Chronic Obstructive Pulmonary Diseases:
Journal of the COPD Foundation

Journal Club

Journal Club: COPD and Oxygen Therapy

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Citation: Balkissoon R. Journal club: Oxygen therapy. *Chronic Obstr Pulm Dis.* 2017;4(1):71-75. doi: https://doi.org/10.15326/jcopdf.4.1.2016.0181

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Keywords:

chronic obstructive pulmonary disease; COPD; oxygen therapy

Abstract 1
A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation

Long-Term Oxygen Treatment Trial Research Group. *N Engl J Med.* 2016. 375(17):1617-1627.
doi: https://doi.org/10.1056/NEJMoa1604344

BACKGROUND:
Long-term treatment with supplemental oxygen has unknown efficacy in patients with stable chronic obstructive pulmonary disease (COPD) and resting or exercise-induced moderate desaturation.

METHODS:
We originally designed the trial to test whether long-term treatment with supplemental oxygen would result in a longer time to death than no use of supplemental oxygen among patients who had stable COPD with moderate resting desaturation (oxyhemoglobin saturation as measured by pulse oximetry [Spo2], 89% to 93%). After 7 months and the randomization of 34 patients, the trial was redesigned to also include patients who had stable COPD with moderate exercise-induced desaturation (during the 6-minute walk test, Spo2 ≥80% for ≥5 minutes and <90% for ≥10 seconds) and to incorporate the time to the first hospitalization for any cause into the new composite primary outcome. Patients were randomly assigned, in a 1:1 ratio, to receive long-term supplemental oxygen (supplemental-oxygen group) or no long-term supplemental oxygen (no-supplemental-oxygen group). In the supplemental-oxygen group, patients with resting desaturation were prescribed 24-hour oxygen, and those with desaturation only during exercise were prescribed oxygen during exercise and sleep. The trial-group assignment was not masked.

RESULTS:
A total of 738 patients at 42 centers were followed for 1 to 6 years. In a time-to-event analysis, we found no significant difference between the supplemental-oxygen group and the no-supplemental-oxygen group in the time to death or first hospitalization (hazard ratio, 0.94; 95% confidence interval [CI], 0.79 to 1.12; P=0.52), nor in the rates of all hospitalizations (rate ratio, 1.01; 95% CI, 0.91 to 1.13), COPD exacerbations (rate ratio, 1.08; 95% CI, 0.98 to 1.19), and COPD-related hospitalizations (rate ratio, 0.99; 95% CI, 0.83 to 1.17). We found no consistent between-group differences in measures of quality of life, lung function, and the distance walked in 6 minutes.

CONCLUSIONS:
In patients with stable COPD and resting or exercise-induced moderate desaturation, the prescription of long-term supplemental oxygen did not result in a longer time to death or first hospitalization than no long-term supplemental oxygen, nor did it provide sustained benefit with regard to any of the other measured outcomes. (Funded by the National Heart, Lung, and Blood Institute and the Centers for Medicare and Medicaid Services; LOTT ClinicalTrials.

gov number, NCT00692198).
PMID: 27783918

Comments

Most are familiar with the studies from the early 1980's such as the Nocturnal Oxygen Therapy Trial[1] and the Medical Research Council study of supplemental oxygen in patients with chronic hypoxic cor pulmonale.[2] These studies demonstrated reduced mortality with use of continuous oxygen. Since that time more patients are diagnosed earlier and even patients with moderate levels of hypoxemia have been prescribed supplemental oxygen. The first indication that this sub-group may indeed be different from those with more severe disease was that they had to change the study protocol to include time to first hospitalization in part because there was a lower than projected mortality in this group. This is an important study because many of these patients with moderate disease have been prescribed supplemental oxygen despite their protests to not want it. There were 51 adverse events including 23 reports of tripping over equipment, and 2 patients required hospitalization. Five patients reported a total of 6 instances of fires or burns, with one of these patients hospitalized. Further, the costs of supplemental oxygen are not insignificant.

This study, appropriately, does not attempt to define stricter criteria as to what should be the appropriate cutoffs for qualifying for supplemental oxygen. There are patients that fit into this moderate group who will claim that they have fewer symptoms or sleep better with supplemental oxygen. Should they not be prescribed supplemental oxygen? This study does not stratify for patients with significant comorbidities such as coronary artery disease and obstructive sleep apnea. They did not measure nocturnal desaturation, nor did they assess the immediate effects of oxygen on exercise performance or symptoms. Further, as the authors noted, patients who met study criteria but felt they benefited from supplemental oxygen may have been reluctant to enter a trial where they may be randomized to the non-oxygen group. While the primary outcomes were not likely to be affected, it is possible that the lack of masking in the study could have influenced patient-reported outcomes. This study is instructive for the clinical scenario of the patient who fits these moderate criteria but is reluctant to be put on supplemental oxygen. We do not need to feel compelled to convince them to go on it. This study does not rule out potential benefits for patients with certain comorbidities or that report symptomatic improvement. For now, clinicians will have discretion to individualize care. It will be interesting to see how the various guidelines incorporate the findings of this study into their recommendations with regard to supplemental oxygen therapy.

Abstract 2
Oxygen for Breathlessness in Patients With Chronic Obstructive Pulmonary Disease Who Do Not Qualify for Home Oxygen Therapy

Ekström M, Ahmadi Z, Bornefalk-Hermansson A, Abernethy A, Currow D. *Cochrane Database Syst Rev*. 2016;11:CD006429.

BACKGROUND:
Breathlessness is a cardinal symptom of chronic obstructive pulmonary disease (COPD). Long-term oxygen therapy (LTOT) is given to improve survival time in people with COPD and severe chronic hypoxaemia at rest. The efficacy of oxygen therapy for breathlessness and health-related quality of life (HRQOL) in people with COPD and mild or no hypoxaemia who do not meet the criteria for LTOT has not been established.

OBJECTIVES:
To determine the efficacy of oxygen versus air in mildly hypoxaemic or non-hypoxaemic patients with COPD in terms of (1) breathlessness; (2) HRQOL; (3) patient preference whether to continue therapy; and (4) oxygen-related adverse events.

SEARCH METHODS:
We searched the Cochrane Airways Group Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and Embase, to 12 July 2016, for randomised controlled trials (RCTs). We hand searched the reference lists of included articles.

SELECTION CRITERIA:
We included RCTs of the effects of non-invasive oxygen versus air on breathlessness, HRQOL or patient preference to continue therapy among people with COPD and mild or no hypoxaemia (partial pressure

of oxygen (PaO2) > 7.3 kPa) who were not already receiving LTOT. Two review authors independently assessed articles for inclusion in the review.

DATA COLLECTION AND ANALYSIS:
Two review authors independently collected and analysed data. We assessed risk of bias by using the Cochrane 'Risk of bias tool'. We pooled effects recorded on different scales as standardised mean differences (SMDs) with 95% confidence intervals (CIs) using random-effects models. Lower SMDs indicated decreased breathlessness and reduced HRQOL. We performed subanalyses and sensitivity analyses and assessed the quality of evidence according to the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach.

MAIN RESULTS:
Compared with the previous review, which was published in 2011, we included 14 additional studies (493 participants), excluded one study and included data for meta-analysis of HRQOL. In total, we included in this review 44 studies including 1195 participants, and we included 33 of these (901 participants) in the meta-analysis. We found that breathlessness during exercise or daily activities was reduced by oxygen compared with air (32 studies; 865 participants; SMD -0.34, 95% CI -0.48 to -0.21; I2 = 37%; low-quality evidence). This translates to a decrease in breathlessness of about 0.7 points on a 0 to 10 numerical rating scale. In contrast, we found no effect of short-burst oxygen given before exercise (four studies; 90 participants; SMD 0.01, 95% CI -0.26 to 0.28; I2 = 0%; low-quality evidence). Oxygen reduced breathlessness measured during exercise tests (25 studies; 442 participants; SMD -0.34, 95% CI -0.46 to -0.22; I2 = 29%; moderate-quality evidence), whereas evidence of an effect on breathlessness measured in daily life was limited (two studies; 274 participants; SMD -0.13, 95% CI, -0.37 to 0.11; I2 = 0%; low-quality evidence).Oxygen did not clearly affect HRQOL (five studies; 267 participants; SMD 0.10, 95% CI -0.06 to 0.26; I2 = 0%; low-quality evidence). Patient preference and adverse events could not be analysed owing to insufficient data.

AUTHORS' CONCLUSIONS:
We are moderately confident that oxygen can relieve breathlessness when given during exercise to mildly hypoxaemic and non-hypoxaemic people with chronic obstructive pulmonary disease who would not otherwise qualify for home oxygen therapy. Most evidence pertains to acute effects during exercise tests, and no evidence indicates that oxygen decreases breathlessness in the daily life setting. Findings show that oxygen does not affect health-related quality of life.

Comments

This study lends credence to the contention that setting oxygen qualification criteria based on level of desaturation alone is unlikely to be sufficient. This needs to be put into the overall context of benefits to patients remaining active and participating in daily exercise as opposed to the benefits of the supplemental oxygen therapy itself.

Abstract 3
Long-Term Oxygen Therapy 24 vs 15h/day and Mortality in Chronic Obstructive Pulmonary Disease

Ahmadi Z, Sundh J, Bornefalk-Hermansson A, Ekström M. *PLoS One*. 2016;11(9):e0163293. doi: https://doi.org/10.1371/journal.pone.0163293

Long-term oxygen therapy (LTOT) ≥ 15 h/day improves survival in hypoxemic chronic obstructive pulmonary disease (COPD). LTOT 24 h/day is often recommended but may pose an unnecessary burden with no clear survival benefit compared with LTOT 15 h/day. The aim was to test the hypothesis that LTOT 24 h/day decreases all-cause, respiratory, and cardiovascular mortality compared to LTOT 15 h/day in hypoxemic COPD. This was a prospective, observational, population-based study of COPD patients starting LTOT between October 1, 2005 and June 30, 2009 in Sweden. Overall and cause-specific mortality was analyzed using Cox and Fine-Gray regression, controlling for age, sex, prescribed oxygen dose, PaO2 (air), PaCO2 (air), Forced Expiratory Volume in one second (FEV1), WHO performance status, body mass index, comorbidity, and oral glucocorticoids. A total of 2,249 included patients were included with a median follow-up of 1.1 years

(interquartile range, 0.6-2.1). 1,129 (50%) patients died and no patient was lost to follow-up. Higher LTOT duration analyzed as a continuous variable was not associated with any change in mortality rate (hazard ratio [HR] 1.00; (95% confidence interval [CI], 0.98 to 1.02) per 1 h/day increase above 15 h/day. LTOT exactly 24 h/day was prescribed in 539 (24%) patients and LTOT 15-16 h/day in 1,231 (55%) patients. Mortality was similar between the groups for all-cause, respiratory and cardiovascular mortality. In hypoxemic COPD, LTOT 24 h/day was not associated with a survival benefit compared with treatment 15-16 h/day. A design for a registry-based randomized trial (R-RCT) is proposed.

Comments

In terms of cost and patient adherence this question is an important clinical question and it is encouraging that they have plans to perform a proper randomized trial to address this issue.

References

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