Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial

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Lancet 2010; 376: 784–93

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Summary

Background Palliative oxygen therapy is widely used for treatment of dyspnoea in individuals with life-limiting illness who are ineligible for long-term oxygen therapy. We assessed the effectiveness of oxygen compared with room air delivered by nasal cannula for relief of breathlessness in this population of patients.

Methods Adults from outpatient clinics at nine sites in Australia, the USA, and the UK were eligible for enrolment in this double-blind, randomised controlled trial if they had life-limiting illness, refractory dyspnoea, and partial pressure of oxygen in arterial blood (PaO_2) more than 7·3 kPa. Participants were randomly assigned in a 1:1 ratio by a central computer-generated system to receive oxygen or room air via a concentrator through a nasal cannula at 2 L per min for 7 days. Participants were instructed to use the concentrator for at least 15 h per day. The randomisation sequence was stratified by baseline PaO_2 with balanced blocks of four patients. The primary outcome measure was breathlessness (0–10 numerical rating scale [NRS]), measured twice a day (morning and evening). All randomised patients who completed an assessment were included in the primary analysis for that data point (no data were imputed). This study is registered, numbers NCT00327873 and ISRCTN67448752.

Findings 239 participants were randomly assigned to treatment (oxygen, n=120; room air, n=119). 112 (93%) patients assigned to receive oxygen and 99 (83%) assigned to receive room air completed all 7 days of assessments. From baseline to day 6, mean morning breathlessness changed by –0·9 points (95% CI –1·3 to –0·5) in patients assigned to receive oxygen and by –0·7 points (–1·2 to –0·2) in patients assigned to receive room air (p=0·504). Mean evening breathlessness changed by –0·3 points (–0·7 to 0·1) in the oxygen group and by –0·5 (–0·9 to –0·1) in the room air group (p=0·554). The frequency of side-effects did not differ between groups. Extreme drowsiness was reported by 12 (10%) of 116 patients assigned to receive oxygen compared with 14 (13%) of 108 patients assigned to receive room air. Two (2%) patients in the oxygen group reported extreme symptoms of nasal irritation compared with seven (6%) in the room air group. One patient reported an extremely troublesome nose bleed (oxygen group).

Interpretation Since oxygen delivered by a nasal cannula provides no additional symptomatic benefit for relief of refractory dyspnoea in patients with life-limiting illness compared with room air, less burdensome strategies should be considered after brief assessment of the effect of oxygen therapy on the individual patient.

Funding US National Institutes of Health, Australian National Health and Medical Research Council, Duke Institute for Care at the End of Life, and Doris Duke Charitable Foundation.

Introduction

Dyspnoea has been defined as "a subjective experience of breathing discomfort that consists of qualitatively distinct sensations varying in intensity. The experience derives from interactions among multiple physiological, psychological, social, and environmental factors".[1] Prevalence of severe dyspnoea has been reported as 65%, 70%, and 90% in terminally ill patients with heart failure, lung cancer, and chronic obstructive pulmonary disease (COPD), respectively.[2] Dyspnoea often presents as a chronic disorder that intensifies during the dying process;[3] it can erode quality of life, psychological wellbeing, and social functioning.[4]

The exact nature and cause, and therefore appropriate treatment, of dyspnoea remain elusive. Objective measures, such as desaturation with exercise, hint at underlying pathology, but do not reliably indicate subjective experience. Current pharmacological treatments for dyspnoea include opioids, psychotropic drugs, inhaled furosemide, helium-oxygen mixture (heliox 28; 72% helium, 28% oxygen), and oxygen; opioids remain the mainstay of treatment.[5,6] Palliative interventions seek to alleviate the sensation of breathlessness; they are generally applied in palliative care irrespective of underlying pathology and respiratory functioning.[7]

Long-term oxygen therapy is indicated for COPD patients with severe hypoxaemia (partial pressure of oxygen in arterial blood [PaO_2] ≤7·3 kPa at rest); such treatment improves survival, dyspnoea, and functional

status.[8–10] Palliative oxygen is frequently prescribed to manage dyspnoea in people with advanced life-limiting illness, irrespective of PaO_2, and is generally considered standard of care.[11,12] More than 70% of physicians caring for patients with dyspnoea in palliative care prescribe palliative oxygen, usually for refractory symptoms (65%) or at the patient's request (30%).[13] There is not, however, clear evidence showing symptomatic benefit of palliative oxygen,[14–16] although the intervention entails cost and logistical burden. Hospices worldwide commonly prescribe oxygen on the basis of symptomatic criteria, rather than on the basis of pulse oximetry readings. In Canada, compassionate use of oxygen that does not meet criteria for long-term oxygen therapy represents 30% of the budget for oxygen therapy.[9] Lack of evidence to support use of palliative oxygen and absence of available clinical practice guidelines have led to inconsistent access and variable use.[17]

This study assessed the symptomatic effectiveness of palliative oxygen for patients with life-limiting illness, refractory breathlessness, and PaO_2 more than 7·3 kPa. The comparator was room air provided via a modified concentrator (altered according to a standard protocol); the null hypothesis was that oxygen therapy is not superior to room air in this setting.

Methods

Participants

This international, multicentre, double-blind, randomised controlled trial was undertaken from April, 2006, to March, 2008. The study protocol was approved by the Duke University Health System Institutional Review Board, and local research and ethics committees or institutional review boards of all participating sites. The full protocol for the trial is available from the corresponding author.

Participants were recruited from outpatient pulmonary, palliative care, oncology, and primary care clinics at five sites in Australia, two in the USA, and two in the UK. Patients older than 18 years of age were eligible for inclusion if they had PaO_2 more than 7·3 kPa, refractory dyspnoea related to life-limiting illness (determined by the referring physicians), received maximum treatment for underlying disease, reported dyspnoea at rest or with negligible exertion of 3 or more on the Medical Research Council (MRC) categorical dyspnoea scale,[18] were on stable medications for 1 week before participation, and were judged by their physicians to have expected survival of at least 1 month. Patients were excluded if they met international eligibility guidelines for long-term oxygen therapy, had a history of hypercarbic respiratory failure with oxygen, had anaemia (haemoglobin <100 g/L), hypercarbia ($PaCO_2$ >6·7 kPa), or cognitive impairment (Folstein mini-mental status examination[19] score <24/30), smoked, or had had a respiratory or cardiac event in the previous 7 days. All participants provided written informed consent.

Randomisation and masking

Participants who provided consent and met screening criteria underwent arterial blood gas assessment either in the outpatient clinic or at home by use of a standard protocol. Patients with PaO_2 more than 7·3 kPa and who met all eligibility criteria were randomly assigned in a 1:1 ratio to receive oxygen or room air delivered by a concentrator and nasal cannula. Participants were stratified by baseline PaO_2 (≤9·3, 9·4 to ≤10·7, 10·8 to ≤12·0, 12·1 to ≤13·3 kPa) and randomised to treatment by a central computer-generated system available (via web or telephone) through the pharmacy service at Repatriation General Hospital (Adelaide, Australia) with balanced blocks of four patients per stratum, on the basis of Fisher and Yates' statistical tables.[20] Intervention assignment was communicated from the randomisation service to the medical gas company who prepared the concentrators and delivered masked concentrators to the patients' homes.

Patients, individuals delivering the interventions, investigators, and nurses were masked to treatment assignments. Oxygen and room air concentrators were identical in appearance.

Procedures

The intervention lasted 7 days. This duration was selected because, in a preparatory survey, palliative care physicians said that a definitive study of palliative oxygen that would provide compelling evidence about dyspnoea and quality of life would require 3–7 days.[13] Although dyspnoea caused by hypoxaemia or hypoxygenation can be relieved by oxygen within a short period of a few minutes or hours, we chose the conservative estimate provided by practising clinicians because such physicians represent the practical audience for the results of this study.

A medical gas concentrator was delivered to the participant's home in the afternoon on day 0 and retrieved in the afternoon on day 7. By use of a standard protocol, the medical gas company serving each site modified half the concentrators to dispense room air without setting off the internal alarm that sounds when oxygen concentrations are low. Medical gas was administered continuously at 2 L per min through the nasal cannula. Participants were instructed to use the concentrator for at least 15 h per day. No substantial modifications were made to the protocol after study commencement.

Outcomes

The primary outcome was "breathlessness right now", recorded by the patient twice a day (within 30 min of waking up [morning] and going to bed [evening]) in a diary with a 0–10 numerical rating scale (NRS; 0="not breathless at all", 10="breathlessness as bad as you can imagine"), which is a valid instrument for this population of patients.[21] A 1-point reduction in self-reported dyspnoea is generally deemed a clinically relevant change;[22]

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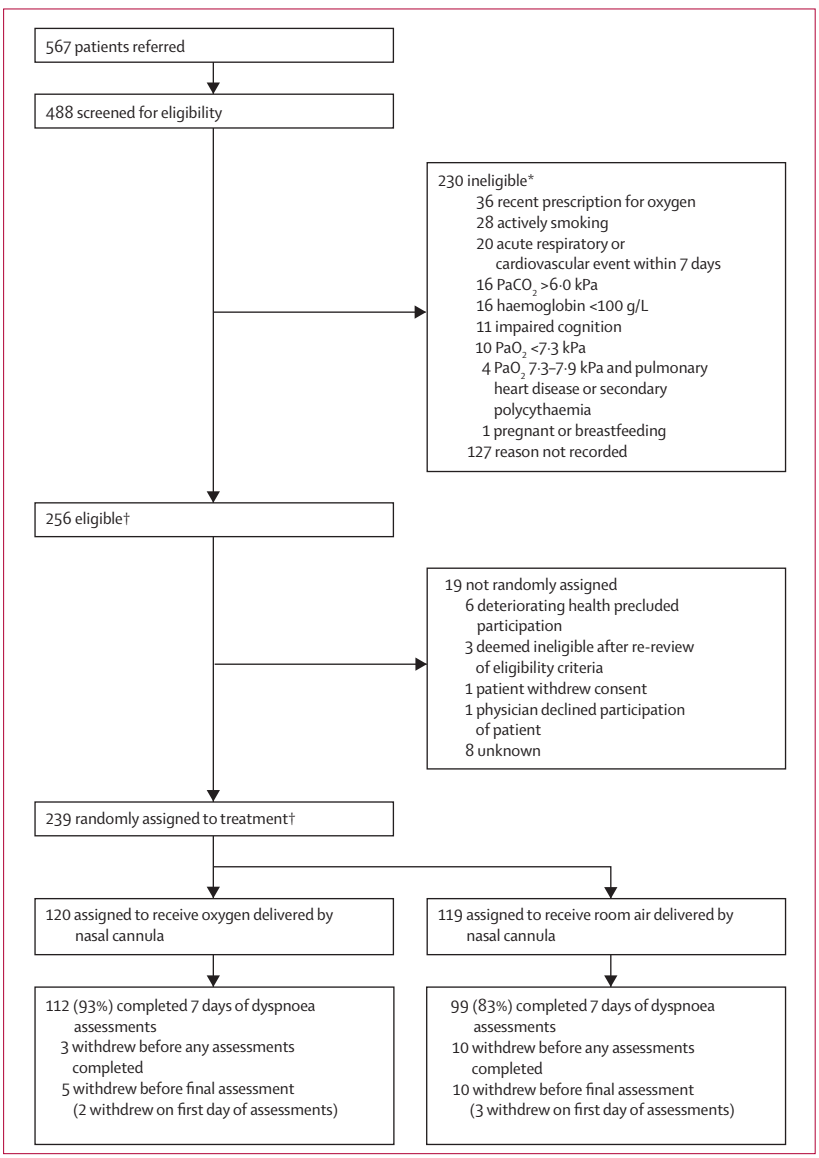

Figure 1: **Trial profile**
$PaCO_2$=partial pressure of carbon dioxide in arterial blood. PaO_2=partial pressure of oxygen in arterial blood. *A patient could have more than one reason for ineligibility. †237 eligible patients plus two ineligible patients were randomly assigned to treatment. One ineligible patient had $PaCO_2$ 6·3 kPa, and the other had an acute respiratory or cardiovascular event in the past 7 days. Both patients were included in the analysis.

therefore, a 1-point reduction was used to define response for all NRS measures in the study.

Diaries also captured secondary outcomes: average dyspnoea in the previous 24 h (0–10 NRS), worst breathlessness in the previous 24 h (0–10 NRS), relief of dyspnoea during the previous 24 h (0–10 NRS), and ordered categorical scales for functional impact, sleep disturbance, drowsiness, anxiety, nasal irritation, and nose bleeds. Quality of life was assessed every day by use of the McGill quality of life questionnaire (MQoLQ),[23] which consists of 17 items and includes a single-item measure of global quality of life (0–10 NRS). Functional changes were assessed with the modified Medical Research Council (MRC) 4-point categorical dyspnoea scale[24] and dyspnoea exertion scale.[25] Participants were asked to record secondary measures once a day, generally in the evening unless when more relevant to morning (eg, sleep).

Participants began to complete diaries 2 days before the intervention started (day –2). Research personnel assessed the full MQoLQ and performance status (Eastern Cooperative Oncology Group [ECOG] performance status scale[26]) on days –2, 0, and 6. At the end of the study, respondents were asked to rate their overall experience with the intervention and to state whether they wished to continue with oxygen therapy (via concentrator).

Side-effects were patient-reported and measured by use of 5-point Likert-type categorical scales. No changes were made to study outcomes after commencement of the trial.

Statistical analysis

The sample size estimate of 240 participants was based on the primary outcome variable, previous experience in a trial of morphine compared with placebo in patients with dyspnoea,[7] and use of a Student's *t* test to compare interventions at day 6. Assumptions were a 20% attrition rate, NRS variance of 6, and a 1-point NRS change to define clinical relevance. A sample size of 240 participants would provide 80% power to detect a 1-point difference with α=0·05. Actual NRS variance and attrition were less than expected. Repeated-measures analyses were used rather than the Student's *t* test.

All randomised patients who completed an assessment were included in the primary analysis for that data point (no data were imputed). Analyses were done with SAS version 9.1. Descriptive statistics were used to characterise populations. Internal consistency of each subscale of the MQoLQ was confirmed with Cronbach's α before we proceeded with analyses.

Repeated-measures models were used to estimate the effect of time and intervention on all efficacy endpoints. Mixed-model repeated-measures analysis (SAS PROC MIXED) with an unstructured covariance matrix was used to estimate the effect of time on mean dyspnoea and quality of life score by intervention. Separate repeated-measures logistic regression models were used to estimate change over time by intervention in participants with high MRC scores, and in participants reporting sleep disturbance because of breathlessness. These models were created with generalised estimating equations (GEE, SAS PROC GENMOD), on the assumption of an unstructured covariance matrix and with categorical variables of time (days –1 to 6), intervention (oxygen *vs* air), and interaction (time by treatment intervention). The interaction term was included to assess the consistency of treatment effect over time. All models included participants who

completed the baseline assessment, whether or not they received the assigned intervention. Missing assessments were few and assumed to be missing at random.

To identify variables that best predicted response, proportions of responders were calculated, with response defined as a 1-point NRS or more decrease from day –1 to day 6 (ie, participants still showing improvement at end of intervention). This post-hoc analysis included only participants who completed both baseline and day 6 assessments. A series of logistic regression models estimated the effect of each predictor on response and the difference in effect between treatment groups. Each model included treatment group, one predictor, and interaction. Potential predictors were baseline dyspnoea (low [0–3 points], moderate [4–6 points], severe [7–10 points]), age, sex, COPD status (yes or no), PaO_2 at enrolment, rapid decline in breathlessness before enrolment (declining MRC scores over 4 weeks), ECOG at day 0, opioid use, previous oxygen use, and study site. Predictors that had a potential effect on response (type III Wald χ^2 test with $p \leq 0 \cdot 2$) were included in a full interaction model. Predictive variables in the interaction model were identified through stepwise selection. Morning and evening changes in breathlessness were modelled separately.

This study is registered, numbers NCT00327873 and ISRCTN67448752.

Role of the funding source

The sponsors of the study had no role in study design, protocol development, data collection, review, data analysis, or writing of the report, apart from through delegated oversight to a data safety monitoring board appointed by the US National Institutes of Health. Study investigators and statisticians (APA, DCC, JEH, and JM), as well as the data safety monitoring board, had full access to the primary data. The study investigators had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Table 1 shows baseline characteristics of study participants. 13 (5%) participants withdrew before the study started and completed no assessments. Additionally, 15 (6%) patients withdrew before completing the final (day 6) assessment.

The primary outcome, breathlessness, did not differ between groups at any time during the study period (figure 2). For morning dyspnoea, 58 (52%) of 112 patients assigned to oxygen and 40 (40%) of 101 patients assigned to room air responded to the interventions. For evening dyspnoea, response rates were 42% for both interventions (oxygen, n=47; room air, n=42).

Longitudinal analyses explored the clinical effect of the interventions. Over the intervention period, there was significant improvement in morning and evening dyspnoea in both groups (time $p<0 \cdot 0001$, both models; figure 2). Table 2 shows absolute and relative changes in dyspnoea and quality of life during the 7-day study

	Oxygen group (n=120)	Room air group (n=119)
Men	76 (63%)	71 (60%)
Cause of dyspnoea		
COPD	71 (59%)	81 (68%)
Restrictive lung disease	5 (4%)	9 (8%)
Bronchiectasis	4 (3%)	3 (3%)
Primary pulmonary hypertension	0	3 (3%)
Primary lung cancer	18 (15%)	15 (13%)
Known secondary lung cancer	2 (2%)	3 (3%)
Pleural effusion	2 (2%)	0
End-stage cardiomyopathy	2 (2%)	5 (4%)
Other	16 (13%)	0
Age (years)	73 (11)	74 (10)
Baseline morning dyspnoea (day –1; 0–10 NRS)	4·5 (2·2)	4·6 (2·4)
Baseline evening dyspnoea (day –1; 0–10 NRS)	4·7 (2·2)	4·7 (2·3)
Baseline global QoL (day 0; 0–10 NRS)	6·2 (2·2)	5·9 (2·0)
MRC dyspnoea functional scale		
Breathless when walking at own pace	0	1* (1%)
Breathless when walking 100 yards	54 (45%)	59 (50%)
Breathless when dressing or undressing	66 (55%)	59 (49%)
Dyspnoea exertion scale†‡		
1	11 (9%)	9 (8%)
2	54 (46%)	50 (44%)
3	26 (22%)	29 (26%)
4	24 (20%)	23 (20%)
5	4 (3%)	2 (2%)
ECOG performance status‡§		
0	0	1 (1%)
1	40 (34%)	29 (26%)
2	48 (40%)	61 (54%)
3	31 (26%)	22 (19%)
Regular oxygen previously prescribed	56 (47%)	59 (50%)
PaO_2 (kPa), mean (SD; range)	10·3 (1·6; 7·5–16·3)	10·1 (1·6; 7·7–17·6)
$PaCO_2$ (kPa), mean (SD; range)	5·2 (0·5; 3·7–6·8)	5·1 (0·7; 3·6–6·8)
Strata for randomisation (PaO_2 concentration, kPa)		
≤9·3	40 (33%)	44 (37%)
9·4 to ≤10·7	37 (31%)	38 (32%)
10·8 to ≤12·1	27 (23%)	22 (18%)
≥12·2	16 (13%)	15 (13%)
Total time of concentrator use (h)¶	93 (36)	98 (44)

Data are number (%) or mean (SD), unless otherwise indicated. COPD=chronic obstructive pulmonary disease. NRS=numerical rating scale. QoL=quality of life. MRC=Medical Research Council. ECOG=Eastern Cooperative Oncology Group. PaO_2=partial pressure of oxygen in arterial blood. $PaCO_2$=partial pressure of carbon dioxide in arterial blood. *This individual met the MRC eligibility criteria during enrolment. †Dyspnoea exertion scale: 1=able to walk at own pace on the level without getting out of breath; 2=becomes breathless when walking around the house or on the hospital ward on the level at own pace; 3=becomes breathless if moves around in bed or get out of bed; 4=becomes breathless when talking; 5=is breathless at rest. ‡Oxygen group, n=119; room air group, n=113. §ECOG performance status: 0=fully active, able to carry on all pre-disease performance without restriction; 1=restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (eg, light house work, office work); 2=ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours; 3=capable of only limited self-care, confined to bed or chair more than 50% of waking hours. ¶15 h per day, per protocol=105 h.

Table 1: **Characteristics of the study population**

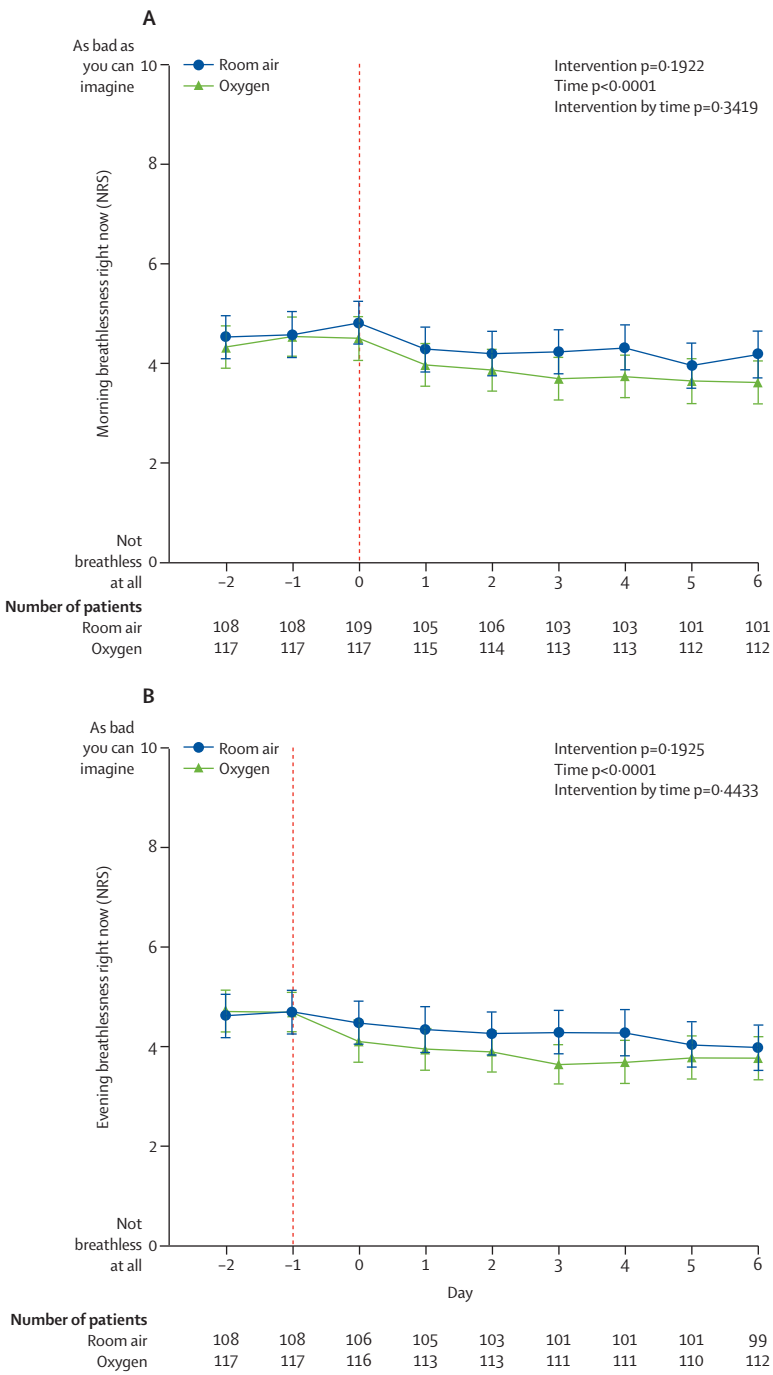

Figure 2: **Morning and evening dyspnoea during the study**
Dyspnoea was measured on a 0–10 numerical rating scale (NRS), with which the patient reported "breathlessness right now". The baseline assessment (dotted line) was the last assessment completed before initiation of the intervention on day 0. All non-missing assessments were included in the analysis; the number of patients per group indicates how many assessments were available at each timepoint. Error bars represent 95% CIs. p values are from repeated-measures mixed models. Intervention is the main effect for treatment group, time is the main effect for time period, and intervention by time is the statistical interaction for the main effects.

See Online for webappendix

period in oxygen and room air groups and in both groups combined. Assignment to oxygen seemed to have greater effect on relative change in morning dyspnoea, whereas room air had greater effect on relative change in evening dyspnoea (table 2). The greatest decrease in morning dyspnoea was between day 0 and day 1 and for evening dyspnoea between day –1 and day 0 (figure 2), both less than a day after arrival of the concentrator. Of the 177 (74%) patients whose evening breathlessness decreased by 1 point or more, 97 (55%) improved within the first 24 h of the intervention and 156 (88%) improved within the first 72 h. Relief of dyspnoea in the previous 24 h, measured on a 0–10 NRS based on the Brief Pain Inventory,[27] showed similar results (figure 3).

Change in quality of life did not differ between groups (figure 4). Results of MQoLQ individual items and subscales were similar between groups. Overall, the absolute increase in global quality of life scores was 0·7 points (95% CI 0·5–0·9; table 2); 87% of improvement in quality of life occurred within the first 3 days after receipt of the concentrator.

All other patient-reported outcomes reflected the trends in dyspnoea and quality of life. The proportion of patients reporting the worst level of functioning on the MRC dyspnoea scale (MRC=4; "breathless when undressing"), and sleep disturbed by breathlessness, decreased during the 7-day study, without differences between groups (webappendix).

Significant predictors of morning response were intervention (oxygen *vs* air) and baseline dyspnoea (severe *vs* moderate *vs* low; table 3). Compared with those in the room air group, participants in the oxygen group were more likely to have an improvement in morning dyspnoea (odds ratio [OR] 2·0; 95% CI 1·1–3·5); participants with severe baseline dyspnoea were more likely to have a response than were participants with low baseline dyspnoea (OR 5·3, 2·2–12·8); participants with severe baseline dyspnoea were more likely to have a response than were those with moderate baseline breathlessness (OR 3·4, 0·8–3·0). Baseline dyspnoea, but not intervention, similarly predicted evening response. No other participant characteristics predicted response. The effect of the interventions was similar irrespective of cause of dyspnoea, performance status, opioid use, and baseline oxygenation.

43 (18%) of all 239 participants did not want to receive oxygen after the study; 63 (26%) said that they derived no benefit from the intervention; 41 (17%) requested and received unblinded oxygen after the study; 74 (31%) requested oxygen but did not receive it; 18 (8%) did not respond to the question. Distributions of preferences were similar between groups.

There were few adverse events and no clinically meaningful difference between groups in frequency of side-effects (table 4). In the questionnaire, participants had the option to report additional side-effects, which were reviewed by the data safety monitoring board. No other side-effects were reported.

Discussion

This study shows that compared with room air delivered by a nasal cannula, oxygen provides no additional symptomatic benefit for relief of refractory breathlessness in patients with PaO_2 more than 7·3 kPa. Intensity of dyspnoea decreased during the study in both groups, temporally related to the provision of the concentrator; improvement in quality of life scores and exertional capacity mirrored changes in breathlessness. Breathlessness scores of patients with moderate to severe baseline dyspnoea improved most, irrespective of intervention assignment.

Historically, a compassion-based rationale has underpinned clinical decisions about use of palliative oxygen. Physicians often prescribe palliative oxygen for patients with refractory dyspnoea and PaO_2 more than 7·3 kPa despite a paucity of definitive evidence to support efficacy in this setting. Previous studies of palliative oxygen and room air have been difficult to interpret because they were small, inadequately controlled, or had unclear outcomes. This effectiveness study ensured masked identical standard interventions, adequate sample size, sufficient study duration to assess outcomes, and patient-centred outcomes that were meaningful for the target population.

The temporal relation between gas delivery and reduction in breathlessness suggests that room air delivered by a nasal cannula can be considered as an intervention rather than as a placebo. Previous small studies of palliative oxygen compared with room air have also shown improvements with both gases.[28,29] Possible reasons for these findings are that the movement of any gas across the nasal passages affects the sensation of dyspnoea; the presence of an intervention alleviates the patient's anxiety and related breathlessness; the concentrator itself might function as a placebo, inducing expectation of benefit; or, the extra attention that the patient receives during study participation improves psychological status, thereby reducing breathlessness. In a similar longitudinal study, dyspnoea gradually worsened over an 8-day period, suggesting that study participation does not, in itself, lessen dyspnoea.[7]

In both study groups, a temporal relation between dyspnoea, quality of life, exertional capacity, and sleep improvement after introduction of the intervention was recorded. Because patients with intractable symptoms showed substantial benefit from both interventions, these results warrant further investigation to establish the gases' relative effect and feasibility, and to determine whether this finding was a placebo effect from study participation or a meaningful medical intervention. Additionally, these results should serve to guide clinicians in the best use of medical gases to relieve patients' breathlessness.

Are these results clinically significant? The absolute mean change in morning and evening dyspnoea (–0·8, 95% CI –1·1 to –0·5 in the morning; –0·4, –0·7 to –0·1 in the evening) reflects an 18% and 9% relative reduction, respectively. In patients with refractory symptoms, a 9% reduction in intensity might be clinically meaningful and most individuals would find an 18% improvement important. Overall, 46% and 42% of individuals responded to the intervention in the morning and evening, respectively. These proportions are similar to the proportions of patients who respond to opioids.[7,30] Subgroup analyses showed that the effect of the interventions was similar irrespective of current opioid

	Oxygen group	Room air group	Overall	p value
Change in morning dyspnoea (baseline to day 6)				
Absolute change (95% CI)	–0·9 (–1·3 to –0·5)	–0·7 (–1·2 to –0·2)	–0·8 (–1·1 to –0·5)	0·504
Relative change (%)	–20%	–15%	–18%	..
Change in evening dyspnoea (baseline to day 6)				
Absolute change (95% CI)	–0·3 (–0·7 to 0·1)	–0·5 (–0·9 to –0·1)	–0·4 (–0·7 to –0·1)	0·554
Relative change (%)	–7%	–11%	–9%	..
Change in global QoL (baseline to day 6)				
Absolute change (95% CI)	0·7 (0·4 to 1·0)	0·7 (0·4 to 1·0)	0·7 (0·5 to 0·9)	0·966
Relative change (%)	11%	12%	12%	..

Dyspnoea was measured on a 0–10 numerical rating scale. Relative change in dyspnoea is the absolute change in dyspnoea during the study period divided by the baseline mean dyspnoea score. Global quality of life (QoL) was reported daily on a single-item 0–10 numerical rating scale. Relative change in QoL is the absolute change in QoL during the study period divided by the baseline mean QoL score.

Table 2: **Absolute and relative changes in dyspnoea and quality of life during the 7-day study period**

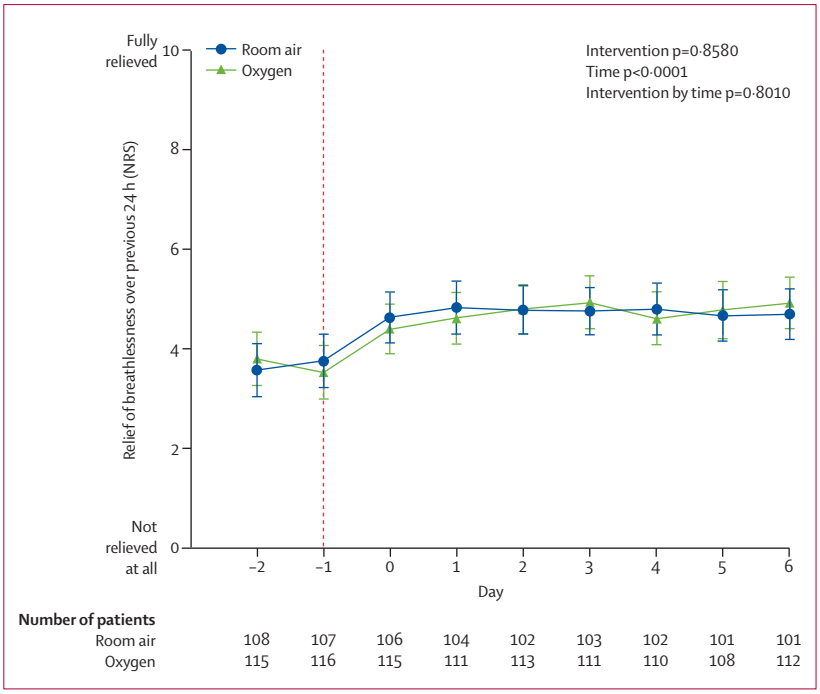

Figure 3: **Relief of dyspnoea during the previous 24 h**

Patients reported their "relief of breathlessness over the previous 24 hours" by use of a 0–10 numerical rating scale (NRS). Baseline is day –1 (dotted line), since the assessment showed the experience of dyspnoea during the previous day. All non-missing assessments were included in the analysis; the number of patients per group indicates how many assessments were available at each timepoint. Error bars represent 95% CIs. p values are from repeated-measures mixed models. Intervention is the main effect for treatment group, time is the main effect for time period, and intervention by time is the statistical interaction for the main effects.

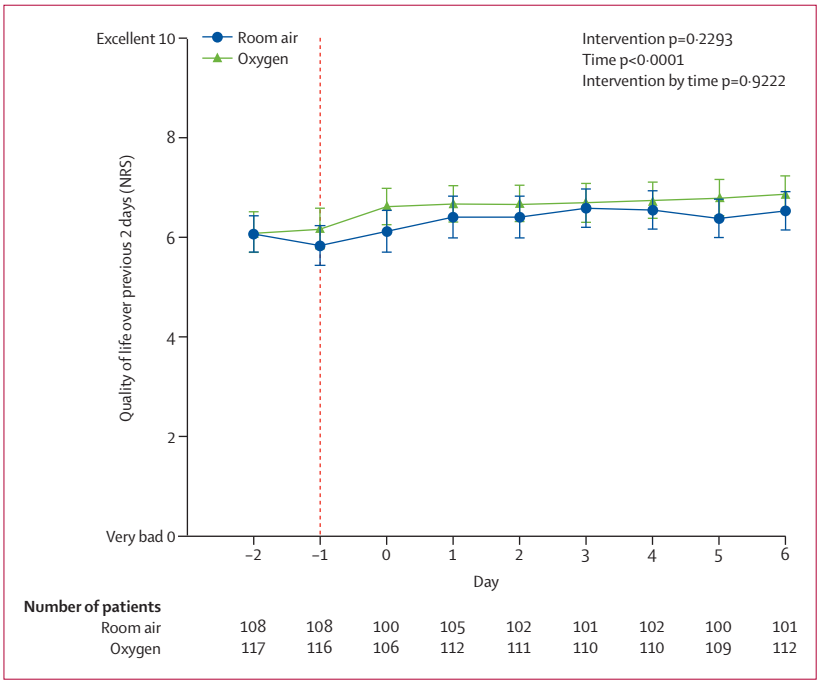

Figure 4: **Quality of life**
Global quality of life was reported daily on a single-item 0–10 numerical rating scale (NRS) patterned after the McGill Quality of Life Questionnaire.[23] The baseline (dotted line) reflects the timing of the survey in relation to initiation of the intervention. All non-missing assessments were included in the analysis; the number of patients per group indicates how many assessments were available at each timepoint. Error bars represent 95% CIs. p values are from repeated-measures mixed models. Intervention is the main effect for treatment group, time is the main effect for time period, and intervention by time is the statistical interaction for the main effects.

use. The morning effect, given anecdotal evidence that most people used oxygen at night, could warrant further investigation, in conjunction with study of breathlessness on exertion, to establish potential windows of time when a medical gas intervention is most likely to benefit the patient.

How do these results compare with other intervention studies of air movement to treat breathlessness? Studies in animals dating back to the 1960s have reported the role of upper airway receptors associated with the trigeminal nerve in reduction of ventilation requirements.[31] In people with COPD, air blown on the face (eg, from an open window or fan) substantially diminished the sensation of dyspnoea induced by a resistive load and hypercapnia without substantial reduction in ventilation.[31] Low temperature seems to improve efficacy of ventilation,[32] although the relative roles of mechanics and temperature remain unclear. Exploratory studies showed that use of a hand-held fan improved dyspnoea when air was blown towards the face, but not towards the leg;[33,34] a randomised controlled crossover trial has recently substantiated that a hand-held fan directed at the face is effective in reducing the symptom of breathlessness compared with the same fan directed at the leg.[33] Our study adds to the evidence by showing change over time in dyspnoea after medical gas delivery by nasal cannula, and corollary effect on quality of life and physical functioning.

How do we interpret the conflicting findings that there were no differences in the effects of the two gases, and yet the oxygen intervention predicted improvement in morning dyspnoea? The graphs provide insight; there was a non-significant trend for oxygen to confer more benefit than room air (figure 2, figure 4, webappendix); predictor analysis upheld this trend. The interventions were equivalent in proportional improvement (figure 3).

Oxygen therapy is widely prescribed in palliative care. These results should therefore be placed in clinical context, providing practical guidance to inform care of patients with refractory breathlessness and advanced life-limiting illness. Interpreted cautiously, these results suggest that moving gas near the nasal passages, and specifically delivered via a nasal cannula, can lead to improved symptoms. The gas, however, need not be oxygen. An effect can be achieved in the setting of other palliative interventions, such as opioids (the option best supported by evidence). Currently, prescription of room air is difficult because of ethical concerns, cost, and lack of availability of concentrated room air as a treatment option; oxygen can be substituted, but with important caveats. Oxygen is flammable; patients who smoke, and patients with carers who smoke, should not be prescribed oxygen.[35] Oxygen is expensive and can be difficult to obtain. Potentially hypercarbic patients, and especially people with central hypoventilation syndromes, should have close supervision when they are prescribed oxygen. Since air motion seems to be an operative factor in relief of breathlessness, a simple hand-held or table-top fan could be a helpful, inexpensive, first step. Treatment of breathlessness with a medical gas—whether oxygen or moving air—might be advisable to alleviate other related symptoms in addition to dyspnoea, such as fatigue. Additionally, and especially for patients with less severe dyspnoea, non-pharmacological options such as pulmonary rehabilitation should be considered.

If medical gas is prescribed, treatment should focus on patients with dyspnoea scores on the 0–10 NRS of 4 points or more, and especially on those with scores of 7 points or more. Recurrent assessment with standardised scales is prudent, especially when undertaking trials in individual patients, since prediction of which patients will benefit is difficult.[16] This study shows that most benefit occurred in the first 24 h after delivery of the concentrator, and nearly all symptomatic and functional improvements happened in the first 3 days. Assessment in an n=1 study should therefore happen during the first 72 h after the start of the intervention. Discontinuation of the intervention after 3 days, if ineffective in that time, will require substantial re-education of clinicians and carers, who often perceive palliative oxygen as a crucial element for relief of suffering. The logistical burden of this intervention, as well as its burden in terms of social stigma and potential negative effect on social relationships,[36] should be considered. Clinical practice guidelines should be updated to avoid offering a

burdensome treatment, or continuing it, if patients are unlikely to benefit through symptom relief.

This study has some limitations. We did not record the exact time of morning and evening assessments, nor did we know the exact times during which participants used the gases; we omitted these details to reduce burden on participants. Our inclusion and exclusion criteria prevented extrapolation of study results to terminally ill patients with dyspnoea who were expected to survive less than a month, and to patients eligible for long-term oxygen therapy.

We considered palliative oxygen within the context of general clinical practice, irrespective of the cause of dyspnoea, and therefore we deliberately enrolled a heterogeneous population. This approach reflects standard practice in palliative medicine, in which the symptom is treated similarly for patients with different underlying diseases. Palliative oxygen is possibly more beneficial than is room air for some subgroups (eg, patients with COPD *vs* patients with cancer), and our study might not have been adequately powered to identify these patients. We plan to combine results from this trial with the main systematic reviews for palliative oxygen in cancer and COPD to explore this issue.[14,37] Because most participants had ECOG performance status of 2 or 3, and did not show breathlessness at rest, this population might not be representative of the sickest patients in palliative care who frequently receive palliative oxygen.

Another limitation of the study was that more randomised participants withdrew from the room air group than did participants in the oxygen group, thereby introducing potential for skewing; however, most withdrawals occurred before the intervention began. The fairly small definition of response (1-point change on NRS) calls into question the clinical significance of demonstrated benefit. Each patient should be the final arbiter judging relative benefit versus burden; patients can and do exercise this role discerningly.[38] Secondary analyses might be underpowered, and, given multiple comparisons, some findings might occur by chance. Since our focus was on subjective experiences of breathlessness, we did not track objective measures of oxygen saturation, haemodynamics, and sleep, which might have provided insight into the benefits of the interventions. Finally, although participants were instructed to use the intervention for 15 h per day, total hours of use recorded by concentrator meters suggest a slightly lower daily usage (14 h per day). Since most of the response occurred in the first 24 h, when participants were presumably most likely to use the intervention, it is unlikely that stricter adherence would have changed outcomes. In predictor analyses, we did not see a dose-response between level of PaO_2 and dyspnoea relief by intervention, although underuse of concentrators might have contributed to this lack of effect.

High-quality care for people with life-limiting illness and refractory symptoms requires the judicious use of interventions that provide greatest patient-defined benefit with least harm. Palliative oxygen does not provide incremental benefit over room air when provided at 2 L per min by a nasal cannula, for patients with PaO_2 more than 7·3 kPa. There was a temporal relation between provision of medical gas, symptomatic benefit, and improved quality of life, especially for people with moderate to severe dyspnoea. Results can be efficiently defined through careful monitoring of symptoms by use

	Reference group (number of responders)	Odds ratio (95% CI)	Wald χ^2 p value
Morning dyspnoea (111 responders, 102 non-responders)			
Intercept	..	..	0·008
Oxygen (n=66)	Room air (n=45)	2·0 (1·1–3·5)	0·019
Severe baseline dyspnoea (n=32)	Low baseline dyspnoea (n=27)	5·3 (2·2–12·8)	0·0002
Moderate baseline dyspnoea (n=52)	Low baseline dyspnoea (n=27)	1·6 (0·8–3·0)	0·155
Severe baseline dyspnoea (n=32)	Moderate baseline dyspnoea (n=52)	3·4 (1·5–7·7)	0·004
Evening dyspnoea (112 responders, 99 non-responders)			
Intercept	..	..	0·010
Oxygen (n=64)	Room air (n=48)	1·5 (0·8–2·6)	0·197
Severe baseline dyspnoea (n=38)	Low baseline dyspnoea (n=22)	8·7 (3·4–22·0)	<0·0001
Moderate baseline dyspnoea (n=52)	Low baseline dyspnoea (n=22)	1·8 (1·0–3·5)	0·070
Severe baseline dyspnoea (n=38)	Moderate baseline dyspnoea (n=52)	4·8 (2·0–11·3)	0·0004

Response was defined as a 1-point or more decrease in the numerical rating scale from baseline. Logistic regression was used to identify predictors of response.

Table 3: **Predictors of response to medical gas**

	Oxygen group (n=116*)	Room air group (n=108*)
How drowsy have you felt today?		
Not drowsy at all	14 (12%)	14 (13%)
Mildly drowsy	47 (41%)	39 (36%)
Moderately drowsy	43 (37%)	41 (38%)
Extremely drowsy	12 (10%)	14 (13%)
How much nasal irritation have you experienced today?		
None at all	21 (18%)	26 (24%)
Mild symptoms	62 (53%)	44 (41%)
Moderate symptoms	31 (27%)	31 (29%)
Extreme symptoms	2 (2%)	7 (6%)
Have you experienced any nose bleeds today?		
No	89 (77%)	69 (64%)
Yes but not troublesome	21 (18%)	27 (25%)
Yes and mildly troublesome	3 (3%)	9 (8%)
Yes moderately troublesome	2 (2%)	3 (3%)
Yes and extremely troublesome	1 (1%)	0
How anxious have you felt today?		
Not anxious at all	31 (27%)	17 (16%)
Mildly anxious	54 (47%)	48 (44%)
Moderately anxious	27 (23%)	37 (34%)
Extremely anxious	4 (3%)	6 (6%)

*Number of participants who answered the questions in the questionnaire. During the intervention period, the worst score for each patient was tabulated; these scores are shown here.

Table 4: **Patient-reported rating of side-effects**

of basic standardised scales (eg, 0–10 NRS), with patients' preference being a guiding factor in decisions to continue or discontinue therapy. A future research agenda should explore these findings in the context of health service use, carer confidence, exertional breathlessness, and additional interventions for refractory dyspnoea in the setting of life-limiting illness.

Contributors

APA and DCC contributed to conception and design; acquisition of data; analysis and interpretation of data; drafting of the report; critical revision of the report; obtaining funding; administrative, technical, or material support; and supervision. APA was the principal investigator, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of data analyses. CFM, PAF, KC, IHY, and SB contributed to conception and design; acquisition of data; analysis and interpretation of data; critical revision of the report; obtaining funding; and supervision. JEH contributed to conception and design; statistical analyses; analysis and interpretation of data; drafting of the report; critical revision of the report; and supervision. JM contributed to conception and design; statistical analyses; analysis and interpretation of data; drafting of the report; and critical revision of the report. JB contributed to acquisition of data; analysis and interpretation of data; critical revision of the report; and supervision. AW, JAT, and AJC contributed to conception and design; analysis and interpretation of data; critical revision of the report; and obtaining funding. JLW contributed to analysis and interpretation of data; drafting of the report; and critical revision of the report.

Conflicts of interest

CFM has received honoraria for presenting at scientific meetings sponsored by AstraZeneca, GlaxoSmithKline, and Boehringer Ingelheim, and has served as an advisory board member for these same corporations. JB is on the speaker's bureau for Wyeth Pharmaceuticals, Pfizer, and Meda Pharmaceuticals. All other authors declare that they have no conflicts of interest.

Acknowledgments

This study was funded through grants from the US National Institutes of Health (NIH; R01 AG026469), Australian National Health and Medical Research Council (324770 and 375127), Duke Institute for Care at the End of Life, and Doris Duke Charitable Foundation. None of the study sponsors had a role in the conduct of this study or its reporting, except through the input of the Data Safety Monitoring Board as mandated by the NIH. We thank the many patients with advanced life-limiting illness who generously participated in this study, and their carers. We also thank Bernadette Kenny and Belinda Fazekas (Southern Adelaide Palliative Services, Adelaide, Australia) for their important contributions in study and data management, and David Woods (Tasmania Statewide Palliative Care Service, Australia) for his assistance with participant recruitment in Tasmania, Australia.

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