Original Article

A Randomized, Double-Blind, Crossover Trial of the Effect of Oxygen on Dyspnea in Patients with Advanced Cancer

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Abstract

Dyspnea is a common symptom in palliative care. Despite this, there is uncertainty regarding the role of oxygen to treat the symptom in patients with advanced illness. This randomized, double-blind, crossover trial examined the effect of oxygen versus air on the relief of dyspnea in patients with advanced cancer. Following the blinded administration of air and oxygen via nasal prongs, 51 patients rated dyspnea and indicated preferences for the blinded treatments. On average, patients improved symptomatically with both air and oxygen, and there were no significant differences between the treatments. The subgroup of 17 hypoxic patients overall did not demonstrate a significant difference between air and oxygen, despite having improved oxygen saturations when administered oxygen. Hypoxia was corrected in 13 of 17 patients using the treatment dose of 4 L/min of oxygen. The experience of dyspnea is a complex, multifactorial phenomenon, with oxygen tension not correlating with the subjective experience. The administration of either air or oxygen via nasal prongs on average confers improvement of the symptom. J Pain Symptom Manage 2006;32:541–550.

Key Words

Dyspnea, cancer, oxygen, palliative care

Introduction

Dyspnea is a common symptom in patients with advanced cancer, rated as a moderate or severe problem in 46% of those admitted to a palliative care program, and affecting 70% of hospice inpatients.[1,2] At the Peter MacCallum Cancer Center, the incidence of dyspnea among all patients with a cancer diagnosis was 33%.[3] The presence of dyspnea indicates a poor prognosis for patients with pancreatic

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or lung cancer.[4,5] In one study, this prognostic association was so strong for some patients with a cancer diagnosis presenting to the emergency department of a North American center, the presence of dyspnea may have heralded a shift in treatment focus from acute intervention to palliative measures.[6]

Dyspnea is one of the most distressing symptoms experienced by patients. It is a combination of a "sensation" (neural activation resulting from stimulation of a receptor) and a "perception" (reaction of the individual to that sensation).[7] A consensus statement of the American Thoracic Society has defined dyspnea as "a term used to characterize a subjective experience of breathing discomfort that is comprised of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioral responses."[7]

The development of dyspnea is a complex phenomenon and is related to activation of sensory systems involved with respiration. The main mechanisms involve feedback from chemoreceptors, mechanoreceptors, and vagal afferents in the lung and chest wall, which project to higher brain centers to provide a direct review of the chemical state of the body and the mechanical state of the lungs. Efferent copies of brainstem respiratory motor output also appear to be transmitted to higher brain centers and result in a conscious awareness of the motor command.[8] Behavioral style and emotional state influence the perception of the stimulus. These factors all play a role in shaping the perception of dyspnea, and, therefore, this symptom, like pain, should be understood to be a multidimensional experience.

The management of dyspnea involves attention to the etiology of the symptom and where possible, correction of causative factors. Management of the symptom itself may include behavioral approaches, pharmacological agents, and the use of airflow and oxygen. A number of small studies have demonstrated the benefit of behavioral techniques,[9,10] while the body of literature supporting pharmacological management, principally opioids, is well established.[11–17]

Oxygen plays an important role in the management of the hypoxic patient with chronic obstructive pulmonary disease (COPD), being associated with improvements in survival, quality of life, and neuropsychologic function.[18] There have been few studies addressing the role of oxygen in hypoxic and normoxic dyspneic patients with advanced cancer. Bruera et al. conducted a randomized, double-blind, crossover trial in 14 patients with advanced cancer and hypoxemia, defined as oxygen saturation of less than 90% on pulse oximetry.[19] These patients received oxygen or air at 5 L/min by mask and then were twice crossed over to the other treatment. The average dyspnea score, measured by visual analogue scale (VAS), was significantly less when patients received oxygen ($P < 0.001$), and 12 of 14 patients consistently preferred oxygen ($P < 0.001$). The blinded investigator also chose oxygen for 12 of 14 patients. According to a global well-being scale, patients felt little or no benefit with air but moderate to much benefit when receiving oxygen. The authors concluded that hypoxic patients with cancer receive symptomatic benefit from oxygen therapy.[19] In 1994, Booth et al. did not obtain these findings when they conducted a single-blind, crossover trial of oxygen and air administered in random order to 38 hospice patients who reported dyspnea at rest.[20] These patients completed a VAS for dyspnea, oxygen saturation measures, and limited lung function tests before and after 15 minutes on each gas. On average, dyspnea improved significantly with both treatments, with the air group having a reduction of dyspnea from a mean of 59 to 48 mm on a 100 mm scale ($P < 0.001$) and the oxygen group having a reduction of dyspnea from a mean of 59 to 45 mm ($P < 0.001$). While the average response to oxygen was quantitatively better than the response to air, there was no statistically significant difference between the treatments.[20] It is noteworthy that the analysis performed in this study did not appear to make use of statistical methods appropriate for crossover trials. The discrepancy between these two studies may, therefore, be explained by the different patient groups (hypoxic versus mixed hypoxic and normoxic patients on no routine inhaled treatment) or the analysis methodology, or may be a spurious result due to the small numbers in each study.

We proposed, therefore, to clarify the role of oxygen when used to relieve dyspnea in patients with advanced cancer, focusing on the clinically relevant group of patients who

present with the symptom and, therefore, including both hypoxic and normoxic patients.

Methods

The primary aim of this randomized, double-blind, crossover study was to determine blinded patient preference for oxygen or air, following 15-minute administration of both. Secondary aims were to compare the response to oxygen and air in hypoxic and normoxic patient groups, and to identify factors other than hypoxia that may affect the experience of dyspnea and the response to oxygen.

The study took place in two centers in Australia (The Alfred Hospital and the Peter MacCallum Cancer Center) and recruited both inpatients and outpatients. Patients were eligible if they had a diagnosis of cancer, were dyspneic and had a main etiology for dyspnea that was clinically deemed to be related to cancer, had a dyspnea intensity score of at least 30 mm on a 0−100 mm VAS, were on stable medication doses (including opioids), had normal cognitive status defined according to the Blessed Orientation Memory & Concentration mental status examination, were over 18 years of age, had no contraindications to oxygen, and signed a written informed consent.[21] Patients were ineligible if they had evidence of acute respiratory distress, were thought to be unable to complete the trial, or were oxygen dependent.

Eligible patients completed a VAS for dyspnea and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 dyspnea measurement, providing verbal ratings of intensity,[22] and underwent oxygen saturation pulse oximetry. The investigator collected demographic data and determined the most likely pathological causes of the symptom, to a maximum of three causes. Patients were then randomized to receive either air or oxygen at 4 L/min via nasal prongs for 15 minutes, following which dyspnea intensity ratings and oximetry were repeated. Then, following a 30-minute interval without gas, repeat measurements were taken with crossover to the other gas for a further 15 minutes. Measurements of symptom intensity and oximetry were then repeated, and the blinded patient and investigator nominated the preferred gas. Patients were asked to select qualitative descriptors of their experience of dyspnea according to the Dyspnea Assessment Questionnaire.[23] The results of these qualitative data will be presented elsewhere.

Four-liters-per-minute of gas administration is generally the maximum amount that is tolerated for longer-term use when given via nasal prongs and is also the maximum amount that can be achieved via standard home oxygen therapy delivery systems. Thus, 4 L/min was chosen for practical reasons and because this most closely mimics the clinical situation for patients at home. Since the trial was attempting to answer the clinical problem of improvement of dyspnea, gas flows required to correct hypoxia were not conducted for patients prior to trial enrollment.

Institutional ethics committee approval was granted at both centers. The trial was registered with the Clinical Trials Registry. All data were collected on study-specific case record forms and entered into a Microsoft Access database. Data consistency checks were made at the time of data entry and prior to statistical analysis.

Statistical Methods

A sample size of 50 was chosen based upon the primary objective of the study, which was to determine patient preference for oxygen or air. Given a two-sided significance level of 0.05, the study had 90% power to detect a significant difference between the two gases if 60% of patients preferred oxygen, 20% preferred air, and 20% had no preference.

Descriptive statistics of baseline patient characteristics were computed for all patients and by randomized gas sequence. For all patients and the subgroup of hypoxic patients, the change in VAS score and oxygen saturation from pre- to postadministration of gas was analyzed using analysis of variance for a 2×2 crossover design.[24] In a 2×2 crossover trial, it is necessary to consider the effects of carry-over and period. Carry-over refers to the possibility that the effect of the treatment given in the first period (e.g., oxygen) may be carried over to the second period when the next treatment is given (e.g., air), and so might influence response to the second treatment. The period effect refers to the possibility that the response in the first treatment period may

tend to be different from the response in the second period irrespective of the treatment given. In the analysis of variance, an estimate and test for the carry-over effect, the period effect, and the treatment effect were undertaken. Treatment comparisons were then made allowing for the effects of carry-over and period. Results are presented according to the gas received first in accordance with appropriate statistical analysis for a 2×2 cross-over design. Pearson's Chi-squared test was used to assess if the change in EORTC verbal rating was dependent on the gas used, both before the first and the second gas. Patient preference for oxygen or air was compared using Prescott's test.[24] Cohen's kappa statistic was used to measure agreement between patient and investigator assessment of gas preference. The Spearman rank correlation coefficient was computed between VAS score and oxygen saturation after administration of the first and second gas.

Two-tailed *P*-values were reported for all statistical tests. Hypoxic patients were defined as those with oxygen saturation <90% prior to commencing treatment. Statistical analysis was performed using Genstat for Windows 7th edition (VSN International, UK, 2003) and StatXact 6.0 (Cytel Software Corporation, USA, 2003) software.

Results

A total of 51 eligible patients were accrued to the study between August 13, 2001 and January 12, 2005, 17 from The Alfred Hospital and 34 from the Peter MacCallum Cancer Center. Twenty-seven patients (53%) were randomized to the "Air first" arm and 24 (47%) to the "Oxygen first" arm. The patient baseline characteristics are outlined in Table 1. All patients had been exposed to intermittent oxygen therapy prior to trial enrollment.

For 47 patients (92%), cancer was directly responsible for dyspnea. Of these, cancer was deemed to be solely responsible for the symptom in 29. The remaining patients had other causes of dyspnea related either to complications of cancer, such as pneumonia (five patients), or to the treatment of cancer, such as radiation pneumonitis (two patients). Fifteen patients (29%) had unrelated causes contributing to dyspnea, including 11 with COPD. In total, 32 patients had a single cause of dyspnea, 17 had two causes, and 2 had three or more causes.

Response to Gas—VAS

Descriptive statistics are presented in Table 2 of VAS scores prior to and after 15 minutes on each gas. For the "Air first" arm, the median change was an improvement in VAS score of 3 mm (range, −19 to 70 mm) after air and 10 mm (range, −19 to 63 mm) after oxygen. For the "Oxygen first" arm, the median change was an improvement of 11.5 mm (range, −20 to 45 mm) after air and 7 mm (range, −33 to 71 mm) after oxygen. After allowing for carry-over and period effects, there was no significant difference between the two gas types in the mean change in VAS score ($P = 0.622$, air = 8.7 mm, oxygen = 10.5 mm). Mean VAS scores before and after administration of the first and second gas are shown in Fig. 1.

Response to Gas—EORTC Verbal Rating

A summary of EORTC verbal ratings before and after administration of each gas is presented in Tables 2 and 3. According to the EORTC descriptors, patients were assessed as having "improved," "stayed the same," or "worsened" in their shortness of breath from pre- to post-intake of gas. After the first gas, 12 patients (44%) who received air reported an improvement in their shortness of breath, compared to 10 (42%) of those who received oxygen ($P = 0.888$). After the second gas, 9 patients (38%) improved with air and 7 patients (26%) with oxygen ($P = 0.767$) (Fig. 2).

Response to Gas—Oxygen Saturation

Oxygen saturation levels pre- and post-administration of gas are shown in Table 2. The change in oxygen saturation levels from pre- to post-intake of gas was computed for all patients after they received each of the two gas types. There is a significant difference between the two gas types in the mean increase in oxygen saturation ($P < 0.001$, air = 0.94%, oxygen = 5.43%). There was no evidence of a significant correlation between VAS score and oxygen saturation. The Spearman rank correlation coefficient was 0.019 ($P = 0.895$)

Table 1
Patient Baseline Characteristics

		Overall ($n=51$)		Air First ($n=27$)		Oxygen First ($n=24$)	
Characteristic	Category	*n*	%	*n*	%	*n*	%
Sex	Male	31	61	19	70	12	50
	Female	20	39	8	30	12	50
Age (years)	Median	65		65		64	
	Range	33–82		33–81		37–82	
ECOG performance status	2	13	25	7	26	6	25
	3	37	73	19	70	18	75
	4	1	2	1	4	0	0
Cancer diagnosis	NSCLC	22	43	15	56	7	29
	Small cell lung cancer	6	12	2	7	4	17
	Breast cancer	8	16	3	11	5	21
	Colorectal cancer	4	8	1	4	3	13
	Other[a]	11	22	6	22	5	21
Time since diagnosis of cancer (months)	Median	10.7		12.9		9.7	
	Range	0.1–247.4		0.3–186.2		0.1–247.4	

NSCLC = non-small-cell lung cancer.
[a]Other diagnoses include lymphoma, melanoma, sarcoma, carcinoid tumors, and cancers from skin, bladder, and pharyngeal origins.

after the first gas and 0.056 ($P=0.695$) after the second gas.

Gas Preference

Twenty-one patients (41%) expressed a preference for oxygen, 15 (29%) expressed a preference for air, and 15 (29%) expressed no preference. There was no evidence of a significant difference in patient preference for air or oxygen ($P=0.357$). The investigator assessment of patient preference was 20% for air, 35% for oxygen, 43% no preference, and one patient was not assessed. Using Cohen's kappa statistic, the agreement between patient and investigator in their assessment of gas preference was significant ($P<0.001$, kappa = 0.501, 95% confidence interval: 0.305–0.697).

Hypoxic Patients

In the subgroup of 17 hypoxic patients, mean change in VAS score did not differ significantly between air and oxygen ($P=0.812$, air = 15.4 mm, oxygen = 13.3 mm) but mean oxygen saturation levels increased significantly more for oxygen than for air ($P=0.005$, air = 2.7%, oxygen = 10.7%). Following oxygen administration, hypoxia was corrected in 13 of the 17 patients. Of the 17 hypoxic patients, 35% expressed a preference for air, 24% expressed a preference for oxygen, and 41% expressed no preference.

Discussion

A number of authors have commented upon the difficulties in conducting clinical research in palliative care. The problems encountered have included the difficulties of recruitment and attrition of patients.[25,26] Having enrolled patients, difficulties arise with the problems of isolating the effect of a single intervention from the complexities of an ever-changing disease state and the heterogeneity of the patient group.[27,28] In an attempt to circumvent some of these difficulties encountered by other researchers, the intervention in this trial was simple and brief, with the data collection completed within 2 hours of enrollment. In addition, the symptom examined was one that is common in a cancer population. Despite this, recruitment continued for almost 5 years until the required 50 participants were enrolled. A significant component of this related to the clinical fragility of the patients. Many patients were screened and complained of dyspnea, and for reasons of accessibility, these were largely inpatients. But unless patients identified as eligible were able to be enrolled in the trial within 24 hours, most deteriorated, with cognitive impairment or increasing oxygen

Table 2
Patient Responses Pre- and Post-administration of Gas

		Overall ($n=51$)		Air First ($n=27$)		Oxygen First ($n=24$)	
Assessment	Category	*n*	%	*n*	%	*n*	%
Breathlessness immediately before first gas (mm)	Median	45		52		43	
	Range	23–92		23–92		31–78	
Breathlessness after 15 minutes on first gas (mm)	Median	43		45		34.5	
	Range	0–83		10–83		0–68	
Breathlessness immediately before second gas (mm)	Median	53		57		42	
	Range	10–88		15–88		10–70	
Breathlessness after 15 minutes on second gas (mm)	Median	34		40		30.5	
	Range	0–92		4–92		0–90	
Shortness of breath immediately before first gas	Not at all	1	2	1	4	0	0
	A little	22	43	10	37	12	50
	Quite a bit	23	45	13	48	10	42
	Very much	4	8	2	7	2	8
	Not recorded	1	2	1	4	0	0
Shortness of breath after 15 minutes on first gas	Not at all	6	12	3	11	3	13
	A little	33	65	17	65	16	67
	Quite a bit	12	24	7	26	5	21
	Very much	0	0	0	0	0	0
Shortness of breath immediately before second gas	Not at all	1	2	1	4	0	0
	A little	35	69	17	63	18	75
	Quite a bit	15	29	9	33	6	25
	Very much	0	0	0	0	0	0
Shortness of breath after 15 minutes on second gas	Not at all	8	16	3	11	5	21
	A little	37	73	20	74	17	71
	Quite a bit	5	10	4	15	1	4
	Very much	1	2	0	0	1	4
Oxygen saturation immediately before first gas	Median	93		93		93	
	Range	70–98		70–98		71–98	
Oxygen saturation after 15 minutes on first gas	Median	94		93		97	
	Range	69–100		69–98		73–100	
Oxygen saturation immediately before second gas	Median	92		93		90	
	Range	69–98		74–98		69–98	
Oxygen saturation after 15 minutes on second gas	Median	97		98		93	
	Range	73–99		86–99		73–98	
Hypoxic prior to first gas		17	33	8	30	9	38
Hypoxic after first gas		13	25	9	33	4	17
Hypoxic prior to second gas		18	35	8	30	10	42
Hypoxic after second gas		12	24	4	15	8	33

requirements, to the point where they were unable to participate in the study. Despite this study being specifically designed to cater to this particular group of patients, it nevertheless proved difficult for them to participate in the intervention.

The experience of the researchers was that dyspnea in an inpatient cancer population indicated an extremely poor prognosis. This was confirmed by the Eastern Cooperative Oncology Group (ECOG) Performance Status, with the majority of patients (73%) having an ECOG performance status rating of 3. In addition, they had extensive malignant disease, with nearly half of the participants having multiple causes for the complaint of dyspnea. However, it is a particular strength of this trial that it did in fact study the palliative care population of interest.

The improvement of oxygen saturation when oxygen was administered indicated effective delivery of oxygen within the short study time of 15 minutes. While hypoxia was not corrected in all cases, with four patients remaining hypoxic despite oxygen administration, the oxygen flow mimicked the standard application of oxygen administered in the domiciliary setting. Under these conditions, the improvement of mean oxygen saturations did not correlate with a reduction of mean VAS ratings of dyspnea. Instead, average VAS scores improved with both interventions. It should not be anticipated that there would be a linear relationship between oxygen saturations and

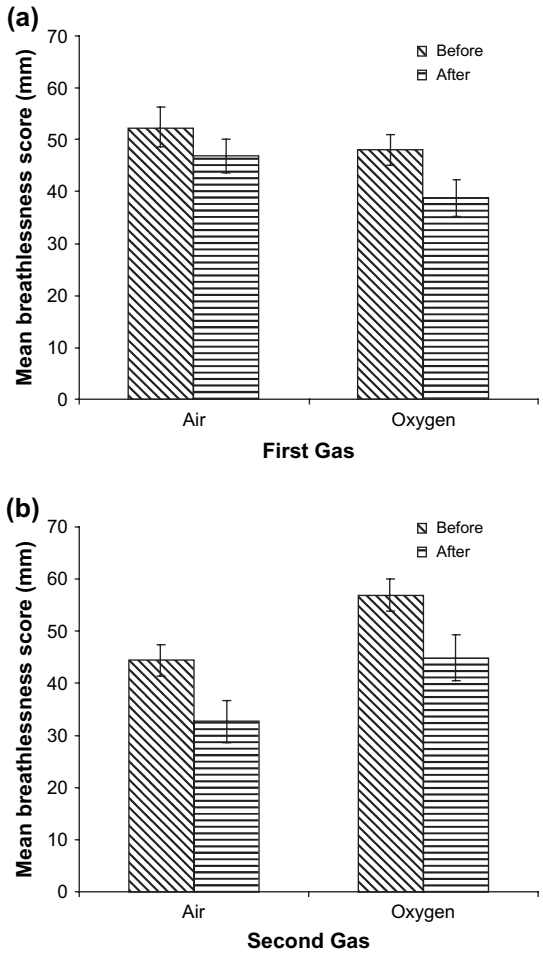

Fig. 1. Mean VAS score before and after administration of the first (a) and second (b) gas. The error bar represents standard error of mean.

complaints of dyspnea in view of the subjective nature of symptom reporting, the multiple factors contributing to the generation of dyspnea, and the complexity of the physiology of oxygen-hemoglobin binding, which does not occur according to linear dynamics. Nevertheless, the lack of correlation between oxygen saturation and dyspnea complaints is an important finding of this study to disseminate, since much practice in acute hospitals revolves around "treating" dyspnea by responding to oxygen saturation levels. Other authors have similarly demonstrated that standard clinical tools, such as forced expiratory volume in one second and forced vital capacity, do not correlate with the experience of dyspnea in patients with advanced cancer.[29] The results of this study add further weight to the statement

Table 3
Change in EORTC Verbal Rating

	Improved		Same		Worse	
	n	%	*n*	%	*n*	%
First gas						
Air[a]	12	44	13	48	1	4
Oxygen	10	42	13	54	1	4
Second gas						
Air	9	38	14	58	1	4
Oxygen	7	26	19	70	1	4

[a]One patient was not assessed prior to first gas.

that dyspnea is a subjective symptom and its adequate management requires full inquiry of the patient, not simply responding to abnormal investigations. Appropriate management of patients with advanced cancer must include an evaluation of the burden of symptoms irrespective of the results of investigations.

Consistent with the results of Booth et al., patients on average improved with gas administration.[20] Air was not considered a placebo arm in this trial, with air administration on average conferring considerable benefit. The benefits of air and oxygen were not significantly different. Since hypoxia was not corrected with oxygen in 4 of the 17 patients, the lack of significant difference between the gases in this group needs to be interpreted with caution. But this finding has clinical implications, because while using the equivalent of standard domiciliary oxygen flow, patients demonstrated no difference in response between air and oxygen. Importantly, no clear preference expressed for either treatment arm according to the criteria set for the trial. It appears that the act of treatment is important, with treatment in this study consisting of gas administration via nasal prongs. The mechanism by which this improvement is achieved is not clear.

The possibility of a placebo response to any treatment including air must be considered. Since all these patients had previously been exposed to gas administration, it is not treatment naivety informing the results. The trial was conducted over a short treatment period, and it may be that the initial response to air would lessen during longer-term administration, as would be expected in a placebo response.

Another possible explanation for the lack of differential response is that mechanoreceptors

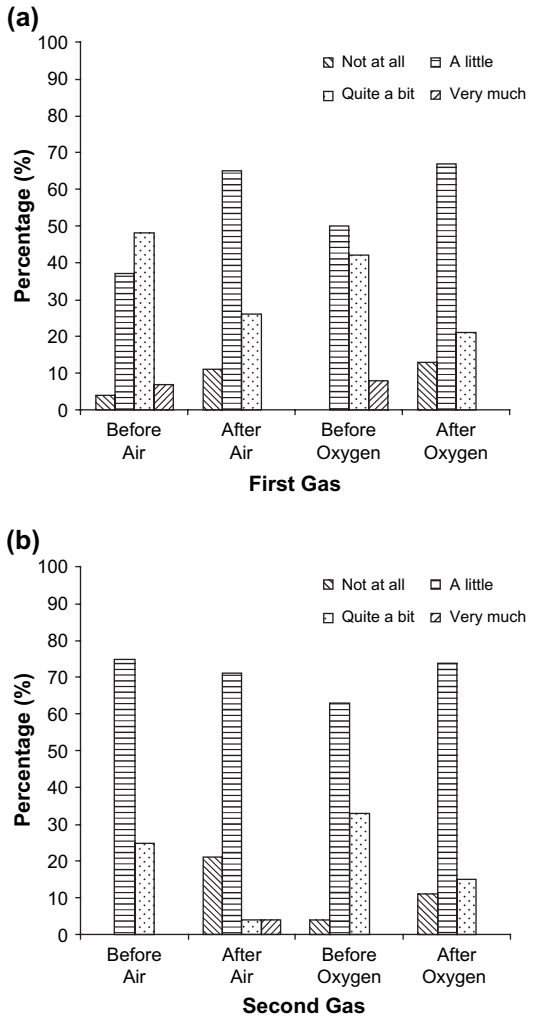

Fig. 2. EORTC verbal rating before and after administration of the first (a) and second (b) gas.

are stimulated by gas administration, bringing about a reduction in the sensation of dyspnea. In studies on normal subjects, breathlessness has been found to be reduced by oral mucosal stimulation and cold facial stimulation, suggesting the mechanism by which open windows and fans may be useful.[30,31] Others have suggested that wearing nasal prongs appears to bring about a reduction of breathlessness in patients with COPD.[32] The role of the establishment of a therapeutic environment may also be important in this trial. The presence of an interested researcher throughout the intervention may lead to a reduction of anxiety and fear, which, in turn, may result in a reduction of symptom intensity.

There were limitations to this study that may influence the results. First, eligible patients had to record a dyspnea score at rest of 30 mm on VAS. A number of patients complained of significant dyspnea with activity but at rest did not reach this score, rendering them ineligible for study inclusion. In order to control for differing levels of activity, the study required patients to remain at rest for the study duration. It is possible that if gases were administered to patients during activity, there may have been a differential preference and response to the gases that were not apparent at rest. Second, the investigators defined a clinically significant response to oxygen to be a preference for oxygen chosen by 60% of patients. However, the exact nature of what constitutes a clinically significant improvement in this symptom is uncertain. While there has been some discussion and attention to this issue in pain research,[33] the same remains to be established for other symptoms, including dyspnea. If a clinically significant improvement occurred at lower increments of improvement, then this study may not have been adequately powered. The study methodology and response criteria were informed by the considerable clinical experience of the investigators, and, therefore, this study represents the best available evidence at the time.

Conclusion

In agreement with the findings of Booth et al.,[20] this study established that both oxygen and air administered intranasally improve the mean sensation of dyspnea for patients with advanced cancer. There is no significant difference between the gases in either VAS or preferences expressed. This is despite oxygen significantly improving mean oxygen saturation measures. Nor did the group of hypoxic patients show mean greater improvement with, or preference for, oxygen. Notably, oxygen saturation measures do not correlate with ratings of dyspnea, which is in keeping with the knowledge that dyspnea in advanced cancer is the expression of multiple sensations and experiences, and not simply related to oxygen tension.

This study has highlighted the need to establish what constitutes a clinically significant

improvement of the symptom of dyspnea. This requires investigation as a matter of urgency such that future studies may be designed and powered to reflect clinically relevant outcomes. Once established, the role of oxygen to relieve dyspnea in advanced cancer may require further investigation, with particular attention given to longer-term studies. Until such time, the current state of evidence suggests that the administration of intranasal gas, either air or oxygen, improves the sensation of dyspnea in advanced cancer.

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