Is the Liberal Use of Oxygen Associated With Worse Outcomes Among Critically Ill Patients?

TAKE-HOME MESSAGE

Compared with conservative oxygen therapy, liberal oxygen therapy is associated with increased mortality without improving other patient-relevant outcomes.

METHODS

DATA SOURCES

The authors searched the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, HealthSTAR, Latin American and Caribbean Health Sciences Literature, PapersFirst, and the World Health Organization International Clinical Trials Registry, without language restrictions, from inception to October 25, 2017, for studies comparing liberal versus conservative oxygen therapy in acutely ill adults. Database searches were supplemented by screening the reference lists of relevant studies and reviews. They also contacted study authors for unpublished data and in all instances with missing or unclear data.

STUDY SELECTION

Studies were included if they were randomized controlled trials comparing liberal and conservative oxygenation strategies in acutely ill adults (≥18 years) and assessed either mortality (inhospital, at 30 days, and at the longest follow-up) or morbidity (ie, disability measured by the modified Rankin Scale score at longest follow-up, risk of hospital-acquired pneumonia, risk of any hospital-acquired infection, and hospital length of stay). Patients were defined as acutely ill if they had any

EBEM Commentators
Michael Gottlieb, MD
Corey Goldstein, MD
Edward J. Ward, MD, MPH
Department of Emergency Medicine
Rush University Medical Center
Chicago, IL

Jestin N. Carlson, MD, MS, and Alan Jones, MD, serve as editors of the SRS series.

Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **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: 1693-1705.**

Results

Summary of findings comparing liberal oxygen therapy with conservative oxygen therapy.

Outcome	No. of Studies (No. of Participants)	Relative Risk (95% CI)	Heterogeneity, %
Inhospital mortality	19 (15,071)	1.21 (1.03–1.43)	0
30-day mortality	14 (15,053)	1.14 (1.01–1.28)	0
Mortality at longest follow-up	23 (15,754)	1.10 (1.00–1.20)	0

The search strategy identified 1,784 total records, of which 25 studies (16,037 patients) met the inclusion criteria. Studies included 3 trials of oxygen in critical illness, 1 trauma study, 2 sepsis studies, 7 stroke studies, 6 myocardial infarction studies, 2 cardiac arrest studies, and 4 emergency surgery studies. Twelve of 25 trials excluded patients with hypoxemia at baseline, whereas the remainder excluded only those with severe baseline hypoxemia (PaO_2 to FiO_2 ratio <100). Median follow-up duration was 3 months, with a range of 14 days to 12 months. The mean age of all subjects was 64 years and 64% were men. The oxygen delivery method was by nasal prongs in 4 trials, face mask in 13 trials, and invasive mechanical ventilation in 8 trials. Liberal oxygen supplementation constituted a median FiO_2 of 0.52 (range 0.28 to 1.00), which corresponds to approximately 6 L of oxygen flow by face mask. Conservative oxygen supplementation consisted of a median FiO_2 of 0.21 (range 0.21 to 0.50), which corresponds to that of room air.

condition requiring nonelective hospital admission and had the potential to be exposed to supplemental oxygen. The treatment group with the higher oxygen target was defined as the liberal arm, whereas the group with the lower oxygen target was defined as the conservative arm. Two reviewers independently screened titles for inclusion, with disagreements resolved by consensus.

DATA EXTRACTION AND SYNTHESIS

Two reviewers independently abstracted data, using a standardized data collection form, with disagreements resolved by consensus. For dichotomous outcomes, the authors calculated the relative risk with 95% confidence interval (CI). For continuous outcomes, the mean difference with 95% CI was calculated. For ordinal outcomes, odds ratio and 95% CI were calculated. Heterogeneity between studies was calculated with χ^2 and the I^2 statistic. Publication bias was determined with funnel plots and the Egger's test. Quality assessment was performed with the Cochrane Risk of Bias tool.

Compared with a conservative approach, liberal oxygen therapy was associated with a higher risk of mortality inhospital, at 30 days, and at longest follow-up (Table). There was no significant difference in morbidity or rates of hospital-acquired infections between the 2 groups. There were no significant differences in the subgroup analyses of ICU versus non-ICU, invasive versus noninvasive oxygen delivery, duration of oxygen exposure, or whether trials excluded patients with hypoxemia at baseline. Eighteen of the trials were considered to be at overall low risk of bias, whereas the remainder were considered to be at high risk of bias because of early termination as a result of interim analyses showing apparent benefit or harm (5 studies), quasi-randomization (1 study), or missing outcome data (1 study).

Commentary

Oxygen therapy was first described for the treatment of pneumonia in 1885.[1] Since then, oxygen has been increasingly administered to acutely ill patients, with studies finding that 34% of patients in ambulances, 23% of those in emergency departments, and 47% of those in cardiac care units received supplemental oxygen therapy.[2,3] In these settings, studies have found that 50% to 84% of patients were exposed to hyperoxemia because of excessive oxygen.[4-6] Although adequate oxygen therapy is essential for treating hypoxemia, excessive oxygen therapy can cause a number of problems, including inflammatory cytokine production, absorption atelectasis, acute lung injury, reduced cardiac output, cerebral and coronary vasoconstriction, and central nervous system toxicity.[7] Therefore, it is important to understand the potential risks and benefits of oxygen therapy for acutely ill patients.

This systematic review and meta-analysis found that liberal oxygen therapy was associated with an increased risk of mortality in the hospital, at 30-day follow-up, and at the longest follow-up. The authors noted that for every 1% increase in the pulse oximetry, there was a 25% increase in the relative risk of inhospital mortality and a 17% increase in the relative risk of mortality at longest follow-up. The mean number needed to harm resulting in one death with liberal oxygen therapy was 71. The authors also found that there was no difference in morbidity outcomes (eg, worsening disability after acute stroke, development of hospital-acquired infections). Although previous small studies have suggested that oxygen supplementation may improve outcomes in patients with acute stroke,[8] the current meta-analysis provides stronger evidence suggesting no significant benefit in this group.

It is important to consider several limitations with respect to this review. First, there was variability in the study settings and the definitions of liberal versus conservative oxygen therapy. Additionally, there was variation in the patient groups (eg, trauma, myocardial infarction, stroke) and it is unclear whether oxygen may be more harmful or beneficial in specific groups. There were also variations in the follow-up periods between studies, although the outcomes appeared similar regardless of the follow-up period. While benefit was found in all 3 mortality times, the 95% CI for the relative risk was close to 1.0. Consequently, it is possible that the actual benefit is small. Finally, 7 of the studies were at high risk of bias, with 5 having early termination of the study because of the results of the interim analysis.

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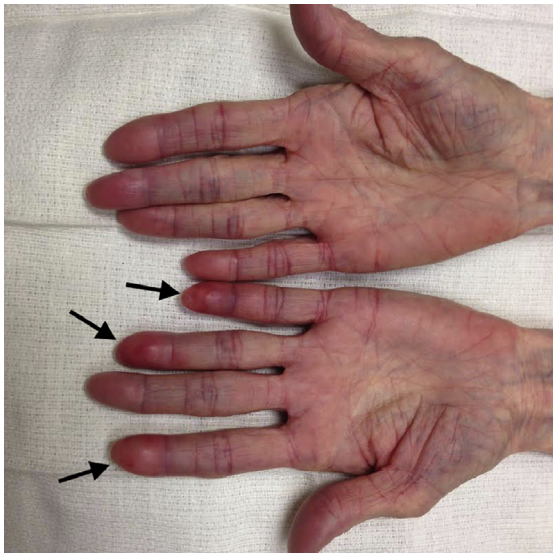

"Elderly Woman With Painful Swollen Fingers" by Bickel et al, March 2017, Volume 69, #3, pp. 297, 314.