ORIGINAL ARTICLE

Heliox in the treatment of chronic obstructive pulmonary disease

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Objective: To determine if breathing helium oxygen mixtures in addition to conventional therapy in non-intubated adult chronic obstructive airways disease (COPD) patients reduces the arterial partial pressure of carbon dioxide (PaCO_2) more than conventional treatment alone, and confers an advantage in terms of the odds of intubation in the acute setting.

Design: Meta-analysis.

Setting: Diverse settings.

Participants: Adult patients with a diagnosis of either stable severe or acute COPD.

Main outcome measures: Decrease in partial pressure of arterial PaCO_2 and intubation rates.

Results: Combination of the results from trials measuring change in PaCO_2 in COPD subjects receiving conventional therapy but breathing helium-oxygen estimated a reduction of 0.78 KPa (1.44–0.13) beyond that produced by conventional therapy with air-oxygen breathing ($n=234$). Using quantitative and qualitative measures of validity it was found that most trials were unsatisfactory. Chief concerns were poor concealment of allocation and lack of blinding. Analysis excluding all papers with low methodological quality (Jadad <2) estimated the reduction in PaCO_2 conferred by use of Heliox breathing to be 0.22 KPa ($+0.57$ to -0.14). A non-significant reduction ($p=0.2$). When combined, the results from trials measuring the intubation rates of patients treated conventionally or with Heliox ($n=121$) the odds ratio of intubation was 0.096 (0.03–0.27).

Conclusion: Definitive evidence of a beneficial role of Heliox in treatment of severe COPD is lacking and therefore its wide scale use cannot be recommended based on this analysis. However, as a beneficial effect of Heliox breathing was reported in all trials, further investigation with a well conducted randomised controlled trial is warranted.

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Treatment in acute chronic obstructive pulmonary disease (COPD) is directed at improving gas exchange and decreasing the work of breathing. In the most severe exacerbations of COPD this is achieved by intubation and mechanical ventilation. However this approach is associated with several problems including ventilator associated pneumonia, ventilator induced lung injury, and deconditioning of respiratory muscles leading to ventilator dependence. Recently strategies to avoid intubation and mechanical ventilation have been examined. Much success has been seen with non-invasive ventilation (NIV) in selected COPD patients who would have otherwise been intubated and mechanically ventilated. Another strategy in severe COPD entails changing the physical properties of the gas the patient inspires. Substituting helium for nitrogen results in a lighter carrier gas for oxygen, Heliox, this can be used in conjunction with all conventional treatments including NIV.

The behaviour of gas flows in the lungs determines the pressure required to drive the gas. Gas movement may be: laminar, where the molecules flow in parallel lines; turbulent, where the molecules flow in a haphazard fashion or transitional, where there is a combination of both laminar and turbulent flow. Laminar flow is far more energy efficient and requires lower pressures to achieve a given flow rate. Gases are more likely to flow in a laminar pattern if they are of low density and high viscosity. Because Heliox has a significantly lower density (and a slightly higher viscosity) than air it is more likely to exhibit laminar flow when travelling through the bronchial tree. Additionally, when there is turbulent or transitional flow gases of lower density require less pressure to drive ventilation. As Heliox has lower density than air it will flow more efficiently in turbulent

conditions. Papamoschou, using a fluid mechanical model of the human lung, described a theoretical analysis comparing flow rates of Heliox and air-oxygen mixtures. The author found there was a 50% improvement in flow rates if nitrogen was substituted with helium.¹

Several case reports in the literature attest to the benefits of Heliox in severe COPD.^{2–4} In one, an American patient was being treated in an emergency department with maximal conventional treatment (including NIV). Despite this he continued to deteriorate. Within 20 minutes of introduction of Heliox therapy his arterial blood gas parameters had improved and he was objectively and subjectively less breathless. Intubation was avoided and he was discharged within six days.⁴ This case illustrates the potential of the treatment. However in a rigorous systematic review performed by the Cochrane group⁵ the reviewers concluded that there was insufficient evidence to support use of Heliox in COPD treatment. Many trials were excluded from this review and it has been criticised as the conclusion was based on just two trials, one of which did not examine continuous Heliox breathing. This review attempts to incorporate all levels of evidence to reduce the likelihood of a type II statistical error in assessing the value of Heliox in COPD management.

CRITERIA FOR INCLUSION

Types of studies

Only controlled studies were considered for inclusion. In the case of parallel groups historical controls were accepted.

Abbreviations: COPD, chronic obstructive pulmonary disease; NIV, non-invasive ventilation

Table 1 Summary of the papers included in the study

Study	Objective	Design	Setting	Subjects	Intervention	Measurements	Results
Jaber ¹⁰	Assess short term physiological effects of Heliox and NIV in patients with acute COPD	Randomised crossover single blind study	Medical ICU	n = 10. Recent exacerbation Of COPD with either tachypnoea, acidosis, or hypoxia.	NIV with 15-25 cm H ₂ O PS breathing air-oxygen then 78:22 Heliox for 20 min measurements made in final 5 min of treatment.	Paco ₂ (ABG)	Paco ₂ fell by 2 mm Hg without oxygenation being affected
Joliet ¹⁶	Assess short term physiological effects of Heliox and NIV in patients with acute COPD	Randomised crossover single blind study	Medical ICU	n = 20. Acute decompensated COPD managed to a stable point in their course with NIV	NIV with air-oxygen and 70:30 Heliox given in random order with a 45 min washout period.	Paco ₂ (ABG)	Paco ₂ fell by 0.8 mm Hg more on Heliox than air-oxygen. Paco ₂ reduced by more when baseline Paco ₂ higher (that is, more ill)
Gerbeaux ¹³	To assess whether patients with acute exacerbations of COPD treated with Heliox have better outcomes than those receiving standard treatments	Retrospective case note review with historical control group	Emergency department	n = 81. Patients with final diagnosis of COPD with respiratory acidosis. 39 Heliox. 42 non-Heliox	78:22 Heliox in the treatment group administered by face mask with supplemental O ₂ . O ₂ only in the standard group.	Incidence of intubation	Significant reduction in intubation (50 v 8%) and mortality rates (24 v 3%)
Albernoz ¹⁴	To assess effect of 80:20 Heliox breathing in exacerbation of COPD on gas exchange and intubation rates	Retrospective case note review with historical control group	ICU	n = 20 Asthma and COPD patients. 15 Heliox. 25 non-Heliox	80:20 Heliox breathing compared with air-oxygen in addition to conventional treatment.	Paco ₂ (ABG) incidence of intubation	Paco ₂ (12.7 mm Hg) and intubation rates (56 v 13.3%) fell in Heliox group.
Swidwa ¹⁵	To assess effect of Heliox breathing in stable severe COPD on gas exchange	Non-randomised non-blinded crossover study	Respiratory outpatients	n = 15. Male volunteers. Stable but severe COPD	80:20 Heliox breathing for 15 min compared with baseline air-oxygen breathing	Paco ₂ (ABG)	Reduction of Paco ₂ of 2 mm Hg
Nyarko-Adomfeh ¹¹	To assess effect of Heliox breathing in exacerbations of COPD on gas exchange	Non-randomised non-blinded crossover study	Ward	n = 6. COPD with hypercapnia in acute exacerbation	70:30 Heliox breathing compared with air-oxygen in addition to conventional treatment.	Paco ₂ (ABG)	27 mm Hg fall in Paco ₂ with breathing Heliox v 10 mm Hg on air-oxygen
Harrison ¹²	To assess effect of Heliox breathing in exacerbations of COPD on gas exchange	Non-randomised non-blinded crossover study	ICU	n = 10. COPD acute exacerbations	70:30 Heliox breathing compared with air-oxygen in addition to conventional treatment.	Paco ₂ (ABG)	52 v 44 mm Hg decrease in Paco ₂ in Heliox 70:30 but also fall in Paco ₂ 129 to 73 mm Hg
Thiriet ¹⁷	To assess effect of Heliox breathing in exacerbations of COPD on gas exchange	Randomised crossover single blind study	ICU	n = 23. COPD acute exacerbations	70:30 Heliox breathing for 20 min compared with 20 min air-oxygen	Paco ₂ (ABG)	Paco ₂ fell by 0.076 KPa on Heliox treatment

NIV, non-invasive ventilation; ABG, arterial blood gas; ICU, intensive care unit; PS, pressure support. 7.5 mm Hg = 1 KPa.

Table 2 Summary of the study appraisal

	Swidwa ¹⁵	Jaber ¹⁰	Harrison ¹²	Nyarko-Adomfeh ¹¹	Jolliet ¹⁶	Gerbeaux ¹³	Albornoz ¹⁴	Thiriet ¹⁷
Internal validity								
Randomisation	Non-randomised	Randomised but no details of allocation sequence generation or concealment	Non-randomised	Non-randomised	Randomised concealment achieved using sealed envelopes	Non-randomised. Subjects allocated according to clinician preference	Non-randomised	Randomised but no details of concealment of allocation
Blinding	No blinding	Subjects blinded but no blinding of clinicians. No blinding of statisticians to results	No blinding	No blinding	Subjects blinded but no blinding of clinicians. No blinding of statisticians to results	Blinding of observers to evolution of patient but not Heliox, blinding of authors to use of Heliox, but not of evolution	No blinding	No blinding
Patient attrition	No attrition	Attrition <10%: one patient refused consent. One patient withdrawn due to condition. Appropriate tests	No attrition	No details supplied	No attrition	No attrition	No attrition	No attrition
Statistical analysis	No details	Appropriate tests	No details	No details	Appropriate test	Appropriate tests	No details	Appropriate tests
External validity								
Inclusion/exclusion criteria supplied	Yes	Yes	No details	No details	Yes	Yes	Yes	No details
Treatment regimens described	Yes	Yes	Yes but no indication of duration of treatment	Yes but no indication of duration of treatment	Yes	Yes	Yes but no indication of duration of treatment	Yes
Summary Jadad quality assessment scale (0–3)	1	2	1	0	3	1	1	2

Randomisation and blinding although desirable were not mandatory.

Participants and settings

Adults, aged over 18 years, with a clinical diagnosis of COPD or emphysema. The patients were ideally being treated for acute exacerbations however if their condition was stable at the time of study their underlying COPD should be severe according to pulmonary function testing.

Studies involving asthmatic subjects exclusively were excluded. Studies involving both COPD and asthma were included if the proportions of each condition were similar in the intervention and control group. Studies examining mechanically ventilated subjects were excluded.

The ideal setting would be the emergency department; however there were too few studies conducted in this environment to make this feasible as an inclusion criterion. Many diverse settings were included.

Types of intervention

Self ventilation with Heliox-oxygen mixtures, the oxygen composition of which should not exceed 40%. All co-interventions should be the same between control and treatment groups in the study.

No restrictions on types of co-intervention were applied and trials of Heliox used with NIV and given via facemask without pressure support were included.

Studies using helium-oxygen as a driving gas for nebulised drugs were excluded as this does not examine Heliox breathing as a treatment in its own right.

Types of outcome measures

Decrease in Paco_2 was chosen as a marker of improved alveolar ventilation.

The clinical outcome of intubation of the patient taken to represent a failure of treatment.

SEARCH STRATEGY AND RESULTS OF SEARCH

Embase and Medline databases were searched from 1966 to 2002 using the Ovid and Zetoc (Athens) interphase. No restrictions were made on language or publication type.

The search strategy used the following terms

- (1) COPD OR COAD OR CAL OR chronic bronchitis OR emphysema
- (2) Heliox OR Helium and oxygen

Search 1 and 2 were combined using the Ovid interphase

A further search was also conducted using the search term Heliox. References including the term in any medical context were examined for suitability.

Citations taken from publications retrieved were also examined for suitability if not already located in the database searches.

BOC medical was contacted for additional references.

Tables of contents for key medical journals were examined using the Zetoc notification system over a six month period (September 2002–February 2003).

The database searches revealed 29 publications (17 Embase and 20 Medline). Where possible, studies were excluded by examination of the title or abstract. Nine publications were retrieved from the British Library and a search of the citations in these papers yielded three further studies. By hand searching archives of respiratory journals a further two abstracts of

interest were retrieved. Exclusion criteria were applied to all papers in the set.

Two papers were not available (although the parent journal was contacted) as they were published as reports from conference proceedings. One paper in Russian was excluded as translation could not be arranged. From the remaining papers five were excluded and an exclusion log was kept (see appendix, available on the journal web site <http://www.emjonline.com/supplemental>).

Table 1 summarises the papers included.

METHODS

An assessment of study qualities was made using the criteria laid out in the Chalmers scale, a checklist of best practice in therapy trials.⁶ This qualitative assessment was further supplemented by quantitative scoring based on a scale devised by Jadad. This scale returns one point each for adequate sequence allocation, blinding, and handling of patient attrition if recorded, giving a score of 0–5 with 5 being the best. Table 2 shows a summary of this appraisal.

Data were extracted from the trial summary statistics and weighting was applied according to the precision of the study.

Because of heterogeneity of design combination was possible in six studies for the outcome measure of reduction in PaCO_2 . In these studies reductions in partial pressure of arterial carbon dioxide after addition of Heliox was reported. The assumption is made that any improvement in PaCO_2 occurs instantly due to improved alveolar ventilation. These results were combined to give a summary statistic reflecting true decrease in PaCO_2 . The Hedges' adjusted g standardised mean difference method was used to determine the size of the treatment effect in each trial. These were then combined using the DerSimonian and Laird random effects model to give a final summary statistic.

A sensitivity analysis was then performed on methodological grounds, followed by an investigation of the heterogeneity in the study trials.

Two further studies reported the effect of Heliox on intubation rates in COPD exacerbations in the acute setting. Using trial data the odds ratios for intubation with Heliox

and conventional treatment were calculated and combined using the Mantel-Haenszel estimate.

All calculations were performed by hand and then checked using Comprehensive Meta Analysis, a commercial medical meta analysis software package.

RESULTS

Table 2 summarises the methodological properties of each paper.

The internal and external validity of all the studies was examined and significant sources of bias, based on Chalmers scale⁶ were apparent. These were attributable to non-randomisation and lack of blinding. Using the Jadad scale of validity⁷ it was found that most trials were unsatisfactory, scoring lower than 2. Studies published in abstract form lacked the information required to perform a detailed critical analysis, however in a complete systematic review it is recommended they be included⁸ to avoid exclusion of important data.

The results of examination and manipulation of the data for the outcome of reduction in PaCO_2 in Heliox treated and conventionally treated patients ($n = 234$) for the six trials is displayed in a forest plot (fig 1).

Combination of data from all trials suggests a reduction of PaCO_2 of 0.78 KPa (1.44 to 0.13) beyond that produced by conventional treatment.

In the study by Jolliet it was further noted that the magnitude of reduction in PaCO_2 may be correlated with baseline PaCO_2 . That is, sicker patients with a higher initial PaCO_2 benefited more from the use of Heliox.

Figure 2 shows the result of combination of data from trials measuring intubation rates of patients treated conventionally or with Heliox ($n = 121$).

The odds ratio of intubation for all patients treated with Heliox during an acute exacerbation of COPD compared with conventionally treated patients was 0.096 (0.03 to 0.27). That is the odds of intubation in a severe exacerbation are reduced by a factor of 10. Converting this to risk ratios, an 82% reduction in risk of intubation may be conferred by addition of Heliox in patients with exacerbations of COPD.

A sensitivity analysis excluding all papers with low methodological quality (Jadad < 2) estimated the reduction

in PaCO_2 conferred by use of Heliox breathing to be 0.22 KPa (+0.57 to -0.14) (fig 3).

A further analysis removing trials that did not explicitly exclude asthmatic subjects estimated the reduction in PaCO_2 to be 0.40 (0.76 to 0.05).

Heterogeneity in the trials of reduction in PaCO_2 was examined and the Q statistic (measure of heterogeneity following a χ^2 probability distribution) was 37.23 meaning that the studies were highly heterogeneous. Examining the subgroup of the most methodologically robust studies, statistical tests suggested little heterogeneity. For the subgroup of lower quality studies heterogeneity remained suggesting a property of these studies that increased their variability beyond the play of chance. This may be explained by the variety of settings and protocols used in these studies (more robust studies were all ITU based).

One possible source of heterogeneity is the co-intervention of NIV. When reduction in PaCO_2 in studies using NIV was compared with those not using NIV, the effect attributable to Heliox was less in the studies using NIV and this difference approached statistical significance ($p = 0.16$). That is, there appeared to be a proportional reduction in benefit of Heliox when used in combination with NIV.

DISCUSSION

Unfortunately much of the evidence in this review is of low methodological quality. With regard to the end point of reduction in PaCO_2 , once low quality evidence was excluded the estimate of treatment effect became quite modest with confidence intervals crossing the line of no effect ($p = 0.2$). However, one must accept the difficulties associated with studying Heliox making rigorous scientific assessment problematic. Blinding is difficult as investigator and patient can easily detect the change in voice when breathing Heliox and technical details in administration of Heliox prevent blinding of the investigator. Satisfactory randomisation, however, could have been attempted. This was only achieved in three trials (Jaber, Thiriet, and Jolliet) and has the effect of undermining the validity of the analysis. Therefore for future trials proper randomisation is mandatory to add new evidence.

The absence of blinding and randomisation does not totally invalidate trials of treatment but it is estimated that it may exaggerate the treatment effect by up to 40%.⁹ If the results are adjusted to take this into account there is only an insignificant treatment effect.

Many of the trials used stable patients rather than patients with acute severe COPD in whom benefits may be greater, thus it is possible that the data used for the outcome of reduction in PaCO_2 may underestimate the clinical value of Heliox treatment. Also it is highly probable that the way Heliox breathing affects the pathophysiology of COPD is multifactorial and other processes outside the scope of this analysis may contribute to overall improvement in clinical outcome such as reduced dynamic hyperinflation and work of breathing. These are not directly assessed by PaCO_2 and

may explain why despite a modest reduction in PaCO_2 there is a striking effect on odds of intubation.

The estimation of the true odds ratios for intubation in intervention and control groups was also biased because of poor methodology. Most importantly both studies were retrospective case note reviews and used historical control groups, resembling more a cross sectional study than a true trial in that the participants were not assigned to control or intervention groups by methods that are bias averse. These groups could easily have varied in ways other than the intervention under investigation. This is especially true for the Gerbeaux study, where the type of intervention the patient received was determined by the emergency physician treating the patient. The authors admit that only three of seven clinicians in their department favoured the use of Heliox, thus the variability of skills of the clinician treating the patient in the trial becomes highly significant, and as there was no attempt to standardise this by protocol, the variability pollutes the overall study results.

An investigation into heterogeneity showed differences between Heliox delivered by NIV and by face mask, which although not significant might suggest that only modest additional benefits in alveolar ventilation are achieved by adding Heliox to the NIV regimen.

The cost of Heliox treatment is about £500 per day depending on the oxygen concentration the patient requires. If this is compared with the cost of mechanical ventilation in the ITU (about £1500 per day) there is an overall cost saving for Heliox treatment. However, comparing Heliox and NIV in a high dependency setting the costs are probably comparable.

Two of the trials (Thiriet and Harrison) reported a decrease in partial pressure of oxygen when Heliox treatment was started but this effect was not seen in any of the other trials. No other adverse effects are reported.

In conclusion, definitive evidence of a beneficial role of Heliox in treatment of severe COPD is lacking and therefore its wide scale use cannot be recommended based on this analysis. Heliox may improve alveolar ventilation and gas transfer but a randomised controlled trial without NIV as a co-intervention is needed to further elucidate its role. Heliox may confer a benefit in reduced odds of intubation. Based on this, in the individual case of severe COPD where intubation is required but would be undesirable, it is a treatment worthy of consideration.

The appendix showing the exclusion log is available on the journal web site (<http://www.emjonline.com/supplemental>).

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