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REVIEW ARTICLE

The long-term effects of lower versus higher oxygenation levels in adult ICU patients – protocol for a systematic review

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Abstract

Background: Many organs can remain impaired after discharge from the intensive care unit (ICU) leading to temporal or permanent dysfunctions. Long-term impairments may be affected by supplemental oxygen, a common treatment in ICU, having both potential beneficial and harmful long-lasting effects. This systematic review aims to assess the long-term outcomes of lower versus higher oxygen supplementation and/or oxygenation levels in adults admitted to ICU.

Methods: We will include trials differentiating between a lower and a higher oxygen supplementation or a lower and a higher oxygenation strategy in adults admitted to the ICU. We will search major electronic databases and trial registers for randomised clinical trials. Two authors will independently screen and select references for inclusion using Covidence and predefined data will be extracted. The methodological quality and risk of bias of included trials will be evaluated using the Cochrane Risk of Bias tool 2. Meta-analysis will be performed if two or more trials with comparable outcome measures will be included. Otherwise, a narrative description of the trials' results will be presented instead. To assess the certainty of evidence, we will create a 'Summary of findings' table containing all prespecified outcomes using the GRADE system. The protocol is submitted on the PROSPERO database (ID 223630).

Conclusion: No systematic reviews on the impact of oxygen treatment in the ICU on long-term outcomes, other than mortality and quality of life, have been reported yet. This systematic review will provide an overview of the current evidence and will help future research in the field.

KEYWORDS

critical care outcomes, intensive care units, oxygen, systematic review

1 | INTRODUCTION

During the last decades the number of survivors after admission to an intensive care unit (ICU) has increased and post-ICU long-term outcomes have gained interest.[1,2] Critical illness should be considered an entity that exceeds the borders of the ICU and thus demands a multidisciplinary approach to improve long-term outcomes in ICU survivors.[3] Among the longstanding organ dysfunctions, psychiatric, cognitive, pulmonary, neuromuscular and physical impairments have been described.[4] Psychiatric

complications occur frequently, with depression and anxiety being the most common.[4] Cognitive disability, including delirium, is also prevalent in ICU patients[4] and up to half of ICU patients discharged from hospital have altered mental status with potential long-lasting neurocognitive consequences.[5–7] Regarding post-ICU pulmonary function, most studies have been conducted in patients with acute respiratory distress syndrome (ARDS).[8,9] The severity of impairments have predominantly been mild, but the degree of dysfunction directly related to ARDS has been difficult to quantify.[4] Neuromuscular complications of critical illness are increasingly recognised and termed ICU-acquired weakness.[10] Finally, limitations in physical function, typically measured by surveying patients in activities of daily living, are commonly reported after hospital discharge and may persist.[4] Given the high frequency of multiple impairments after critical illness, the term 'post intensive care syndrome' has been coined to describe new or worsening impairments in physical, cognitive, or mental health status arising after critical illness and persisting beyond acute care hospitalisation.[11]

1.1 | Targeted oxygen therapy in the ICU

Supplemental oxygen therapy is one of the most commonly prescribed medications in the ICU and supranormal values of arterial oxygen tension (PaO_2) (i.e. hyperoxaemia) have been tolerated and perceived as a safety buffer against hypoxaemia (i.e. low blood oxygen content).[12,13] In recent years, there has been an increasing focus on targeted oxygen administration in acutely ill adults leading to conflicting results regarding the optimum oxygenation target to pursue. The IOTA systematic review and meta-analysis suggested that liberal oxygen therapy as compared with conservative oxygen therapy might be harmful in acutely ill adults, with indications of a dose-dependent increase in mortality.[14] Conversely, such findings were not supported in an updated meta-analysis by Barbateskovic et al. with a similar set-up.[15] Among randomised clinical trials (RCTs) performed in the ICU-setting, neither a lower nor a higher oxygenation strategy, when treating adult ICU patients with acute hypoxaemic respiratory failure, has proven to be superior in terms of effects on short-term mortality.[16–19] Finally, the lack of international consensus is also reflected by divergent guidelines on the topic[20–23] and by the absence of formal recommendation on oxygenation targets in mechanically ventilated ARDS-patients.[24,25]

1.2 | Why it is important to do this review

The increasing number of ICU survivors has demanded a research focus on long-term complications that persists after hospital discharge.[4,11] Simultaneously, supplemental oxygen therapy is common practice in critical illness and it has been challenging to define the optimum oxygenation target balancing the potential beneficial and harmful effects.[26] Presently, no systematic review on the impact of oxygen treatment in the ICU on long-term outcomes, other than mortality and quality of life[27], has been reported, but no data for the latter outcome were identified. Therefore, we will conduct a systematic review of the scientific literature on the effects of lower versus higher oxygen supplementation and/or oxygenation levels in adult ICU patients on all long-term outcomes.

1.3 | Objectives

We aim to assess the long-term effects of lower versus higher oxygen supplementation and/or oxygenation levels in adult ICU survivors. We *a priori* hypothesise that lower oxygen supplementation and/or oxygenation levels result in poorer long-term cognitive function, whereas higher oxygen supplementation and/or oxygenation levels result in poorer long-term pulmonary function, poorer standardised 6-minute walk test[28] and reduced health-related quality of life (HRQoL).

2 | METHODS

The following protocol has been written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols checklist (PRISMA-P)[29] (the checklist is presented in Appendix S1) and the principles of Cochrane Handbook including the Methodological Expectations of Cochrane Intervention Reviews standards.[30,31] The protocol has been submitted at the International Prospective Register of Systematic Reviews (ID 223630).

2.1 | Criteria for considering trials for inclusion in the review

2.1.1 | Types of trials

We will include RCTs, irrespective of language, publication status and date. Unpublished data, however, will only be included if methodological descriptions and trial data are provided in written form, or by direct contact with study authors. We will exclude cross-over trials, quasi-randomised trials and non-interventional studies.

2.1.2 | Types of participants

We will include trials on adults, as defined by the trial authors, admitted to the ICU. If trials are not limited to adults only or if this is unspecified, we will include trials if the majority of patients are over 18 years old based on presented population characteristics. Patients must be allocated to lower versus higher oxygen supplementation or lower versus higher oxygenation target strategies.

2.1.3 | Types of setting

The setting will be confined to the ICU for inclusion of trials, that is, the intervention of lower versus higher oxygen supplementation or oxygenation targets must be applied in the ICU. We will assume an ICU facility if more than half of the patients receives typical ICU interventions, for example, mechanical ventilation, vasopressors/inotropes, and invasive hemodynamic monitoring.

2.1.4 | Types of intervention

We will include trials differentiating between a lower and a higher oxygen supplementation or a lower and a higher oxygenation strategy. Oxygen supplementation is defined by fraction of inspired oxygen (FiO_2) including separate oxygen flow levels in open systems, or by oxygenation targets or levels such as PaO_2, SaO_2 or peripheral oxygen saturation (SpO_2). We will not determine *a priori* thresholds of oxygenation for the two groups to ensure inclusion of all relevant trials. We will exclude trials on hyperbaric oxygen.

Lower oxygen group

Participants allocated to the lower oxygen supplementation or lower oxygenation strategy, administered by any device, will be defined as the lower oxygen group (L group).

Higher oxygen group

Participants allocated to the higher oxygen supplementation or higher oxygenation strategy, administered by any device, will be defined as the higher oxygen group (H group).

2.1.5 | Types of outcomes measures

We will include all long-term outcomes other than mortality. We will define long-term as any assessment following hospital discharge, or any follow-up period where most patients are expected to have been discharged, for example, at 90 days. If a trial includes several post-discharge assessment time points, only the assessment at longest follow-up will be included in the analysis.

Co-primary outcomes

1. Long-term cognitive function measure: the overall cognitive score on any valid scale of cognitive assessment such as (but not limited to) Repeatable Battery for the Assessment of Neuropsychological Status[32], or Mini-Mental State Exam;[33]
2. HRQoL assessment: the overall score on any valid scale such as (but not limited to) EuroQol 5 dimensions 5 level questionnaire, or EQ visual analogue scale;[34]
3. Standardised 6-minute walk test;[28]
4. Diffusion capacity test: diffusing capacity of lung for carbon monoxide, transfer factor of the lung for carbon monoxide, or diffusing capacity of lung for nitric oxide[35]

All long-term outcomes, other than those mentioned above, will be reported as exploratory outcomes. Examples of explorative outcomes are (but not limited to): forced expiratory volume measured during the first second (FEV_1); forced vital capacity (FVC); FEV_1/FVC ratio.

2.2 | Search methods for identification of studies

2.2.1 | Electronic searches

RCTs that fulfil the inclusion criteria will be identified through a systematic literature search, using a population and intervention-based approach. We will use the search strategy designed by Barbateskovic et al. in their Cochrane Review.[27] No restriction will be applied on publication date, language and journal. We will search the following databases: Cochrane Central Register of Controlled Trials, MEDLINE, Embase, Science Citation Index, BIOSIS Previews, Latin American and Caribbean Health Science Information database. Full search strategies are included in Appendix S2.

2.2.2 | Other resources

Reference lists of relevant reviews and papers will be manually screened for potentially relevant trials missed in the systematic electronic searches.Furthermore, we will search for ongoing and unpublished trials using the following trial registers: US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov), World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/), EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/), Australian New Zealand Clinical Trials Registry (ANZCTR) (www.anzctr.org.au/).

2.3 | Data collection and analysis

2.3.1 | Selection of studies

Two authors (TLK and FMN) will independently screen titles and abstracts of all reports found in the systematic search using Covidence.[36] Reports which are presumed to be potentially eligible will be obtained in full text, and the same two authors will independently assess these for inclusion. Any disagreement will be resolved by consensus. If no agreement can be reached, co-authors (OLS, MB or BSR) will resolve the issue. The selection of trials will be illustrated in a PRISMA flow diagram.

2.3.2 | Data extraction

The authors (EC and KUK) will independently extract predefined data from the included trials using a standardised data collection form designed and piloted by the review team. Any disagreement will be discussed between the authors (EC and KUK). If no agreement

can be reached, a third author (OLS or BSR) will resolve the issue. The following data will be collected when available:

1. Trial: country, duration of the trial, date of publication, type of trial;
2. Participants: number randomised, number analysed, number lost to follow-up or withdrawn, type of population, mean or median age, proportion of male sex, inclusion and exclusion criteria, setting;
3. Interventions: oxygenation strategies employed, that is, as defined by FiO_2, PaO_2 and/or SaO_2/SpO_2;
4. Outcomes: any data on long-term outcomes and reported time points

Trial investigators of the original reports will be contacted for important missing data. The characteristics of all trials will be summarised in a 'Characteristics of trials' table.

2.3.3 | Risk of bias

The authors (EC and KUK) will independently assess risk of bias of each of the included trials. Any disagreement will be resolved by consensus between the two authors. If no agreement can be reached, a third author (OLS, MB or BSR) will resolve the issue. The risk of bias will be assessed according to the Cochrane Handbook for Systematic Reviews of Interventions using the revised Risk of Bias 2 tool.[31,37]

We will assess the risk of bias in all five mandatory risk of bias domains: bias arising for the randomisation process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in measurement of the outcome; and bias in the selection of the reported results. The effect of interest within the domain 'bias due to deviations from intended interventions' will be the effect of assignment to the intervention (i.e. intention to treat effect). Each domain will be adjudicated as 'low risk of bias', 'some concerns' or 'high risk of bias'. RCTs with 'low risk of bias' in all domains will be classified as overall 'low risk of bias' trials. RCTs with one domain adjudicated at 'some concerns', but no domain adjudicated at 'high risk of bias', will be classified as overall causing 'some concerns' of risk of bias. RCTs will be classified as overall 'high risk of bias' trials if at least one domain is adjudicated at 'high risk of bias'. However, if a study is judged to have 'some concerns' of risk of bias for multiple domains, it may be judged as 'high risk of bias' overall if the assessors judge that the multiple concerns amount to a serious risk of bias.[38,39] Risk of bias tables, including summarised rationales, will be presented in a supplement to the final manuscript. We will base our primary conclusions on results from RCTs with an overall low risk of bias for the outcome of interest.

2.3.4 | Measures of intervention effect

We will calculate the mean difference with a 95% confidence interval (CI) for continuous data. For continuous outcomes, we plan to include both end-scores and change-scores in the analyses; we will use end-scores if both are reported. We will calculate the mean differences and consider calculating the standardised mean difference[31] with 95% CI for continuous outcomes. We will calculate risk ratios (RR) with 95% CIs for dichotomous outcomes.

2.3.5 | Assessment of heterogeneity

We will assess forest plots for visual signs of heterogeneity. Statistical heterogeneity will be assessed using Chi squared test with significance at $P < 0.1$ and the quantities of heterogeneity will be measured by calculations of I^2, where a $I^2 > 50\%$ will be categorised as substantial heterogeneity.[40] The tool Clinical Diversity in Meta-analyses (CDIM) of interventions will be used to assess clinical heterogeneity.[41] CDIM covers the following four domains: setting, population, intervention and outcome diversity. Furthermore, clinical heterogeneity will be evaluated by pre-specified sub-group analyses (see below).

2.4 | Data synthesis

2.4.1 | Meta-analysis

We will undertake the systematic review according to the recommendations stated in the Cochrane Handbook for Systematic Review of interventions.[31] If two or more RCTs are included with comparable outcome measures, we will assess intervention effects with both random-effects model meta-analyses[42-44] and fixed-effect model meta-analyses.[44,45] We will use the more conservative point estimate of the two with the highest p-value. Review Manager 5.4 will be used to meta-analyse data and results will be illustrated using forest plots.[46] We will perform an adjustment of the CIs of our co-primary outcomes due to multiplicity according to the procedure specified by Jakobsen et al[47]. With four predefined outcomes, significance in the adjusted P-value will be below 0.02, equivalent of an adjusted CI of 98%, in order to preserve a family wise error rate below 5%. Thus, if the adjusted 98% CI for any of the co-primary outcomes does not include the null effect, the result will be considered statistically significant. Exploratory outcomes will not be adjusted for multiplicity and a p-value below 0.05 will be assumed significant. For outcome measures reported by only one RCT, no meta-analysis will be conducted. A narrative description of the trials' results will be presented instead. We will present our findings in a 'Summary of findings' table.

2.4.2 | Trial sequential analysis

We will analyse our prespecified co-primary outcomes with trial sequential analyses (TSA).[48] For dichotomous outcomes, we will estimate the required information size based on the observed proportion of patients with an outcome in the control group (the cumulative proportion of patients with an event in the control groups relative to all patients in the control groups), a relative risk reduction

or a relative risk increase of 20%, an alpha of 2% for all our outcomes, a beta of 10% (i.e. power of 90%), and the observed diversity as suggested by the trials in the meta-analysis. For continuous outcomes, we will in the TSA use the observed standard deviation (SD) in the control group, the observed SD/2, an alpha of 2% for all outcomes, a beta of 10%, and the observed diversity as suggested by the trials in the meta-analysis.

2.4.3 | Subgroup analysis

If data permit, we will undertake a subgroup analysis comparing estimates of the pooled intervention effect according to the type of ICU population: medical versus surgical versus mixed. We hypothesise a successively greater detrimental effect on long-term cognitive function in the lower oxygenation group in surgical, mixed and medical population respectively; whereas we hypothesise a successively greater detrimental effect on long-term pulmonary function and HRQoL in the higher oxygenation group in surgical, mixed and medical population respectively.

2.4.4 | Sensitivity analysis

We will perform sensitivity analyses to assess the potential impact of missing data by performing best-worst and worst-best case scenarios.[47]

When analysing our co-primary outcomes, a 'beneficial outcome' will be the group mean plus two SDs of the group mean and a 'harmful outcome' will be the group mean minus two SDs of the group mean.[47]

Moreover, to assess the potential impact of missing SDs for continuous outcomes, we will perform the following sensitivity analysis: where SDs are missing or it is not possible to calculate them, we will impute SDs from trials with similar populations and being at overall low risk of bias. If we find no such trials, we will impute SDs from trials with a similar population. As a final option, we will impute the mean SD from all included trials.

2.4.5 | Certainty of evidence

We will assess the certainty of evidence for all prespecified outcomes according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[49-51] We will present the results of the GRADE assessment for long-term cognitive function, HRQoL, 6-minute walking test and diffusion capacity in the 'Summary of findings' table[50], using the GRADE software.[52] The GRADE approach appraises the certainty of evidence based on the extent to which one can be confident that the estimate of effect or association reflects the item being assessed. We will assess the following domains: within-trial risk of bias[53], imprecision[54], inconsistency[55], indirectness[56] and publication bias.[57] The latter domain will be assessed by examination of funnel plots. Accordingly, the overall certainty of evidence for all outcomes will be classified as 'high', 'moderate', 'low' or 'very low'.

3 | DISCUSSION

The outlined systematic review will provide an overview of the available data regarding long-term outcomes after lower versus higher oxygen supplementation and/or levels of oxygen therapy in the adult ICU survivors. The review holds several strengths. It will be written in accordance with the PRISMA-statement[29] and we have prepared the methodology based on the Cochrane Handbook for Systematic Reviews of Interventions,[30,31] and the GRADE approach.[49] A limitation of our review stems from the lack of international consensus regarding targeted oxygen therapy and no formal recommendations for ICU patients. Consequently, we have not defined a priori oxygenation thresholds and statistical results must be interpreted with caution. Furthermore, we expect an extreme heterogeneity within the long-term dysfunctions after the ICU stay, and subsequently, all long-term outcomes, other than the predefined, will be reported as exploratory and not subjected to certainty of evidence assessment. Finally, it is also important to mention that mortality at the longest follow-up has not been included in our outcomes, since it has been earlier explored in a recent meta-analysis[27] and the focus of our review lies on the ICU survivors. In conclusion, we plan to perform a systematic review of the clinical literature assessing the impact of lower versus higher oxygen supplementation and/or oxygenation levels in the ICU on long-term outcomes. The review will provide an overview of the current evidence and it will help future research in the field.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of the article at the publisher's website.

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