

# Higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the intensive care unit: a Cochrane Review

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## Background

The mainstay treatment for hypoxaemia is oxygen therapy, which is given to the vast majority of adults admitted to the intensive care unit (ICU). The practice of oxygen administration has been liberal, which may result in hyperoxaemia. Some studies have indicated an association between hyperoxaemia and mortality, whilst other studies have not. The ideal target for supplemental oxygen for adults admitted to the ICU is uncertain. Despite a lack of robust evidence of effectiveness, oxygen administration is widely recommended in international clinical practice guidelines. The potential benefit of supplemental oxygen must be weighed against the potentially harmful effects of hyperoxaemia.

## Objectives

To assess the benefits and harms of higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the ICU.

## Search methods

We identified trials through electronic searches of CENTRAL, MEDLINE, Embase, Science Citation Index Expanded, BIOSIS Previews, CINAHL, and LILACS. We searched for ongoing or unpublished trials in clinical trials registers. We also scanned the reference lists of included studies. We ran the searches in December 2018.

## Selection criteria

We included randomized controlled trials (RCTs) that compared higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the ICU. We included trials irrespective of publication type, publication status, and language.

We included trials with a difference between the intervention and control groups of a minimum 1 kPa in partial pressure of arterial oxygen (PaO<sub>2</sub>), minimum 10% in fraction of inspired oxygen (FiO<sub>2</sub>), or minimum 2% in arterial oxygen saturation of haemoglobin/non-invasive peripheral oxygen saturation (SaO<sub>2</sub>/SpO<sub>2</sub>).

We excluded trials randomizing participants to hypoxaemia (FiO<sub>2</sub> below 0.21, SaO<sub>2</sub>/SpO<sub>2</sub> below 80%, and PaO<sub>2</sub> below 6 kPa) and to hyperbaric oxygen.

## Data collection and analysis

Three review authors independently, and in pairs, screened the references retrieved in the literature searches and extracted data. Our primary outcomes were all-cause mortality, the proportion of participants with one or more serious adverse events, and quality of life. None of the trials reported the proportion of participants with one or more serious adverse events according to the International Conference on Harmonisation Good Clinical Practice (ICH-GCP) criteria. Nonetheless, most trials reported

several serious adverse events. We therefore included an analysis of the effect of higher versus lower fraction of inspired oxygen, or targets using the highest reported proportion of participants with a serious adverse event in each trial. Our secondary outcomes were lung injury, acute myocardial infarction, stroke, and sepsis.

None of the trials reported on lung injury as a composite outcome, however some trials reported on acute respiratory distress syndrome (ARDS) and pneumonia. We included an analysis of the effect of higher versus lower fraction of inspired oxygen or targets using the highest reported proportion of participants with ARDS or pneumonia in each trial. To assess the risk of systematic errors, we evaluated the risk of bias of the included trials. We used GRADE to assess the overall certainty of the evidence.

## Main results

We included 10 RCTs (1458 participants), seven of which reported relevant outcomes for this review (1285 participants). All included trials had an overall high risk of bias, whilst two trials had a low risk of bias for all domains except blinding of participants and personnel.

Meta-analysis indicated harm from higher fraction of inspired oxygen or targets as compared with lower fraction or targets of arterial oxygenation regarding mortality at the time point closest to three months (risk ratio (RR) 1.18, 95% confidence interval (CI) 1.01 to 1.37;  $I^2 = 0\%$ ; 4 trials; 1135 participants; very low-certainty evidence). Meta-analysis indicated harm from higher fraction of inspired oxygen or targets as compared with lower fraction or targets of arterial oxygenation regarding serious adverse events at the time point closest to three months (estimated highest proportion of specific serious adverse events in each trial RR 1.13, 95% CI 1.04 to 1.23;  $I^2 = 0\%$ ; 1234 participants; 6 trials; very low-certainty evidence). These findings should be interpreted with caution given that they are based on very low-certainty evidence.

None of the included trials reported any data on quality of life at any time point.

Meta-analysis indicated no evidence of a difference between higher fraction of inspired oxygen or targets as compared with lower fraction or targets of arterial oxygenation on lung injury at the time point closest to three months (estimated highest reported proportion of lung injury RR 1.03, 95% CI 0.78 to 1.36;  $I^2 = 0\%$ ; 1167 participants; 5 trials; very low-certainty evidence).

None of the included trials reported any data on acute myocardial infarction or stroke, and only one trial reported data on the effects on sepsis.

## Authors' conclusions

We are very uncertain about the effects of higher versus lower fraction of inspired oxygen or targets of arterial oxygenation for adults admitted to the ICU on all-cause mortality, serious adverse events, and lung injuries at the time point closest to three months due to very low-certainty evidence. Our results indicate that oxygen supplementation with higher versus lower fractions or oxygenation targets may increase mortality. None of the trials reported the proportion of participants with one or more serious adverse events according to the ICH-GCP criteria, however we found that the trials reported an increase in the number of serious adverse events with higher fractions or oxygenation targets. The effects on quality of life, acute myocardial infarction, stroke, and sepsis are unknown due to insufficient data.

## Section Info

This section reproduces articles previously published by Cochrane Database of Systematic Reviews and is carried out in coordination with Patricia Jabre, Yannick Auffret, Sebastien Beroud, Julie Dumouchel, Virginie-Eve Lvovschi, Kirk Magee, Daniel Meyran, Patrick Miroux, Nordine Nekhili and Youri Yourdanov from the Cochrane Pre-hospital and Emergency Care group.