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A randomized controlled trial of supplemental oxygen versus air in cancer patients with dyspnea

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Context: The symptomatic benefits of oxygen in patients with cancer who have nonhypoxic dyspnea are not well defined. **Objective:** To determine whether or not oxygen is more effective than air in decreasing dyspnea and fatigue and increasing distance walked during a 6-minute walk test. **Patients and methods:** Patients with advanced cancer who had no severe hypoxemia (i.e., had an O_2 saturation level of $\geq 90\%$) at rest and had a dyspnea intensity of ≥ 3 on a scale of 0–10 (0 = no shortness of breath, 10 = worst imaginable shortness of breath) were recruited from an outpatient thoracic clinic at a comprehensive cancer center. This was a double-blind, randomized crossover trial. Supplemental oxygen or air (5 L/min) was administered via nasal cannula during a 6-minute walk test. The outcome measures were dyspnea at 3 and 6 minutes, fatigue at 6 minutes, and distance walked. We also measured oxygen saturation levels at baseline, before second treatment phase, and at the end of study. **Results:** In 33 evaluable patients (31 with lung cancer), no significant differences between treatment groups were observed in dyspnea, fatigue, or distance walked (dyspnea at 3 minutes: $P = 0.61$; dyspnea, fatigue, and distance walked at 6 minutes: $P = 0.81$, 0.37, and 0.23, respectively). **Conclusions:** Currently, the routine use of supplemental oxygen for dyspnea during exercise in this patient population cannot be recommended. *Palliative Medicine* 2003; **17:** 659–663

Key words: air; cancer; dyspnea; oxygen

Introduction

Dyspnea is a frequent and distressing symptom in patients with advanced cancer and is often difficult to control.[1–3] Studies have shown that the incidence of dyspnea in terminally ill patients with cancer ranges from 20% to 80%.[1,2,4,5]

The effects of oxygen on dyspnea symptoms in patients with terminal cancer have not been clearly defined, and the decision to administer oxygen to these patients is often made on a case-by-case basis.[6] Nonetheless, studies by our group have suggested that supplemental oxygen in patients with terminal cancer decreases the intensity of dyspnea in those with hypoxemia and dyspnea at rest.[6,7]

In patients with muscle loss due to cachexia and deconditioning, oxygen debt can increase with normal or minimal activities. Supplemental oxygen can decrease oxygen debt and recovery time,[8] and should result in decreased dyspnea. However, the effects of supplemental oxygen on physical function and performance in patients with nonhypoxic dyspnea associated with cancer have not been established. In addition, the cost of home oxygen is not reimbursed for cancer patients with dyspnea who do not have hypoxemia on room air.

The purpose of this double-blind, randomized, controlled crossover trial was to determine whether supplemental oxygen is more effective than air in decreasing the intensity of dyspnea and fatigue or in increasing the distance walked during a 6-minute walk test by cancer patients with dyspnea who do not have severe hypoxemia.

Patients and methods

Patients were recruited and enrolled by the research nurse from the outpatient clinic in the Thoracic Center at the University of Texas M. D. Anderson Cancer Center from May to November 2001. The institutional review board approved the study, and all participants provided written informed consent.

Patients were eligible for inclusion in the study if they had advanced (locally recurrent or metastatic) cancer and had had dyspnea at rest or upon mild exertion (i.e., dyspnea caused by activities of daily living), with intensity levels of at least 3 on a scale of 0–10 (0 = no

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shortness of breath; 10 = worst imaginable shortness of breath) within the previous 24 hours. To be included, patients were required to be ambulatory and to have normal cognitive status, defined by a normal state of arousal and the absence of obvious clinical findings of confusion, memory deficit, or concentration deficit. A hemoglobin level of ≥ 10 g/L measured within two weeks of the study was also required. Patients with a history of chronic obstructive pulmonary disease (COPD) were eligible if they had not previously required oxygen therapy. Patients were excluded if they had evidence of acute respiratory distress, which was defined as dyspnea of recent onset (within the previous 24 hours), and if the intensity of the dyspnea as described by the patient was severe enough to interfere with the 6-minute walking test, if the patient had required oxygen supplementation at any point during the last four weeks (including at rest or during exercise), or if the patient had a resting oxygen saturation level of $< 90\%$. Oxygen saturation was measured by pulse oximetry, using Oxisensor II (Nellcor Puritan Bennett, Preston, CA, USA). Patients with dyspnea that was obviously due to a condition other than cancer (such as congestive heart failure, pericardial effusion, or cardiomyopathy) were also excluded.

The baseline assessment consisted of an evaluation of patient's fatigue and dyspnea (using a numerical rating scale of 0–10; 0 = absence of symptoms and 10 = worst possible symptoms) and a measurement of oxygen saturation, respiratory rate, and heart rate. Patients were randomized in a double-blind crossover fashion to receive either oxygen or air in the first treatment phase and air or oxygen in the second treatment phase; each gas was delivered by nasal cannula at 5 L/min. The statistician created a randomization list using the software Ranlist, developed at the Department of Biostatistics, M. D. Anderson Cancer Center. The investigators, research nurses, and patients were blinded to the randomization. The respiratory therapist was not blinded to the contents of the 697-L 'E'-type gas tanks. The oxygen and air tanks were concealed by the respiratory therapist using identical covers and labeled them with the numbers 1 or 2, indicating which was to be used first or second. Patients were asked to rest while receiving either oxygen or air for 5 minutes and then to perform a 6-minute walking test while receiving the gas. The walk was on level ground, and the patients were asked to walk as fast as they could do so comfortably. All patients received standardized instructions with a short practice walk and no verbal encouragement. The intensity of dyspnea (measured on a 0–10 numerical rating scale) and the patient's ability to continue walking were assessed after 3 minutes of walking. At the end of the 6-minute walk, each patient was asked to rest. The intensity of dyspnea and fatigue was evaluated immediately after completion of the 6-minute walk using numerical rating scale (0–10) by the research nurse. The research nurse also recorded the distance walked by each patient using a pedometer (Trumeter, Radcliffe, UK), and the number of stops during the 6-minute walk. Treatment continued after the walk, and the patients were asked to rate their dyspnea every 5 minutes for a minimum of 15 minutes or until the intensity of dyspnea returned to baseline. Oxygen saturation was measured at this point.

After the first treatment phase, patients were crossed over to the opposite treatment and the same assessments were performed as were done with the first treatment. At the end of the study, the patients chose their preferred treatment and the research nurses chose their preferred treatment for the patients. If a patient had a preference for one treatment, the patient was asked to rate the difference in benefit between the two treatments on a scale of 1–7; 1 = no important benefit, 2 = slightly important benefit, 3 = some important, consistent benefit, 4 = moderately important, consistent benefit, 5 = much important, good deal of benefit, 6 = very important benefit, and 7 = greatly important benefit.

Statistical considerations

The differences in benefits between the two treatments were calculated and then averaged for each treatment group. Three two-sample t-tests were used for comparisons. Before comparing treatment groups for the main effects, first period (time) effects and treatment–period interactions were tested to rule out complications in analyses or reporting of results.

The study was powered to detect differences between the two treatment groups as large as or larger than 75% of the standard deviation of the means, with a two-sided significance level of 0.05, and 80% power with 30 evaluable patients. The dropout rate (one of 34 patients) was lower than expected, and therefore the study had more than adequate power to detect the expected estimated differences.

We used t-tests to compare differences in dyspnea, fatigue, and distance walked between oxygen and air in patients with a baseline oxygen saturation level of $\leq 97\%$ and patients with a baseline oxygen saturation level of $> 97\%$. We also compared outcomes between patients grouped by patients' assessment of relative benefit. Finally, in the subgroup of patients with oxygen saturation levels of $\leq 97\%$, we used analysis of variance to compare oxygen saturation levels at baseline and second treatment phases and at the end of the study. Duncan's multiple range test was then used to determine the points at which significant differences occurred.

Results

Thirty-four eligible patients consented to participate in the study. Thirty-three of the 34 patients were evaluable; one patient did not continue after the first phase of the study because of personal time constraints. Patient demographic information is summarized in Table 1.

The baseline pulse rates, respiratory rates, and oxygen saturation levels did not differ significantly between the two treatment groups. During the first phase of treatment, 17 patients received air and 16 received oxygen. Table 2 summarizes the results of each treatment. No significant differences existed between treatment groups in dyspnea at 3 minutes ($P = 0.78$) or in dyspnea, fatigue, and distance walked at 6 minutes ($P = 0.52$, 0.64, and 0.95, respectively). These outcomes also did not differ significantly between patients with baseline oxygen saturation levels of $\leq 97\%$ ($n = 15$) and those with baseline saturation levels of $> 97\%$ (dyspnea at 3 minutes: $P = 0.61$; dyspnea, fatigue, and distance walked at 6 minutes: $P = 0.81$, 0.37, and 0.23, respectively). In the subgroup of patients with baseline oxygen saturation levels of $\leq 97\%$, analysis of variance showed significant differences ($P = 0.0009$) in the oxygen saturation levels at baseline and before second treatment phase and at the end of the study. Multiple comparison tests found that the average oxygen saturation at initial baseline was significantly lower ($P < 0.01$) than that measured after completion of the first or second phase of treatment. The average oxygen saturation levels after the first and second treatment phases did not significantly differ from each other.

The number of patients who reported more benefit from oxygen than from air ($n = 19$) was significantly greater than the number of patients who reported more benefit from air than from oxygen ($n = 11$; $P < 0.05$). Patients who reported a lot of benefit or very important benefits from oxygen walked significantly greater distances while receiving either treatment than did those who reported a lot of benefit or very important benefits from air ($P < 0.05$).

According to the current study results, we calculated that in order to detect a difference of 0.4 cm (0.4 on a 0–10 scale) in dyspnea intensity between the oxygen and air groups after a 6-minute walk at a significance level of ≤ 0.05 (assuming a standard deviation of 2.45), we would have needed approximately 600 patients in our study.

Table 1 Demographic information for 33 patients

Patient characteristic ($n = 33$)	Number (%)[a]
Median age (range); years	64 (41–79)
Sex	
Male	21 (64)
Female	12 (36)
Current cancer status	
Primary lung cancer	31 (94)
Other cancers	2 (6)
Metastatic disease	31 (94)
Pleural effusion	3 (9)
Median hemoglobin concentration (range); g/dL	12.3 (10.2–14.6)
Median baseline oxygen saturation (range); %	98 (91–100)
Oxygen saturation $\leq 97\%$ at baseline	15 (45)
Oxygen saturation $\leq 95\%$ at baseline	6 (18)
Median usual dyspnea upon activity (range) 0–10	5 (3–8)

[a] Value reflects number patients (%) except as otherwise stated.

Discussion

Our results showed no significant differences between oxygen and air in reducing the intensity of dyspnea or fatigue or in increasing the distance walked during a 6-minute walk test by cancer patients with dyspnea.

In previous studies of patients with cancer who had hypoxemia and dyspnea at rest, we found that oxygen decreases the intensity of dyspnea.[6,7] The likely mechanism is the reduction of afferent stimulation from the endocarotid chemoreceptors. Because the pO_2 that is capable of influencing these receptors varies widely, we hypothesized that patients with dyspnea and normal oxygen saturation who are not normally considered to be candidates for oxygen therapy might benefit from supplemental oxygen therapy. Oxygen could also have symptomatic benefits by reducing anaerobic glycolysis and oxygen debt induced by exercise. Future studies should investigate the possibility that individuals doing more strenuous exercise resulting in more intense dyspnea or oxygen debt might benefit from oxygen therapy.

Table 2 Dyspnea, fatigue, and distance walked during a 6-minute walk

Variable	Treatment		
	Air	Oxygen	P value
Dyspnea score at 3 minutes, mean (SD)	3.8 (2.2)	3.7 (2.1)	0.78
Dyspnea score at 6 minutes, mean (SD)	4.9 (2.7)	4.5 (2.2)	0.52
Fatigue score at 6 minutes, mean (SD)	4.1 (2.6)	3.8 (2.3)	0.64
Distance in feet walked at 6 minutes, mean (SD)	1085 (189)	1088 (180)	0.95

The 6-minute walk test is a reliable modality for assessing dyspnea and its treatment with supplemental oxygen,[9–11] and the level of dyspnea produced by the 6-minute walk test is a good predictor of clinical outcome.

In a previous study, both oxygen and air significantly reduced dyspnea scores at rest in patients with cancer, and the effectiveness of the two treatments did not differ significantly.[12] In addition, the investigators in that study found no evidence that the improvement in dyspnea differed significantly by the levels of initial oxygen saturation. Possible explanations for the reduced dyspnea scores in that study are that the airflow produced by nasal prongs stimulates nasal receptors or that wearing nasal prongs has a placebo effect.[13]

In our study, patients with lower oxygen saturation at baseline ($\leq 97\%$) appeared to benefit in terms of oxygen saturation from both gases. This benefit was apparent after the first phase of the study and was sustained after the second phase. One possible reason for this could be that mild exercise improves oxygen saturation in these patients.

Our study has a number of limitations. A control group who received no treatment with oxygen or air during the 6-minute walk test might have allowed us to better determine the extent to which treatments were beneficial and whether or not some of the beneficial effect was due to exercise itself. In addition, oxygen saturation was not measured during or at the end of the 6-minute walks; hence patients who desaturated on exercise cannot be identified. All these patients had to be able to complete a 6-minute as a criterion for inclusion. Therefore, they may represent a subgroup of more 'fit' patients, less likely to benefit from oxygen. However, the group did develop considerable dyspnea after a 3- and 6-minute walk (Table 2).

The overall oxygen saturation was high in our study participants; only six patients had oxygen saturations of $\leq 95\%$. A baseline saturation of $\leq 95\%$ has been found to be a useful screening tool for determining which patients with COPD are likely to desaturate with exercise.[14] In palliative care populations, the use of supplemental oxygen therapy should be considered to help improve symptoms and quality of life, and thus should be measured by clear symptomatic improvement. This is in contrast to patients with chronic lung diseases, in whom long-term outcomes – such as prevention of pulmonary hypertension and heart failure – are important considerations. Intermittent oxygen therapy to activities that cause dyspnea may be more acceptable than continuous oxygen therapy in palliative care patients. However, our current data do not support the use of oxygen for treatment of exercise-related dyspnea in patients with cancer who do not have hypoxemia. In patients with COPD not receiving oxygen who desaturate with exercise, supplemental oxygen has been found to acutely improve dyspnea and exercise tolerance.[15–18] In COPD patients, treatment with oxygen as compared with air has been found to have a small beneficial effect on dyspnea.[18] The trend for the slightly greater choice for oxygen treatment ($P < 0.05$) and longer distance walked by patients expressing subjective benefit suggests that there may be a subgroup of patients likely to benefit from oxygen treatment. Unfortunately, this study is not able to identify the characteristics of this subgroup due to the small number of participants. Future studies should examine the effects of oxygen therapy on exercise tolerance and dyspnea in patients who have oxygen saturation levels below 95% and those with borderline saturation levels at rest, who may be likely to desaturate with exercise. This will require measurement of oxygen saturation during exercise instead of only after completion of the exercise as done in this study. In addition, the short- and long-term effects of exercise on dyspnea in patients with advanced cancer should also be studied.

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