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Original Articles

A review of long-term oxygen therapy for chronic obstructive pulmonary disease

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This study aimed to review the evidence for the use of long-term oxygen therapy for patients with chronic obstructive pulmonary disease (COPD).

The design was a systematic Cochrane review of randomized controlled trials (RCTs) of long-term oxygen therapy for COPD and main outcome measure was survival on home oxygen therapy.

Five RCTs were identified. Data from two trials of nocturnal oxygen therapy in mild to moderate hypoxaemia were aggregated. Data from the other three trials could not be aggregated because of differences in trial design and patient selection. Treatment with continuous versus nocturnal oxygen therapy produced a significant improvement in mortality after 24 months [Peto odds ratio 0·45, 95% confidence interval (95% CI) 0·25–0·81] for the continuous therapy group. Treatment with oxygen therapy versus no oxygen therapy showed a significant improvement in mortality after five years in the group receiving oxygen therapy (Peto odds ratio 0·42, 95% CI 0·18–0·98). There was no difference in mortality for patients with COPD and mild to moderate daytime hypoxaemia and nocturnal desaturation receiving nocturnal oxygen therapy versus no oxygen therapy or sham treatment. Long-term oxygen therapy versus no oxygen therapy in patients with COPD and moderate hypoxaemia had no effect on survival.

In conclusion, long-term oxygen therapy improved survival in a selected group of COPD patients with severe hypoxaemia but few co-morbidities. Long-term oxygen therapy did not improve survival in patients with moderate hypoxaemia or in those with mild to moderate hypoxaemia and arterial desaturation at night.

Key words: long-term oxygen therapy; survival; chronic obstructive pulmonary disease.

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Introduction

Patients with chronic obstructive pulmonary disease (COPD) develop chronic hypoxaemia which is related to the progression of their underlying lung condition. Over the last 20 years domiciliary long-term oxygen therapy (LTOT) has become one of the major forms of treatment for hypoxaemic COPD patients. A frequently held clinical belief exists, from early studies in the United Kingdom, that LTOT will give COPD patients an additional 5 years of life (1).

To determine the effect of domiciliary oxygen therapy on the survival and quality of life of patients with COPD and hypoxaemia we conducted a systematic Cochrane review of randomized controlled trials (RCTs).

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Materials and methods

IDENTIFICATION OF TRIALS

We sought to identify all relevant RCTs in adult patients with hypoxaemia and COPD, chronic airflow limitation (CAL), chronic obstructive airways disease (COAD) or chronic airflow obstruction (CAO) that compared long-term domiciliary or home oxygen therapy with a control group. The intervention in the active treatment group covered all forms of LTOT, including provision of oxygen using cylinders, concentrators or liquid oxygen therapy. In the control group, the intervention was either placebo air by the same method of delivery or no specific intervention. The majority of the patients had chronic hypoxaemia, an arterial oxygen tension (PaO_2) <55 mmHg (7·3 kPa), but some of the patients had a $PaO_2 > 55$ mmHg (7·3 kPa) at rest with evidence of nocturnal hypoxaemia or desaturation with exercise.

SEARCH STRATEGY

Trials were identified with assistance from the Cochrane Airways Group, London, U.K. using the Cochrane

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Airways Group COPD register and the search terms: home *or* domiciliary *and* oxygen. This register is regularly updated by electronic searches and hand searches of relevant journals. Following this, the bibliographies of each RCT were searched for additional papers that may have contained RCTs. Authors of identified RCTs were contacted for additional data. In addition, companies who supply the oxygen delivery devices and members of the International Respiratory Care Association were contacted for unpublished studies.

Two reviewers assessed all RCTs that appeared potentially relevant, and then independently selected the trials for inclusion in this review. Disagreement was resolved by consensus. The trials were rated for the quality of allocation concealment according to the method proposed by Schulz (2).

OUTCOME MEASURES

The outcome measures determined in advance for the review were:

- Survival from the commencement of home oxygen therapy as measured by all cause mortality.
- Health related quality of life as measured by a validated instrument.
- Improvement in physiological parameters.

DATA EXTRACTION, ANALYSIS AND STATISTICAL METHODS

Two reviewers, using a standard form, extracted data on the types of study, participants, methodology, interventions and outcomes. Subgroup analysis included, where possible, a comparison of:

(1) Male with female patients;
(2) Continuous oxygen therapy versus nocturnal oxygen therapy;
(3) Oxygen therapy versus no oxygen therapy;
(4) Nocturnal oxygen therapy versus room air for arterial oxygen desaturation during sleep;
(5) Long-term oxygen therapy versus no oxygen therapy for moderate hypoxaemia.

RevMan 4·0 statistical software provided by the Cochrane Collaboration was used in the analysis (3). We calculated Peto odds ratios with 95% confidence interval (95% CI) using a fixed effects model on an intention to treat basis.

Results

Seven abstracts were identified from the comprehensive searches of the databases. The full text was obtained for all of the abstracts (4–10). Three papers were found to be reports on various aspects of one RCT (Nocturnal Oxygen Therapy Trial; NOTT) (4–6). One of these was excluded as it contained baseline data only (5). The physiological data from another of these papers were combined with data from the original NOTT study report (6). Five RCTs were considered suitable for inclusion in the review (4,7–10). Table 1 summarizes these trials and includes the number of participants, the intervention and the control regime. The trials are described in more detail below. No additional data could be obtained from the authors of the studies.

Two studies (7,9) treated subjects with COPD with long-term oxygen therapy versus no oxygen therapy. However, these two studies were not combined as the MRC study included subjects with severe hypoxaemia (PaO_2, 40–60 mmHg, 5·3–8·0 kPa) while the study by Górecka *et al*. included subjects with moderate hypoxaemia (PaO_2 56–65 mmHg, 7·4–8·7 kPa). Although both studies included a small number of female subjects, survival was stratified by gender for the MRC study but not for study by Górecka *et al*.

Data from the two studies of nocturnal oxygen therapy in patients with COPD and mild to moderate hypoxaemia were combined (8,10).

Four of the trials were scored as having adequate concealment. One trial described the method of randomization as 'blind draw' with the vendor and respiratory therapist knowing the treatment code and so was given a rating of unclear concealment (8).

NOTT STUDY

A total of 1043 patients from six centres in North America were screened for inclusion in the Nocturnal Oxygen Therapy Trial (NOTT) (4). Eight hundred and nine patients were excluded for a variety of reasons including other major concomitant disease, refusal to participate or because patients were already using oxygen therapy or had a PaO_2 greater than 59 mmHg (7·9 kPa). The study was not blinded. Two hundred and three patients with hypoxaemic chronic obstructive lung disease were randomly allocated to nocturnal oxygen therapy (n=102) or continuous oxygen therapy (n=101) at a flow-rate of 1–4 l min^{-1}. The oxygen source was an oxygen concentrator, liquid oxygen or compressed gas. The mean age was 65·7 years in the nocturnal oxygen therapy group and 65·2 years in the continuous oxygen therapy group. Most patients were male: 80·4% in the nocturnal oxygen therapy group and 77·2% in the continuous oxygen therapy group. Mean baseline forced expiratory volume in 1 sec (FEV_1) was 29·9% predicted for the nocturnal oxygen therapy group and 29·5% predicted for the continuous oxygen therapy group. Mean baseline PaO_2 was 51·5 mmHg (nocturnal group) and 50·8 mmHg for the continuous oxygen therapy group.

Figure 1 shows the odds ratios for each of the treatment categories by trial included in this meta-analysis. For the NOTT study the survival at 12 months was not significant (Peto odds ratio 0·53; 95% CI: 0·25–1·11). At 24 months there was a significant improvement in mortality for the continuous oxygen treatment group (Peto odds ratio 0·45; 95% CI: 0·25–0·81).

In this RCT, quality of life parameters and several physiological variables were studied, but the number of patients in each group was not defined and could not be

TABLE 1. Table of included studies

Trial	No. of patients	Treatment groups	Treatment	Control
NOTT (4)	203	101 patients (77·2% male) received continuous oxygen therapy and 102 patients (80·4%) male received nocturnal oxygen therapy	1–4 l min^{-1} by concentrator, liquid oxygen or compressed gas	Mean of 12 h day^{-1} nocturnal oxygen therapy
MRC (7)	87	66 males (33 treated and 33 controls) and 21 females (9 treated and 12 controls) were included in the trial	Domiciliary oxygen therapy (at least 15 h day^{-1}, at least 2 l min^{-1}) by concentrator, cylinder or liquid oxygen. Flow rate adjusted to raise PaO_2 above 60 mmHg	No oxygen therapy
Fletcher *et al.* (8)	38	19 patients were sham-treated, 19 patients were treated with oxygen therapy (gender not given)	Oxygen therapy at 3 l min^{-1} was administered during sleep versus compressed air at 3 l min^{-1}	Treatment with compressed air with an oxygen concentration no greater than 25%
Górecka *et al.* (9)	135	103 males (51 treated and 52 controls) and 32 females (17 treated and 15 controls) and included in the trial	Patients treated with long-term oxygen therapy received concentrator oxygen adjusted to raise PaO_2 above 65 mmHg (8·7 kPa)	No oxygen therapy
Chaouat *et al.* (10)	76	41 patients received nocturnal oxygen therapy 35 no oxygen therapy, gender not given	Concentrator oxygen therapy at usually 2 l min^{-1} for 8–10 h at night	No oxygen therapy

PaO_2: arterial oxygen tension.

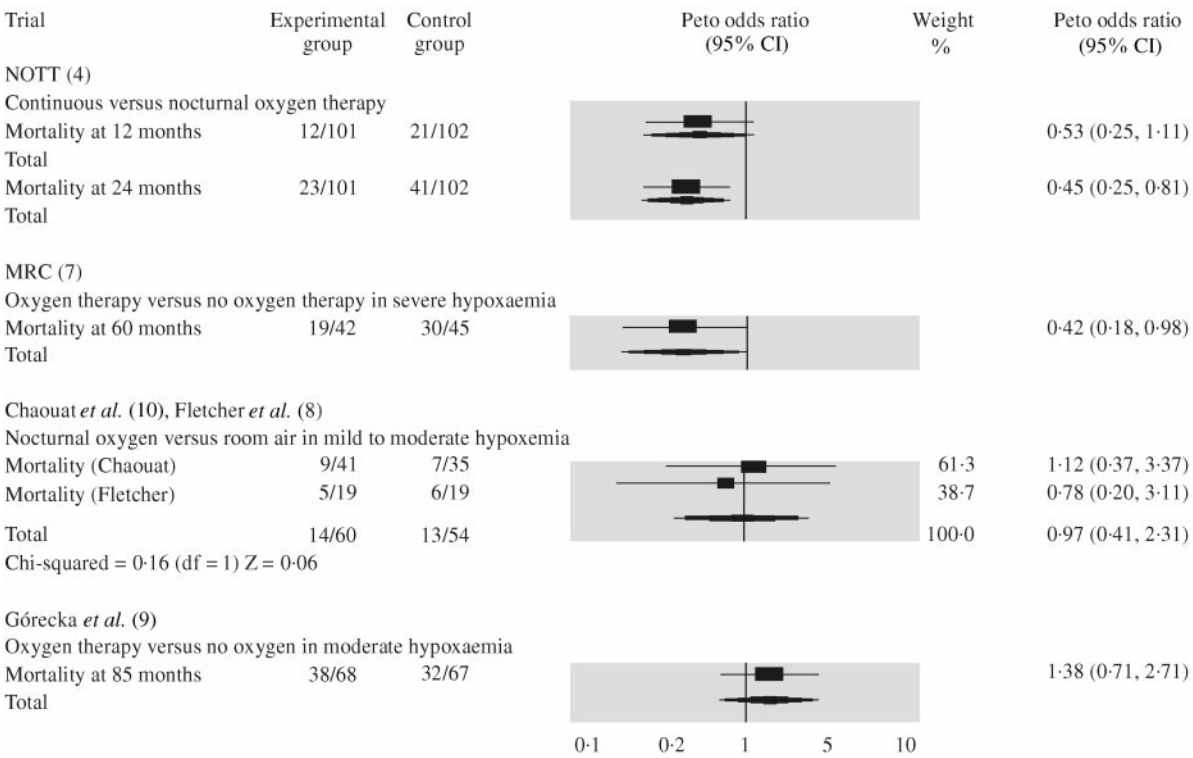

FIG. 1. Quantitative effects of domiciliary oxygen on survival in COPD.

assessed using this meta-analysis protocol. Timm's paper on the NOTT study reported no significant difference between the treated and nocturnal groups of patients for the physiological parameters right atrial pressure, pulmonary capillary wedge pressure, cardiac index and right ventricular stroke work index. However, the continuous oxygen therapy group was reported to show improvement in stroke volume index, pulmonary vascular resistance and pulmonary artery pressure.

The study speculated that those patients most likely to benefit from continuous oxygen therapy would have relatively severely impaired quality of life and brain dysfunction but relatively mild disturbances of pulmonary haemodynamics and exercise capacity.

MRC TRIAL

The Medical Research Council (MRC) trial of long-term domiciliary oxygen therapy took place in three centres in the U.K. (7). The patients had a diagnosis of chronic bronchitis and emphysema, and were randomized to receive oxygen therapy or no oxygen (controls). The study was not blinded. Patients were enrolled in the study if they had a PaO_2 of between 40 and 60 mmHg (5·3 and 8 kPa) and one or more recorded episodes of heart failure with ankle oedema, and so were highly selected. Thirty-three men and nine women received oxygen therapy for at least 15 h day^{-1} at a flow rate of a minimum of 2 l min^{-1}. Eight subjects received liquid oxygen therapy and all but one of the patients (total number not disclosed) in one centre received oxygen via an oxygen concentrator. The remaining subjects received oxygen from cylinders. A total of 33 men and 12 women formed the control group.

Mean (range) age was 58·2 (44–69) years for the male treated group, 56·2 (42–68) years for the male control group, 59·4 (55–67) years for the female treated group and 59·3 (50–69) years for the female controls. Mean baseline FEV_1 was 0·76 l and 0·58 l for the treated male and female groups and 0·65 l and 0·63 l for the control male and female groups. Mean baseline forced vital capacity (FVC) was 1·92 l and 1·31 l for the treated male and female groups and 1·88 l and 1·46 l for the control male and female groups. Mean baseline PaO_2 was 50·4 mmHg (6·7 kPa) and 49·4 mmHg (6·6 kPa) for the treated male and female groups, and 51·5 mmHg (6·9 kPa) and 51·8 mmHg (6·9 kPa) for the control male and female groups.

There was an improvement over 5 years in mortality in the group receiving oxygen therapy (Peto odds ratio 0·42, 95% Cl: 0·18–0·98) as shown in Fig. 1. However, there was no difference in mortality for male patients in both treated and control groups up to 500 days from commencement of treatment. In female patients, mortality was improved for the oxygen-treated group from the commencement of treatment. However, the number of female patients in each of the treated and control groups was small (n=9 and n=12, respectively).

Physiological variables could not be assessed using this meta-analysis protocol. The study found that the male subjects most likely to benefit from oxygen therapy had a sum of the red cell mass and $PaCO_2$ less than 98.

FLETCHER STUDY

Thirty-eight subjects with COPD, a daytime $PaO_2 > 60$ mmHg and nocturnal sleep desaturation agreed to participate in the Fletcher double-blind RCT and were randomized into the study (8). An additional 13 patients with similar baseline pulmonary function who did not desaturate were also followed up but not randomized. In the 'sham-treated' group of 19 patients, six died and four were excluded (two withdrew, one developed daytime hypoxaemia, one was non-compliant). Of the original 19 treated subjects, six developed significant daytime hypoxaemia, one developed worsening of sleep apnoea and there were five deaths.

Oxygen was supplied in the active group by an oxygen concentrator. The control group received gas from an oxygen concentrator rendered ineffective. However, some control group patients received an oxygen concentration of 25% rather than the ambient concentration of 21%, equivalent to an inspired oxygen tension of approximately 30 mmHg (4 kPa) greater than if they had received room air. Mean age in the control group was 61·2 years and mean age in the oxygen-treated group was 62·1 years. The gender of the subjects was not given.

Physiological parameters could not be assessed using this meta-analysis protocol.

There was no difference in mortality after 36 months between the oxygen-treated and sham-treated groups. However, the possibility of a type 2 error occurring could not be rejected due to the small study size even though the point estimate of mortality was very close to the odds ratio of 1·0.

GÓRECKA STUDY

One hundred and thirty-five patients with COPD and moderate hypoxaemia referred to nine regional centres in Poland were included in the unblinded RCT (9). Patients with concomitant disease that might impact on survival were excluded from the study.

Sixty-seven patients (52 males, 15 females, mean age 62·4 years) formed the control group and 68 patients (51 males 17 females, mean age 60·1 years), formed the treatment group. Both treated and control groups received 'usual treatment' which consisted of bronchodilators, antibiotics, corticosteroids and diuretics as required. The oxygen group were prescribed at least 17 h of oxygen per day from an oxygen concentrator at a flow rate that raised their resting PaO_2 greater than 8·7 kPa (65 mmHg). This group used a mean of 13·5 h of oxygen therapy per day. The patients were followed for 3 years or until death.

No difference in mortality during the study period was found between COPD patients with moderate hypoxaemia under conventional treatment plus long-term oxygen therapy versus conventional treatment only. In the intervention group, duration of oxygen therapy (over 15 h day^{-1}) did not affect survival.

Physiological parameters could not be assessed because these were not reported by treatment group.

CHAOUAT STUDY

Seventy-six patients with COPD and mild to moderate daytime hypoxaemia, PaO_2 56–69 mmHg (7·4–9·2 kPa) exhibiting significant nocturnal desaturation were randomized into this unblinded study (10). The patients were recruited from six hospital outpatient clinics of four European countries.

Thirty-five patients, mean age 64 ± 6 years, gender not defined, formed the control group and 41 patients, mean age 63 ± 8 years the treatment group. Patients were excluded if they had a variety of co-morbidities including left heart or congenital heart disease, interstitial lung disease, bronchiectasis, lung carcinoma or other severe disease that could influence survival. Patients with obstructive sleep apnoea were also excluded. Patients in the treatment group were given concentrator oxygen for 8–10 h per night at a flow rate usually of $2\,l\,min^{-1}$. The control group received no oxygen therapy. There was no difference in mortality between the treated and control groups on an intention to treat basis.

Nocturnal oxygen did not allow delay in the prescription of long-term oxygen therapy. Twelve patients in the nocturnal oxygen group and 10 control group patients deteriorated and required treatment with conventional long-term oxygen therapy during the follow-up period of from 2·5 to 60 months. Five of these patients subsequently died, two in the treated group and three in the control group.

Pulmonary haemodynamic parameters could not be assessed due to limitations in the meta-analysis protocol. However, no significant difference between treated and control groups in the evolution of any of these parameters was reported over a 2-year period.

There was no difference in mortality between the treated and control groups when the Chaouat and Fletcher data were aggregated, with the summary Peto odds ratio moving close to unity than the individual odds ratios (0·97, 95% CI: 0·41–2·31).

Discussion

SURVIVAL

Two of the five RCTs included in this review demonstrated a significant survival advantage for the selected COPD subjects receiving long-term oxygen therapy (4,7). In the NOTT study there was a significant improvement in mortality for hypoxaemic COPD patients after 24 months of treatment with continuous long-term oxygen therapy when compared to the nocturnal oxygen therapy group. In the MRC study long-term oxygen therapy produced a small but significant overall improvement in survival in both male and female patients with severe hypoxic cor pulmonale complicating chronic bronchitis and emphysema. However, the authors reported a different survival response between males and females. Survival for treated and control male patients was similar until 500 days from the commencement of treatment probably due to small numbers and inadequate resolution. However, the mortality of the control female patients was reported to be significantly greater than that of the treated females from the commencement of home oxygen therapy.

A number-needed-to-treat estimate (1/absolute risk reduction) of 4·5 can be calculated for the MRC study where the risk of death in the control group is 0·67, the risk of death for the oxygen group is 0·45 and the absolute risk reduction is 0·22. Thus, for the MRC study, five patients with severe hypoxaemic COPD with long-term oxygen therapy needed to be treated to save one life over the 5-year study period.

Nocturnal supplemental oxygen for COPD patients with nocturnal sleep desaturation but mild to moderate daytime hypoxaemia did not improve mortality. Nocturnal oxygen therapy did not delay the requirement for long-term oxygen therapy, which was similar in both the treated and control group patients for the Chaouat study. In the Fletcher study one sham group patient and six patients in the treatment group developed daytime hypoxaemia. The number of patients included in the Chaouat study was too small to determine if the cross-over to long-term oxygen therapy had an effect on survival.

Supplemental oxygen therapy for COPD patients with moderate hypoxaemia (9) did not prolong survival.

The relatively small numbers of patients, their young age and their lack of co-morbidities in most of the above studies raise concerns about the applicability of the survival outcomes to current clinical situations. Unselected patients with COPD fulfilling prescription guidelines for domiciliary oxygen therapy appear to be older than the subjects included in these studies and the majority of them have multiple co-morbidities (11). The assumption that home oxygen therapy has a beneficial effect in these patients has not been tested.

QUALITY OF LIFE ISSUES

Quality of life and other health outcome variables such as physiological parameters could not be included in this review due to limitations in the available software at this point in time. The Chaouat study concluded that nocturnal oxygen therapy in patients with COPD and mild to moderate daytime hypoxaemia did not modify the evolution of pulmonary haemodynamics. This was in contrast to the Fletcher study where it was reported that nocturnal oxygen therapy resulted in improved haemodynamics. However, the number of patients included in the Fletcher study was small.

Physiological variables should be considered intermediate outcomes, while survival and quality of life should be considered as the more definitive outcomes. It is possible that statistically significant improvement in some physiological variables may have little measurable impact on the subjects' perceived quality of life or survival.

The MRC study reported that indicators such as general improvement in the sense of well being, improved appetite, and general alertness were frequently found in those patients treated with oxygen therapy (7). However, no data

were given. The NOTT study reported neuropsychological deficits in hypoxic COPD patient groups and observed small improvements in neuropsychological function and quality of life when data from all patients were combined (4,5).

LIMITATIONS OF THE STUDIES

This systematic review has highlighted several problems with patient selection and study design. Only one of the studies was double-blinded due to the inability to blind liquid oxygen therapy (8). The treatment regime for the control groups of the studies varied from none for the Górecka study, to nocturnal oxygen therapy for the NOTT study, to sham treatment through a disabled oxygen concentrator equivalent to 25% oxygen therapy in the Fletcher study. In the Fletcher study this level of oxygen therapy for the control subjects may have confounded the results as this higher oxygen tension may have been reflected in the PaO_2 in this group. The control group in the MRC study did not receive a sham treatment regime.

In the NOTT study the numbers of patients receiving the different modes of oxygen treatment were not given. There were some differences between treatment and control groups at baseline in the MRC study. Females in the treated group appeared to have more compromised lung function than those of the control group, while the reverse appeared to be apparent for the male patient groups. The mean number of hospitalizations and hospitalized days in the Fletcher study could not be included in this review as standard deviations were not given. The Górecka study reported differences in studied variables by survivors and non-survivors.

No data were reported in the two major studies (NOTT and MRC) about the effects of continuing or ceasing smoking or indeed if smoking status affected the outcomes. The mean arterial CO_2 tension at baseline was higher in the MRC study than in the NOTT study. This did not appear to influence the results. Other known prognostic indicators such as body mass index were not discussed in either of the studies. The lack of exacerbation data is also a further limiting factor in interpreting the results.

IMPLICATIONS FOR RESEARCH

The role of long-term oxygen therapy prescribed for a longer time period (at least $19\,h\,day^{-1}$) in COPD with moderate hypoxaemia and/or nocturnal desaturation requires further investigation, with larger numbers of participants included in the studies.

Ethical concerns have been raised about the randomization of patients to placebo and this may be a barrier to obtaining more appropriate health status data about the effects of oxygen in more severely hypoxaemic subjects.

Further development of the Revman software package is required to enable more comprehensive comparisons of the available data.

Conclusions

Long-term oxygen therapy improved survival in a selected group of COPD patients with severe hypoxaemia but few co-morbidities. Although many physiological outcomes were measured in the NOTT and MRC trials, none clearly indicated a plausible mechanism for the effect on mortality. Long-term oxygen therapy did not appear to improve survival in patients with COPD and moderate hypoxaemia nor in COPD patients with nocturnal desaturation but resting daytime oxygenation above that to qualify for oxygen therapy.

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