Editorial

Long term oxygen therapy—it is still relevant?

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Long term oxygen therapy (LTOT) at home is almost the standard of care for domiciliary management of chronic obstructive pulmonary disease (COPD) with severe hypoxemia. LTOT is widely practiced all over the world for several other chronic conditions, with or without hypoxemia. It is not only a costly mode of therapy, but also poses several logistic and psychosocial issues for the patient as well as the care-givers. "Whether the LTOT prescription is medically useful and indicated" is the core question which every physician needs to answer before prescribing this treatment.

Survival benefit of LTOT in COPD was first shown in the two landmark studies which were published in the early 1980 and laid the foundation for long-term domiciliary management of hypoxemia (1,2). The survival benefit was not replicated in some of the later trials which appeared afterwards, even through a number of other studies continued to report benefits in breathlessness and/or other clinical symptoms (3-5).

The first two trials included patients with oxy haemoglobin saturation of less than 89% when measured by pulse oximetry (1,2). Of the two trials, the Nocturnal Oxygen Therapy Trial (NOTT) included 203 out of 1,043 COPD patients who were screened from six centres in the United States. The study-patients were randomly allocated either to nocturnal oxygen therapy (NOT) group who were administered with daily nocturnal oxygen for 13 hours or less, or to continuous oxygen therapy (COT) group who were administered oxygen for 19 hours or more every day (1). The overall mortality in the NOT group was 1.94 times that of the COT group (1). The other study, Medical Research Council (MRC) oxygen therapy trial included 87 patients with right heart failure and chronic cor-pulmonale with PaO2 of 40–60 mmHg (2). The study group received oxygen for at least 15 hours a day while no oxygen was given to the control group; there was improvement in survival in the oxygen-therapy group after 500 days of treatment (2). It was therefore concluded from these studies that continuous oxygen improved survival but "some oxygen was better than no oxygen". Both of these two studies however were un-blinded in design.

The issue of LTOT for patients of COPD with moderate hypoxemia, those with hypoxemia only during sleep and in those with only exercise-induced hypoxemia has remained controversial. Some of the earlier studies, including a Cochrane database systemic review did not show any survival benefit with LTOT in COPD patients with resting SpO_2 of over 88 percent (6,7). A recently published, randomized trial by the Long Term Oxygen Treatment Trial (LOTT) Research Group seems to have settled the controversy—at least for the present (8).

The LOTT study was initially aimed to study the time-to-death as the primary outcome in COPD patients with moderate desaturation (SpO_2 between 89% to 93%) at rest. But the mortality observed over a 7-month period was lower than what was projected. The trial was therefore redesigned to include patients with exercise induced desaturation as well as to expand the primary outcome to include the secondary outcome of hospitalization (8). After a follow up period of 1 to 6 years, the LOTT concluded that LTOT

did not result in any survival benefit. Factually, the study did not show if LTOT provided any benefit in terms of time-to-death or first hospitalization or any other outcome parameters in patients with stable COPD with resting or exercise induced moderate desaturation (8).

With 738 patients from 42 centres, the LOTT is the largest study to date on domiciliary oxygen for COPD patients. It is quite robust in design as well as in analysis even though a few changes were considered necessary in the recruitment and outcome parameters. These changes however are unlikely to have affected the study outcome.

On the other hand, there are a few limitations of the study some of which have been pointed out by the investigators themselves. LOTT, like the initial two studies was un-blinded in design which may have introduced bias in results. As on example, patients not receiving LTOT may have tended to either overplay or underplay their symptomatic responses. Moreover, patients with greater clinical symptom might have refused to enrol themselves in the trial for the fear of possible inclusion in the no-oxygen group.

Blinding is essential to answer long debated and controversial issues. But blinding for such a study would have involved sham therapy to the no-oxygen group. This will be generally unacceptable to the hospital boards in the current scenario in most of the countries. A few other limitations have been also listed by the investigators which I believe, do not seem to have played a major role in the study conclusion.

It seems a bit premature for pulmonologists to abandon the current practice of prescribing domiciliary, long term oxygen to patients with exercise induced desaturation or persistent moderate desaturation as has been also advocated in accompanying editorial in the same issue of the journal (9). The editorial stresses upon the need for a fair trial with LTOT in such a group of patients. It seems important to corroborate the results from another large study to make final conclusions. Recently, the authors of a Cochrane database systemic review on oxygen for breathlessness have also concluded that oxygen could relieve breathlessness during exercise in such COPD patients with mild or moderate hypoxemia, who do not otherwise qualify for home oxygen therapy (10).

It is also likely that some of the subjective benefits of oxygen to reduce breathlessness in clinical practice are only palliative benefits in nature induced by placebo administration. For example, the care-givers of patients with terminal or life limiting illnesses find LTOT as often beneficial for refractory breathlessness even in the absence of demonstrable hypoxemia (11). There is no good evidence to support this practice.

In another unrelated study from Sweden, LTOT benefits were compared in a prospective, observational, population based study amongst COPD patients with hypoxemia with a median follow-up period of 1.1 years (12). In one group of 539 patients, oxygen was given for 24 hours per day while the other group of 1,231 patients received oxygen for 15–16 hours per day. The all-cause, respiratory and cardiovascular mortality were found to be similar in the two groups supporting the hypothesis that 15 hours/day oxygen was as good as 24 hours/day continuous oxygen (12). This report in COPD patients with hypoxia seems to further challenges the earlier observations that continuous oxygen was best in patients with hypoxemia in reducing mortality.

It is possible that the benefits of LTOT in COPD and/or other conditions shown in the earlier studies were over estimated or attributed to inclusion and assessment biases? Alternatively, are we now biased against the domiciliary, long-term use of oxygen with an overall focus on attempts to reduce the health-care costs? Both these fears seem merely presumptive. What is more likely is the possibility that there was an over enthusiastic response of clinician to use supplemental oxygen for diverse medical condition with or without hypoxemia. As a result, there was a significant dilution of clinical criteria for inclusion of patients for treatment indications. As an example, the practice of unregulated use of domiciliary oxygen in India as well as in many other countries has been popular (11,13).

It is important to keep in mind that long term domiciliary oxygen is a significant additional burden on health-care infrastructure. For the patients and the care givers, it is not only an expensive treatment but also a psychological and social burden. The patient, who gets tied to machines, feels depressed and socially constrained. Prolonged oxygen therapy is also associated with physical risks as well as physiological and structural damage to the lungs.

In the light of the newly emerging evidence through different reports, the entire issue of LTOT needs a close relook to define indications based on stringent scientific criteria than its use as a placebo (or a ritual) for terminal condition. It is extremely important to revise the earlier concepts about use of chronic domiciliary oxygen. Physicians need to change their prescription habits as per new standards. There is also need to create fresh evidence through controlled clinical and laboratory studies.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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