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[Intervention Review]

Permissive hypoxaemia versus normoxaemia for mechanically ventilated critically ill patients

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ABSTRACT

Background

Permissive hypoxaemia describes a concept in which a lower level of arterial oxygenation (PaO₂) than usual is accepted to avoid the detrimental effects of high fractional inspired oxygen and invasive mechanical ventilation. Currently however, no specific threshold is known that defines permissive hypoxaemia, and its use in adults remains formally untested. The importance of this systematic review is thus to determine whether any substantial evidence is available to support the notion that permissive hypoxaemia may improve clinical outcomes in mechanically ventilated critically ill patients.

Objectives

We assessed whether permissive hypoxaemia (accepting a lower PaO₂ than is current practice) in mechanically ventilated critically ill patients affects patient morbidity and mortality. We planned to conduct subgroup and sensitivity analyses and to examine the role of bias to determine the level of evidence provided.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 11, part of *The Cochrane Library*; MEDLINE (1954 to November 2013); EMBASE (1980 to November 2013); CINAHL (1982 to November 2013) and ISI Web of Science (1946 to November 2013). We combined the sensitive search strategies described in the *Cochrane Handbook for Systematic Reviews of Interventions* to search for randomized controlled trials (RCTs) in MEDLINE and EMBASE. For ongoing trials, we also searched the following databases: MetaRegister of Controlled Trials and the National Research Register. We applied no language restrictions.

Selection criteria

RCTs and quasi-RCTs that compared outcomes for mechanically ventilated critically ill participants, in which the intervention group was targeted to be hypoxaemic relative to the control group, and the control group was normoxaemic or was mildly hypoxaemic, were eligible for inclusion in this review. Exact values defining 'conventional' and 'permissive hypoxaemia' groupings were purposely not specified, and the manner in which these oxygenation goals were achieved also was not specified. We did state however that the intervention group required a target oxygenation level lower than that of the control group, and that the control group target levels should be in the range of normoxaemia or mild hypoxaemia (not hyperoxaemia).

Data collection and analysis

We used standard methodological procedures expected by The Cochrane Collaboration. Using the results of the above searches, two review authors (EG-K and KM) independently screened all titles and abstracts for eligibility and duplication. No discrepancies were encountered, nor was it necessary for review authors to contact the first author of any trial to ask for additional information.

Main results

Our search strategy yielded a total of 2419 results. After exclusion of duplications, 1651 candidate studies were identified. Screening of titles and abstracts revealed that no studies met our inclusion criteria.

Authors' conclusions

This comprehensive review failed to identify any relevant studies evaluating permissive hypoxaemia versus normoxaemia in mechanically ventilated critically ill participants. Therefore we are unable to support or refute the hypothesis that this treatment strategy is of benefit to patients.

Given the substantial amount of provocative evidence derived from related clinical contexts (resuscitation, myocardial infarction, stroke), we believe that this review highlights an important unanswered question within critical care. In the presence of two competing harms (hypoxia and hyperoxia), it will be important to carefully evaluate the safety and feasibility of permissive hypoxaemia before proceeding to efficacy and effectiveness trials.

PLAIN LANGUAGE SUMMARY

Low blood oxygen levels versus normal blood oxygen levels in ventilated severely ill people

Review questions

We reviewed the evidence to see whether allowing for low blood oxygen levels, as opposed to normal blood oxygen levels, in severely ill people on mechanical breathing machines (ventilators) in intensive care units (ICUs) (otherwise known as critical care units (CCUs)) changed their chances of recovery (morbidity) and survival rate (mortality). We found no studies eligible for inclusion in this review.

Background

A common feature of people who become severely unwell and require admission to the ICU/CCU is lack of oxygen in the blood. Regardless of the initial reason that caused them to become unwell, people on the ICU/CCU suffer from the effects of low oxygen levels; however the treatments that we can currently offer are frequently ineffective and may even be harmful. High levels of oxygen are toxic, and the ventilators used to deliver oxygen may cause physical damage to the lungs. Conversely, lower levels of oxygen in the blood than are considered normal are not necessarily harmful and may be seen in people who subsequently fully recover, or in healthy people at altitude. We therefore wanted to ascertain whether any research had been done to examine whether allowing low blood oxygen levels, as opposed to normal blood oxygen levels, in ventilated severely ill people on the ICU/CCU altered their morbidity and mortality.

Study characteristics

We were looking for studies that assessed the morbidity and mortality of ventilated people who were at least one year old. We were looking for studies in which the intention in one group of people was to maintain low levels of blood oxygen, and the intention in the other group of people was to maintain normal levels of blood oxygen. We included studies involving people irrespective of gender, ethnicity and past medical history. The evidence is current to November 2013.

Key results

Our search yielded 2419 results. After exclusion of duplications, 1651 candidate studies were identified. Upon assessing the titles and abstracts of candidate studies, we found that none met our inclusion criteria. We are therefore unable to identify or comment as to whether allowing for low blood oxygen levels is beneficial.

Quality of evidence

Permissive hypoxaemia versus normoxaemia for mechanically ventilated critically ill patients (Review)

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As no studies were included in our review, we cannot comment on the quality of evidence. Given the lack of evidence related to safety issues regarding allowing for low, as opposed to normal, levels of blood oxygen, we recommend caution with respect to changing current medical practice in this area. We do believe however that future research into this question is necessary.

BACKGROUND

Description of the condition

Hypoxaemia is defined as a deficiency of oxygen within the arterial circulation, that is, at a level below that which has been determined to be normal. Oxygen level is commonly described in terms of oxygen partial pressure (PaO₂) or oxygen haemoglobin saturation (SaO₂) derived from arterial blood gas samples. The latter can also be measured by pulse oximetry and is referred to as peripheral oxygen saturation (SpO₂). The PaO₂ or SaO₂ at which clinicians deem hypoxaemia to be significant varies widely, as does a patient's subsequent response (Mao 1999).

Hypoxaemia is common amongst critically ill patients (De Jonge 2008) and usually is treated via the instigation of combinations of ventilatory (Esan 2010) and non-ventilatory (Raouf 2010) strategies. The aim is to restore arterial oxygenation to normal values and thereby reduce morbidity and mortality associated with hypoxaemia. This said, strategies used to treat hypoxaemic critically ill patients are also associated with harm, and this harm may outweigh the benefit of an increase in arterial oxygenation. For example, both ventilator-induced lung injury and oxygen toxicity occurring with high inspired concentrations of oxygen (FiO₂) are known to be associated with harm, which may in some cases outweigh the benefit of normalizing oxygenation (PaO₂ and SaO₂). Although a substantial proportion of critically ill patients require these interventions to achieve normoxaemia, permissive hypoxaemia describes a concept in which a lower level of arterial oxygenation than usual is accepted to avoid the detrimental effects of high fractional inspired oxygen (FiO₂) and invasive mechanical ventilation (Abdelsalam 2006; Abdelsalam 2010; Cheifetz 2006). No specific threshold is known that defines permissive hypoxaemia, and its use in adults remains formally untested.

Description of the intervention

The intervention under investigation is permissive hypoxaemia, which is the tolerance of arterial oxygenation levels lower than would normally be acceptable in patients suffering severe hypoxaemia. Limited evidence suggests that hypoxaemia per se is directly linked to poor outcomes in mechanically ventilated critically ill patients. However, numerous case reports describe patients surviving extreme hypoxaemia without morbidity (Cohen 2001; Lund 1984; Pytte 2007) and acclimatization in healthy volunteers exposed to hypobaric hypoxia (Grocott 2009; Sutton 1988). Although hypoxaemia is an essential component of the diagnostic criteria of acute respiratory distress syndrome (ARDS), few patients die as a direct result of hypoxaemia; patients more commonly die from the underlying cause of ARDS: sepsis (Montgomery 1985; Stapleton 2005). Conversely, the harmful effects of excessive oxygen administration (Auten 2009; Clark 1971; Crapo 1985) and mechanical ventilation (Slutsky 1999) are well described. The combined insult of oxygen free radical release, biophysical injury (including barotrauma, volutrauma and atelectatrauma) and cytokine-mediated inflammation may be responsible for local and systemic harm in mechanically ventilated patients receiving high inspired concentrations of oxygen. Given the marginal risk/benefit profile of some strategies in reoxygenating critically ill patients to a PaO₂ that is generally accepted to be 'normal,' permissive hypoxaemia may offer an alternative

that has the potential to improve patient outcomes by avoiding unnecessary harm.

How the intervention might work

Accepting lower levels of arterial oxygenation may remove the need to resort to treatments that although successful in increasing PaO₂ have little or no effect on mortality and morbidity. Furthermore, in the light of recent discoveries, an additional benefit may be derived from reduction of arterial oxygenation. It has been demonstrated that better outcomes are achieved if hyperoxaemia is avoided in those who have sustained a myocardial infarction (Cabello 2010), stroke (Ronning 1999) or cardiac arrest (Kilgannon 2010). However, the PaO₂ threshold that determines outcome differences between normoxaemia and hyperoxaemia is unknown.

Why it is important to do this review

The purpose of this systematic review was to determine whether any substantial evidence is available to support the notion that permissive hypoxaemia may improve clinical outcomes in mechanically ventilated critically ill patients. Twenty per cent of the population is admitted to critical care at some time in life; among those with a diagnosis of ARDS, the mortality rate is approximately 25% to 30%. Epidemiological data suggest that a large proportion of patients cared for on critical care units are administered high FiO₂ or are hypoxaemic; therefore they might be candidates for permissive hypoxaemia. Whilst others have suggested the possible benefits of permissive hypoxaemia in narrative reviews, to our knowledge no previous systematic reviews have examined this topic.

OBJECTIVES

We assessed whether permissive hypoxaemia (accepting a lower PaO₂ than is current practice) in mechanically ventilated critically ill patients affects patient morbidity and mortality. We planned to conduct subgroup and sensitivity analyses and to examine the role of bias to determine the level of evidence provided.

METHODS

Criteria for considering studies for this review

Types of studies

We planned to identify randomized controlled trials (RCTs) that have compared the outcomes for mechanically ventilated critically ill participants when the intervention group was targeted to be hypoxaemic relative to the control group, and the control group was either normoxaemic or mildly hypoxaemic. Exact values defining 'conventional' and 'permissive hypoxaemia' groupings were purposely not specified; the manner in which these oxygenation goals were achieved also was not specified. However, the intervention group must have had a target oxygenation level (PaO₂, SaO₂ or SpO₂) lower than that of the control group, and control group target levels should be in the range of normoxaemia or mild hypoxaemia (not hyperoxaemia). Arterial oxygenation levels were defined using the following measures.

SaO₂: arterial oxyhaemoglobin saturation, directly measured in arterial blood samples.

SpO₂: peripheral oxyhaemoglobin saturation, measured by pulse oximetry.

PaO₂: partial pressure of oxygen in arterial blood, measured in arterial blood samples.

We planned to include RCTs and quasi-RCTs comparing permissive hypoxaemia and conventional therapy in mechanically ventilated participants. We planned to include studies irrespective of language and publication status.

Types of participants

We planned to include studies involving participants from the age of one year upwards who have been mechanically ventilated in a hospital critical care setting, irrespective of gender, ethnicity and past medical history. Participants were to be defined as children (one year to 18 years) and adults (> 18 years old). We planned to exclude neonates (< 28 days) and infants (< one year) in view of their recent exposure to extreme hypoxia in utero. We planned to include all critical care settings in the review.

Types of interventions

The interventions to be included will require clear differentiation of participants into 'conventional' and 'low' targets of arterial oxygenation, that is, permissive hypoxaemia versus 'standard' care. The threshold of oxygenation determining these groups will not be specified to allow inclusion of a range of studies and to explore the relationship between oxygenation threshold and outcome.

Types of outcome measures

Primary outcomes

1. Mortality at longest follow-up and overall 28-day mortality.

Secondary outcomes

1. Number of days ventilated (invasive and non-invasive).
2. Ventilator-free days.
3. Requirement for inotrope support.
4. Resolution of multi-organ failure (according to different organ dysfunction scores).
5. Need for haemofiltration or dialysis.
6. Improvement in neurological functioning of participant.
7. Improvement in mean pulmonary arterial pressure.
8. Length of intensive care unit (ICU) stay.
9. Length of stay in hospital.
10. Participant-reported outcome measures (quality of life).
11. Cost/benefit analyses.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2013, Issue 11, part of *The Cochrane Library* (see [Appendix 1](#)), MEDLINE (Ovid SP, 1954 to November 2013; see [Appendix 2](#)); EMBASE (Ovid SP, 1980 to November 2013; see [Appendix 3](#)); CINAHL (EBSCO host, 1982 to November 2013; see [Appendix 4](#)) and ISI Web of Science (1946 to November 2013; see [Appendix 5](#)).

We combined the sensitive search strategies described in Section 6.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)) to search for RCTs in MEDLINE and EMBASE. We used an iterative search strategy of free text and associated exploded Medical Subject Heading (MeSH) terms, which was modified as search terms were added during the course of the search. We planned to list the final iterations when the review was to be published. We searched CENTRAL in the above manner and adapted our MEDLINE search strategy to reflect subject headings found in the thesauri used by EMBASE, CINAHL and Web of Science. For ongoing trials, we searched the following databases: MetaRegister of Controlled Trials and the National Research Register.

We applied no language restrictions.

Searching other resources

We screened the reference lists of all eligible trials and reviews. We contacted the main authors of relevant studies and experts to ask about any missed, unreported or ongoing studies.

Data collection and analysis

Selection of studies

Using the results of the above searches, we screened all titles and abstracts for eligibility and any duplication. Two review authors independently performed this screening (EG-K and KM). We independently documented the reason for exclusion of a trial. We planned to resolve disagreements by consulting with a third review author (DM), who would have decided on inclusion or not. In the case of insufficient published information, we would have contacted the first author of the relevant trial to make a decision about inclusion. We would have compiled a list of eligible trials, along with a unique identifier, on a Form for Eligible Trials (see [Appendix 6](#); [Appendix 7](#); [Appendix 8](#); [Appendix 9](#)).

Data extraction and management

Two review authors planned to independently extract and collect data on a paper form (EG-K and KM). EG-K and KM would have resolved discrepancies in the extracted data by discussion. In cases in which additional information was required, EG-K would have contacted the first author of the relevant trial (see [Appendix 10](#)).

Assessment of risk of bias in included studies

Two review authors would have independently assessed the methodological quality of eligible trials (EG-K and KM). We would have resolved disagreements by discussion with a third review author (DM).

We planned to perform the assessment as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)) and to describe each bias as 'low risk', 'high risk' or 'unclear risk.'

We would have considered a trial as having low risk of bias, and thus as adequate, if all of the following criteria were assessed as 'low risk.' We would have considered a trial as having high risk of bias, and thus as inadequate, if one or more of the following criteria were 'high risk' or 'unclear risk.'

1. Random sequence generation

We would have considered allocation as low risk if it was generated by a computer or a random number table algorithm. We planned to judge other processes, such as tossing of a coin, as adequate if the whole sequence was generated before the start of the trial, and if it was performed by a person not otherwise involved in participant recruitment. We planned to consider allocation as high risk if a non-random system was utilized.

2. Allocation concealment

We would have considered concealment as low risk if the process used prevented participant recruiters, investigators and participants from knowing the intervention allocation of the next participant to be enrolled in the study. Acceptable systems include a central allocation system, sealed opaque envelopes and an on-site locked computer. We would have considered concealment as inadequate and of high risk if the allocation method used allowed participant recruiters, investigators or participants to know the treatment allocation of the next participant to be enrolled in the study.

3. Blinding of participants and personnel, and of outcome assessment

We would have considered blinding as low risk if the participant and the outcome assessor were blinded to the intervention. We would have considered blinding as high risk if participants and outcome assessors were not blinded to the intervention. Participants are likely to be unaware of their entry into a trial because of the nature and severity of their disease and the influence of sedative drugs.

4. Incomplete outcome data and intention-to-treat

We planned to consider trials satisfactory if rate of data loss during follow-up was low, and if investigators took into account intention-to-treat through withdrawal from the studies due to lack of tolerance to the intervention. Any missing data not accounted for would have been classified as high risk.

5. Selective reporting

We would have considered trial reporting to be at low risk of bias if the study protocol was available on request and if all of the study's prespecified outcomes of interest for the review had been reported in the prespecified way.

6. Other bias

We planned to apply the criteria described in Table 8.5d of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) to assess whether attrition bias was likely to result in low, high or unclear risk of bias (see Appendix 11).

Measures of treatment effect

We planned to present categorical data as risk ratio and risk difference. We planned to calculate number needed to treat for an additional beneficial outcome (NNTB) and number needed to treat for an additional harmful outcome (NNTH) when appropriate. We planned to present numerical comparisons as the differences between means.

Unit of analysis issues

Categorical primary and secondary outcomes would have been analysed as having happened to participants once. Continuous variables would have been analysed only once for each participant.

Dealing with missing data

We planned to contact trial authors to try to retrieve missing data.

We planned to model the effects of missing data in the following sensitivity analyses.

1. Assuming outcomes in missing participants were equal to average for the relevant allocation group.
2. Assuming outcomes in missing participants were equal to average for all participants irrespective of allocation group.
3. Assuming outcomes in missing participants reflected the distribution of results for the relevant allocation group.
4. Assuming outcomes in missing participants reflected the distribution of results for all participants irrespective of allocation group.
5. Assuming outcomes in missing participants were the most extreme reported for each allocation group, both bad and good.
6. Assuming outcomes in missing participants were the most extreme reported for all participants irrespective of allocation group.

Assessment of heterogeneity

We planned to quantify statistical inconsistency using the I^2 statistic. We would have categorized I^2 values of 30% to 49% as moderate heterogeneity, 50% to 79% as substantial heterogeneity and 80% to 100% as considerable heterogeneity.

Heterogeneity > 29% would have triggered checking of data to confirm correct data entry.

Our intention was to analyse combined studies irrespective of clinical differences, as evidence is insufficient to show that this is inappropriate for permissive hypoxaemia. The calculated statistical heterogeneity and its exploration may have given useful indications as to which clinical features might interact with the intervention. We would have observed whether any of the prespecified subgroup analyses reduced the measured heterogeneity.

Heterogeneity > 29% for continuous variables would have triggered assessment of the contribution of the variation of effect measure to heterogeneity.

We planned to explore whether clinical variations in studies, hypothesized in the protocol as possibly interacting with the intervention effect, could have explained the observed heterogeneity of > 29%.

Assessment of reporting biases

We planned to construct unmodified and contour-enhanced funnel plots for all outcomes. We would have tested for asymmetry of funnel plots containing at least 10 RCTs. We planned to test asymmetry of categorical and continuous variables expressed as odds ratios using tests proposed by Harbord 2006.

Data synthesis

We planned to report categorical variables as the risk ratio with 95% confidence interval (CI) using the Mantel-Haenszel fixed-effect model and the DerSimonian and Laird random-effects model. We planned to report continuous variables as standardized mean differences (95% CI) by using both fixed-effect and random-effects models. We would have considered statistical significance as P value < 0.05 . We planned to follow Chapters 10.4.4.1 and 9.5.3 of the *Cochrane Handbook for Systematic Reviews of Interventions*: We planned to discuss the sensitivity analyses from both random-effects and fixed-effect models when $I^2 > 0$. We would have considered reasons for discrepancies, including variation of methodological rigour, with study size and standard errors.

Subgroup analysis and investigation of heterogeneity

When possible, we planned to undertake individual participant data analysis.

1. Subgroups according to intervention

We planned to perform interaction analyses of risk ratios generated by at least two contributing subgroups, whether the summary of complete RCTs or subgroups reported within RCTs. We planned to analyse subgroups defined by the length of time participants in the studies were exposed to hypoxaemia: less than one day; one to seven days; longer than seven days.

2. Subgroup according to participants

We planned to perform interaction analyses of risk ratios generated by at least two contributing subgroups, whether the summary of complete RCTs or subgroups reported within RCTs. We would have analysed subgroups defined by the primary pathology: intracerebral; cardiac; respiratory; sepsis; trauma; postoperative.

3. Subgroup according to distribution of results

We planned to perform interaction analyses of risk ratios generated by at least two contributing subgroups, whether the summary of complete RCTs or subgroups reported within RCTs. We would have analysed subgroups defined by the dispersion of oxygenation in the control group: highest; middle; and lowest terciles. We thought this would have addressed an important scientific question: Do control groups with larger ranges of oxygenation give a stronger signal (greater difference) in control versus permissive hypoxaemia? We hypothesized that this might have been due to more of the harmful intervention (ventilation and O_2) in patients whose values were high (thereby causing greater dispersion of values).

4. Subgroup according to age of participants

We planned to perform interaction analyses of risk ratios generated by at least two contributing subgroups, whether the summary of complete RCTs or subgroups reported within RCTs. We would have analysed subgroups defined by age of participants: children (one to 18 years) and adults (> 18 years).

Sensitivity analysis

We planned to perform sensitivity analyses of trials with low risk of bias versus high risk of bias. In cases of missing data, we would

have used best case and worst case imputation of missing data. We planned to exclude and include any study that appeared to have a large effect size (often the largest or earliest study) to assess its impact on the meta-analysis. If large variations in the control group event rate were noted, we would have also subjected this to sensitivity analysis. In addition, we planned to assess the benefits and harms of the interventions when data from studies published only as an abstract were excluded, and to examine the role of funding bias by excluding trials sponsored by pharmaceutical companies.

Summary of findings

We planned to use the principles of the GRADE system (Guyatt 2008) to assess the quality of the body of evidence associated with the following specific outcomes.

1. Hospital mortality.
2. Number of organ failures.
3. Need for haemofiltration or dialysis.
4. Requirement for inotrope support.
5. Number of days ventilated (invasive and non-invasive).
6. Ventilator-free days.
7. Length of intensive care unit (ICU) stay.
8. Length of stay in hospital.

We planned to construct a 'Summary of findings' (SoF) table.

The GRADE approach assesses the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers study methodological quality, directness of the evidence, heterogeneity of the data, precision of the effect estimates and risk of publication bias.

RESULTS

Description of studies

No eligible studies were identified.

Results of the search

Our search strategy yielded a total of 2419 results. After exclusion of duplications, 1651 candidate studies were identified. After screening of titles and abstracts by two independent review authors (EG-K and KM), no studies met our inclusion criteria (i.e. no studies compared 'permissive' or 'low' vs 'normal' or 'conventional' oxygenation strategies in any study cohort).

Included studies

No eligible studies were identified.

Excluded studies

Of the 1651 trial titles and abstracts screened, none met eligibility criteria; thus all were excluded (Figure 1).

Figure 1. Search flow diagram.

Risk of bias in included studies

No eligible studies were identified.

Allocation

No eligible studies were identified.

Blinding

No eligible studies were identified.

Incomplete outcome data

No eligible studies were identified.

Selective reporting

No eligible studies were identified.

Other potential sources of bias

No eligible studies were identified.

Effects of interventions

No eligible studies were identified.

DISCUSSION

Summary of main results

This comprehensive review failed to identify any relevant studies evaluating permissive hypoxaemia versus normoxaemia in mechanically ventilated critically ill participants.

Overall completeness and applicability of evidence

We found no relevant evidence.

We employed a comprehensive search strategy, with no language restriction that was likely to be sensitive in identifying relevant studies. Although this approach identified a large number of candidate studies, none of them met the review inclusion criteria.

Quality of the evidence

We found no relevant evidence.

Potential biases in the review process

It is possible that our search strategy failed to identify all relevant studies. However, we believe that this is unlikely, given that the search identified relevant articles in other fields as well as comment pieces of relevance to the title of this review.

Agreements and disagreements with other studies or reviews

We were unable to identify any other systematic reviews on this subject.

AUTHORS' CONCLUSIONS

Implications for practice

We found no relevant studies comparing permissive hypoxaemia versus normoxaemia in mechanically ventilated critically ill participants. Therefore, we are unable to support or refute the hypothesis that this treatment strategy is of benefit to patients. Given this lack of evidence related to the safety and efficacy of permissive hypoxaemia, we recommend caution with respect to modifying current practice in this area.

Implications for research

Given the substantial amount of provocative evidence derived from related clinical contexts (resuscitation, myocardial infarction, stroke), we believe that this review highlights an important

unanswered question within critical care. In the presence of two competing harms (hypoxia and hyperoxia), it will be important to carefully evaluate the safety and feasibility of permissive hypoxaemia before proceeding to efficacy and effectiveness trials.

Important issues in clinical trial design that should be considered include the following.

1. Clinician buy-in (feasibility).
2. Comprehensive screening for adverse effects (safety).
3. Careful definition and selection of target patients (inclusion and exclusion criteria).
4. Appropriate comparator therapy.
5. Appropriate outcome measures.
6. Appropriate sample sizes with the statistical power to detect clinically meaningful differences in outcome.
7. Consideration of resource utilization, quality of life and cost-effectiveness.

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REFERENCES

Additional references

Abdelsalam 2006

Abdelsalam M. Permissive hypoxemia: is it time to change our approach. *Chest* 2006;**129**(1):210-1. [MEDLINE: 16424435]

Abdelsalam 2010

Abdelsalam M, Cheifetz IM. Goal-directed therapy for severely hypoxic patients with acute respiratory distress syndrome: permissive hypoxemia. *Respiratory Care* 2010;**55**(11):1483-90. [MEDLINE: 20979676]

Auten 2009

Auten RL, Davis JM. Oxygen toxicity and reactive oxygen species: the devil is in the details. *Pediatric Respiratory Reviews* 2009;**66**(2):121-7. [MEDLINE: 19390491]

Cabello 2010

Cabello JB, Burls A, Emparanza JI, Bayliss S, Quinn T. Oxygen therapy for acute myocardial infarction. *Cochrane Database of Systematic Reviews* 2010, Issue 6. [DOI: [10.1002/14651858.CD007160.pub2](https://doi.org/10.1002/14651858.CD007160.pub2)]

Cheifetz 2006

Cheifetz IM, Hamel DS. Is permissive hypoxemia a beneficial strategy for pediatric acute lung injury?. *Respiratory Care* 2006;**12**(3):359-69. [MEDLINE: 16952798]

Clark 1971

Clark JM, Lambertsen CJ. Pulmonary oxygen toxicity: a review. *Pharmacology Review* 1971;**23**(2):37-133. [MEDLINE: 4948324]

Cohen 2001

Cohen ES, Elpern E, Silver MR. Pulmonary alveolar proteinosis causing severe hypoxemic respiratory failure treated with sequential whole-lung lavage utilizing venovenous extracorporeal membrane oxygenation: a case report and review. *Chest* 2001;**120**(3):1024-6. [MEDLINE: 11555544]

Crapo 1985

Crapo JD. Morphological changes in pulmonary oxygen toxicity. *Annual Review of Physiology* 1986;**48**:721-31.

De Jonge 2008

de Jonge E, Peelen L, Keijzers PJ, Joore H, de Lange D, van der Voort PH, et al. Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Critical Care* 2008;**12**(6):R156. [MEDLINE: 19077208]

Esan 2010

Esan A, Hess DR, Raoof S, George L, Sessler CN. Severe hypoxemic respiratory failure: part 1—ventilatory strategies. *Chest* 2010;**137**(5):1203-16. [MEDLINE: 20442122]

Grocott 2009

Grocott MP, Martin DS, Levett DZ, McMorro R, Windsor J, Montgomery HE. Arterial blood gases and oxygen content in

climbers on Mount Everest. *New England Journal of Medicine* 2009;**360**(2):140-9. [MEDLINE: 19129527]

Guyatt 2008

Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality evidence" and why is it important to clinicians. *BMJ* 2008;**336**:995-8. [MEDLINE: 18456631]

Harbord 2006

Harbord RM, Egger M, Sterne JA. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. *Statistics in Medicine* 2006;**25**:3443-57. [MEDLINE: 16345038]

Higgins 2011

Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Kilgannon 2010

Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, et al. Emergency Medicine Shock Research Network (EMShockNet) Investigators. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA* 2010;**303**(21):2165-71. [PUBMED: 20516417]

Lund 1984

Lund T, Koller ME, Kofstad J. Severe hypoxemia without evidence of tissue hypoxia in adult respiratory distress syndrome. *Critical Care Medicine* 1984;**12**(1):75-6. [MEDLINE: 6690211]

Mao 1999

Mao C, Wong DT, Slutsky AS, Kavanagh BP. A quantitative assessment of how Canadian intensivists believe they utilize oxygen in the intensive care unit. *Critical Care Medicine* 1999;**27**(12):2806-11. [MEDLINE: 10628630]

Montgomery 1985

Montgomery AB, Stager MA, Carrico CJ, Hudson LD. Causes of mortality in patients with the adult respiratory distress syndrome. *American Review of Respiratory Disease* 1985;**132**:485-9. [MEDLINE: 4037521]

Pytte 2007

Pytte M, Opdahl H, Skaga NO. Grave acidosis after severe anaphylactic bronchospasm: friend or foe?. *Acta Anaesthesiologica Scandinavica* 2007;**51**(4):495-500. [MEDLINE: 17229196]

Raoof 2010

Raoof S, Goulet K, Esan A, Hess DR, Sessler CN. Severe hypoxemic respiratory failure: part 2—nonventilatory strategies. *Chest* 2010;**137**(6):1437-48. [MEDLINE: 20525656]

RevMan 5.1 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration.
Review Manager (RevMan). Version 5.1. Copenhagen: The
Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Ronning 1999

Ronning OM, Guldvog B. Should stroke victims routinely receive
supplemental oxygen? A quasi-randomized controlled trial.
Stroke 1999;**30**(10):2033-7. [MEDLINE: 10512903]

Slutsky 1999

Slutsky AS. Lung injury caused by mechanical ventilation. *Chest*
1999;**116**(1):9-15. [MEDLINE: 10424561]

Stapleton 2005

Stapleton RD, Wang BM, Hudson LD, Rubenfeld GD, Caldwell ES,
Steinberg KP. Causes and timing of death in patients with ARDS.
Chest 2005;**128**(2):525-32. [MEDLINE: 16100134]

Sutton 1988

Sutton JR, Reeves JT, Wagner PD, Groves BM, Cymerman A,
Malconian MK. Operation Everest II: oxygen transport during
exercise at extreme simulated altitude. *Journal of Applied
Physiology* 1988;**64**(4):1309-21. [MEDLINE: 3132445]

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Oxygen Consumption explode all trees
#2 hypoxia or normoxia or oxygen deficiency
#3 (#1 OR #2)
#4 MeSH descriptor Respiration, Artificial explode all trees
#5 MeSH descriptor Critical Illness explode all trees
#6 (mechanical* near ventilat*) or (critical* near (sick* or ill*))
#7 (#4 OR #5 OR #6)
#8 (#3 AND #7)

Appendix 2. Ovid MEDLINE search strategy

1. Oxygen Consumption/ or hypoxia.af. or normoxia.af. or oxygen deficiency.mp.
2. Respiration, Artificial/ or Critical Illness/ or (mechanical* adj3 ventilat*).mp. or (critical* adj5 (sick* or ill*)).mp.
3. 1 and 2
4. ((randomised controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
5. 3 and 4

Appendix 3. EMBASE (Ovid SP) search strategy

1. oxygen consumption/ or hypoxia.mp. or normoxia.mp. or oxygen deficiency.mp.
2. artificial ventilation/ or critical illness/ or (mechanical* adj3 ventilat*).mp. or (critical* adj3 (sick* or ill*)).mp.
3. 1 and 2
4. (placebo.sh. or controlled study.ab. or random*.ti.ab. or trial*.ti.ab. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti.ab.) not (animals not (humans and animals)).sh.
5. 3 and 4

Appendix 4. CINAHL (EBSCO host) search strategy

S1 (MH "Oxygen Consumption") OR (hypoxia or normoxia or oxygen deficiency)
S2 ((MH "Respiration, Artificial") OR (MH "Critical Illness")) OR ((mechanical* and ventilat*) or (critical* and (sick* or ill*)))
S3 (MH "Randomized Controlled Trials") OR (MH "Random Assignment") OR "randomised" OR (MH "Clinical Trials") OR (MH "Multicenter Studies") OR (MH "Prospective Studies") OR (MH "Double-Blind Studies") OR (MH "Single-Blind Studies") OR (MH "Triple-Blind Studies") OR (MH "Placebos") OR "placebo"
S4 S1 and S2 and S3

Appendix 5. ISI Web of Science search strategy

#1 TS=(oxygen consumption or hypoxia or normoxia or oxygen deficiency)
#2 TS=(respiration SAME artificial) or TS=critical illness or TS=(mechanical* SAME ventilat*) or TS=(critical* SAME (sick* or ill*))
#3 TS=(random* or (controlled SAME (study or trial*)) or prospective or placebo or multicenter) or TS=((mask* or blind*) SAME (single or double or triple or treble))
#4 #1 and #2 and #3

Appendix 6. Study selection form

First author	Journal	Year

Appendix 7. Study eligibility form

RCT	Relevant participants (mechanically ventilated, intensive care unit)	Relevant interventions (low vs conventional oxygenation)	Relevant outcomes (mortality) (number of organ failures, haemofiltration/dialysis, inotrope support, days ventilated, ventilator-free days, length of ICU stay, length of stay in hospital, participant-reported outcome measures)
Yes/No/Unclear	Yes/No/Unclear	Yes/No/Unclear	Yes/No/Unclear

Appendix 8. Table of excluded studies

Title	Reason for exclusion

(Continued)

Appendix 9. Eligible trials form

Paper code	Author	Journal	Year
1			
2			
3			
3			

Appendix 10. Data extraction form

Outcomes	Cited in paper
Primary outcome—mortality	Yes/No
Secondary outcomes:	
1. Number of organ failures	Yes/No
2. Need for haemofiltration/dialysis	Yes/No
3. Requirement for inotrope support	Yes/No
4. Number of days ventilated	Yes/No
5. Ventilator-free days	Yes/No
6. Length of ICU stay	Yes/No
7. Length of stay in hospital	Yes/No
8. Participant-reported outcome measures	Yes/No

(Continued)

9. Cost/benefit analysis	Yes/No
10. Adverse events	Yes/No
11. Improvement in neurological functioning of participant	Yes/No
Subgroups	Cited in paper
Intervention commenced < 24 hours	Yes/No
Intervention commenced 24 hours to one week	Yes/No
Intervention commenced over one week	Yes/No
Intracerebral pathology	Yes/No
Cardiac pathology	Yes/No
Respiratory pathology	Yes/No
Sepsis	Yes/No
Trauma	Yes/No
Postoperative	Yes/No
Age	Adult/Child

For continuous data (with a separate copy for each relevant subgroup)

Paper code	Outcomes	Unit of measurement	Intervention group (n, mean ($\pm$ SD))	Control group (n, mean ($\pm$ SD))	Details if outcome only described in text

For dichotomous data (with a separate copy for each relevant subgroup)

Paper code	Outcomes	Intervention group (n)	Control group (n)

n = number of participants, not number of events.

Permissive hypoxaemia versus normoxaemia for mechanically ventilated critically ill patients (Review)

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Did this report include any references to published reports of potentially eligible trials not already identified for this review?

First author

Journal

Year of publication

Did this report include any references to unpublished data from potentially eligible trials not already identified for this review? If yes, list contact names and details.

Trial characteristic

Single centre /multi-centre

Country

How was participant eligibility defined

How many people were randomly assigned

Number of participants in each intervention group

Number of participants who received intended treatment

Number of participants who were analysed

Target oxygenation in conventional group

Target oxygenation in low group

Achieved oxygenation in conventional group

Achieved oxygenation in low group

Duration of intervention

Median (range) length of follow-up reported in this paper

Trial design (parallel/cross-over)

Other details

Appendix 11. Quality assessment of eligible trials form

Random sequence generation

Selection bias due to inadequate generation of randomized sequence

Method used to generate allocation?	Low risk
	High risk
	Unclear risk

Allocation concealment

Selection bias due to inadequate concealment of allocations before assignment

Method used to conceal allocation?	Low risk
	High risk
	Unclear risk

Blinding of participants and personnel

Performance bias due to knowledge of allocated interventions by participants and personnel during the study

Method used to blind participants and personnel?	Low risk
	High risk
	Unclear risk

Blinding of outcome assessment

Detection bias due to knowledge of allocated interventions by outcome assessors

Method used to blind assessors?	Low risk
	High risk
	Unclear risk

Incomplete outcome data

Attrition bias due to amount, nature or handling of incomplete outcome data

Method used to minimize attrition bias?	Low risk
	High risk
	Unclear risk

Selective reporting

Reporting bias due to selective outcome reporting

Method used to minimize reporting bias?	Low risk
	High risk

(Continued)

Unclear risk

Other bias

Bias due to problems not covered elsewhere in table

Risk of bias from other sources?

Low risk

High risk

Unclear risk

WHAT'S NEW

Date	Event	Description
20 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

CONTRIBUTIONS OF AUTHORS

Conceiving of the review: Mike Grocott (MG).

Co-ordinating the review: Edward Gilbert-Kawai (EG-K).

Undertaking manual searches: Kay Mitchell (KM) and EG-K.

Screening search results: KM and EG-K.

Organizing retrieval of papers: KM and EG-K.

Screening retrieved papers against inclusion criteria: KM and EG-K.

Appraising quality of papers: Daniel Martin (DM), KM and EG-K.

Abstracting data from papers: KM and EG-K.

Writing to authors of papers for additional information: EG-K.

Providing additional data about papers: EG-K.

Obtaining and screening data on unpublished studies: KM and EG-K.

Managing data for the review: John Carlise (JC), MG, DM, KM and EG-K.

Entering data into Review Manager ([RevMan 5.1](#)): DM and EG-K.

Handling RevMan statistical data: JC and EG-K.

Performing other statistical analysis not using RevMan: JC and EG-K.

Performing double entry of data (data entered by person one: EG-K; data entered by person two: KM).

Interpreting data: MG, JC, DM, EG-K and KM.

Making statistical inferences: JC.

Writing the review: MG, JC, DM, EG-K and KM.

Securing funding for the review: MG.

Permissive hypoxaemia versus normoxaemia for mechanically ventilated critically ill patients (Review)

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Performing previous work that served as the foundation of the present study: MG.

Serving as guarantor for the review (one review author): MG.

Taking responsibility for reading and checking the review before submission: EG-K.

DECLARATIONS OF INTEREST

Dr Grocott has received unrestricted funds to support research and travel to a conference, as well as an honorarium for speaking, from BOC (Linde Gas Therapeutics), which supplies oxygen to hospitals. None of these funds were used to support this Cochrane review.

Dr Martin has received payments to his institution for lectures on high altitude research, along with expenses accompanying this. His institution has received unrestricted sponsorship and donations to conduct high altitude research.

Dr Gilbert-Kawai: none known

Ms Mitchell: none known

Dr Carlisle: none known

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Internal sources

- Nil, Other.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

No differences can be seen between the protocol and the review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Critical Illness; *Hypoxia; *Respiration, Artificial; Oxygen [*blood]; Reference Values

MeSH check words

Adult; Humans