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EDITORIAL

Evidence-based oxygen therapy: Missed and future opportunities

Oxigenoterapia baseada na evidência: Oportunidades perdidas e futuras

Two landmark trials conducted more than 30 years ago provided scientific evidence that, under very specific circumstances, long-term oxygen therapy (LTOT) may prolong life.[1,2] These two trials targeted patients with chronic obstructive pulmonary disease (COPD) and severe daytime hypoxemia documented by direct arterial blood gas measurement.

Although the survival benefits of LTOT in COPD are real, home oxygen is not a panacea. In the British Medical Research Council's trial, 500 days elapsed before any effect of LTOT on survival appeared, when compared to no oxygen therapy at all.[1] Overall, at 5-year follow-up, those who received oxygen had improved survival: 19 of 42 (42%) had died, compared to 30 of the 45 control patients (66%). The difference (24%) corresponds to a number needed to treat (NNT) of 5, which means that 5 patients must receive oxygen during 5 years in order to prevent one death over the same period. Similarly, the American Nocturnal Oxygen Therapy trial randomly assigned patients to receive oxygen for either 12 h a day (nocturnal group) or 24 h a day (continuous group).[2] The latter group actually received oxygen for an average of 19 h a day. All received oxygen therapy during sleep. At 24 months, the overall mortality in the continuous group was 22.4%, whereas it was 40.8% in the nocturnal group (absolute difference: 18.4%; $p = 0.01$). The corresponding NNT was therefore 6.

The good news from both trials was that ''oxygen saves lives''. From this moment, oxygen therapy became a standard of care, and confirmatory trials would be considered by many as unethical. Unfortunately, beyond survival, the effects of LTOT on quality of life remain largely unexplored in randomized controlled trials. Both the British and the American trials were conducted before the era of quality-of-life questionnaires. Although suggestion from uncontrolled studies has been made that oxygen therapy improves quality of life,[3] clinical experience rather suggests that LTOT may limit the patients' ability to remain active and may be detrimental to the rehabilitation process.

Thereafter, oxygen therapy gained widespread acceptance by official organizations for treatment of most chronic cardio-respiratory conditions complicated by severe hypoxemia, even if proof of efficacy is lacking. These conditions now largely go beyond COPD and include, among others, cystic fibrosis,[4] interstitial lung diseases,[5] and pulmonary arterial hypertension.[6] In only rare exceptions (such as obesity hypoventilation[7] and chronic heart failure[8]), the indication of oxygen in patients with severe hypoxemia is questioned. Also, new indications of oxygen therapy in COPD (such as nocturnal oxygen therapy in patients with isolated nocturnal oxygen desaturation, or ambulatory oxygen to correct exercise-induced desaturation) have emerged. To these extended indications of home oxygen, one must add that, even in COPD, inappropriate prescriptions of home oxygen therapy are not unusual.[9] Oxygen is everywhere.

Home oxygen therapy is very expensive. For instance, in the Canadian cohort of the Confronting COPD Survey (3265 individuals; mean age: 63 years; 44% female), oxygen therapy accounted for 17% of the entire annual direct costs of COPD care.[10] Also, home oxygen therapy imposes sacrifices on patients and their families. It is therefore surprising that it is so readily accepted by patients, health care professionals and payers, despite the lack of evidence to support its use in most circumstances. Why is that so? In addition to being safe and readily available, the problem with oxygen is that its prescription always makes sense: if oxygen desaturation exists, its correction should help.

This reasoning was common before the introduction of ''evidence-based medicine'', when the study and understanding of basic mechanisms of disease and pathophysiologic principles were considered sufficient to guide clinical practice.[11] A famous example proved the contrary. Since ventricular arrhythmias are an important cause of death following acute myocardial infarction, their suppression was expected to decrease mortality. The Cardiac Arrhythmia Suppression trial (CAST) was stopped early after patients allocated to receive potent anti-arrhythmic drugs were found to have an increased mortality rate when compared to those receiving placebo.[12] Similar examples, although less dramatic, exist in the field of oxygen therapy. For instance, although oxygen corrects oxygen desaturation

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and improves walked distance in patients with COPD and exercise-induced desaturation in laboratory testing,[13] other trials have failed to demonstrate any long-term benefit.[14–17]

Before the introduction of ''evidence-based medicine'', another assumption guiding clinical practice was that unsystematic observations from clinical experience were a valid way of building and maintaining knowledge about the efficacy of treatment.[11] Clinicians' memory is often selective. The observations they recall are often anecdotal and limited to their best or worst experiences. In the case of oxygen therapy, bad experiences seldom occur. The consequence is that prescriptions of home oxygen therapy are well anchored into clinical practice and almost never challenged.

Twenty years ago, a shift of paradigm operated. Evidence-based medicine was put forward.[18] Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.[19] The assumptions of the new paradigm were then described as follows: (1) the study and understanding of mechanisms of disease are necessary but insufficient guides for clinical practice; (2) systematic observations increase the confidence clinicians can have in knowledge about efficacy of treatments; (3) understanding certain rules of evidence is necessary to correctly interpret the medical literature.[11]

This new paradigm guided us in the development and implementation of the International Nocturnal Oxygen (INOX) trial, a multi-centre, randomized, placebo-controlled trial of nocturnal oxygen therapy in COPD (ClinicalTrtials.gov id: NCT01044628). Prior observations suggested that nocturnal oxygen desaturation may accelerate the natural progression of COPD toward its end stages of severe hypoxemia, right heart failure, and death.[20,21] Until recently, it was often recommended in Canada (and elsewhere around the world) that nocturnal oxygen be considered if desaturation occurs for protracted periods. However, current evidence from two small randomized controlled trials[22,23] and their meta-analysis[24] does not support this recommendation. The cost-effectiveness of nocturnal oxygen is unknown. The INOX trial, in which 4 clinical sites in Portugal (Matosinhos, Vila Nova de Gaia, Coimbra and Lisboa) participate, is intended to address this important clinical question.

Of note, even when data from randomized trials exist, its translation into clinical practice may be problematic. This is seen especially in the case of negative trials. Our experience with a randomized trial of ambulatory oxygen in oxygen-dependent patients with COPD illustrates this situation.[25] In a one-year, randomized, three-period, crossover trial, we allocated 24 patients to one of the 6 possible sequences generated by 3 interventions: (1) standard therapy (home oxygen therapy with an oxygen concentrator only); (2) standard therapy plus as-needed ambulatory oxygen; (3) standard therapy plus ambulatory compressed air. The comparison of ambulatory oxygen vs. ambulatory compressed air was double blind. The main outcomes were quality of life, exercise tolerance and daily duration of exposure to oxygen. The trial was stopped prematurely after a planned interim analysis. On average, the patients used few ambulatory cylinders and ambulatory oxygen had no effect at all on any of the outcomes. Our results did not support the widespread provision of ambulatory oxygen to patients with oxygen-dependent COPD.

The results of our trial challenged the recommendation that active patients receiving LTOT should have both stationary and mobile systems of oxygen delivery.[26,27] The sample size of our trial was small. However, for both quality of life and exercise capacity, the 95% confidence intervals around the mean treatment effect included zero (i.e., no effect) and excluded what is usually considered as the minimal clinically important difference, a clear demonstration that the negative results were not from a lack of power to detect a clinically significant difference. We rather interpreted the negative results as a real indication of no benefit from ambulatory oxygen under the circumstances of the study. Our results were recently confirmed by a related trial.[28] However, we are still facing clinicians' reluctance, even in our own institution, to limit the prescriptions of ambulatory oxygen in oxygen-dependent COPD patients.

Home oxygen therapy still offers a multitude of research opportunities in COPD.[29] The INOX trial is only one of them. The effects of home oxygen therapy in most cardiopulmonary conditions (including interstitial lung diseases, cystic fibrosis, pulmonary arterial hypertension and chronic heart failure) remain unexplored. Randomized trials represent the most powerful method to address these important clinical questions. Cost-effectiveness analyses are also needed. Suggestion has been made that multicenter clinical research networks should be established to perform such clinical trials.[30] Such efforts are challenging as they require time, money and commitment from all investigators to bring the clinical trials to their ends. However, this investment is certainly worth it for the patients and those who will have to financially support LTOT.

Conflicts of interest

The authors have no conflicts of interest to declare.

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