

Is an IOTA of evidence enough?

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ABSTRACT

Clinical question: Do patients with acute illness admitted to the hospital and treated with liberal oxygen therapy compared with those treated with conservative oxygen therapy have differences in mortality and morbidity?

Article chosen: Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet* 2018;391(10131):1693–705.

Objectives: To analyse the existing literature to assess the potential benefits or harms of supplemental oxygen use in acutely ill patients.

Keywords: drug therapy, hyperoxemia, meta-analysis, oxygen therapy

BACKGROUND

Supplemental oxygen is commonly used by emergency medical services and within the hospital setting as a potential treatment that is often felt to have few side effects and little harm.¹ However, the literature is increasingly showing that liberal supplemental oxygen may in fact have a deleterious effect on mortality and morbidity. These effects are thought to potentially be due to inflammatory processes, changes in cardiac output, lung injury, and vasoconstriction.²

POPULATION STUDIED

Meta-analysis of randomized controlled trials (RCTs) of patients admitted to the hospital for non-elective acute illness in which they had potential for exposure to supplemental oxygen.

STUDY DESIGN

Meta-analysis of RCTs comparing liberal with conservative oxygen supplementation.

INTERVENTION

Liberal oxygen therapy, as defined by the treatment arm with the higher oxygen target (FiO₂ 0.28–1.00), by any definition of a fraction of inspired oxygen, arterial partial pressure of oxygen, arterial oxygen saturation or peripheral oxygen saturation, was compared with the arm that had a lower oxygen target (FiO₂ 0.21–0.50).

OUTCOME MEASURES

Mortality (in hospital, 30 days, or longest follow-up) or morbidity (modified Rankin score at longest follow-up, hospital acquired pneumonia, hospital acquired infection, and hospital length of stay).

RESULTS

Studies were included if they were RCTs comparing a liberal oxygen therapy with a conservative oxygen therapy in patients over the age of 18 years who required a non-elective admission to the hospital. The search retrieved 26 publications, with 25 RCTs identified among them. This yielded a total of 16,037 patients admitted with acute illness, of which 43% were admitted for a surgical diagnosis. Median baseline SpO₂ was

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96.4% (range 94.0–99.0) in the liberal arm and 96.7% (range 93.4–98.0) in the conservative arm, although it is not clear whether this was on room air. The median FiO_2 of the liberal arm was 0.52 (range 0.28–1.00), and the median FiO_2 of the conservative arm was 0.21 (range 0.21–0.50). In terms of mortality, liberal oxygen therapy was associated with increased risk of death during hospital admission (relative risk [RR] 1.21, confidence interval [CI] 1.03–1.43, high quality), death at 30 days (RR 1.14, CI 1.01–1.28, high quality), and death at longest follow-up (median 3 months, RR 1.10, CI 1.00–1.20, high quality), compared with the conservative arm. As SpO_2 increased, the RR of in-hospital mortality increased with liberal oxygen therapy.

AUTHOR'S CONCLUSION

The authors concluded that the overall liberal use of supplemental oxygen therapy was harmful in acutely ill patients.

COMMENTARY

Meta-analysis quality

The search strategy was exhaustive, using multiple databases, including all languages, searching references, and getting raw and unpublished data from authors. Two reviewers assessed each article with quality determined by the GRADE scale³ and bias using the Cochrane risk of bias assessment. The I^2 for the various groups was 0%, indicating good homogeneity. The paper adheres very closely to the PRISMA reporting guidelines.⁴ The paper thus meets criteria for a high quality meta-analysis.⁵

Limitations

Baseline saturation. The overall SpO_2 was 96.4%–96.7% in the meta-analysis, meaning that the majority of these patients were already meeting their oxygen requirements without supplemental oxygen. Indeed, studies including patients with chronic respiratory disease were excluded, and many of the studies excluded patients with baseline hypoxia. Therefore, we assume that the conclusions of the present article only apply to patients who are not hypoxemic.

Population

Given that this meta-analysis excluded studies with patients who had chronic respiratory illnesses, were under 18 years of age and pregnant, these results may not apply to every patient in whom emergency physicians may consider oxygen therapy. In particular, patients with chronic respiratory illnesses are common in the emergency department (ED), and this study does not address whether or not they might require a more liberal use of oxygen. The meta-analysis only included data on admitted patients, and not patients in the ED, which further limits the generalizability of the current results to the ED.

Intervention

Although the authors did complete an analysis of the heterogeneity of the samples, finding an I^2 of 0%, various studies still had widely different oxygen targets in the liberal versus conservative arm. Indeed, the liberal arm in some studies was as low as an FiO_2 of 0.28, whereas the conservative arm in other studies was as high as 0.50. This may make the comparison between these studies difficult, and more information may be required to know what would be a useful or harmful FiO_2 .

Statistical versus clinical significance

Although the meta-analysis did reach statistical significance, the RR of the mortality at longest follow-up was 1.1 and the lower limits of the CIs for all outcomes were very close to 1 (1.00–1.03), which may mean these results are not strongly predictive of risk. In addition, the authors found an absolute risk reduction of 1.1% for in-hospital mortality and 1.2% for 30-day mortality, which represent a relatively large number-needed-to-harm (NNH) of 91 and 83, respectively. Given the small RR with CIs bordering 1 in a large sample size and a large NNH, this definitely raises the question as to whether this actually represents a clinically significant difference or only a statistically significant one.⁶

CONCLUSION

Rather than stating that liberal O_2 is harmful, perhaps a more reasonable conclusion to draw from these results is that there appears to be no benefit to supplemental oxygen in patients who have normal room air saturation.

These results cannot be generalized to patients with baseline hypoxia or respiratory disorders, nor patients in the ED specifically.

Competing interests: None declared.

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