Higher Versus Lower Oxygenation Strategies in The General Intensive Care Unit Population: A Systematic Review, Meta-Analysis and Meta-Regression of Randomized Controlled Trials.

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Abstract

Background

Oxygen therapy is vital in intensive care unit (ICU) patients, but it is indistinct whether higher or lower oxygen targets are favorable with regards to patient centered outcomes. Our aim was to systematically evaluate the findings of randomized controlled trials (RCTs) comparing higher and lower oxygen therapy strategies in mechanically ventilated patients.

Methods

A meta-analysis and meta-regression analysis of RCTs published between 2015 and 2021 was conducted. Electronic databases of MEDLINE, EMBASE, and Web of Science were systematically searched. Publications comparing the effects of higher or lower oxygen therapy in adult ICU patients were eligible. Risk of bias was assessed using the Cochrane Risk of Bias tool. The primary outcome was mortality at day 90; secondary outcomes include serious adverse events (SAE), ICU and hospital length of stay and support-free days.

Results

We included nine RCTs enrolling 5807 patients. No significant difference was observed for mortality at day 90. A significantly lower odds ratio (OR) was found for SAEs, favoring lower oxygenation (OR 0.86 [0.77, 0.96], $P=0.009$). Our meta-regression analysis shows that the effect sizes for 90-day mortality may be influenced by both the between-group difference in achieved oxygenation and the severity of hyperoxia in the higher group ($\beta=-0.0022$, $P=0.1$).

Conclusion

In the general ICU population, there was no significant difference in 90-day mortality between higher and lower oxygenation strategies. However, a lower incidence of serious adverse events was found for the lower oxygenation groups. These findings may have clinical implications for practice guidelines, yet it remains of paramount importance to continue conducting clinical trials, ideally comparing groups with a clinically relevant contrast for specific patient groups.

Trial registration

The protocol of this study was registered on PROSPERO (CRD42021286372).

Introduction

Oxygen therapy has been successfully used in the acute care setting for over a century (1). Most critically ill patients are at risk for hypoxemia which may cause tissue damage, organ failure or even death. Owing to these risks, the professional norm among health care specialists is to attentively avoid and sometimes even overcompensate hypoxemic events by liberally administering oxygen or deliberately inducing supranormal arterial oxygen levels (2, 3). Oxygen has proven to be very effective in the treatment of hypoxemic patients, but may not be beneficial in all patients. The deleterious properties of oxygen are increasingly acknowledged. Harmful effects can include cerebral and coronary vasoconstriction, reduction of cardiac output, absorption atelectasis, acute lung injury and central nervous system toxicity (4). In addition, studies repeatedly showed a negative correlation between hyperoxia and patient centered outcomes (5-7). Accordingly, newer guidelines on oxygen therapy generally recommend a more conservative approach (8). However, not all cautions with regards to hyperoxia have been conclusively justified as observational studies and randomized controlled trials (RCTs) comparing higher versus lower oxygen targets show heterogeneous results.

Few systematic reviews have been conducted in order to provide guidance for administering oxygen in a safe and efficient manner to intensive care unit (ICU) patients. The results were unequivocal (5, 9), but new studies have recently been published (10). Furthermore, important data concerning vital secondary outcomes, such as ischemic events, have not been aggregated in detail before. By systematically combining all available evidence from RCTs comparing higher and lower targeted oxygen strategies in mechanically ventilated patients, we aim to provide conclusive insights into favorable oxygen therapy.

Methods

This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses (see Additional file 1) (11). The protocol of this study was registered on PROSPERO (CRD42021286372). Studies were included when meeting the following inclusion criteria: RCTs comparing higher (liberal) and lower (conservative) oxygen therapy strategies in the general ICU population of which the majority is mechanically ventilated.

Information sources and search

After consulting a librarian, the electronic databases of Medline (1962-2021), EMBASE (1970-2021) and Web of Science (1970-2021) were searched. This search was supplemented by manually screened reference lists of relevant studies and reviews. Full search terms and search strategies are presented in Additional file 3 of the Additional files. Main MeSH headings and key words that were used are "oxygen inhalation therapy", "hyperoxia", "hypoxia", "oxygen" and "respiration, artificial". The literature search was last updated October 20th 2021.

Study selection and Data collection process

Two authors (L.I.W, H.J.F.H) independently screened articles on title and abstract. Differences in this process were resolved by consensus. No language restrictions were applied. Studies were excluded using the following criteria: patients younger than 18 years, animal studies, extracorporeal life support, perioperative settings and hyperbaric oxygen therapy. Studies that solely focused on one specific patient group (e.g. myocardial or cerebral infarction) were excluded to improve the comparability of the included study population. Duplicates were removed by using the method of Bramer et al (9).

Data analysis and outcomes

Data abstraction was done by two content area experts using an electronic standardized data abstraction sheet. Extraction was reviewed by two review authors independently. Disagreements were resolved by consensus. If no consensus could be reached, a third co-author would resolve the issue. Data was collected as dichotomous and continuous outcome data. The primary outcome of interest was mortality at day 90; and mortality at day 28, day 180 and ICU and hospital mortality were also analyzed. Secondary outcomes were adverse events, support-free days at day 28 and length of stay (LOS).

If data was available on intended primary or secondary outcomes, studies were included in the meta-analysis. Corresponding authors were contacted to clarify important missing data or for further trial details. The Grading Of Recommendation, Assessment, Development and Evaluation (GRADE) approach was used to grade the certainty of evidence of the included papers (12). Heterogeneity between studies and between subgroups was assessed by using either τ^2 , χ^2 or I^2 statistics, or a combination of the latter and presented as either a p-value, percentages or both. A low p-value was considered as evidence of heterogeneity of intervention effects. An I^2 of 0 to 40% was considered not important, 30 to 60% was considered moderate, 50 to 90% was considered substantial and 75 to 100% considerable (13).

For individual effect estimates, pooling and formal meta-analysis of the data odds ratios (ORs) were used. Pooled estimates are displayed in forest plots and summarized as OR with a 95% CI. For dichotomous data a random-effects model according to Mantel and Haenszel (M-H) was used; continuous data was analyzed by the use of a random-effects inverse variance model. A random-effects model was chosen due to existing heterogeneity. The effects of hyperoxia by achieved oxygenation in the randomized groups were analyzed using a meta-regression framework (16). For this meta-regression analyses we calculated a combined score in order to assess the effects of the achieved difference in PaO_2 (contrast) between the oxygenation groups in combination with the degree of hyperoxia that was achieved in the higher oxygenation group. Hence, the combined score was calculated as: between group difference in achieved PaO_2 plus the achieved PaO_2 in the highest group. The ORs were based on the 90-day mortality. Our hypothesis was that a higher between-group difference and a more severe hyperoxic target in the higher group, increase the effect size for 90-day mortality. Since Yang et al did not report on 90 day mortality, this study was not included in the meta-regression analysis.

In order to assess bias, the Cochrane risk of bias tool for randomized trials was used (14). A funnel plot was used to graphically display reporting bias, using standard errors of the intervention effect estimate. Funnel plot asymmetry was tested by using Egger's exact test.

All analyses were conducted using RevMan 5.3 (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) and R version 4.0.3. (R Foundation for Statistical Computing, Vienna, Austria) with RStudio (RStudio, Boston, MA).

Results

Study selection and study characteristics

Figure 1 depicts the study flowchart. Our search strategy resulted in 1311 studies considered for inclusion after deleting duplicates. In total, 19 full-text articles were assessed for eligibility after title and abstract screening (Figure 1). The most important exclusion reasons were study types other than RCTs, post hoc analyses or lack of comparison between higher and lower oxygenation. For the final analysis, nine studies, in a total of 5807 patients, were included (Table 1) (10, 15-22). In the studies included, data collection took place between 2010 and 2020; the study reports were published between 2015 and 2021. All included studies were RCTs comparing a higher versus a lower oxygenation in mechanically ventilated patients focusing on the general ICU population. Either PaO_2 , SpO_2 , FiO_2 or a combination of these parameters were used to pursue oxygenation targets. The duration of the interventions ranged from 24 hours to 90 days (Table 1).

Risk of bias in studies

Overall, the risk of bias was moderate to low, except for blinding and early stopping bias (see Figure 2 and 3 and Additional file 2 of Additional files). Due to the design of the trials, it was essentially unfeasible to blind clinicians for the assigned treatment group. However, patients were blinded in the majority of the trials. Also, three trials scored high on early stopping bias. The funnel plot regarding publication bias is displayed in Figure 4. Egger's exact test for funnel plot asymmetry was based on Additional 4 of the Additional files. A z-score of 0.83 and a corresponding p-value of 0.41 was found, suggesting no funnel plot asymmetry.

Primary endpoint

Mortality at day 28, day 90, day 180, in the ICU and in the hospital were assessed separately and are listed in a forest plot (Figure 5). No effect of different oxygenation strategies was found for either mortality at day 28 ($P=0.75$), day 90 ($P=0.91$), day 180 ($P=0.70$), ICU mortality ($P=0.55$) or in-hospital mortality ($P=0.53$).

Secondary endpoints

Adverse events were categorized in the following subgroups: myocardial ischemia, intestinal ischemia, ischemic stroke, respiratory infection, systemic infection, shock, organ failure, renal replacement therapy and arrhythmias (Figure 6). Regarding the adverse infectious events, respiratory infection (OR 0.88 [0.63, 1.22], $P=0.45$) showed no significant difference between groups, although lower targets were favorable in cases of systemic infection (OR 0.51 [0.29, 0.88], $P=0.02$). For ischemia, including myocardial ischemia (OR 1.29, [0.61, 2.73], $P=0.50$), intestinal ischemia (OR 1.12, [0.43, 2.93], $P=0.82$) and ischemic stroke (OR 0.94 [0.44, 2.04], $P=0.88$), no difference was detected. Overall, the incidence of adverse events showed a significant OR of 0.86 [0.77, 0.96] ($P=0.009$) in favor of lower targets. Between studies, heterogeneity was considered not important ($I^2=13\%$, $P=0.29$) as well as subgroup heterogeneity ($I^2=23.0\%$, $P=0.24$).

Support-free days were analyzed as ventilator- and vasopressor-free days at day 28 (Figure 7). In general, the support-free days did not show a significant difference (OR 0.20 [-0.45, 0.85] $P=0.55$). Heterogeneity was moderate between all studies ($I^2=33\%$, $P=0.16$) and not important between subgroups ($I^2=0\%$, $P=0.65$).

The analysis of the length of stay (LOS) was categorized according to two subgroups: hospital LOS and ICU LOS (Figure 8). No significant differences were observed in the different subgroups.

Sensitivity analysis

All included studies in this meta-analysis were assessed using the GRADE approach (12). In most cases, the certainty of evidence was high to moderate (Table 1). Despite methodological differences, we mainly observed low heterogeneity and low risk of bias. Due to a variety in the chosen targets of the studies, we performed a meta-regression analysis that compared the odds for lower oxygenation on 90-day mortality for different achieved oxygenation targets. The regression was performed for both the achieved high and low oxygenation groups (see Additional file 5 of Additional files) and for the combined score. The combined score is calculated by combining the achieved difference between the high and low oxygenation targets and the achieved higher oxygenation target (Figure 9). Figure 9 shows that this combined score is in the same order of magnitude for the majority of the trials (10, 15, 17-19, 21, 22) and the OR of mortality in the lower group approximates 1. One trial (16) shows a combined score of 260 mm Hg in combination with a lower OR for mortality in the lower group. Taken together, the risk of mortality after 90 days in the lower group may be dependent on the combined score, i.e. the combination of the difference of achieved oxygenation and the severity of achieved hyperoxia in the higher group. However, the beta associated with this meta-regression analysis did not reach statistical significance.

Discussion

This systematic review and meta-analysis shows no difference in mortality at day 90 when aggregating data from RCTs comparing lower and higher oxygenation targets. For secondary outcomes, a significant effect favoring lower oxygenation targets was identified with regards to serious adverse events..

The following study strengths and limitations should be considered. First, this meta-analysis includes important secondary patient centered outcomes such as support-free days and serious adverse events. Second, in order to ensure comprehensiveness of the data, corresponding authors were contacted for additional data. Also, established guidelines, such as the PRISMA and GRADE approach, were used to ensure the quality of our methodology and certainty of evidence.

A key limitation is that all trials on oxygenation in ICU patients used different targets. Several varying thresholds were used for PaO_2 targets. Moreover, some trials used SpO_2 targets rather than PaO_2 targets and one study managed liberal oxygenation by applying an FiO_2 of 1.0 (irrespective of SpO_2) during the first 24 hours while not using different SpO_2 or PaO_2 targets afterwards. A PaO_2 of 90 mmHg can correspond with a SpO_2 of 100% but also 93%, partially depending on the underlying disease. Therefore, a higher PaO_2 cannot be consistently translated into a fixed SpO_2 (23). As thresholds differ, a patient could be categorized in the higher oxygenation group in one trial, whereas this could be the lower oxygenation group in the other trial. Moreover, in some studies chosen oxygenation targets can overlap (15, 18), suggesting there may not be a true comparison between a 'high' and a 'low' group.

Another limitation is the heterogeneity of the ICU population in combination with the heterogenous treatment effect that can be expected from oxygen therapy in certain subgroups. For example, in vasodilatory septic shock, arterial hyperoxia may be beneficial due to antibacterial properties and the counteraction of vasodilation (24, 25), while in ischemia and reperfusion injuries, such as myocardial infarction, hyperoxia may have detrimental effects (26). Recent reviews explored the optimal oxygen targets per subgroup by underlying disease (27, 28) and no optimal oxygen target per subgroup could be identified, though it seems justifiable to avoid both hypoxemia and excess hyperoxemia. Hence, the key question remains whether we should settle for a one-strategy-that-fits all (optimal) oxygen therapy approach, or whether optimal oxygen strategies can be applied per subgroup.

None of the included trials were blinded, which can be considered a limitation since the latest literature could have imposed bias towards the beneficial effect of lower oxygenation targets (29, 30). Therefore, clinicians may be more prone to adhere to the lower targets, making it more difficult to create contrast in oxygenation between two different groups. However, owing to the design of the trial, it was essentially unfeasible to blind clinicians for the assigned treatment group. Despite lack of blinding and early stopping bias, an overall low risk of bias (Figure 2 and 3) and low heterogeneity was observed with a moderate to high certainty of evidence (Table 1). Taken together, this provides a reasonable degree of certainty that there is no or little evidence for important differences in mortality between compared oxygenation targets.

Our findings are in line with recent systematic reviews showing that different oxygenation strategies did not have a significant impact on mortality (9, 31). However, the findings are in contrast to previously published reviews (5, 32, 33), that support a conservative oxygen strategy. A simple explanation for these contradictions might be that patients either simply do not benefit from a lower oxygenation strategy or that the achieved lower and higher PaO_2 in both groups lack sufficient contrast to be able to detect a difference. In the included trials it has proven to be difficult to accomplish a clinical contrast between the intervention and the control group. The majority of the trials that reported on the achieved oxygenation show a difference of 10 to 20 mmHg (15, 17-19, 21).

Our sensitivity analysis using a meta-regression framework (Figure 9 and additional files) shows that trials with a smaller achieved difference (10-20 mm Hg) (15, 17-19, 21) and studies with a larger achieved difference (25-70 mm Hg) (10, 16, 22) both show heterogeneous results. It should be noted that achieved differences are in the same order of magnitude for most studies (10-30 mm Hg) despite one outlier (70 mm Hg). When a large difference is achieved there is a sign that patients may benefit from a lower oxygenation target. Though, due to lack of significant results, this may also be originated by chance. Furthermore, when specifically targeting a very high or low target a significant clinical difference may be achieved but neither the intervention nor the control group may then represent usual care. Accordingly, the present study may demonstrate that a broad range of less extreme achieved oxygenation falls within a fairly safe category.

The different results amongst included trials can be explained by secondary factors such as early stopping bias, subgroup analysis and not choosing a truly hyperoxic target. Taking all included trials that reported on achieved targets together, an average higher oxygenation around 110 mm Hg was achieved, with an individual maximum of 185 mm Hg (16). The hypothesis that 110 mm Hg is not a truly hyperoxic target is supported by earlier literature that showed a significant increase in mortality in the hyperoxic group, where hyperoxia was defined as $\text{PaO}_2 > 300 \text{ mmHg}$ (26). Our meta-regression analysis (figure 9) shows that when a hyperoxic target of 185 mm Hg is achieved (16), patients may have a lower risk of mortality in the lower oxygenation group. In line, these results are not significant and the more severe the higher target, the less it represents usual care and the higher the chances of mortality.

A new finding in our meta-analysis resulted from studying serious adverse events. We found that adverse events are more likely to occur in the higher oxygenation groups. As in previous studies, serious adverse events should be critically reviewed to evaluate whether the event is consistent with the natural history of the critical illness (34). If a large difference is observed, similar to the difference found in our meta-analysis, it might be attributable to the different interventions. As serious adverse events can highly impair patient health and quality of life the potential negative impact of higher targets may also be a compelling argument to adhere to a lower oxygenation strategy. However, the results on adverse events are dominated by one study (18) and a low number of studies reported on the individual adverse events groups. Even though this finding, concerning adverse events, is an important signal for clinical practice guidelines, more robust data is needed for a compelling conclusion.

Conclusion

In the present meta-analysis comparing higher and lower oxygenation targets we found no difference in 90-day mortality. Importantly, we did find a significant difference in serious adverse events favoring lower oxygenation targets. Differences in methodology, oxygenation targets and primary and secondary endpoints may hamper a comparison of studies, even though the certainty of evidence in the majority of studies was graded relatively high and heterogeneity was generally low. Robust future clinical trials remain of paramount importance, ideally adequately separating the intervention groups based on achieved oxygenation.

Abbreviations

GRADE = Grading of Recommendation, Assessment, Development and Evaluation

ICU = Intensive Care Unit

LOS = Length Of Stay

M-H = Mantel and Haenszel

OR = Odds Ratio

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis

RCT = Randomized Controlled Trial

SAE = Serious Adverse Events

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

All authors declare to have no competing interests.

Funding

Not applicable

Authors' contributions

LIW and HH conducted the search, reviewed the articles for eligibility and performed the statistical analysis. LIW wrote the manuscript. All authors contributed to the writing, critical revision of the manuscript and approved the final version.

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Tables

Table 1. Summary of included studies

Study	Journal	Year	Country	Sample size	Population	Intervention		Primary endpoint	Duration intervention	Certainty of evidence (GRADE)
						Lower oxygenation	Higher oxygenation			
Asfar (16)	Lancet	2017	France	442	Sepsis	SpO ₂ 88%-95%	FiO ₂ 1.0	28 day mortality	24h	Moderate ^a
Barrot (17)	NEJM	2020	France	205	ARDS	PaO ₂ 55-70 mm Hg or SpO ₂ 88-92%	PaO ₂ 90-105 mm Hg or SpO ₂ at least 96%	28 day mortality	7 days	Low ^b
Gelissen (21)	JAMA	2021	Netherlands	400	Total ICU population	PaO ₂ 8-12 kPa	PaO ₂ 14-18 kPa	Cumulative daily delta SOFA score from day 1 to day 14	14 days or ICU discharge	Moderate ^c
Girardis (18)	JAMA	2016	Italy	480	Total ICU population	PaO ₂ 70-100 mm Hg or SpO ₂ 94-98%	PaO ₂ up to 150 mm Hg or SpO ₂ 97-100%	ICU mortality	ICU discharge	Moderate ^a
Mackle (15)	NEJM	2019	New Zealand, Australia	1000	Total ICU population	SpO ₂ 91-97%, FiO ₂ as low as possible	≥ 91% without upper limit	Number of ventilator free days	ICU discharge or day 28	High
Martin (22)	JICS	2021	England	34	Total ICU population	SpO ₂ 88-92%	SpO ₂ ≥ 96%	Feasibility	Until extubation, tracheostomy, transfer or death	Low ^d
Panwar (19)	AJRCCM	2015	Australia, New Zealand, France	104	Total ICU population	SpO ₂ of 88-92%	SpO ₂ ≥ 96%	Mean AUC for SpO ₂ , SaO ₂ , PaO ₂ and FiO ₂ . % spent off target	Entire duration of mechanical ventilation	High
Schjørring (10)	NEJM	2021	Denmark, Switzerland, Finland, The Netherlands, Norway, the United Kingdom, Iceland	2928	Total ICU population	PaO ₂ 60 mm Hg	PaO ₂ 90 mm Hg	90 day mortality	ICU discharge or day 90	High
Yang (20)	J Thorac Dis	2019	China	214	Total ICU population	SpO ₂ of 90-95%	SpO ₂ of 96-100%	28 day mortality	14 days or ICU discharge	Moderate ^c

a. High risk of bias due to early stopping bias, lack of blinding and performance bias (see Fig 2 and 3).

b. High risk of bias due to early stopping bias, lack of blinding and performance bias (see Fig 2 and 3). Imprecision due to wide confidence intervals.

c. High risk of bias due to lack of blinding and selective reporting bias (see Fig 2 and 3).

d. High risk of bias due to lack of blinding, attrition bias and early stopping bias (see Fig 2 and 3). Imprecision due to wide confidence intervals.

Figures

Figure 1

Flowchart study selection

Figure 2

Risk of bias graph

Figure 3

Risk of bias summary

Figure 4

Funnel plot for publication bias based on mortality at day 28, day 90, day 180, ICU mortality and hospital mortality.

Figure 5

Forest plot mortality

Figure 6

Forest plot adverse events. Patients from each study are counted once in the test for overall effect.

Figure 7

Forest plot support free days at day 28

Figure 8

Forest plot length of stay

Figure 9

Meta regression analysis for the crude effects of lower oxygenation on 90-day mortality by combined score. Scatters indicate odds ratios for 90-day mortality for lower oxygenation on a logarithmic scale, according to the combined score in the indicated studies. The combined score is calculated as the difference between achieved oxygenation (PaO_2) of lower and higher group plus the achieved oxygenation (PaO_2) of the higher group. The point sizes are inversely proportional to the standard error of the mean of the individual studies (i.e., larger/more precise studies are shown as larger *circles*). The predicted effect sizes are modeled in a linear mixed-effects model with corresponding 95% CI boundaries and a β -coefficient with p value for the meta-regression line. An OR >1 is beneficial to the lower oxygenation group.

Supplementary Files

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