (2 publications) involving 389 preterm newborns receiving respiratory support at birth, and these revealed no statistically significant difference in starting with lower compared with higher F_{IO_2} (RR = 1.14 [95% CI 0.78 to 1.67]; I^2 = 0%; Supplemental Fig 5C).[34] Because there were limited RCT data, 2 observational cohort studies involving 930 preterm newborns receiving respiratory support at birth were also considered. They revealed no statistically significant difference in starting with lower compared with higher F_{IO_2} (RR = 0.89 [95% CI 0.66 to 1.20]; I^2 = 59%; Supplemental Fig 5D).

Time to HR >100 beats per minute was defined as a secondary outcome, but there was limited direct evidence available. Researchers in only 4 RCTs and 1 observational cohort study reported HR response in the first 10 minutes, and because it was reported differently in those studies, it precluded meta-analysis. One study revealed a significantly lower HR in the lower F_{IO_2} group until 3 to

TABLE 4 Patient Characteristics in Preterm Retrospective Observational Cohort Studies

Study	Oxygen Level	Gestational Age, wk, Mean (SD)	Male Sex, %	Birth Wt, g, Mean (SD)	Antenatal Steroid Administration, %	Cesarean Delivery, %	Intubation and Mechanical Ventilation, %	Chest Compressions, %
Dawson et al[27]								
	Low	27 (1.6)	64	930 (293)	82	N/A	0	0
	High	27 (1.6)	65	915 (300)	90	N/A	40	0
Rabi et al[33]								
	Low	26 (25–27)[a]	54	884 (284)	85	58	36	N/A
	High	26 (25–27)[a]	51	843 (196)	87	55	38	N/A
Soraisham et al[36]								
	Low	26.3 (1.4)	51	917 (216)	93	61	N/A	N/A
	High	25.8 (1.5)	53	851 (217)	92	57	N/A	N/A
Kapadia et al[35]								
	Low	26 (1)	48	983 (224)	51	66	70	2
	High	26 (1)	53	939 (255)	54	67	58	1

N/A, not available (not collected in original study).
[a] Reported as median (IQR).

TABLE 5 RoB According to Cochrane RCT Criteria

Study	Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessors	Incomplete Outcome Data	Selective Outcome Reporting	Other Sources of Bias	Overall Bias
Lundstrøm et al[24]	Unclear	Unclear	High	Unclear	Low	Low	Unclear	Unclear
Harling et al[25]	Low	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Wang et al[26]	Low	Low	High	Unclear	Low	Unclear	Low	Unclear
Vento et al[28]	Low	Low	Unclear	Low	Low	Low	Low	Low
Rabi et al[29]	Low	Low	Low	Low	Low	Low	Unclear	Low
Armanian and Badiee[30]	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High	Unclear
Kapadia et al[31]	Low	Low	High	Unclear	Low	Low	Unclear	Unclear
Aguar et al[32]	Low	Low	Low	Low	Low	Unclear	High	Unclear
Rook et al[37]	Low	Low	Low	Unclear	Low	Low	Unclear	Unclear
Boronat et al[34]	Low	Low	Low	Low	Unclear	Low	Unclear	Unclear
Oei et al[5] (To2rpido)	Low	Low	High	Low	Low	Low	High	High
Thamrin et al[38]	Low	Low	High	Low	Unclear	Low	High	High

TABLE 6 RoB According to ROBINS-I Observational Cohort

Study	Bias Due to Confounding	Bias in Selection of Participants	Bias in Classification of Interventions	Bias Due to Deviations From Intended Interventions	Bias Due to Missing Data	Bias in Measurement of Outcomes	Bias in Selection of the Reported Result	Overall Bias
Dawson et al[27]	Unclear	High	Low	Unclear	Low	Low	Low	Unclear
Rabi et al[33]	Unclear	Low	High	High	Low	Low	Low	Unclear
Soraisham et al[36]	Unclear	Low	Unclear	High	Low	Low	Low	Unclear
Kapadia et al[35]	Unclear	Low	Low	High	Low	Low	Low	Unclear

TABLE 7 Summary of Results for All Preterm Newborns <35 Weeks' Gestation

Outcome	Study Design	No. Studies	No. Participants	Effect Estimate, RR (95% CI)	I^2, %	GRADE Confidence
STM	RCT	10	968	0.83 (0.50 to 1.37)	18	Very low
Long-term mortality	RCT	3	491	1.05 (0.32 to 3.39)	79	Very low
NDI long-term	RCT	3	389	1.14 (0.78 to 1.67)	0	Very low
ROP	RCT	7	806	0.73 (0.42 to 1.27)	0	Very low
NEC	RCT	8	847	1.34 (0.63 to 2.84)	0	Very low
BPD	RCT	8	843	1.00 (0.71 to 1.40)	47	Very low
Major IVH (grade III or IV)	RCT	7	795	0.96 (0.61 to 1.51)	0	Very low

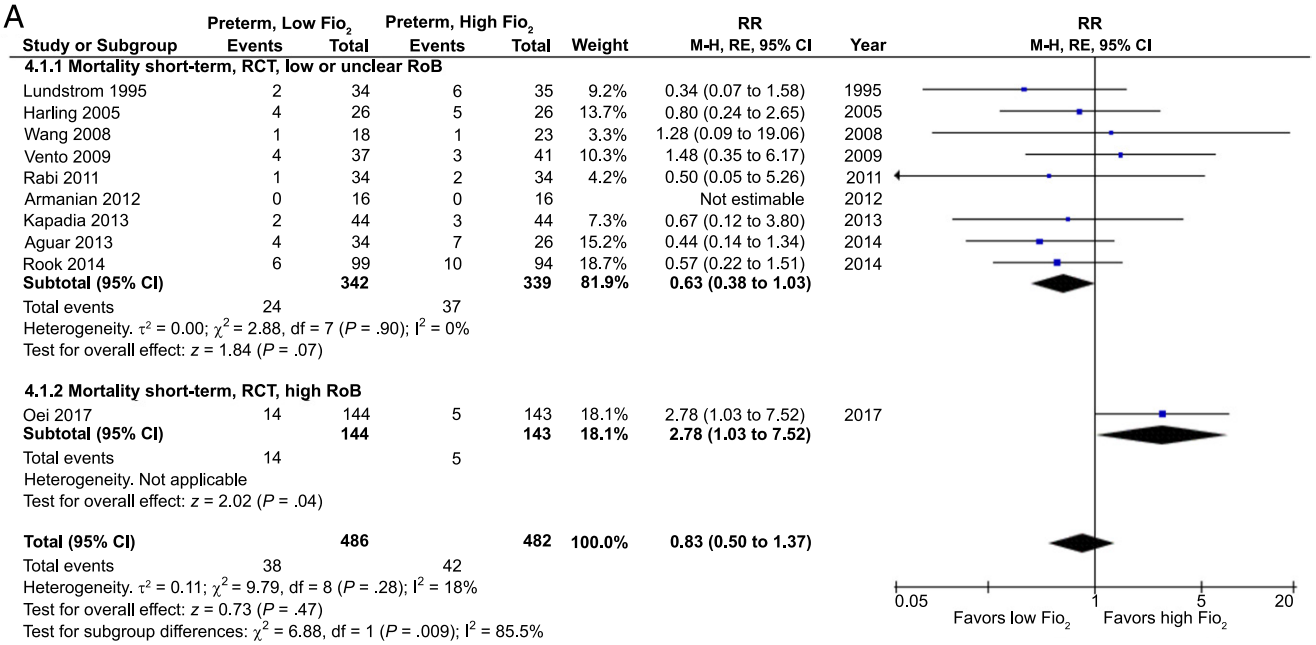

FIGURE 2

Summary of results: Preterm newborns receiving respiratory support when comparing low with high F_{IO_2}. A, STM demonstrating studies by RoB. B, STM sensitivity analysis revealing studies that are blinded and unblinded.

4 minutes of age,[41] and the others revealed no statistically significant difference.[26–28,30] A summary of the data found on HR response within the first 10 minutes is reported in Supplemental Table 15.

None of the additional secondary outcomes that were deemed important markers of morbidity revealed statistically significant differences. Results are detailed in Tables 7 through 11.

Subgroup Analyses

The predetermined subgroup analyses by gestational age (≤32 and ≤28 weeks) all revealed no statistically significant differences when comparing lower with higher F_{IO_2}. The RRs are reported in Tables 8 and 9. Results from 2 observational studies involving 1225 preterm newborns ≤28 weeks' gestation reveal an association with a statistically significant benefit of starting with lower oxygen compared with higher oxygen concentration

TABLE 8 Summary of Results for All Preterm Newborns ≤32 Weeks' Gestation

Outcome	Study Design	No. Studies	No. Participants	Effect Estimate, RR (95% CI)	I^2, %	GRADE Confidence
STM	RCT	8	837	0.93 (0.55 to 1.55)	15	Very low
Long-term mortality	RCT	3	491	1.05 (0.32 to 3.39)	79	Very low
NDI long-term	RCT	3	389	1.14 (0.78 to 1.67)	0	Very low

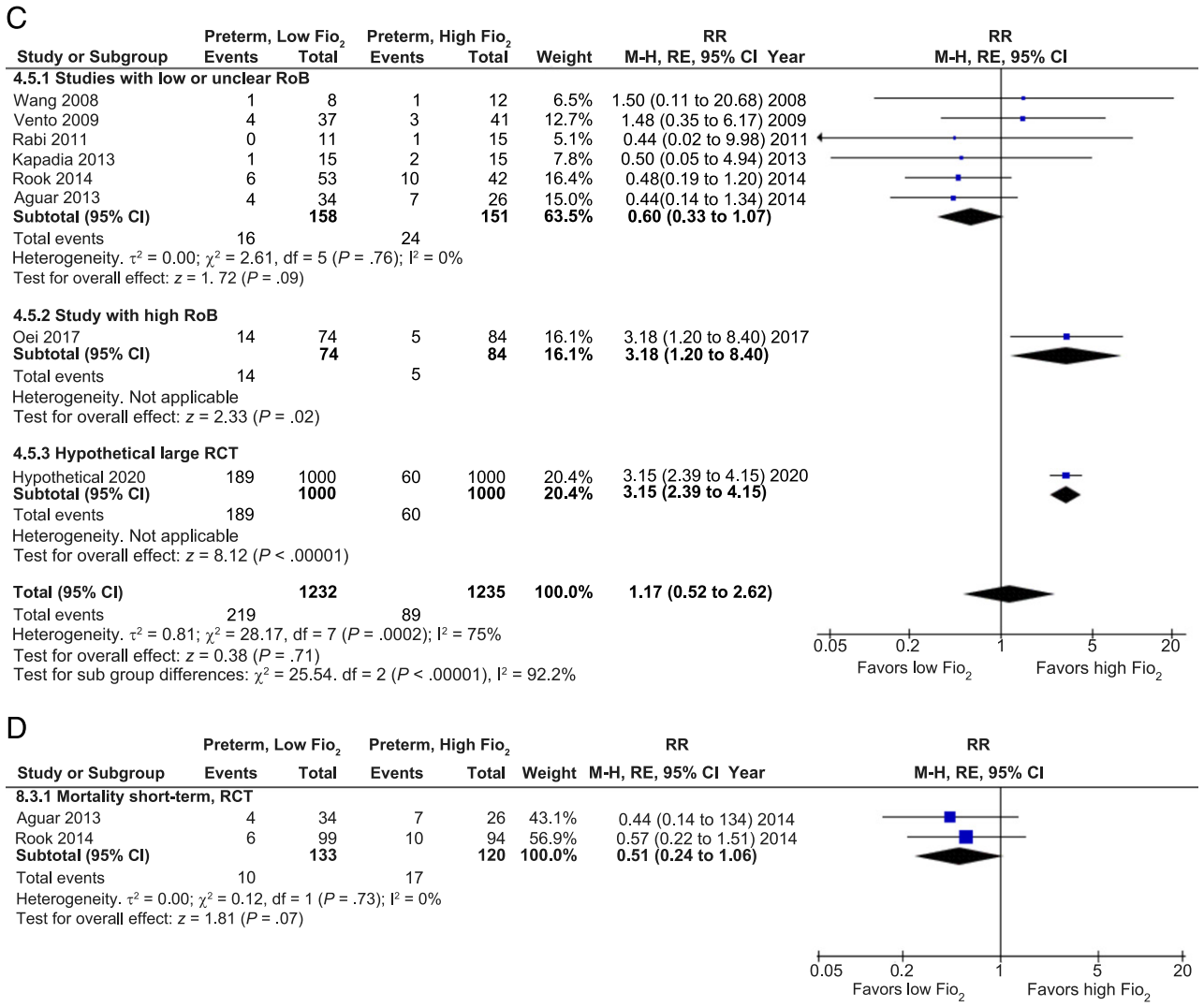

FIGURE 3
Summary of results: Preterm newborns receiving respiratory support when comparing low with high F_{IO_2} (continued). C, STM exploratory analysis, including a hypothetical large study. D, STM subgroup analysis F_{IO_2} 0.3 compared with F_{IO_2} 0.60 to 0.65. df, degrees of freedom; MH, Mantel-Haenszel.

with respect to long-term mortality (RR = 0.77 [95% CI 0.59 to 0.99]; I^2 = 6%).[35,36]

Exploratory analysis was conducted to assess whether an additional large RCT involving 2000 patients ≤28 weeks' gestation (all studies combined have <500 total patients in this age subgroup) with STM results similar to those in the Tor2rpido study would change the point estimate and CI to favor high F_{IO_2} (Fig 3C). If such a sufficiently large RCT were added, the random effectsmeta-analysis result would remain nonsignificant (RR = 1.17 [95% CI: 0.52 to 2.62]; I^2 = 75%).

The predetermined subgroup analyses by F_{IO_2} comparisons are reported in Table 10. Researchers in 2 RCTs with 253 preterm newborns (≤32 weeks' gestation) compared initial F_{IO_2} 0.30 with F_{IO_2} 0.60 to 0.65. The pooled estimate for STM reveals no statistically significant difference (RR = 0.51 [95% CI 0.24 to 1.06]; I^2 = 0%; Fig 3D).[32,37] The other outcomes and subgroups by

TABLE 9 Summary of Results for All Preterm Newborns ≤28 Weeks' Gestation

Outcome	Study Design	No. Studies	No. Participants	Effect Estimate, RR (95% CI)	I^2, %	GRADE Confidence
STM	RCT	7	467	0.92 (0.43 to 1.94)	45	Very low
Long-term mortality	RCT	1	86	2.11 (0.86 to 5.19)	N/A	Very low
NDI long-term	RCT	1	69	1.08 (0.58 to 2.03)	N/A	Very low
ROP	RCT	6	441	0.75 (0.43 to 1.33)	0	Very low
NEC	RCT	6	441	1.62 (0.66 to 3.99)	0	Very low
BPD	RCT	7	467	0.90 (0.64 to 1.28)	31	Very low
Major IVH (grade III or IV)	RCT	6	441	0.84 (0.50 to 1.40)	12	Very low

N/A, not available.

TABLE 10 Summary of Results of F_{IO_2} Subgroup Comparisons

Outcomes	Study Design	No. Studies	No. Participants	Effect Estimate, RR (95% CI)	I^2, %	GRADE Confidence
Subgroup F_{IO_2} 0.21 compared with 1.0 only						
STM	RCT	4	484	1.58 (0.70 to 3.55)	4	Very low
Long-term mortality	RCT	3	491	1.05 (0.32 to 3.39)	79	Very low
NDI long-term	RCT	3	389	1.14 (0.78 to 1.67)	0	Very low
Subgroup F_{IO_2} 0.21–0.30 compared with 0.80–1.00 only						
STM	RCT	7	667	1.24 (0.61 to 2.4)	13	Very low
Long-term mortality	RCT	3	491	1.05 (0.32 to 3.39)	79	Very low
NDI long-term	RCT	3	389	1.146 (0.78 to 1.67)	0	Very low
Subgroup F_{IO_2} 0.30 compared with 0.60–0.65						
STM	RCT	2	253	0.51 (0.24 to 1.06)	0	Moderate
Long-term mortality	RCT	2	253	0.58 (0.28 to 1.20)	N/A	Low
NDI long-term	RCT	2	174	0.96 (0.38 to 2.43)	N/A	Low

N/A, not available.

TABLE 11 Summary of Results for Subgroup Oxygen Saturation Targeting or No Targeting

Outcomes	Study Design	No. Studies	No. Participants	Effect Estimate RR (95% CI)	I^2, %	GRADE Confidence
Subgroup with no explicit oxygen saturation targeting						
STM	RCT	2	121	0.58 (0.23 to 1.49)	0	Very low
Subgroup with explicit oxygen saturation targeting						
STM	RCT	8	847	0.92 (0.50 to 1.71)	28	Very low
Long-term mortality	RCT	3	491	1.05 (0.32 to 3.39)	79	Very low
NDI long-term	RCT	3	389	1.14 (0.78 to 1.67)	0	Very low

N/A, not applicable.

F_{IO_2} comparisons also reveal no statistically significant differences when comparing lower with higher F_{IO_2}.

The last predetermined subgroup analysis was focused on those studies in which oxygen saturation targeting (by using pulse oximetry) was explicitly included as a cointervention (and those in which it was not). The pooled results reveal no statistically significant differences and are reported in Table 11.

Certainty in the Point Estimates (GRADE Analysis)

The GRADE summary for the primary outcomes is presented in Supplemental Table 16. RCTs (n = 10) are started at high certainty, and retrospective cohort studies (n = 4) are started at low certainty. Because of serious concerns with RoB, inconsistency, and imprecision, the certainty of the results was downgraded to very low for the majority of the outcomes. The expert opinion of the ILCOR NLS Task Force was that it would be very unlikely that there were any additional unpublished studies given the intense clinical interest in this topic, the international reach and involvement of the committee, and the extensive search (including uncovering abstracts and conference proceedings). Therefore, the outcomes were not downgraded for publication bias. The rating of the importance of outcomes for the GRADE analysis were all "critical" or "important" and ranged from 6 to 9 on the 9-point scale.

TABLE 12 Comparison With Previous Meta-analyses

	This study, RR (95% CI); *n*	Oei et al,[42,a] RR (95% CI); *n*	Saugstad et al,[43,b] RR (95% CI); *n*	Brown et al,[44,c] RR (95% CI); *n*
STM	0.83 (0.50–1.37); 968	0.99 (0.52–1.91); 509	0.62 (0.37–1.04); 677	0.65 (0.43–0.98); 484
Long-term mortality	1.05 (0.32–3.39); 491	—	—	—
NDI (1–3 y)	1.14 (0.78–1.67); 389	—	—	—
IVH (III–IV)	0.96 (0.61–1.51); 795	—	0.90 (0.53–1.53); 677	1.50 (0.71–3.15); 240
ROP (III–V)	0.73 (0.42–1.27); 806	0.78 (0.48–1.29); 419	—	0.68 (0.24–1.96); 199
NEC (II–III)	1.34 (0.63–2.84); 847	1.61 (0.77–3.36); 483	—	1.74 (0.42–7.20); 199
BPD (moderate to severe)	1.00 (0.71–1.40); 843	0.88 (0.68–1.14); 443	1.11 (0.73–1.68); 677	0.86 (0.62–1.18); 223

RR <1 favors lower compared with higher F_{IO_2}. —, not applicable.

[a] Data were as follows: F_{IO_2} ≤0.3 compared with ≥0.6; age <29 wk; 6 articles and 2 abstracts, 4 were excluded; did not specify moderate to severe BPD; ROP ≥3; and NEC ≥2.

[b] Data were as follows: F_{IO_2} ≤0.3 compared with ≥0.6; age <32 wk; and IVH ≥2.

[c] Data were as follows: F_{IO_2} ≤0.5 vs >0.5; most were age <32 wk; and no definition was given for BPD, ROP, NEC, or severe IVH.

DISCUSSION

In this systematic review and meta-analysis, we identified 10 RCTs involving 1007 preterm newborns (<35 weeks' gestation) and demonstrate no statistically significant improvement in STM when initiating respiratory support in newborns with low compared with high F_{IO_2}. There is also no statistically significant benefit in the other outcomes. However, the GRADE certainty of evidence for all outcomes assessed were very low because of issues with RoB, inconsistency, and imprecision.

Although concealed allocation was a common feature for most of the randomized studies, researchers in only 3 studies used oxygen saturation targeting and adequately masked the study gas from the delivery room personnel.[29,32,37] When considering all-cause STM, none of the studies revealed statistically significant effects of the initial oxygen concentration, but the 3 fully masked studies had similar point estimates, and each favored lower initial oxygen concentrations.

In contrast, the recently published To2rpido study was nonblinded.[41] Although it is the largest RCT reported to date, after 6.5 years of enrollment, the study had to be terminated with only 15% of planned enrollment (292 of 1976) completed. Only 4.6% (292 of 6291) of eligible subjects were enrolled secondary to clinician preference, lack of equipoise, and inability of the study team to attend many births. Therefore, the study was determined to be at an overall high RoB. The study's primary outcome was death or disability at 2 years; however, when the study was terminated, investigators reported a statistically significant increased risk of death before hospital discharge (RR 3.9; 95% CI 1.1 to 13.4) among newborns <28 weeks' gestation who were randomly assigned to the room air group. This was not a prespecified outcome and thus should be interpreted with caution. Comparing STM from the To2rpido study with the other 6 studies in which outcomes for newborns ≤28 weeks' gestation were reported, To2rpido subjects had both the highest reported proportion of deaths in the low F_{IO_2} group (19%) and the lowest proportion of deaths in the high F_{IO_2} group (6%). Because of the small number of extremely preterm subjects, the increased risk of all deaths reported in the To2rpido study reflects a difference in mortality for only 6 subjects over the 6.5 years of study enrollment and may represent a type I (α) error. In sensitivity analysis, removing this study shifts the summary estimate of STM to favor lower oxygen (RR 0.63; 95% CI 0.38 to 1.03) with no heterogeneity (I^2 = 0%), whereas including it shifts the effect estimate toward the null effect line (RR 0.83; 98% CI 0.50 to 1.37) and increases heterogeneity (I^2 = 18%).

The findings in this meta-analysis are seemingly contradictory to the evidence that high F_{IO_2} can be toxic to newborns, especially preterm newborns. As has been recognized for decades, free radical formation from hyperoxia can cause injury to the newborn lungs, eyes, brain, and other organs.[6] Researchers in the original delivery room oxygen studies of term newborns examined only F_{IO_2} 0.21 compared with F_{IO_2} 1.0 and demonstrated evidence of a STM benefit of initial room air resuscitation. However, the more recent preterm studies do not reveal this same effect.

Contemporary practice involves oxygen saturation targeting with pulse oximetry and was included as a cointervention in the 8 most recent RCTs and all 4 observational studies.[5,26–33,36,37] Among RCTs in which researchers used oxygen saturation targeting, nearly all subjects who were randomly assigned to initiate resuscitation with room air required the administration of supplemental oxygen to meet desired targets.[5,26,29,31] With oxygen saturation targeting, control and intervention subjects were exposed to different inspired oxygen concentrations for the first 5 to 7 minutes of life,[5,26,28,31,37] which may have limited the effect of the intervention.

In Table 12, we compare this meta-analysis to key previously published analyses. The STM RRs for low compared with high F_{IO_2} are different in the analyses published before the To2rpido study because that study had a negative point estimate for mortality. This shifted the subsequent point estimates and CIs to a nonsignificant finding of neither harm nor benefit.

In 2010, the ILCOR recommended initial room air for term neonatal resuscitation.[45] Although this was not intended to apply to preterm newborns, there were some publications in which researchers studied preterm subjects that had revealed no apparent harm from starting resuscitation with F_{IO_2} <1.0, and some centers began changing to initial room air resuscitation in preterm newborns in addition to term newborns. Since then, researchers in several RCTs of oxygen administration to preterm newborns found recruitment difficult because clinicians lost equipoise in using F_{IO_2} 1.0 for the initial resuscitation of preterm newborns.[5,27]

In 2015, the ILCOR NLS Task Force made the recommendation to begin the resuscitation of preterm newborns (<35 weeks' gestation) with a low oxygen concentration (F_{IO_2} 0.21–0.30) and recommended against the use of high supplementary oxygen concentrations (F_{IO_2} 0.65–1.0; strong recommendation, moderate quality evidence). This was a major change for many regions of the world that had a long-standing practice of starting with 100% oxygen for respiratory support in all preterm newborns who received respiratory support at birth. In making such a recommendation, high value was placed on not exposing preterm newborns to additional oxygen without proven benefit for critical or important outcomes.

In this analysis in 2018 (in collaboration with the ILCOR), we considered preterm newborns <35 weeks' gestation and defined low oxygen as F_{IO_2} 0.21 to 0.50 and high oxygen as F_{IO_2} 0.51 to 1.0 (with planned subgroup analyses based on specific F_{IO_2} comparisons). Low F_{IO_2} was considered to be the intervention and high F_{IO_2} was the comparison. Thus, the relative risks are the inverse of the previous ILCOR 2015 review. Additional studies and trials have become available since the 2015 CoSTR and included data regarding long-term NDI. However, even with the new information and 1 larger trial in which researchers reported an increased risk of mortality for low oxygen in a secondary analysis of newborns ≤28 weeks' gestation, the outcomes remain similar to those in the previous review. Although the point estimates have shifted somewhat, and CIs have widened, there is no clear advantage in using either low or high F_{IO_2} for the outcomes considered, even the critical outcome of mortality. The ILCOR CoSTR associated with this analysis will be published separately in an ILCOR 2019 update.

The strengths of this systematic review and meta-analysis include a prespecified protocol; a broad search strategy, including additional unpublished data from authors; sensitivity analyses, the use of GRADE to determine certainty in effect estimate; a strong team of expert systematic reviewers coupled with international multidisciplinary experts in neonatology; and adherence to PRISMA reporting.

There are, however, several limitations. Firstly, 8 of the 12 RCT publications have an unclear RoB, and 1 RCT, the To2rpido study, has a high RoB.[5,38] The RoB as well as imprecision make the certainty of the point estimates low or very low. We also observed heterogeneity in several analyses, although this was primarily due to the To2rpido study. Variation in interventions and methods of defining outcomes (eg, NDI) across included studies may have contributed to heterogeneity. Lastly, the included studies enrolled patients from 1991 to 2014. During this time, clinical practice and guidelines have changed considerably. It is unclear if similar results would be found with current clinical practice.

CONCLUSIONS

In this systematic review and meta-analysis, comparison of initial low with high F_{IO_2} for preterm newborns <35 weeks' gestation who receive respiratory support at birth demonstrates no consistent evidence to define the ideal initial F_{IO_2}. The data do reveal, however, that nearly all preterm newborns ≤32 weeks' gestation will require oxygen supplementation in the first 5 minutes after delivery to achieve commonly recommended oxygen saturation targets. Future researchers should focus on identifying the optimum initial F_{IO_2} together with the ideal target oxygen saturation. Adequately powered studies in which researchers report long-term neurodevelopmental outcomes are required.

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ABBREVIATIONS

BPD: bronchopulmonary dysplasia
CI: confidence interval
CINAHL: Cumulative Index to Nursing and Allied Health Literature
CoSTR: consensus on science with treatment recommendations
EBM: Evidence-Based Medicine
FIO_2: fraction of inspired oxygen
GRADE: Grading of Recommendations Assessment, Development and Evaluation
HR: heart rate
ILCOR: International Liaison Committee on Resuscitation
IQR: interquartile range
IVH: intraventricular hemorrhage
NDI: neurodevelopmental impairment
NEC: necrotizing enterocolitis
NLS: Neonatal Life Support
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses
RCT: randomized controlled trial
RoB: risk of bias
ROBINS-I: Risk of Bias in Nonrandomized Studies of Interventions
ROP: retinopathy of prematurity
RR: risk ratio
STM: short-term mortality
To2rpido: Targeted Oxygen in the Resuscitation of Preterm Infants and Their Developmental Outcomes

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Dr Welsford prepared the protocol, screened studies, abstracted data, completed risk-of-bias and Grading of Recommendations Assessment, Development and Evaluation evaluations, completed the analysis, and prepared the first draft of the manuscript; Dr Nishiyama reviewed the protocol, screened studies, abstracted data, completed risk-of-bias and Grading of Recommendations Assessment, Development and Evaluation evaluations, reviewed the analysis, and prepared the first draft of the manuscript; Dr Shortt reviewed the protocol, screened studies, abstracted data, prepared the tables, and was involved in writing and editing the manuscript; Drs Weiner and Roehr reviewed the protocol, completed risk-of-bias and Grading of Recommendations Assessment, Development and Evaluation evaluations, reviewed the analysis, and were involved in writing and editing the manuscript; Drs Isayama, Dawson, Wyckoff, and Rabi were involved in reviewing the protocol, reviewing the analysis, and writing and editing the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

This trial has been registered with the Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/prospero/) (identifier CRD42018084902).

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