Therapeutic Efficacies of Normobaric Oxygen Therapy in Healthcare: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Research

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Abstract

Background

Normobaric oxygen therapy is one of the most commonly used treatments in healthcare; however, oxygen is not a panacea. There is currently a lack of a comprehensive review summarizing different normobaric oxygen therapies and their therapeutic efficacies based on randomized controlled trials across healthcare.

Methods

We systematically searched Ovid MEDLINE, Ovid Embase, Web of Science, and the Cochrane database from inception to April 4, 2019, for randomized controlled trials investigating the therapeutic efficacy of normobaric oxygen therapy compared to usual care. Two investigators independently extracted study data and assessed study quality.

Results

A total of 173 studies involving 81,792 patients were included in qualitative analysis, and 95 of these studies, segregated in 49 bodies of evidence according to methods of oxygen therapy used, patient populations treated, and outcomes measured, were included in meta-analyses. Normobaric oxygen therapy was guided by oxygen flow, inspired oxygen fraction (FiO_2), or an oxygenation monitor. Each method had multiple different protocols. Eighteen different outcome measures were commonly used to assess the therapeutic efficacy. Ten (20%), 2 (4%) and 37 (76%) bodies of evidence suggested a beneficial, harmful, and futile effect, respectively. The quality of only two bodies of evidence (4%) was high, i.e., the significant reduction of prematurity-related mortality and necrotizing enterocolitis by 91-95% pulse oxygen saturation-guided therapy. The quality of the remaining 47 bodies of evidence was moderate (39%), low (43%), or very low (14%). Contrary to the World Health Organization recommendation, 80% FiO_2-guided oxygen therapy did not affect surgical site infection in intubated surgical patients (risk ratio, 0.84; 95% confidence interval, 0.69 to 1.01; p=0.07; moderate quality).

Conclusions

Normobaric oxygen therapy is widely used across healthcare; however, more than 70% of bodies of evidence suggested a futile effect and the quality of more than 50% of bodies of evidence was low or very low. How to best use normobaric oxygen therapy deserves further research.

Introduction

Supplemental oxygen is arguably the most prevalent prescription in healthcare. It is administered to millions of acutely and chronically ill patients daily around the world.[1, 2] Almost every patient inhales either pure oxygen or a gas mixture with an inspired oxygen fraction (FiO_2) much higher than 21% in the intensive care unit or perioperative environment.[3]

Many healthcare providers regard supplemental oxygen as a harmless and potentially beneficial therapy, irrespective of the clinical scenario.[4, 5] However, excessive oxygen may lead to various potentially deleterious effects, including absorption atelectasis,[6] acute lung injury,[7] inflammatory cytokine production,[8] central nervous system toxicity,[9] reduced cardiac output,[10] and cerebral and coronary vasoconstriction.[11] The therapeutic efficacy of normobaric oxygen therapy needs to be critically appraised by randomized controlled trials (RCTs). However, there is currently a lack of a comprehensive review summarizing the therapeutic efficacy of normobaric oxygen therapy based on RCTs across different healthcare fields.

In light of these circumstances, we conducted this systematic review and meta-analysis of RCTs to investigate the therapeutic efficacies of different normobaric oxygen therapies across healthcare. We assessed the quality of different bodies of evidence and discussed the implications of our findings.

Methods

Protocol and Registration

This study was registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42019133989). The present report complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[12]

Eligibility Criteria

RCTs investigating the therapeutic efficacy of normobaric oxygen therapy, compared with usual care, on patient-centered clinical outcomes in any patient population were eligible. The study settings were intensive care unit, perioperative environment, emergency department, regular inpatient setting, and outpatient setting. In this review, oxygen therapy was defined as the administration of oxygen to patients at a pressure of one atmosphere (i.e., normobaric oxygen[13]), in contrast to hyperbaric oxygen therapy which was an exclusion criterion. The oxygen administration was required to be guided by oxygen flow, FiO_2, or an oxygenation monitor measuring SpO_2, arterial oxygen partial pressure (PaO_2), central venous oxygen saturation ($ScvO_2$), cerebral tissue oxygen saturation ($SctO_2$), somatic tissue oxygen saturation ($SstO_2$), the oxygen delivery index (DO_2I), or brain tissue oxygen partial pressure ($PbtO_2$). The therapeutic efficacy was assessed by 18 outcome measures, including mortality, surgical site infection, stroke, postoperative delirium, postoperative cognitive decline, hypoxemia, respiratory failure, respiratory support, intubation, atelectasis, pneumonia, arrythmia, myocardial infarction, retinopathy of prematurity, necrotizing enterocolitis, bronchopulmonary dysplasia, nausea/vomiting, and unclassified complications. Publication year and language were not restricted.

Information Sources

Ovid MEDLINE, Ovid Embase, Web of Science, and the Cochrane database were systematically searched from inception to April 4, 2019, the date of the last search. The reference lists of all relevant articles were manually screened to supplement the systematic search.

Search Strategy

The search strategies are detailed in the eAppendix in Supplementary Files.

Study Selection

We used Covidence (a web-based Cochrane technology platform, https://www.covidence.org) for study screening and selection. Two investigators (H.X. and X.Z.) screened all deduplicated titles and abstracts derived from the systematic search and then evaluated the full texts of the candidate articles to determine their eligibility. These two investigators worked independently and resolved any disagreements by consulting the senior author (L.M.).

Data Collection Process

The same investigators performed data extraction independently using predesigned data forms.

Data Items

The data items extracted from each eligible study were as follows: 1) publication (author and year), 2) patient population (age, patient number, region, and setting), 3) intervention (method, protocol and indication of oxygen therapy, including the level of oxygen flow, range of FiO_2, and type of oxygenation monitor, and details of usual care), 4) outcome (measure and prevalence), and 5) study results (event number).

Risk of Bias in Individual Studies

The risk of bias in each study was assessed using the Cochrane Collaboration tool.[14] A study was rated as having a high risk of bias overall if one or more domains were rated as having a high risk of bias.

Summary Measures

The risk ratio (RR) and 95% confidence interval (CI) were used to measure the therapeutic efficacy of normobaric oxygen therapy compared with usual care.

Synthesis of Results

Random-effects meta-analysis was used for bodies of evidence with at least 5 studies, whereas fixed-effects meta-analysis was used for bodies of evidence with fewer than 5 studies.[15] All meta-analyses were performed using the metafor R package (R version 3.5.2, R Foundation for Statistical Computing, Vienna, Austria).[16]

Risk of Bias (ROB) Across Studies

Funnel plots and Egger's test were used to analyse the potential publication bias.[17] A symmetrical funnel plot indicated the absence of bias, while an asymmetrical plot indicated the presence of bias. Publication bias was also suggested by a p value < 0.1 in Egger's test.[18]

Additional Analyses

Trial sequential analysis was used to account for multiple testing and to evaluate the reliability of a meta-analysis by examining sufficient data to avoid type I (false-positive) and type II (false-negative) errors.[19] Trial sequential analysis was performed using TSA software (version 0.9.5.10 beta; Copenhagen Trial Unit, Copenhagen, Denmark).[20, 21]

Quality of Evidence

The evidence quality, defined as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest, was graded as high, moderate, low, or very low according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.[22]

Results

Study Selection

The study selection process and results were detailed in Figure 1.

Study Characteristics and Results

The 173 eligible studies were published between 1976 and 2019 and involved 81,792 patients, with 40,782 patients in the oxygen therapy arm and 41,010 patients in the usual care arm. Each study's characteristics and suitability for evidence synthesis are presented in Table S1 in Additional file 1. Each study's results are presented in Table S2 in Additional file 1.

Risk of Bias Within Studies

The risk of bias within individual studies is presented in Table S3 in Additional file 1, while the pooled risk of bias for these studies is shown in Figure S1 in Additional file 1. We report the risk of bias only for studies that were eligible for meta-analysis. The overall risk of bias was rated low, high, and unclear in 74%, 20%, and 6% of studies, respectively.

Synthesis of Results

Studies that were based on comparable patient populations, treatment protocols, and outcome measures were included in the meta-analysis. Reports that were post hoc analyses of already included studies[23-34] and reports by authors scrutinized for scientific and ethical misconduct[35-39] were excluded from the meta-analysis. Of the 173 studies, 95 studies segregated in a total of 49 bodies of evidence were qualified for meta-analysis (Table S1 in Additional file 1).

The results of flow-guided oxygen therapy are presented in Figure 2. Flow-guided oxygen therapy with a flow rate of 2 l/min significantly reduced the risk of hypoxemia in patients undergoing a procedure (RR, 0.33; 95% CI, 0.21 to 0.53; p<0.001). Flow-guided oxygen therapy with a flow rate of 4-8 l/min significantly reduced the risk of hypoxemia (RR, 0.28; 95% CI, 0.22 to 0.36; p<0.001), but not the risks of mortality, recurrent myocardial infarction, and arrhythmia, in patients with myocardial infarction. The available evidence failed to show a beneficial effect of high-flow oxygen therapy (greater than 35 l/min) on mortality or respiratory complications in patients with acute respiratory failure or receiving procedural sedation.

The results of FiO_2-guided oxygen therapy are presented in Figure 3. Compared to that with a FiO_2 of 30%, FiO_2-guided oxygen therapy with a FiO_2 of 60-65% significantly reduced the risk of bronchopulmonary dysplasia (RR, 0.66; 95% CI, 0.45 to 0.96; p=0.03) in preterm neonates and infants. In contrast, in the same patient population, FiO_2-guided oxygen therapy with a FiO_2 initiated at 100% and titrated per the prespecified SpO_2 range (i.e., 80-95%), compared with that initiated at 30% and titrated per the same prespecified SpO_2 range, significantly increased the risk of bronchopulmonary dysplasia (RR, 1.41; 95% CI, 1.04 to 1.91; p=0.03). Compared with that with a FiO_2 of 30-35%, FiO_2-guided oxygen therapy with a FiO_2 of 80% significantly reduced the risk of atelectasis (RR, 0.75; 95% CI, 0.60 to 0.93; p=0.008) but had no effects on surgical site infection in intubated surgical patients (RR, 0.84; 95% CI, 0.69 to 1.01; p=0.07) and patients undergoing cesarean delivery (RR, 1.23; 95% CI, 0.91 to 1.66; p=0.18).

The results of monitor-guided oxygen therapy are presented in Figure 4. Compared to that with a SpO_2 of 85-89%, SpO_2-guided oxygen therapy with a SpO_2 of 91-95% significantly reduced the risks of mortality (RR, 0.87; 95% CI, 0.77 to 0.98; p=0.02) and necrotizing enterocolitis (RR, 0.81; 95% CI, 0.68 to 0.95; p=0.009) but increased the risks of retinopathy of prematurity (RR, 1.31; 95% CI, 1.12 to 1.54; p<0.001) and bronchopulmonary dysplasia (RR, 1.16; 95% CI, 1.05 to 1.28; p=0.003) in preterm neonates and infants. In contrast, in the same patient population, SpO_2-guided oxygen therapy with a higher SpO_2 (95-99%), compared to that with a SpO_2 of 85-94%, significantly reduced the risk of retinopathy of prematurity (RR, 0.84; 95% CI, 0.70 to 1.00; p=0.04). Oxygen therapy guided by $SctO_2$ monitoring, compared with that not guided by $SctO_2$ monitoring, significantly reduced the risk of postoperative cognitive decline in surgical patients (RR, 0.51; 95% CI, 0.32 to 0.82; p=0.005). DO_2I-guided oxygen therapy with a DO_2I greater than 600 ml/min/m^2, compared with that not guided by DO_2I monitoring, significantly reduced the risks of mortality (RR, 0.41; 95% CI, 0.22 to 0.73; p=0.003) and unclassified complications (RR, 0.76; 95% CI, 0.62 to 0.93; p=0.008) in surgical patients.

Risk of Bias Across Studies

Among the 49 bodies of evidence analysed, 4 bodies of evidence had publication bias based on the funnel plots (Figure S2 in Additional file 1) and the results of Egger's test (Table).

Additional Analyses

Trial sequential analysis showed that there were only two bodies of evidence which met the required information size, i.e., the effect of SpO_2-guided oxygen therapy with a SpO_2 of 91-95% on mortality (beneficial, Figure 5A) and bronchopulmonary dysplasia (harmful, Figure 5B) in preterm neonates and infants. Trial sequential analysis suggested the futility of oxygen therapy guided by $ScvO_2$ for reducing mortality in septic patients (Figure 5C). It also suggested the beneficial effects of flow-guided oxygen therapy with a flow rate of 4-8 l/min on hypoxemia in patients with myocardial infarction (Figure 5D) and of SpO_2-guided oxygen therapy with a SpO_2 of 91-95% on necrotizing enterocolitis in preterm

neonates and infants (Figure 5E). The therapeutic efficacy of 80% FiO_2-guided oxygen therapy on surgical site infection in intubated surgical patients is uncertain (Figure 5F).

Quality of the Evidence

A summary of the findings along with the quality of the evidence and the levels of confidence in the results of the meta-analysis is presented (Table). Two bodies of evidence (2/49, 4%), including studies on the effect of 91-95% SpO_2 on prematurity-related mortality and necrotizing enterocolitis, exhibited high quality, while 19 bodies of evidence (19/49, 39%) exhibited moderate quality. The remaining bodies of evidence exhibited low (21/49, 43%) or very low (7/49, 14%) quality.

Discussion

Summary of the Evidence

We identified 173 RCTs reported over 43 years investigating the therapeutic efficacy of normobaric oxygen therapy across healthcare. Based on the comparability of patient populations, treatment protocols and outcome measures, the data from 95 studies, segregated in a total of 49 bodies of evidence, were eligible for meta-analysis. Normobaric oxygen therapy is widely used across healthcare; however, more than 70% of bodies of evidence suggested a futile effect and the quality of more than 50% of bodies of evidence was low or very low.

Ten bodies of evidence (10/49, 20%) with varying quality of evidence suggested a beneficial effect of oxygen therapy. 2 l/min and 4-8 l/min flow-guided oxygen therapy significantly reduced the risk of hypoxemia in patients undergoing a procedure (very low quality) and in patients with myocardial infarction (moderate quality), respectively. 80% FiO_2-guided oxygen therapy significantly reduced the risk of atelectasis in surgical patients (low quality). In preterm neonates and infants, 60-65% FiO_2-guided oxygen therapy significantly reduced the risk of bronchopulmonary dysplasia (moderate quality), 91-95% SpO_2-guided oxygen therapy significantly reduced the risk of mortality (high quality) and necrotizing enterocolitis (high quality), and 95-99% SpO_2-guided oxygen therapy significantly reduced the risk of retinopathy of prematurity (moderate quality). In surgical patients, oxygen therapy guided by $SctO_2$ monitoring significantly reduced postoperative cognitive decline (low quality), and oxygen therapy guided by a DO_2I greater than 600 ml/min/m^2 significantly reduced mortality (moderate quality) and unclassified complications (moderate quality).

Two bodies of evidence (2/49, 4%) suggested a harmful effect; 91-95% SpO_2-guided oxygen therapy significantly increased the risks of retinopathy of prematurity (low quality) and bronchopulmonary dysplasia (moderate quality) in preterm neonates and infants.

The remaining 37 bodies of evidence (37/49, 76%) suggested a futility of oxygen therapy with varying quality of evidence. Of note, following the exclusion of three studies as a result of potential scientific misconduct,[36, 37, 39] 80% FiO_2-guided oxygen therapy had no effect on surgical site infection in intubated surgical patients based on 13 studies (moderate quality). This is in contrast to the conditional recommendation made by the 2018 edition of the World Health Organization (WHO) guidelines.[40] The missing of the two studies published between 2018 and 2019[41, 42] in the revised WHO guidelines may be primarily responsible for this discrepancy.

Implications

Our findings have several valuable implications for healthcare providers, policymakers, and researchers. First, oxygen therapies are not created equal. Although essential to life, oxygen is not a panacea; on most occasions, oxygen therapy is likely futile, and under specific circumstances, it may be harmful. The administration of oxygen to the right patient via the right approach for the right outcome constitutes the right oxygen therapy. Second, oxygen therapy incurs significant costs. Based on an estimate published in 1995, approximately 241 individuals per 100,000 persons use home oxygen therapy in

the United States, with a total annual cost of $1.4 billion.[43] An updated comprehensive estimate is not available, but it is reasonable to speculate that the overall cost could now be higher. Therefore, it is important to determine how to reduce the cost of oxygen therapy without depriving patients who would benefit from this therapy. Third, practice guidelines and medical directives on oxygen therapy have been mostly inconsistent across healthcare. Although our work provides certain clarifications on this front, multiple areas merit further investigation, as suggested by the inadequate quality of most of the bodies of evidence. Given the routine use of supplemental oxygen in healthcare, the diverse therapeutic efficacies of oxygen therapy, and the uncertainty of the value of this treatment in most clinical scenarios, the findings of our study have immediate and significant implications.

Limitations

Our study may have some limitations in addition to those that are inherent to systematic reviews and meta-analyses. We attempted to cover all patient populations in which the therapeutic efficacy of oxygen therapy had been compared with that of usual care; as a result, we introduced heterogeneities in domains of patients, protocols, and outcomes, which can lead to extraction of useless, misleading, or erroneous information. To counter this limitation, we rigorously stratified the evidence and only performed evidence synthesis when patients, protocols, and outcomes were comparable within a body of evidence. The quality assessment showed that only 2 bodies of evidence (2/49, 4%) exhibited high quality, while the remaining 47 bodies of evidence (47/49, 96%) exhibited moderate, low or very low quality. This limitation prevents us from drawing confident conclusions from the data synthesized from most of the bodies of evidence.

Conclusions

Normobaric oxygen therapy is widely used in healthcare; however, the majority of oxygen therapies are likely futile. The quality of more than 50% of bodies of evidence is low or very low. Only 2 bodies of evidence exhibited high quality, i.e., in preterm neonates and infants, 91-95% SpO_2-guided oxygen therapy, compared with 85-89% SpO_2-guided oxygen therapy, reduces mortality and necrotizing enterocolitis. Oxygen therapy in most healthcare scenarios warrants further investigation due to inadequate quality of the available evidence. We here provide a comprehensive review of normobaric oxygen therapy across healthcare. Our findings have valuable implications for healthcare providers, policymakers, and researchers.

Declarations

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Authors' contributions: HX conceived the study, screened all studies for eligibility, extracted, analysed and interpreted the data, assessed the quality of evidence, and was a major contributor in writing the manuscript. XZ screened all studies for eligibility, extracted, analysed and interpreted the data, assessed the quality of evidence, performed meta-analysis, and was a major contributor in writing the manuscript. AB participated in the design of this study, performed systematic literature search, and provided Covidence for record screening. FD analysed and interpreted the data and participated in the editing of the manuscript. LM conceived the study, participated in the data analysis and interpretation, and drafted the manuscript. All authors participated in critical revision of the manuscript for important intellectual content and read and approved the final manuscript.

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Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Table

Table. Summary of findings comparing normobaric oxygen therapy with usual care*

* Only bodies of evidence included in the meta-analysis are presented in this table. The risk ratio (RR), 95% confidence interval (CI), and heterogeneity (I^2) were based on meta-analysis. The actual sample size is the sum of patients included in the body of evidence. The required information size was calculated by trial sequential analysis[19] based on the pooled event rates from the control groups of the included studies, a two-sided alpha of 0.05, a beta of 0.80, and a relative risk reduction of 20%, with adjustment for heterogeneity.[1] The evidence quality was graded as high, moderate, low, or very low according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines.[22] The confidence level was based on the evidence quality (high quality = confident; moderate quality = likely; low and very low = uncertain).

† Downgraded one level for imprecision because trial sequential analysis indicated that the required information size was not met.[44]

‡ Downgraded one level for inconsistency as a result of high statistical heterogeneity ($I^2 \geq 40\%$) that could not be explained by subgroup analyses.[18]

§ Downgraded one level for high overall risk of bias within studies if the percentage of the studies with a high overall risk of bias within the body of evidence was 50%.[45] The overall risk of bias within individual studies was based on the assessment of the risks of bias for different domains.[14]

¶ Downgraded one level for publication bias. The publication bias was determined by visual inspection of the funnel plots, with asymmetry suggesting the existence of publication bias, and by Egger's test, with a p value <0.10 suggesting the existence of publication bias.[46]

|| Heterogeneity (I^2 40%) could be explained by subgroup analyses.[18]

** The required information size was not met as a result of high heterogeneity. However, we downgraded the rating only one level for inconsistency instead of two levels for both imprecision and inconsistency to account for the interaction between the required information size and heterogeneity.[1]

†† Visual inspection of the funnel plots did not suggest asymmetry.[46]

‡‡ Downgraded one level for imprecision because the 95% CI included both important benefit (RR < 0.75) and harm (RR > 1.25) predictions.[44]

§§ Although the required information size was not met, we did not downgrade the rating for imprecision. The trial sequential analysis indicated that, if we proceeded to include more trials until the required information size was reached, the result would be likely to remain statistically significant,[19] with the cumulative Z-curve surpassing the O'Brien-Fleming monitoring boundary.[21]

COPD, chronic obstructive pulmonary disease; ED, emergency department; ICU, intensive care unit; MI, myocardial infarction; FiO_2, inspired oxygen fraction; NICU, neonatal intensive care unit; SpO_2, pulse oxygen saturation; $ScvO_2$, central venous blood oxygen saturation; $SctO_2$, cerebral tissue oxygen saturation; POCD, postoperative cognitive dysfunction; DO_2I, oxygen delivery index; $PbtO_2$, tissue oxygen partial pressure; TBI, traumatic brain injury.

Figures

Setting (condition)	Outcome (studies, n)	Risk ratio (95% CI)	Actual sample size (patients, n)	Required information size (patients, n)	Overall ROB (high, %)	I^2	Egger's test (p value)	Evidence quality	Clinical implication	
									Effect (intervention vs. control)	Confidence level
Flow < 4 l/min										
Home (COPD)	Mortality (n = 3)	0.84 (0.67-1.05)	841	2,113	0	0	0.78	Moderate†	No difference	Likely
Procedure	Hypoxaemia (n = 4)	0.33 (0.21-0.53)	285	3,483	50	60	0.007	Very low†‡§¶‖	Improvement	Uncertain
Flow 4–9 l/min										
ED/ICU (MI)	Mortality (n = 4)	1.07 (0.79-1.44)	7,459	129,233	0	41	0.87	Moderate†‖	No difference	Likely
	Recurrent MI (n = 3)	1.22 (0.95-1.56)	7,302	1,088,660	0	78	0.003	Very low†‡¶	No difference	Uncertain
	Arrhythmia (n = 2)	1.22 (0.97-1.53)	483	1,486	0	14	0.28	Moderate†	No difference	Likely
	Hypoxaemia (n = 3)	0.28 (0.22-0.36)	6,775	28,098	33	53	0.05	Moderate‡**††	Improvement	Likely
Flow ≥ 20 l/min										
ED/ICU (acute respiratory failure)	Mortality (n = 4)	0.95 (0.82-1.11)	1,326	4,752	0	23	0.38	Moderate†	No difference	Likely
	Respiratory support (n = 4)	0.87 (0.74-1.02)	1,279	23,531	25	53	0.32	Low†‡	No difference	Uncertain
	Intubation (n = 4)	0.76 (0.56-1.04)	708	27,507	0	48	0.29	Low†‡	No difference	Uncertain
Surgery	Mortality (n = 2)	0.77 (0.17-3.43)	560	50,212	0	0	0.82	Low†‡‡	No difference	Uncertain
	Hypoxaemia (n = 2)	0.92 (0.62-1.35)	330	2,295	50	0	0.67	Very low†§‡‡	No difference	Uncertain
	Reintubation (n = 2)	1.30 (0.70-2.41)	330	94,747	50	72	0.06	Very low †‡§‡‡††	No difference	Uncertain
	Pneumonia (n = 2)	1.03 (0.48-2.21)	330	9,082	50	0	0.95	Very low †§‡‡	No difference	Uncertain
Procedure	Hypoxaemia (n = 2)	0.72 (0.43-1.21)	119	2,350	0	37	0.21	Moderate†	No difference	Likely
FiO_2 = 60-79%										
NICU (preterm)	Mortality (n = 2)	1.72 (0.97-3.05)	401	4,302	0	0	0.96	Moderate†	No difference	Likely
	Retinopathy of prematurity (n = 2)	1.07 (0.42-2.72)	401	15,527	0	0	0.36	Low†‡‡	No difference	Uncertain
	Necrotizing enterocolitis (n = 2)	0.76 (0.29-1.95)	401	14,113	0	0	0.94	Low†‡‡	No difference	Uncertain
	Bronchopulmonary dysplasia (n = 2)	0.66 (0.45-0.96)	401	1,991	0	0	0.92	Moderate†	Improvement	Likely
FiO_2 = 80-99%										
Surgery	Mortality (n = 4)	1.38 (0.91- 2.10)	9,712	278,664	25	52	0.07	Low†‡††	No difference	Uncertain
	Surgical site infection (n = 14)	0.84 (0.69-1.01)	11,784	18,899	14	44	0.28	Moderate‡**	No difference	Likely
	Myocardial infarction (n = 2)	0.51 (0.22-1.19)	2,072	44,304	0	0	0.68	Moderate†	No difference	Likely
	Atelectasis (n = 3)	0.75 (0.60-0.93)	3,478	42,506	0	71	0.41	Low†‡	Improvement	Uncertain
	Pneumonia (n = 3)	0.89 (0.60-1.33)	3,458	24,242	0	0	0.21	Low†‡‡	No difference	Uncertain
	Nausea and vomiting (n = 8)	0.84 (0.61-1.15)	3,149	23,994	0	84	0.74	Moderate‡**	No difference	Likely

Caesarean delivery	Surgical site infection (n = 4)	1.23 (0.91-1.66)	1,719	8,052	25	0	0.94	Moderate†	No difference	Likely
NICU (preterm)	Mortality (n = 2)	0.65 (0.24-1.74)	120	4,302	0	0	0.93	Low†‡‡	No difference	Uncertain
FiO_2 = 100%										
NICU (preterm)	Mortality (n = 2)	1.32 (0.92-1.91)	635	4,581	100	0	0.47	Low†§	No difference	Uncertain
FiO_2 initiated with 100% (titrated per SpO_2)										
NICU (preterm)	Mortality (n = 4)	0.80 (0.59-1.10)	681	3,154	50	0	0.75	Low†§	No difference	Uncertain
	Retinopathy of prematurity (n = 2)	2.36 (0.84-6.63)	375	130,254	50	0	0.58	Low†§	No difference	Uncertain
	Necrotizing enterocolitis (n = 2)	1.44 (0.27-7.77)	375	130,254	50	81	0.02	Very low†‡††‡‡	No difference	Uncertain
	Bronchopulmonary dysplasia (n = 3)	1.41 (1.04-1.91)	443	9,383	33	52	0.097	Low†‡	No difference	Uncertain
SpO_2 = 91-95%										
NICU (preterm)	Mortality (n = 4)	0.87 (0.77-0.98)	5,248	3,174	0	0	0.41	High	Improvement	Confident
	Retinopathy of prematurity (n = 4)	1.31 (1.12-1.54)	5,248	33,503	0	75	0.63	Low†‡	Deterioration	Uncertain
	Necrotizing enterocolitis (n = 4)	0.81 (0.68-0.95)	5,248	5,690	0	0	0.92	High§§	Improvement	Confident
	Bronchopulmonary dysplasia (n = 3)	1.16 (1.05-1.28)	4,908	4,850	0	43	0.08	Moderate‡††	Deterioration	Likely
SpO_2 = 95-99%										
NICU (preterm)	Mortality (n = 2)	1.49 (0.72-3.07)	1,007	28,668	0	0	0.66	Low†‡‡	No difference	Uncertain
	Retinopathy of prematurity (n = 2)	0.84 (0.70-1.00)	1,007	1,418	0	0	0.77	Moderate†	Improvement	Likely
$ScvO_2 \geq 70\%$										
ED/ICU (sepsis)	Mortality (n = 4)	0.97 (0.87-1.09)	4,000	5,769	0	55	0.10	Moderate‡**	No difference	Likely
$SctO_2$										
Surgery	Mortality (n = 5)	0.90 (0.41-2.00)	804	21,790	20	0	0.99	Low†‡‡	No difference	Uncertain
	Stroke (n = 4)	1.08 (0.41-2.84)	719	30,241	25	13	0.64	Low†‡‡	No difference	Uncertain
	POCD (n = 6)	0.51 (0.32-0.82)	778	6,525	33	81	<0.001	Low‡¶**	Improvement	Uncertain
	Delirium (n = 3)	0.89 (0.61-1.28)	519	3,070	33	0	0.43	Low†‡‡	No difference	Uncertain
	Myocardial infarction (n = 3)	0.98 (0.46-2.06)	639	15,604	0	0	0.34	Low†‡‡	No difference	Uncertain
	Unclassified complications (n = 4)	0.88 (0.64-1.20)	389	2,312	0	15	0.61	Moderate†	No difference	Likely
DO_2I > 450-600 ml/min/m^2										
Surgery	Mortality (n = 2)	0.50 (0.23-1.11)	262	4,764	0	0	0.55	Moderate†	No difference	Likely
DO_2I > 600 ml/min/m^2										
Surgery	Mortality (n = 4)	0.41 (0.22-0.73)	358	3,295	25	11	0.18	Moderate†	Improvement	Likely
	Unclassified complications (n =	0.76 (0.62-0.93)	467	990	0	34	0.90	Moderate†	Improvement	Likely

	5)									
Sepsis	Mortality (n = 2)	1.09 (0.81-1.47)	130	824	50	0	0.60	Low†§	No difference	Uncertain
$PbtO_2$ ≥ 20 mmHg										
ICU (TBI)	Mortality (n = 3)	0.68 (0.38-1.21)	198	9,185	67	40	0.33	Very low†‡§	No difference	Uncertain

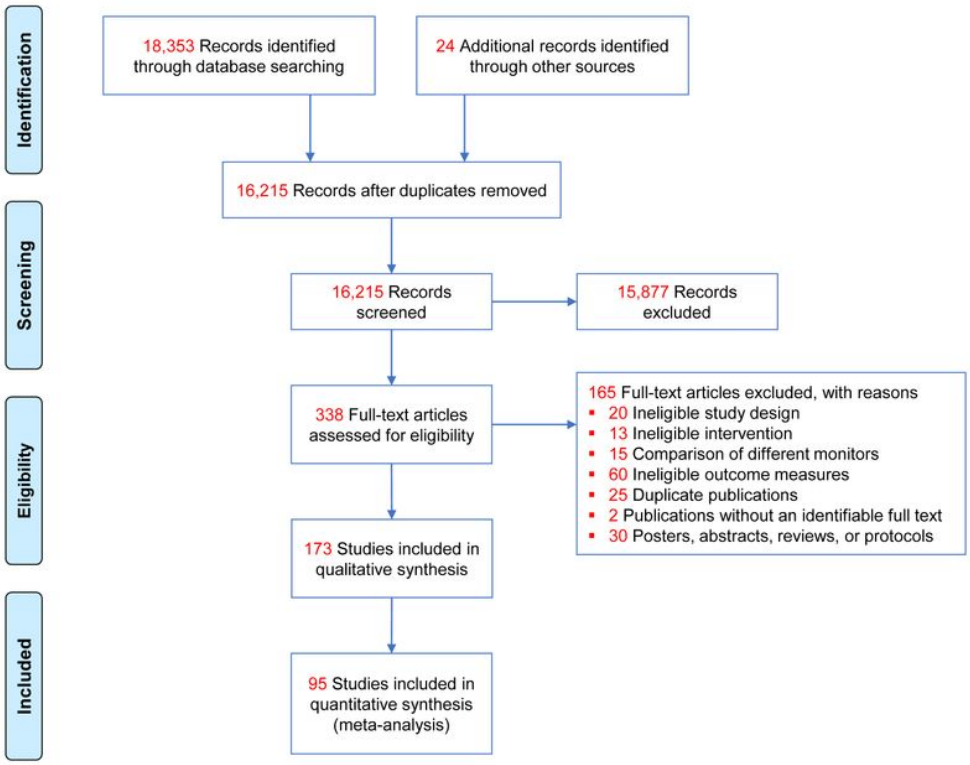

Figure 1

Study identification and selection

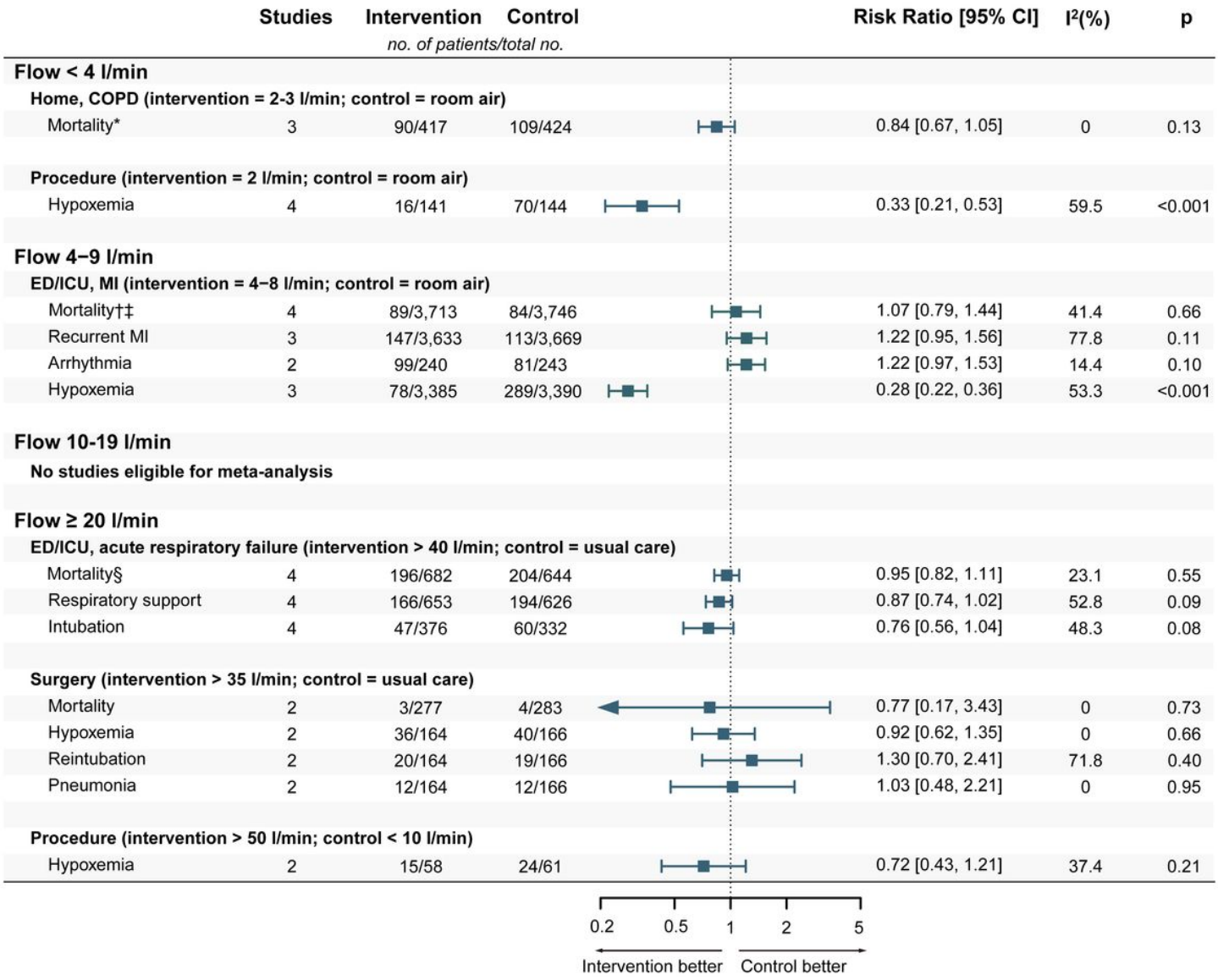

Figure 2

Clinical effectiveness of flow-guided oxygen therapy CI, confidence interval; COPD, chronic obstructive pulmonary disease; ED, emergency department; ICU, intensive care unit; MI, myocardial infarction. * Mortality was assessed at different time points among these studies. † We used the data for short-term mortality when mortalities at different time points were reported for 2 studies.[47, 48] ‡ We excluded two studies that reported post hoc analyses of long-term mortality of the same patient population whose short-term mortalities had already been reported and included in our analysis.[23, 24] § We used the data for short-term mortality when mortalities at different time points were reported for one study.[49]

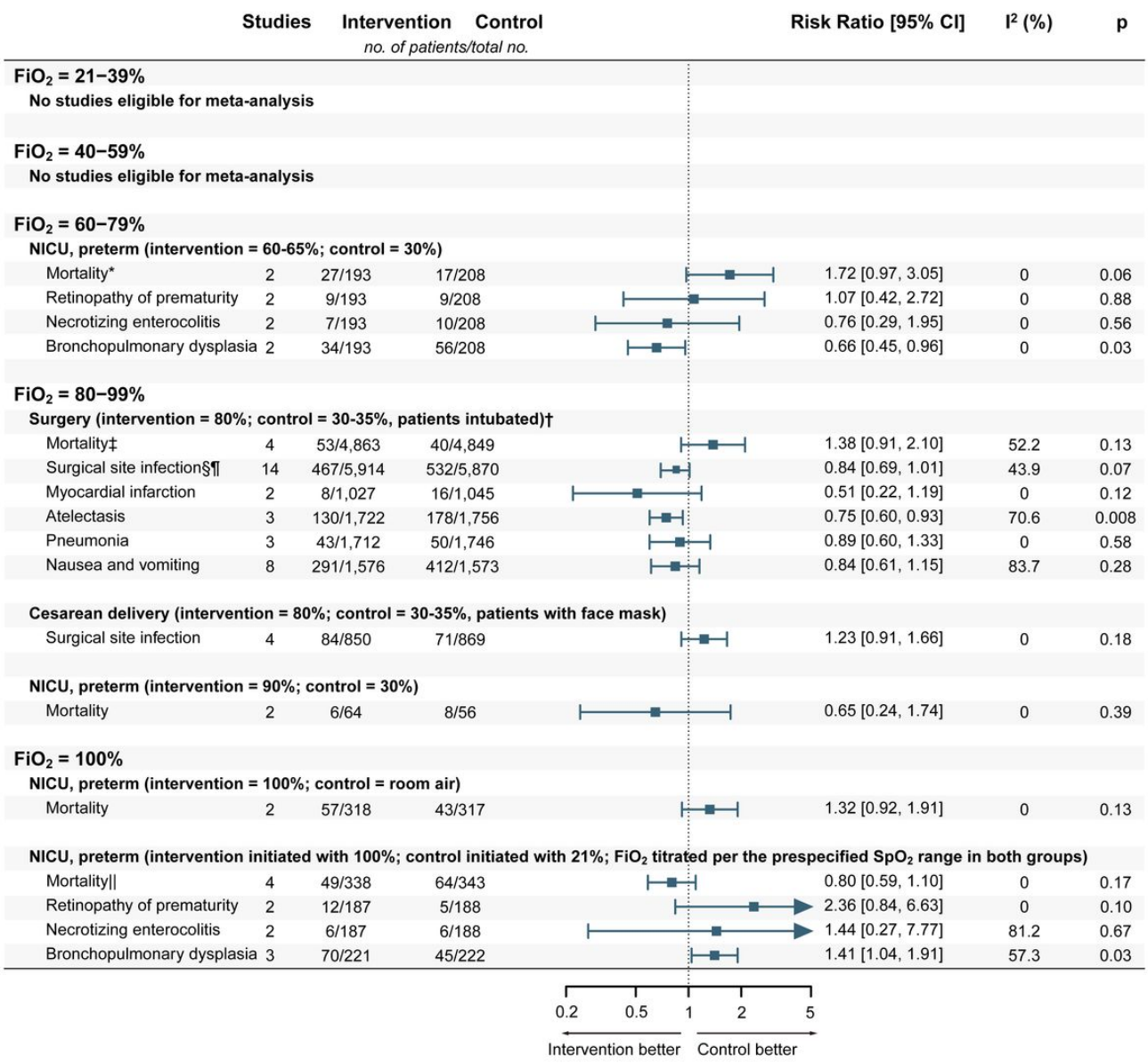

Figure 3

Clinical effectiveness of FiO2-guided oxygen therapy CI, confidence interval; FiO2, inspired oxygen fraction; NICU, neonatal intensive care unit. * Mortality was assessed at different time points for these two studies. † We excluded five studies by an author who has been scrutinized for scientific and ethical misconduct (https://retractionwatch.com/2018/03/26/paper-used-to-support-who-guidelines-on-preventing-infections-has-no-scientific-validity/).[35-39] ‡ We excluded two studies that reported post hoc analyses of long-term mortality of the same patient population whose short-term mortality had already been reported and included in our analysis.[26, 27] § The study by Chen et al. had three groups with two groups using oxygen and nitrogen mixture and one group using oxygen and nitrous oxide mixture.[50] We only chose the groups using oxygen and nitrogen mixture for consistency. We did not sum up the events for different surgical site infections (in Table 5 of Chen et al.'s article) because the abstract of this article stated 2 and 2 patients had postoperative wound infection in high and low FiO2 groups, respectively. ¶ The result is statistically significant (RR, 0.80; 95% CI, 0.65 to 0.99; p=0.044) following the exclusion of the study based on an alternating intervention controlled design (n=5,759), in which the FiO2

was alternated between 30% and 80% at 2-week intervals for 39 months.[51] || Mortality was assessed at different time points among these studies.

Figure 4

Clinical effectiveness of monitor-guided oxygen therapy CI, confidence interval; SpO2, pulse oxygen saturation; PaO2, arterial partial pressure of oxygen; ScvO2, central venous oxygen saturation; SctO2, cerebral tissue oxygen saturation; SstO2, somatic tissue oxygen saturation; DO2I, oxygen delivery index; PbtO2, brain tissue partial pressure of oxygen. * We excluded three studies that reported post hoc analyses of long-term mortality of the same patient population whose short-term mortalities had already been reported and included in our analysis.[31, 33, 34] † Mortality was assessed at different time points for these studies. ‡ We used the data for short-term mortality when mortalities at different time points were reported for one study.[52]

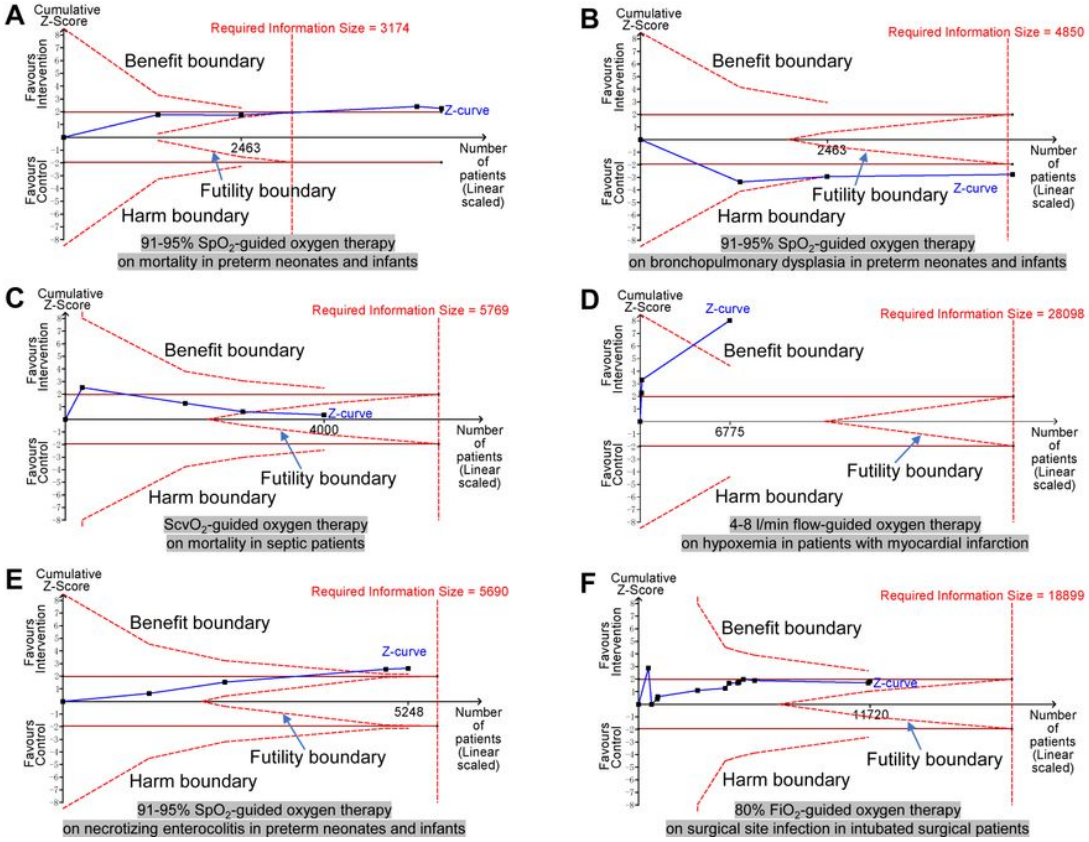

Figure 5

Trial sequential analysis The abscissa indicates the number of patients (linear scale), while the ordinate indicates the cumulative Z-score. The Z-score is the test statistic, with a |Z| of 1.96 corresponding to a p value of 0.05, as indicated by the solid brown horizontal lines. A higher Z-score corresponds to a lower p value. The red vertical dashed line on the right side indicates the required information size which was calculated based on a two-sided alpha of 0.05, a beta of 0.80, the pooled event rate across the control groups of the included studies, and a relative risk reduction of 20%, with adjustment for heterogeneity. The O'Brien-Fleming monitoring boundaries for benefit, harm and futility are indicated with red dashed lines. The black filled squares connected by the solid blue lines (Z-curves) represent the trials. Trial sequential analysis confirmed that the required information size was met (the Z-curve surpassed the required information size boundary) for studies on the effect of SpO2-guided oxygen therapy with a SpO2 of 91-95% on mortality (A) and bronchopulmonary dysplasia (B) in preterm neonates and infants. Trial sequential analysis confirmed the futility (as the Z-score surpassed the futility boundary) of oxygen therapy guided by ScvO2 on mortality in septic patients (C). The analysis also confirmed the

beneficial effects (as the Z-score surpassed the benefit boundary) of flow-guided oxygen therapy with a flow rate of 4-8 l/min on hypoxaemia in patients with myocardial infarction (D) and of SpO2-guided oxygen therapy with a SpO2 of 91-95% on necrotizing enterocolitis in preterm neonates and infants (E). Trial sequential analysis further indicated inconclusive results (as the required information size was unmet and the O'Brien-Fleming monitoring boundaries were not surpassed) regarding the effect of 80% FiO2 on surgical site infection in intubated surgical patients (F). SpO2, pulse oxygen saturation; ScvO2, central venous oxygen saturation; FiO2, inspired oxygen fraction.

Supplementary Files

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