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Role of long-term oxygen therapy in interstitial lung diseases

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Abstract

Background Long-term oxygen therapy in patients with interstitial lung diseases is frequently given in order to enhance gas exchange, lessen dyspnea, and increase physical activity.

Objective To evaluate how individuals with hypoxemia and interstitial lung disease respond to long-term oxygen therapy.

Results Between October 2019 and July 2021, this prospective analytical (cross-sectional) study was carried out at the Assiut University Hospital's Chest Department. Seventy ILD patients were evaluated utilizing a 6-min walk test (SMWT), the St. George respiratory questionnaire (SGRQ), MMRC, and echocardiography and follow-up was done at 1, 3, 6, and 12 months for ABG, SMWT, and MMRC. As regards echocardiography and SGRQ, a follow-up was done on admission and 1 year after starting LTOT. Significant improvement in St. George's respiratory questionnaire score, MMRC, and EF by echocardiography was observed meanwhile PASP showed insignificant reduction.

Conclusion Long-term oxygen therapy is beneficial for patients with ILD and hypoxemia.

Trial registration Long-term oxygen therapy in patients with interstitial lung disease: ClinicalTrials.gov ID: NCT04089826 Registered on September 12, 2019.

Keywords LTOT, ILD, Hypoxemia, SMWT, SGRQ, MMRC, Echocardiography

Background

Interstitial lung disease (ILD) comprises a heterogeneous group of diseases characterized by inflammation and/or fibrosis of the lung parenchyma. Some forms of ILD are irreversible, characterized by progressive hypoxemia and frequent early mortality, and with few pharmacotherapies of proven benefit. Supplemental oxygen is often prescribed for patients with advanced ILD [1].

The use of LTOT in patients with ILD may improve survival and tissue oxygenation, and prevent complications associated with hypoxemia such as worsening pulmonary hypertension [2].

Duration of long-term oxygen therapy, a minimum of 15 h and up to 24 h may be desirable. The advantages of LTOT result from the normalization of improper physiology caused by prolonged hypoxemia [3].

The danger of explosion/burns (61 individuals per 100,000 person-years [4] for smoking during LTOT) must be explained to individuals who still smoke. Moreover, possible LTOT adverse reactions include epistaxis, drowsiness, and a weakened sense of taste and smell [4].

Before prescribing LTOT, we considered the diagnosis, the degree of hypercapnia and hypoxemia, the patient's activity, the oxygen flow rate necessary to attain $PaO_2 \geq 60$ mm Hg (at rest, during activity, or at night), and the preferred delivery method [5].

Our primary outcome measure was the assessment of dyspnea by the Modified Medical Research Council in patients with ILD after LTOT. The secondary outcome

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measure was the assessment of quality of life by the St. George Questionnaire in those patients.

Methods

Study design

This prospective cross-sectional analytic study has been filed with (ClinicalTrials.gov ID: NCT04089826) study. Between October 2019 and July 2021, this research was carried out at the Chest Department of the Assiut University Hospital, Faculty of Medicine. The Scientific Ethics Committee of the Faculty of Medicine at Assiut University gave its approval to the study's design. All participants gave their informed consent after fulfilling the requirements for inclusion.

Patient selection

In this study, 70 ILD cases (52 women and 18 men) were randomly chosen among those hospitalized at the chest department of the Assiut University Hospital.

Inclusion criteria

1- Patients equal to or more than 18 years old
2- Interstitial lung disease (ILD) patients having a resting PaO_2 of less than 7.3 kPa
3- ILD patients with a resting $PaO_2 \leq 8$ kPa, polycythemia (hematocrit $\geq 55\%$), peripheral edema, or pulmonary hypertension symptomatology [3].
4- Interstitial lung disease in those patients diagnosed according to HRCT guideline (1) and PFT. (2)

Diagnostic criteria for ILD on HRCT [1]

- High-resolution computed tomography scanning patterns according to consensus statement updated in 2018.
- 2018 guidelines
- UIP pattern
- Subpleural, basal predominant; distribution is often heterogeneous
- Honeycombing with or without traction bronchiectasis or bronchiolectasis
- Probable UIP pattern
- Subpleural, basal predominant; distribution is often heterogeneous
- Reticular pattern with traction bronchiectasis or bronchiolectasis
- May have mild GGO
- Indeterminate UIP pattern
- Subpleural and basal predominant
- Subtle reticulation may have GGO or distortion ("early UIP pattern")
- CT features and/or distribution of lung fibrosis that do not suggest any specific etiology ("truly indeterminate for UIP")
- Alternative diagnosis

Findings suggestive of another diagnosis, include the following:

- CT features (cysts, marked mosaic attenuation, predominant GGO, profuse micronodules, centrilobular nodules, nodules, consolidation)
- Predominant distribution (peribronchovascular, perilymphatic, upper or mid-lung)
- Other (pleural plaques, dilated esophagus, distal clavicular erosion, extensive lymph node enlargement, pleural effusion, or thickening)

CT, computed tomography; GGO, ground-glass opacities; UIP, usual interstitial pneumonia

Diagnostic criteria for ILD on PFT

Abnormal lung function studies that include evidence of the following:

1. Restriction (reduced vital capacity, often with an increased forced expiratory volume in 1 s/forced vital capacity ratio)
2. Impaired gas exchange (increased alveolar–arterial oxygen tension difference with rest or exercise or decreased diffusing capacity of the lung for carbon monoxide) [2].

Exclusion criteria

If there are other than ILD causes of chronic respiratory failure.

Sample size calculation

With G Power software version 3.1.3, the sample size was calculated based on the following assumptions: an alpha error probability of 0.05, an effect size of 0.5, and a power of 0.80. Given that the frequency of ILD was previously reported to be 4.1/100,000 persons per year (Hyldgaard, 2015) [6], the minimal sample size was 61 individuals, and because 10% dropout was anticipated, a total of 70 patients with ILD were recruited for this research.

Baseline data

All research participants had the following:

History taking which included the following:

- Demographic data as residence, age, smoking, and smoking habits.

- Medical history involving the current complaint, present and past history, and therapeutic history.

Clinical examination included the following:

- General examination
- Local chest examination

Six-min walking test (SMWT): on admission, 1, 3, and 6 months and 1 year after starting LTOT

Each participant was given a 6-m time limit and a 30-m route to complete our indoor hospital corridor, then taking at least 30 min of relaxation. The subjects received standardized instructions and verbal praise. Throughout the test, positive reinforcement was given each minute until the participant fell exhausted. The participant or the doctor decided when the test was finished. Chest pain, acute dyspnea, diaphoresis, stumbling, leg cramps, and a pale look were all reasons to quit the 6MWT right away [7].

St. George's respiratory questionnaire (SGRQ)

In our research, we used the Arabic version of SGRQ [8]. The patient was asked to reply to the questionnaire before and 1 year after the usage of LTOT.

Arterial blood gases (ABG)

An arterial sample on RA was taken under complete aseptic condition on prescription of LTOT to obtain accurate result for arterial oxygen tension and saturation and at 1, 3, 6, and 12 months on follow-up after prescription of LTOT.

Echocardiography: on prescription of LTOT and after 1 year follow-up—measurement of EF and PASP was done

Oxygen flow rate (L/min) was adjusted according to the level of desaturation to reach the target SO_2, and 92% mostly ranged from 5 to 10 L/min, 15 h per day. Oxygen delivery devices were either oxygen concentrators or cylinders, and central oxygen during hospital admission patient interface was a nasal cannula in patients with type 1 respiratory failure and a venturi mask in patients with type 2 respiratory failure.

Some patients needed other respiratory support as CPAP or BiPAP during hospital admission, but on home discharge, they were on long-term oxygen therapy only and did not need ventilator support at home.

PFT was done only for a few patients at the start of the study then could not be done due to the major spread of COVID-19.

Research outcome measures

The primary outcome measure was dyspnea by Modified Medical Research Counsel. The secondary (subsidiary) outcome measure was the quality of life by the St. George Questionnaire.

Statistical analysis

SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York) was used to gather and analyze the data. The mean ± standard deviation (SD) of quantitative data was reported and compared using the paired *t* test and repeated ANOVA test. Number (*n*) and percentage (%) were used to represent numeric. Those data were subjected to the chi^2 test. As the confidence level was maintained at 95%, a *P* value of less than 0.05 was deemed significant.

Results

This study included 70 ILD patients (52 females, 18 males) with a mean age of enrolled cases was 51.02 ± 12.61 years with a range between 30 and 70 years. During a follow-up of those patients over a 1-year duration, there was a marked enhancement in the oxygen saturation during a 6-m walk test ($p < 0.001$). There was a significant improvement in the ejection fraction (EF) at 1 year of follow-up (66.40 ± 4.91 vs. 63.51 ± 5.33 (%); $p < 0.001$) while PASP showed insignificant reduction (47 ± 24.59 vs. 47.53 ± 25.63 (mmHg); $p = 0.64$). Based on MMRC, there was a significant improvement in the grade of dyspnea. None of the studied patients had grade-0 dyspnea at any time of assessment. At baseline majority (81.4%) of patients had dyspnea-IV while after 1 year of LTOT, only 11 (15.7%) patients had grade-IV dyspnea. There was a decrease in St. George's Respiratory Questionnaire Score in studied patients after 1 year of follow-up (21.47 ± 1.11 vs. 20.10 ± 1.41; $p < 0.001$). In addition, there was obvious elevation in 6-MWD in studied patients after 1 year of follow-up (144.34 ± 93.51 vs. 271.78 ± 100.13; $p < 0.001$). It was noticed that there were significant changes in all parameters of ABG except pH values. There was a marked elevation in arterial oxygen tension and saturation while carbon dioxide tension showed significant reduction.

Discussion

In the present study, during a follow-up in 1, 3, and 6 months and one year after starting oxygen therapy, there was obvious improvement in the oxygen saturation during a 6-m walk test ($p < 0.001$). In addition, there was a marked rise in 6-MWD in studied patients after 1 year of

follow-up (144.34 ± 93.51 vs. 271.78 ± 100.13; $p < 0.001$). This agrees with Lancaster et al. who support that the use of supplemental oxygen can prevent desaturation during the test [9].

Also, it was noticed through a follow-up by St. George Respiratory Questionnaire that there was marked improvement in the quality of life as the score changed in studied patients after 1 year of follow-up (21.47 ± 1.11 vs. 20.10 ± 1.41; $p < 0.001$), and this agrees with Poloński et al. who found that the overall health-linked quality of life was enhanced with oxygen therapy (difference 3.7 points; $p < 0.0001$) [10].

Regarding dyspnea follow-up in our research, there was an obvious improvement in the grade of dyspnea based on MMRC. This agrees with Swinburn study which revealed diminishes in dyspnea at rest with oxygen in cases that were severely diseased [11]. In contrast, according to Emily et al., the modified Borg dyspnea score at the termination of exercise did not change as a result of oxygen therapy (mean difference (MD) − 0.06 units, 95% CI − 0.24–0.13; two trials, $n = 27$) [12].

The techniques by which additional oxygen enhances dyspnea in hypoxemic cases are not understood fully, but they may involve modifications in chemoreceptor stimulation, the associated decrease in respiratory drive and modifications to breathing pattern, and/or stimulation of upper airway receptors by gas flow [13].

In this study, there was a significant improvement in the ejection fraction (EF) at 1 year of follow-up (66.40 ± 4.91 vs. 63.51 ± 5.33 (%); $p < 0.001$) while PASP showed insignificant reduction (47 ± 24.59 vs. 47.53 ± 25.63 (mmHg); $p = 0.64$) and this agreed with Poloński et al. These results suggest that persistent home oxygen therapy delays cardiac malfunction in cases with idiopathic interstitial lung fibrosis [14]. Also there is an agreement with Karthikeyan et al. who studied the response to LTOT in cases with pulmonary hypertension because of chronic lung disease [15]. The typical LTOT lasted 16 h per day, and the average PASP decline was 3.2 mm Hg each year [15]. The Zinman trial, on the contrary, assessed if continuous nocturnal oxygen administration slowed the progression of right-sided heart failure and pulmonary hypertension [12]. Four out of fourteen subjects in the oxygen group and six out of fourteen in the non-oxygen group had the onset of at least one physical symptom suggestive of cor pulmonale (Zinman 1989) [16].

Regarding survival in this study, it was noticed that 65 (92.9%) patients were alive till the end of the study while only 5 (7.1%) patients deteriorated and died before the end of the study. Three LTOT trials reported on survival [17–19]. These investigations all showed that people with ILD had disappointing survival rates. According to one research, 50% of fibrosis or pneumoconiosis patients died within a year after starting home oxygen or ventilation [18]. Research of 487 IPF patients, however, used an indirect comparison to show that those who had been counseled to use oxygen treatment had a higher chance of dying than those who had not (relative risk 2.0, 95% CI 1.5–2.6) [19].

Table 1 Baseline data of enrolled patients

	***N* = 70**
Age (years)	51.02 ± 12.61
Range	30–70
Sex	
Male	18 (25.7%)
Female	52 (74.3%)
Comorbidities	
None	48 (68.6%)
Diabetes mellitus	11 (15.7%)
Hypertension	6 (8.6%)
Both	5 (7.1%)

Data expressed as frequency (percentage), mean (SD), and range

Conclusion

We concluded that LTOT significantly improved the quality of life of patients with ILDs. Also, LTOT improved oxygen saturation, arterial oxygen tension, decreased carbon dioxide tension, and improved cardiac function for those patients, so there was a significant improvement in survival outcomes.

Table 2 Baseline and one year follow up echocardiography in studied patients

	Baseline	**One year**	***P* value**
Ejection fraction (%)	63.51 ± 5.33	66.40 ± 4.91	**< 0.001**
PASP (mmHg)	47.53 ± 25.63	47 ± 24.59	0.64
Dimensions			
Normal	44 (62.9%)		
DRS	23 (32.9%)		
LVH	3 (4.3%)		

Data expressed as mean (SD) and frequency (percentage). *P* value was significant if < 0.05 *PASP* pulmonary artery systolic pressure, *DRS* dilated right side, *LVH* left ventricular hypertrophy

Table 3 Changes in arterial blood gases during follow-up in studied patients

Parameters	Baseline	1st month	3rd month	6th month	One year	*P* value
pH	7.44 ± 0.05	7.45 ± 0.04	7.44 ± 0.03	7.44 ± 0.05	7.45 ± 0.09	0.25
PCO_2	49.18 ± 7.69	48.54 ± 7.44	47.78 ± 13.21	47.64 ± 9.47	46.07 ± 10.13	0.02
PaO_2	36.92 ± 9.05	42.65 ± 6.67	45.92 ± 4.95	49.05 ± 4.61	50.77 ± 4.82	< 0.001
SO_2	70.20 ± 12.07	77.53 ± 8.51	79.08 ± 7.03	81.60 ± 6.05	83.74 ± 6.33	< 0.001
HCO_3	32.62 ± 7.51	32.10 ± 6.32	33.54 ± 5.22	34.45 ± 4.77	35.20 ± 4.39	< 0.001

Table 4 Oxygen saturation on a six-min walk test during follow-up of patients

Time of assessment	Oxygen saturation
Baseline	60.61 ± 12.41
1st month	65.34 ± 10.45
3rd month	69.12 ± 8.39
6th month	72.70 ± 7.32
One year	75.95 ± 7.29
***P* value**	**< 0.001**

Table 5 Modified medical research council during follow up of studied patients

Dyspnea	Baseline	1st month	3rd month	6th month	One year
Grade-I	0	0	0	0	0
Grade-II	0	2 (2.9%)	7 (10%)	7 (10%)	7 (10%)
Grade-III	13 (18.6%)	30 (42.9%)	33 (47.1%)	49 (70%)	52 (74.3%)
Grade-IV	57 (81.4%)	38 (54.3%)	30 (42.9%)	14 (20%)	11 (15.7%)
***P* value**	**0.03**				

Table 6 Baseline and 1 year 6-MWD and St. George's respiratory questionnaire in patients

	Time of assessment		*P* value
	Baseline	After 1 year	
SGRQ	21.47 ± 1.11	20.10 ± 1.41	**< 0.001**
6-MWD (m)	144.34 ± 93.51	271.78 ± 100.13	**< 0.001**

Data expressed as mean (SD). *P* value significant if < 0.05. *SGRQ* St. George's Respiratory Questionnaire, *6-MWD* 6-min walk distance

Table 7 Baseline HRCT pattern among enrolled patients

	N = 70
High-resolution CT chest	
Reticulonodular shadow	43 (61.4%)
Ground glass opacity	21 (30%)
Honeycombing	20 (28.6%)
Cystic air space	14 (20%)

Strengths of this study

1. Relatively few studies have focused on the role of long-term oxygen therapy in interstitial lung diseases.
2. The marked improvement in the quality of life after using LTOT in the studied patients.

Limitations of the current study

1. A small number of patients were included in the study.
2. A short duration of follow-up and longer follow-up may validate results.

Recommendations

Further larger and multicentric studies are needed to examine the findings of this study prospectively as well as to investigate the utility of LTOT in a larger number of patients with ILD (Tables 1, 2, 3, 4, 5, 6 and 7).

Abbreviations

ILDs	Interstitial lung diseases
LTOT	Long-term oxygen therapy
ABG	Arterial blood gas
SGRQ	St. George Respiratory Questionnaire
SMWT	6-Minute walk test
EF	Ejection fraction
mMRC	Modified Medical Research Council
PASP	Pulmonary arterial systolic pressure
kPa	Kilopascal
pH	Potential of hydrogen

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Authors' contributions
All the authors contributed to the continuous monitoring and step-by-step close observation during the collection of sample sizes, writing the paper, and trial for publication.

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Availability of data and materials
All data and materials used are available at the Chest Department of Assiut University Hospital.

Declarations

Ethics approval and consent to participate
The research is ethically approved and does not make any hazard to the participants as well consent from each patient was taken before starting.

Consent for publication
All authors participating in this research agree on publication and want it.

Competing interests
The authors declare that they have no competing interests.

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