Heliox vs air-oxygen mixtures for the treatment of patients with acute asthma: a systematic overview
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CRD summary
This review assessed the effectiveness of heliox on respiratory ventilation and outcomes in patients with acute asthma. The authors concluded that heliox may offer mild-to-moderate benefits within the first hour of use, and may be more pronounced in severe cases. The authors' conclusions appear overly optimistic and should not be viewed as being reliable.

Authors' objectives
To assess the effectiveness of heliox on respiratory ventilation and outcomes in patients with acute asthma.

Searching
MEDLINE (from 1966 to June 2002), EMBASE (from 1989 to June 2002) and the Cochrane Controlled Trials Register were searched for articles published in English; the search terms were reported. In addition, the references of identified studies were checked. A further search without language restrictions was undertaken to identify any further RCTs.

Study selection
Study designs of evaluations included in the review
Systematic reviews, randomised controlled trials (RCTs), cohort studies, case-control studies, cross-sectional studies, case series and case reports were eligible for inclusion.

Specific interventions included in the review
Studies that compared any mixture of heliox versus air-oxygen mixtures, with or without concurrent beta-agonists, parasympatholytics and corticosteroids, and with or without invasive ventilation, were included.

Participants included in the review
Adults and children with acute asthma requiring hospital treatment were included. Patients with disease without acute exacerbations, who were studied with or without artificially induced peripheral airway obstruction, were excluded. The age of the patients ranged from 16 months to 70 years across the studies.

Outcomes assessed in the review
Studies that reported the peak expiratory flow rate (PEFR), the PEFR as a percentage of predicted expiratory flow rate (PEFR%), forced expiratory flow rate between 25 and 75% of vital capacity, forced expiratory volume in 1 second, forced vital capacity, respiratory rate, clinical asthma scores, dyspnoea index scores, arterial blood gas, alveolar-arterial oxygen tension gradient, pulsus paradoxus, arterial blood oxygenation (SpO2), length of hospital stay, or incidence of tracheal intubation and mechanical ventilation, were eligible for inclusion.

How were decisions on the relevance of primary studies made?
At least two reviewers independently assessed studies for inclusion in the review. Any discrepancies were resolved by discussion.

Assessment of study quality
The quality of the RCTs was assessed according to the level of allocation concealment, double-blinding and withdrawals. Each of these was rated as adequate, inadequate, or unclear. The authors did not state how the papers were assessed for quality, or how many reviewers performed the quality assessment.
Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

The results were presented as means with standard deviations for each study. Where crossover trials were combined with parallel-group RCTs, the data from the first arm of the trial were used if there was evidence of a carry-over effect. The level of confidence was estimated for any improvement in PEFR% using the method outlined by Shakespeare et al. (see Other Publications of Related Interest).

Methods of synthesis
How were the studies combined?
The studies were combined using a random-effects meta-analysis for the commonly reported outcomes of PEFR%, dyspnoea index scores, hospital admission rate and SpO2. A narrative review was also performed to assess any further outcomes that could not be pooled in the meta-analysis.

How were differences between studies investigated?
Differences between the studies were examined using a fixed-effect meta-regression model, to investigate whether baseline PEFR% affected the efficacy of heliox treatment. The trials were weighted in the linear regression model according to the inverse variance in treatment effect.

Results of the review
Fifteen studies (n=490) were included; eight RCTs (n=393), one non-randomised controlled clinical trial (n=27), one case-control study (n=22), four case series (n=42) and one case report (n=1).

PEFR% (4 RCTs, n=278): no significant difference was observed within the first hour of treatment for heliox compared with the air-oxygen mixture (weighted mean difference, WMD=+3%, 95% confidence interval, CI: -2, +8). The level of confidence that heliox provided a treatment benefit when used as an adjunct to standard medical care was 92%.

Arterial blood oxygenation (2 RCTs, n=50): there was no significant difference between heliox and air-oxygen treatment in relation to arterial blood oxygenation levels (WMD 0%, 95% CI: -1.4, +1.4).

Dyspnea index scores (2 RCTs, n=44): there was a slight significant improvement in dyspnoea index scores with heliox compared with air-oxygen (WMD 0.60, 95% CI: 0.04, 1.16).

An examination of the relationship between baseline PEFR% and treatment effect suggested that there was a slight association between baseline PEFR% and PEFR% readings obtained after treatment for both heliox and air-oxygen. The results of the model also suggested that patients with more severe acute asthma (less than 43% PERF) may benefit more from heliox than patients with less severe acute asthma.

Overall, the narrative synthesis of the results showed that five of the eight RCTs, the one non-randomised controlled trial, one retrospective case-control study, three case series, and one case report had at least one outcome measure that favoured treatment with heliox. One RCT and one case series showed no differences between treatment with heliox and air-oxygen on any of the outcome measures assessed. One RCT showed a possible detrimental effect of treatment with heliox, while one small RCT was inconclusive.

Authors’ conclusions
Based on surrogate respiratory parameters, heliox may offer mild-to-moderate benefits in patients with acute asthma within the first hour of use, but its advantages become less apparent beyond one hour as most conventionally treated patients improve to similar levels, with or without it. The effect of heliox may be more pronounced in more severe cases.
The review question was reasonably well defined in terms of the interventions, participants, study designs and outcome measures. Several sources were searched for relevant studies, but no attempts to identify unpublished material were made; some potentially relevant studies might, therefore, have been missed. Efforts were made to minimise reviewer bias and errors in the study selection process. However, it was unclear how many reviewers were involved in the assessment of study quality and data extraction, and it is therefore possible that errors and bias might have been introduced into the review process.

Some data were presented in tabular format, but more results from the primary studies would have been useful: it appears that the results for only a selection of outcomes were reported. The use of a meta-analysis to combine the common end points across the studies appears to have been appropriate, and this was further supplemented by a narrative discussion of the studies. Some differences between the studies were also appropriately assessed by meta-regression analysis. The results of the review indicated that there were no significant differences between treatment with heliox and air-oxygen mixture within the first hour of treatment. Thus, the authors' conclusions appear overly optimistic and should not be viewed as being reliable.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that in view of the insufficient data available, future studies should focus on whether heliox can reduce tracheal intubation rates, the duration of mechanical ventilation, intensive care and hospital lengths of stay, and mortality. In addition, future studies should improve on the levels of allocation concealment; prevent air entrainment during heliox administration; consider the use of higher heliox flow to compensate for its lower nebulising efficiency; and allow a period for washout of the test gas before spirometry is performed, to minimise the effects of helium on such measurements.

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