Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

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Long-term oxygen in COPD: Time to revisit?

A randomised study in the USA has found that providing long-term oxygen treatment to patients with stable chronic obstructive pulmonary disease (COPD) and moderate desaturation, either at rest or during exercise, does not extend the time to death or first admission, or improve lung function or exercise capacity. Nor did it provide sustained benefit with regard to any of the other measured outcomes. Taken together with previous evidence, this suggests that long-term oxygen should only be prescribed with the intent to prolong survival in patients with COPD who have chronic severe resting hypoxaemia. The results of the study may result in some alterations to current UK guidelines on oxygen use in COPD.

Reference: The Long-Term Oxygen Treatment Trial (LOTT) Research Group. A Randomized Trial of Long-Term Oxygen for COPD with Moderate Desaturation. N Engl J Med 2016; 375:1617-1627.

What do we know already?

- Evidence for long-term oxygen therapy in people with COPD and hypoxaemia is mainly limited to two trials, which recruited patients in the 1970s. The total number of patients in these two trials was 290.
- The Nocturnal Oxygen Therapy Trial was a randomised trial involving 203 patients in the USA. These patients had either severe hypoxaemia, or moderate hypoxaemia and either signs of right heart failure or raised haematocrit. It compared 12 hours of nocturnal oxygen with 24 hours of continuous oxygen. At 12 months there was a reduction in mortality in the 24-hour oxygen group.
- The other study was a Medical Research Council study involving 87 patients in the UK. These patients had chronic bronchitis and emphysema (now called COPD) who had severe hypoxaemia and some also had CO_2 retention (hypercapnia). Patients were randomised to 15 hours per day of oxygen therapy (with a flow rate of enough to give a measured increase in oxygen saturation) or to no therapy. Over 5 years of follow up there was a significant reduction in mortality in those on long-term oxygen compared to no oxygen.
- These two studies have largely driven the policy and criteria for provision of long-term oxygen in patients with COPD in the UK since that time. However, there have been concerns about the size of these studies, their quality and how they relate to the types of patients we now see with COPD in the UK. There are some subsequent small studies that did not show benefit from long-term oxygen therapy in those with lesser degrees of hypoxaemia. However, they were probably underpowered to detect any difference in mortality.
- The National Institute for Health and Care Excellence (NICE) advise that long-term therapy with supplemental oxygen for at least 15 hours a day should be used:
  - in patients who have a PaO_2 less than 7.3 kPa when stable
  - *or* those with a PaO_2 greater than 7.3 and less than 8 kPa when stable and one of: secondary polycythaemia; nocturnal hypoxaemia (oxygen saturation of arterial blood [SaO_2] less than 90% for more than 30% of the time); peripheral oedema; or, pulmonary hypertension.
- They advise that greater benefits are seen in patients receiving oxygen for 20 hours per day.
- There are harms associated with oxygen therapy; for example, it can cause respiratory depression, and it can be a burden for some people. The British Thoracic Society advise that people on oxygen therapy should not smoke because of risk of fire or explosion. They suggest a risk assessment should be undertaken in those who remain active smokers.

What does this evidence add?

- The LOTT study is the first study to examine the effects of long-term oxygen in people with COPD for several decades. A weakness was lack of blinding but it is likely this would cause greater beneficial effects in those on active treatment. The validity of the study is supported by the consistent lack of effects across all outcomes.
- Most of the people included in the LOTT study had lesser degrees of hypoxaemia due to COPD than the main trials from the 1970s. It provides strong evidence that oxygen does not benefit people with moderate degrees of hypoxaemia.
- Further research is needed to re-examine the effects of long-term oxygen in people with more severe hypoxaemia, in particular with regard to its effect on quality of life given that long-term oxygen therapy can be a chore for some.
- NICE are currently updating guidance on COPD (*expected publication date is November 2018*). In the meantime, clinicians should still adhere to the recommendations on oxygen use in the 2010 NICE guideline on COPD. The temptation to use oxygen for lesser degrees of hypoxaemia should be resisted. For example, the British Thoracic Society report that 24-hour 'hypoxaemia burden' is used to guide prescribing of home oxygen in some centres and have advised against it. NICE also gives guidance on appropriate use in their 'Do Not Do' recommendations.
- Perhaps the most important thing is to enable eligible patients or their carers to make an informed choice on whether to use long-term oxygen. This new evidence can assist this process.

Study details

Participants:

- A total of 738 patients at 42 centres in the USA were followed for 1 to 6 years.
- The average age of patients was 68-69 years. 73.5% were male. 32% had cardiovascular disease.
- Between 25-30% were smokers at study entry. All subjects signed a 'contract' not to smoke.

Intervention and comparison:

- Patients were randomly assigned, in a 1:1 ratio, to receive long-term supplemental oxygen or no long-term supplemental oxygen. Most received 2 litres/minute of oxygen.
- The trial group assignment was not masked/blinded.
- The trial was originally designed to examine the use of supplemental oxygen among patients who had stable COPD with moderate resting desaturation (haemoglobin oxygen saturation as measured by pulse oximetry [SaO_2], 89-to-93%). Due to slow recruitment, after 7 months and the randomization of 34 patients, the trial was redesigned:
  - It included patients who had stable COPD with moderate exercise-induced desaturation (during the 6-minute walk test, $SaO_2 \geq 80\%$ for ≥ 5 minutes and $< 90\%$ for ≥ 10 seconds).
  - In the supplemental oxygen group, 220 patients with resting desaturation were prescribed 24-hour oxygen.
  - 148 patients with desaturation only during exercise were prescribed oxygen during exercise and sleep.

Outcomes and results:

- The average hours of oxygen use in those assigned to 24 hours of oxygen was 15.1 ± 6.2 hours per day, and 11.3 ± 5.0 hours per day in the sleep exercise group.
- The initial outcome was time to death. On trial redesign at 7 months, it also incorporated the time to the first hospitalisation for any cause (a composite primary outcome).
- The median time of follow-up was 18 months. There was no significant difference between:
  - the supplemental oxygen group and the no-supplemental oxygen group in the time to death or first hospitalisation (hazard ratio 0.94; 95% confidence interval [CI], 0.79 to 1.12; p = 0.52). The event rate for this composite outcome was 34.2 per 100 patient-years *vs.* 36.4 per 100 patient-years in the respective groups.
  - the rates of all hospitalisations (rate ratio 1.01; 95% CI, 0.91 to 1.13; p = 0.81)
  - rates of COPD exacerbations (rate ratio 1.08; 95% CI, 0.98 to 1.19; p = 0.12)
  - rates of COPD-related hospitalisations (rate ratio 0.99; 95% CI, 0.83 to 1.17; p = 0.86)
- There was also no consistent between-group differences in measures of quality of life, lung function, and the distance walked in 6 minutes.
- There were 51 adverse events associated with oxygen therapy, primarily in the form of patients tripping over medical equipment, which occurred in 23 patients. 5 patients reported fires or burns (one required hospitalisation).

Level of evidence: Level 1 (good quality patient-oriented evidence) according to the SORT criteria.

Study funding: Funded by the National Heart, Lung and Blood Institute and the Centers for Medicare and Medicaid Services. These are not 'commercial' companies.