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Original Article

Internal Medicine Section

Effect of Long-term Oxygen Therapy in Chronic Obstructive Pulmonary Disease: A Prospective Clinical Study

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ABSTRACT

Introduction: Long-Term Oxygen Therapy (LTOT) has the potential to improve the mortality and morbidity in Chronic Obstructive Pulmonary Disease (COPD) patients.

Aim: To assess the effect of LTOT on the Quality of Life (QoL) in stable COPD patients with severe resting hypoxemia.

Materials and Methods: This was a prospective observational study conducted in a tertiary care teaching hospital in Kozhikode, Kerala, India on stable COPD patients with severe hypoxemia who were newly initiated on home LTOT for ≥15 hours per day. Health Related Quality of Life (HRQoL), modified Medical Research Council (mMRC) grade of dyspnoea, frequency of exacerbations and adherence to treatment on LTOT were studied. Total of 60 patients were followed-up for one year. Significance of mean was tested using paired t-test and association between qualitative variables was tested using Chi-square test. The p-value <0.05 was considered statistically significant.

Results: Out of all, 7 patients died during the study period and 53 patients were included in the final analysis. The mean total St.George's Respiratory Questionnaire (SGRQ) scores at 3, 6 and 12 months improved to 53.73±13.2, 53.97±13.22 and 54.63±13.16, respectively, from a baseline score of 72.51±8.88. At the end of 12 months of LTOT, 22 (41.51%) patients did not have exacerbations and 31 (58.49%) patients had exacerbations. There was no statistically significant improvement in dyspnoea after one year of LTOT. Among the 53 patients, who completed one year follow-up, 36 (67.92%) participants were adherent and remaining 17 (32.07%) participants were non adherent to LTOT.

Conclusion: The LTOT improves the HRQoL in stable COPD patients with severe hypoxemia. Use of domiciliary oxygen for atleast 15 hours per day can reduce the number of COPD exacerbations.

Keywords: Adherence, Exacerbation, Quality of life

INTRODUCTION

Long-Term Oxygen Therapy (LTOT), defined as oxygen use for atleast 15 hours per day in chronically hypoxemic patients, is the cornerstone of treatment in stable COPD patients with severe resting hypoxemia. Severe hypoxemia is defined as meeting either of the following criteria: 1) PaO_2≤55 mmHg or oxygen saturation as measured by pulse oximetry (SpO_2)≤88%, with or without hypercapnia; or 2) PaO_2=56-59 mmHg or SpO_2=89% along with one of the following- peripheral oedema, polycythemia (haematocrit≥55%), or P pulmonale [1]. LTOT use in hypercapnic respiratory patients with COPD does not lead to increased morbidity or mortality. Assessment of need for LTOT has to be done when the patient is clinically stable and free from exacerbations, i.e., clinical and arterial blood gas assessments are to be done on two occasions, atleast three weeks apart [2].

The beneficial effects of LTOT in COPD are manifold. In addition to a clear survival benefit, LTOT improves exercise capacity, pulmonary haemodynamics and secondary polycythemia. It has the potential to improve neuropsychological function and sleep quality [3-5]. The two landmark studies on LTOT, Nocturnal Oxygen Therapy Trial (NOTT) and British Medical Research Council (BMRC) trial have demonstrated a clear survival benefit in severely hypoxemic COPD patients on LTOT [6,7]. The NOTT also concluded that those patients with severely impaired QoL and brain dysfunction were most likely to benefit from oxygen therapy.

There are only a few longitudinal studies that have studied the impact of LTOT on the HRQoL in COPD patients with severe hypoxemia, possibly due to the ethical issues in obtaining a placebo control group as well as the logistic difficulties of long-term studies [8,9]. Limited studies have been done in the Indian setting to assess the effect of LTOT in COPD patients with chronic respiratory failure. A retrospective study by Karthikeyan G et al., assessed the reduction in pulmonary artery systolic pressure with LTOT in 41 patients who had pulmonary hypertension due to chronic lung disease and found that response was better with post tuberculosis obstructive airway disease and interstitial lung diseases than with COPD. However, QoL assessment was not done in that particular study [10].

The present study was carried out to assess the effect of long-term domiciliary oxygen therapy on the QoL, grade of dyspnoea and frequency of exacerbations in stable COPD patients with severe resting hypoxemia. Adherence to LTOT and factors responsible for poor adherence were also studied.

MATERIALS AND METHODS

This was a prospective observational clinical study conducted in a tertiary care teaching hospital in Kozhikode, Kerala, India from January 2019 to September 2020. Institutional Ethics Committee clearance was obtained from hospital (GMCKKD/RP2019/IEC65) and written informed consent from all patients.

Inclusion criteria: Stable COPD patients who were on standard medical management and newly initiated on home LTOT ≥15 hours/day, for severe resting hypoxemia as per the standard criteria were included in the study [1].

Exclusion criteria: Patients on intermittent home oxygen therapy only for exertional desaturation, nocturnal only oxygen therapy, concomitant use of home non invasive ventilator for hypercapnic respiratory failure at screening visit, recent COPD exacerbation within four weeks, current smokers, patients with significant lung diseases other than COPD, active tuberculosis, malignancy and unstable cardiovascular disease were excluded from the study.

Sample size calculation: Sample size was calculated as 48, based on a previous study by Eaton T et al., that assessed the improvement in QoL in patients on LTOT [8]. Sample size 'n' was calculated based on the formula:

$$n=(z_{\alpha}+z_{\beta})^2SD^2/d^2$$

where SD=standard deviation=7.3, Z_{α} is 1.96 for an alpha error of 5%, Z_{β} is 0.84 for a beta error of 20% and d is the effect size, taken as 3.

Study Procedure

At enrollment, detailed history was taken and frequency of exacerbations was recorded from patient history and medical records. All patients were prescribed atleast 15 hours of home oxygen therapy using electrically driven oxygen concentrators. Baseline assessment included mMRC dyspnoea score, arterial blood gas PaO_2 and $PaCO_2$ and six-minute walk test. QoL assessment was done using SGRQ [11]. This questionnaire has three subscales or domains, one each for symptoms, activity, and the impact of disease on daily life. SGRQ scores range from 0-100, with higher scores indicating more limitation. The total SGRQ score as well as scores for each domain was calculated.

Patients who were offered LTOT were educated regarding its use and safety measures to be taken. Strict avoidance of smoking was insisted upon and risk of fire hazard was also explained. A minimum of 15 hours in all patients and for greater duration, upto 24 hours of oxygen use, on a case-by-case basis, was advised, using a home oxygen concentrator titrated to keep SpO_2 ≥90%. The patients' concerns regarding home oxygen use were addressed. All patients were asked to keep a diary to record the exacerbations, hours of use of LTOT per day and to record the reasons, if it was not being used for the recommended duration.

The study subjects came for follow-up visits at 3 months, 6 months and 12 months. During each follow-up visit, QoL was assessed and frequency of exacerbations recorded. Adherence to LTOT and reasons for non compliance were recorded. Adherence to LTOT was defined as oxygen usage for atleast 15 hours duration per day. The QoL and frequency of exacerbations were compared with the baseline characteristics recorded during the first visit and each follow-up visit. SGRQ scores before LTOT, after 3 months, 6 months and 12 months of LTOT were considered as the primary outcome variable. The secondary outcome variables included the number of exacerbations and mMRC dyspnoea score at 12 months follow-up.

STATISTICAL ANALYSIS

Descriptive analysis was carried out by mean and standard deviation estimation for quantitative variables and frequency and proportion for categorical variables. Significance of mean was tested using paired t-test and association between qualitative variables was tested using Chi-square test. The p-value <0.05 was considered statistically significant. IBM Statistical Package for Social Sciences (SPSS) version 22.0 was used for statistical analysis.

RESULTS

A total of 60 patients were enrolled in the study. Among them, 7 patients died during the study period. Five out of the seven patients died within the first 3 months and did not report for follow-up. Two patients died during the 4th and 5th months of the study, respectively. Hence, 53 patients completed 12 months of follow-up and were included in the final analysis. Baseline demographics and disease characteristics are given in [Table/Fig-1].

Characteristic	At baseline assessment
Age (in years) (mean±SD)	64.78±5.92
Male [n (%)]	38 (71.70%)
Smoking score (in pack years)	20.4±11.8
Body mass index (kg/m²)	24.2±1.4
Co-morbidities n(%)	
Systemic hypertension	18 (33.96%)
Dyslipidemia	17 (32.08%)
Neuropsychiatric disease	14 (26.42%)
Coronary artery disease	13 (24.53%)
Diabetes mellitus	9 (16.98%)
Obstructive sleep apnoea	6 (11.32%)
None	14 (26.42%)
Duration of COPD (in years)	18.74±4.30
Post bronchodilator FEV_1 (% predicted value)	36.8±12.1
Six-minute walk distance (metres)*	198±87
PaO_2 at rest in room air (mmHg)	54.2±1.5
$PaCO_2$ at rest in room air (mmHg)	42.5±1.8

[Table/Fig-1]: Baseline demographics and disease characteristics (N=53).
*n=22 for six minute walk distance; FEV1: Forced expiratory volume in first second; PaO_2: Partial pressure of oxygen in arterial blood; $PaCO_2$: Partial pressure of carbon dioxide in arterial blood

A comparison of the SGRQ scores for symptoms, activity and impact domains as well as total scores at baseline and follow-up visits was made using paired t-test. There was a statistically significant improvement in all the SGRQ domains at 3 months of LTOT and in the symptoms and activity domains at 12 months [Table/Fig-2].

The number of exacerbations at one year follow-up was compared with the number of exacerbations in the preceding year in the 53 patients who completed 12 months of follow-up using the Chi-square test [Table/Fig-3]. There was a statistically significant reduction in the number of exacerbations on using LTOT. There was no significant improvement in mMRC dyspnoea grade at 12 months of LTOT when compared with the baseline grades when compared using Chi-square test [Table/Fig-4].

Among the 53 patients who completed one year follow-up, 36 (67.92%) participants were adherent to LTOT [Table/Fig-5]. The reasons for non adherence included restriction of ambulation, fear of dependence, nasal discomfort and expenses incurred [Table/Fig-6].

SGRQ domain	At baseline (Time 0)	After 3 months	p-value (0-3 months)	After 6 months	p-value (3-6 months)	After 12 months	p-value (6-12 months)
Symptoms	73.24±6.87	61.82±8.57	0	61.92±8.66	0.3213	62.56±8.57	0.028
Activity	74.11±11.48	60.68±10.64	0	60.78±10.6	0.3210	61.55±10.71	0.047
Impact	71.41±9.35	47.65±16.65	0	47.99±16.68	0.3211	48.62±16.7	0.225
Total	72.51±8.88	53.73±13.2	0	53.97±13.22	0.3217	54.63±13.16	0.114

[Table/Fig-2]: Comparison of SGRQ scores* (baseline- 3 months, 3-6 months and 6-12 months) N=53.
The p-value <0.05 was considered statistically significant; *SGRQ scores are presented as mean±standard deviation

Timing of assessment of exacerbations	No. of exacerbations in previous one year			p-value
	≥2 exacerbations	≥1 exacerbations	No exacerbation	
At baseline	8 (13.33%)	50 (83.33%)	2 (3.33%)	<0.00001
At 12 months	8 (15.09%)	23 (43.40%)	22 (41.51%)	

[Table/Fig-3]: Comparison of exacerbations at baseline and at one-year follow-up (N=53).
The p-value <0.05 was considered statistically significant

mMRC Grade of dyspnoea	At baseline	At 12 months	p-value
Grade II	11 (20.57%)	15 (28.30%)	0.511
Grade III	29 (54.72%)	29 (54.72%)	
Grade IV	13 (24.53%)	9 (16.98%)	

[Table/Fig-4]: Comparison of mMRC dyspnoea scores at baseline and at 12 months (n=53).
The p-value <0.05 was considered statistically significant

LTOT	After 3 months	After 6 months	After 12 months
Adherent	48 (90.57%)	39 (73.58%)	36 (67.92%)
Non adherent	5 (9.43%)	14 (26.42%)	17 (32.07%)

[Table/Fig-5]: Adherence to LTOT after 3, 6 and 12 months (N=53).

Reason for non adherence	Number (Percentage)
Restriction of ambulation	4 (25.53%)
Expenses incurred	8 (47.06%)
Nasal discomfort	3 (17.65%)
Fear of dependence	2 (11.76%)

[Table/Fig-6]: Reason for non adherence to LTOT (N=17).

DISCUSSION

The COPD is a progressive condition with a variable time course for evolution of the disease process. Severe chronic hypoxemia is a sign of advanced disease in COPD and is a predictor of limited survival. The HRQoL is often impaired in patients with COPD as a result of reduced lung function, progressive dyspnoea, recurrent exacerbations and adverse effects of medications.

The QoL was impaired in our study subjects as evidenced by high SGRQ scores at baseline. The mean scores for symptoms, activity, impact subscales and total SGRQ score were 73.24±6.87, 74.11±11.48, 71.41±9.35 and 72.51±8.88, respectively at baseline. A decrease of 4 units in the SGRQ score is generally accepted as Minimum Clinically Important Difference (MCID). This means that if an intervention has produced atleast four units improvement in SGRQ, it is likely to be useful in clinical practice. A change of eight units is moderately efficacious while a change of 12 units is very efficacious treatment [12-14]. The SGRQ symptoms, activity, impact and total scores improved at three months of LTOT. These scores were 62.56±8.57, 61.55±10.71, 48.62±16.7 and 54.63±13.16, respectively at the end of 12 months of LTOT. The use of LTOT in this study has produced clinically important difference in all three subscales and total score of SGRQ questionnaire.

Long-term domiciliary oxygen therapy in COPD patients produced a statistically significant improvement in symptoms, activity, impact and total SGRQ scores within three months as well as in the symptoms and activity scores at 12 months. Although there was no further significant improvement in SGRQ scores at six months, mean of the total SGRQ scores remained below 60 at each of the follow-up visits indicating sustained improvement in overall HRQoL in response to domiciliary oxygen therapy. The present study did not demonstrate an improvement in mMRC dyspnoea scores in spite of improvement in overall HRQoL. This is possibly due to the progressive nature of the disease with gradual decline in lung function.

There are conflicting data regarding the benefits of LTOT in COPD patients. A prospective, longitudinal study by Eaton T et al., in 43 COPD patients on LTOT, found that patients on LTOT had significant improvement in all domains of the Chronic Respiratory Questionnaire (CRQ) by two months, which were either maintained or further improved at six months [8]. In a study from Brazil, LTOT appears to have a beneficial effect on COPD symptoms as assessed by SGRQ scores when patients were followed-up for one year [15]. In contrast, Okubadejo AA et al., were unable to show a change in HRQoL as assessed by the Saint George's Respiratory Questionnaire, in hypoxemic COPD patients on domiciliary oxygen for six months [16]. Unlike the study group, the control group in this study had only moderate hypoxemia and did not use an oxygen concentrator. Similarly, Moore RP et al., could not demonstrate a significant improvement in HRQoL or dyspnoea in 143 COPD patients with exertional breathlessness on domiciliary ambulatory oxygen [17]. However, this study utilised oxygen cylinders as the source of oxygen and also excluded subjects with severe hypoxemia.

COPD exacerbations contribute to disease progression and have a negative impact on the overall health. The strongest predictor of COPD exacerbation is the number of exacerbations in the previous year and patients who have frequent exacerbations (defined as two or more exacerbations per year) have greater morbidity [18]. A study by Türkoğlu N et al., showed that the use of LTOT could reduce one-year hospital admissions and improves arterial blood gases [19]. According to the present study, home oxygen therapy could produce a significant reduction in the frequency of exacerbations in patients with severe hypoxemia. The reduction in the number of exacerbations with oxygen therapy could be a factor contributing to the improved QoL in COPD. However, in a multicentre study on 738 stable COPD patients with moderate desaturation alone, the prescription of long-term supplemental oxygen did not result in reduction in exacerbations or improvement in QoL [20].

Adherence to LTOT was assessed after 12 months in our study. Majority of the 53 patients who completed the one year follow-up were adherent to treatment 36 (67.92%). Various studies have reported adherence rates to LTOT ranging from 45-70% [21]. The perceived clinical benefits, adequate patient education and reinforcement of the need to continue on home oxygen therapy during follow-up visits could be factors contributing to the high adherence rates in our study. Limitation of physical activities, social stigma and fear of oxygen addiction has been described by patients as factors that could be deterrents to home oxygen therapy [22]. Some of these factors are easily modifiable with timely intervention of the healthcare provider. Pépin JL et al., assessed the daily use of oxygen therapy in 930 COPD patients and found that more hypoxic and severely diseased patients had a better adherence to treatment. Other factors identified with good compliance were a proper oxygen prescription, supplementary education on oxygen therapy by a nurse or physiotherapist, cessation of smoking, use of oxygen in all domestic situations and absence of side-effects [23].

Limitation(s)

The final study cohort was small and therefore, the external validity of these results is probably low. Adherence was assessed from patient reported data, which is liable to be inaccurate or under reported. The follow-up period of one year was not sufficient for assessing the long-term QoL. A longitudinal study of longer duration with a larger sample size and with a non LTOT comparison group could address these issues. Considering the long-term requirement of LTOT in COPD and logistic difficulties encountered, a cost-benefit analysis is recommended.

CONCLUSION(S)

The introduction of LTOT in COPD patients with severe hypoxemia produces improvement in HRQoL as early as three months. Continued adherence to oxygen usage sustains this improvement in QoL for atleast one year. An appropriate prescription for LTOT and effective patient education can result in good adherence to domiciliary oxygen therapy. LTOT could also have a positive impact on the prognosis in COPD by reducing the number of exacerbations.

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