Heliox inhalation therapy for bronchiolitis in infants (Review)

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[Intervention Review]

Heliox inhalation therapy for bronchiolitis in infants

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ABSTRACT

Background

Acute viral bronchiolitis is associated with airway obstruction and turbulent gas flow. Heliox, a mixture of oxygen and the inert gas helium, may improve gas flow through high-resistance airways and decrease the work of breathing.

Objectives

To assess heliox in addition to standard medical care for acute bronchiolitis in infants.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 2), which includes the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (1966 to June 2009), EMBASE (June 2009), LILACS (May 2009) and the NIH web site (May 2009).

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs of heliox in infants with acute bronchiolitis.

Data collection and analysis

Two review authors independently extracted data and assessed trial quality. We pooled data from individual trials.

Main results

We included four trials involving 84 infants under two years of age with respiratory distress secondary to bronchiolitis caused by respiratory syncytial virus (RSV) and requiring paediatric intensive care unit (PICU) hospitalisation. We found that infants treated with heliox inhalation had a significantly lower mean clinical respiratory score in the first hour after starting treatment when compared to those treated with air or oxygen inhalation (mean difference (MD) -1.15, 95% confidence interval (CI) -1.98 to -0.33, P = 0.006, n = 69). There was no clinically significant reduction in the rate of intubation (risk ratio (RR) 1.38, 95% CI 0.41 to 4.56, P = 0.60, n = 58), in the need for mechanical ventilation (RR 1.11, 95% CI 0.36 to 3.38, P = 0.86, n = 58), or in the length of stay in a PICU (MD = -0.15 days, 95% CI -0.92 to 0.61, P = 0.69, n = 58). No adverse events related to heliox inhalation were reported.

Authors' conclusions

Current evidence suggests that the addition of heliox therapy may significantly reduce a clinical score evaluating respiratory distress in the first hour after starting treatment in infants with acute RSV bronchiolitis. Nevertheless, there was no reduction in the rate of intubation, in the need for mechanical ventilation, or in the length of PICU stay. Further studies with homogeneous logistics in their heliox application are needed. Such studies would provide necessary information as to the appropriate place for heliox in the therapeutic schedule for severe bronchiolitis.

PLAIN LANGUAGE SUMMARY

Heliox inhalation therapy for bronchiolitis in infants

Bronchiolitis is the leading cause of hospitalisation among infants in high-income countries. Common symptoms include a runny nose, cough and dyspnoea (difficulty breathing) often with bronchospasm (sudden narrowing of the airways) and resultant wheezing. Approximately 20% of all infants experience wheezing associated with respiratory syncytial virus in the first year of life, and 2% to 3% require hospitalisation for this illness. In this review, we selected trials that objectively assessed the effect of the addition of heliox to standard medical care for acute bronchiolitis. Heliox is a mixture of oxygen and the gas helium.

We retrieved four trials involving children under two years of age with respiratory distress secondary to bronchiolitis, which was sufficiently life-threatening to lead to hospitalisation in a paediatric intensive care unit. Pooled results from two trials (where the following data were available) failed to demonstrate a reduction in the need for mechanical ventilation, the rate of intubation (placement of a tube in the airway) or in the length of stay in a paediatric intensive care unit. However, three trials, involving 69 infants, used a clinical respiratory score system, with increased severity receiving a higher score. The pooled results show that infants treated with heliox inhalation had a statistically significant reduction in this respiratory score in the first hour. The only trial which assessed changes after 24 hours of heliox treatment failed to demonstrate any significant reduction in any of our outcome measures.

The trials included in this review had several potential biases and also used four different methods for delivering heliox. Also, importantly, only two trials assessed the reduction in the need for intubation for infants with acute bronchiolitis (58 infants, all hospitalised in a paediatric intensive care unit).

Further studies which all use the same method of heliox application are needed. Such studies would provide necessary information about the appropriate place of heliox in the management of severe bronchiolitis.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

	Experimental events	Experimental total	Control events	Control total
Cambonie 2006	0	10	0	9
Liet 2005	1	18	0	21

BACKGROUND

Description of the condition

Bronchiolitis, an acute inflammatory process of the small airways, is the leading cause of hospitalisation among infants in high-income countries (Welliver 2003). Common symptoms include a runny nose, cough and dyspnoea often with bronchospasm, mucus production and wheezing. Respiratory syncytial virus (RSV) is the most common pathogen (85%) isolated. In fact, approximately 20% of all infants have RSV-associated wheezing in the first year of life, and 2% to 3% require hospitalisation as part of the management strategy (AAP 2006).

Even though there are many treatments, there is no evidence to endorse a specific treatment other than supportive care (Davison 2004). Recent data suggest a possible role for nebulised hypertonic saline in select cases (Zhang 2008). Supplemental oxygen and judicious fluid management remain the mainstays of therapy. Endotracheal intubation, positive pressure ventilation (PPV), or both, are necessary in 3% to 9% of children (Wang 1995).

Premature or low birth weight infants, infants with bronchopulmonary dysplasia and patients with haemodynamically significant congenital heart disease merit special attention. The relatively smaller airways of select infant groups places them at higher risk of respiratory failure and need for specialised management. For example, the percentage of patients requiring endotracheal intubation or PPV is higher in infants with congenital heart disease (19% to 24%), immunocompromised status (14%) (Wang 1995), chronic lung disease (17% to 25%) or those born prematurely (Meert 1990). For infants weighing less than 5 kg the relative risk for mechanical ventilation has been shown to be 4.4 (95% confidential interval (CI) 1.3 to 13.9) (Tissing 1993). Mortality rates of infants hospitalised in a PICU for RSV-bronchiolitis range from 0% to 3% if patients have no risk factors, and 2.5% to 6% if they have at least one risk factor (Chevret 2005; Prais 2003; Wang 1995).

Description of the intervention

Helium-oxygen gas mixtures (heliox) were first described in 1934 by Barach for the treatment of upper airway obstruction (Barach 1934) and heliox has subsequently been shown to be a useful adjunctive therapy in patients with asthma (Carter 1996; Kudukis 1997), chronic obstructive pulmonary disease (Jaber 2001; Jolliet 1999; Laude 2006), bronchiolitis (Holmann 1998; Martinon-Torres 2002), upper airway obstruction (Tobias 1997), acute respiratory distress (Winters 2000) and in children with post-extubation stridor (Kemper 1991). Although heliox can be an effective treatment option, the existing evidence does not provide support for the administration of heliox mixtures to all emergency department patients with acute asthma (Rodrigo 2007a), and there is currently insufficient evidence to support the use of heliox mixtures to treat acute exacerbations of chronic obstructive pulmonary disease in either ventilated or non-ventilated patients (Rodrigo 2007b).

How the intervention might work

In bronchiolitis breathing becomes more difficult due to an increased end-expiratory lung volume, decreased lung compliance and relative upper airway obstruction with increased airway resistance. Infection of bronchiolar respiratory and ciliated epithelial cells produces increased mucus secretion, cell death and sloughing. This is followed by a peribronchiolar lymphocytic infiltrate and submucosal oedema (AAP 2006). The combination of debris and oedema produces obstruction of the smaller airways. This critical narrowing results in turbulent flow and increased airway resistance. Decreased ventilation in effected areas causes ventilation/perfusion mismatching, resulting in hypoxia. During the expiratory phase of respiration, dynamic collapse of the airways produces a disproportionate decrease in airflow and resultant air trapping.

Since bronchiolitis is associated with airway obstruction and turbulent gas flow, this disease process could theoretically be improved by heliox, which improves gas flow through high-resistance airways because of the lower density of helium compared to air

(Gupta 2005; Panitch 2003). Helium is an inert gas with no intrinsic bronchodilatory or anti-inflammatory properties. Helium has the lowest density of any gas other than hydrogen, which is unfortunately not medically useful because of its flammable properties. Helium acts as a 'carrier gas', resulting in lower resistance to gas flow allowing for increased bulk flow, increased oxygen flow and decreased work of breathing (Wolfson 1984). Equally important is the fact that carbon dioxide diffuses through helium four to five times faster than through air, which aids ventilation and carbon dioxide removal.

The effects of heliox are relatively rapid and therefore any significant clinical effects are expected to be seen within minutes. Thus, the clinician quickly knows if heliox therapy will be beneficial for an individual patient or if it should be abandoned for other possible therapies.

For non-ventilated patients, it is also essential to ensure that there is no accidental contamination of the heliox mixture with air or oxygen. For instance, heliox administration via a standard high-concentration reservoir mask leads to significant dilution by room air (Standley 2008).

Tanks of 100% helium are available but require a blender to dilute the helium in order to provide the patient with a stable source of oxygen. Any interruption in oxygen delivery could result in the accidental administration of a hypoxic gas mixture, including the possibility of delivering 100% helium. The use of premixed heliox tanks with at least a 21% oxygen concentration avoids this potentially fatal complication. Administration with premixed 70% helium and 30% oxygen can provide additional oxygen for patients with respiratory distress who need higher fraction of inspired oxygen (FiO_2).

The administration of heliox during mechanical ventilation must be carried out with vigilance and accurate, continuous monitoring. Helium can interfere with the accuracy of pneumotachometer and ventilator function, which are typically calibrated for nitrogen instead of helium as the primary balance gas (Berkenbosch 2003). A new generation helium/oxygen administration system (Heliontix Vent^{TM}) has been recently developed by Linde Gas Therapeutics to help circumvent these issues.

Why it is important to do this review

The hypothesis of this review is that heliox inhalation is beneficial in the management of acute bronchiolitis as assessed by clinically relevant outcomes. In order to critically evaluate the clinical data, we undertook a systematic review of trials that use heliox for the treatment of bronchiolitis.

OBJECTIVES

To determine the effect of heliox in addition to standard medical care on the course of acute bronchiolitis in infants, as measured by clinical endpoints and pulmonary function testing.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs. Both parallel group and cross-over designs were considered. We excluded studies where heliox was used as a vector for nebulisation (to improve aerosol drug delivery), or studies where helium was used to assess lung volumes.

Types of participants

Infants hospitalised for acute bronchiolitis. For the purpose of this review, acute bronchiolitis is defined by the presence of signs of respiratory distress secondary to respiratory syncytial virus (RSV) infection and/or those patients with respiratory distress and symptoms that occur within RSV epidemic periods and are not due to other medical conditions.

Types of interventions

Treatment with inhaled heliox versus a placebo (oxygen or air).

Types of outcome measures

Primary outcomes

1. In-hospital mortality.
2. Need for mechanical ventilation.
3. Need for endotracheal intubation.
4. Length of paediatric intensive care unit (PICU) stay.

Adverse effects were also analysed.

Secondary outcomes

1. Gas exchange (effects on oxygenation and CO_2 elimination) within the first 24 hours after starting heliox treatment.
2. Respiratory mechanics (effects on pulmonary compliance and resistance of airways) within the first 24 hours after starting heliox treatment.
3. Clinical respiratory scores within the first 24 hours after starting heliox treatment.
4. Total duration of hospitalisation (including duration in PICU).

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 2), which includes the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (1966 to June Week 3 2009), EMBASE (June 2009), LILACS (May 2009) and the NIH web site (ClinicalTrials.gov) (May 2009).

We used the following search terms to search MEDLINE and CENTRAL. The MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying RCTs in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2008). The search terms were adapted to search EMBASE (see Appendix 1) and LILACS (see Appendix 2).

MEDLINE (Ovid)

1 Helium/
2 helium.tw,nm.
3 heliox.tw,nm.
4 heo2.tw.
5 he-o2.tw.
6 or/1-5

Searching other resources

We checked references of relevant systematic reviews and identified RCTs. Two review authors (VG, JML) contacted trial authors of all studies to locate other unpublished or in progress studies which met the inclusion criteria. There were no language or publication restrictions.

Data collection and analysis

Selection of studies

Two review authors (JML, GC) independently reviewed titles, abstracts and citations to assess potential relevance for full review. From the full text, both review authors independently assessed studies for inclusion based on the criteria for study design, population, intervention and outcomes. We excluded articles that did not meet the inclusion criteria and noted the reasons for their exclusion (see Characteristics of excluded studies table). We resolved any disagreement between the two review authors about study inclusion by discussion.

Data extraction and management

Two review authors (JML, GC) independently extracted data from the included trials using a standardised data extraction form. We resolved any disagreement between the two review authors by discussion. Results were then entered into the Cochrane Collaboration software program (Review Manager 5.0) (RevMan 2008). Data extraction included the following items.

1. Methods (method of randomisation, allocation concealment, blinding, analysis by intention-to-treat (ITT), withdrawals).
2. Participants (age, gender, number of patients studied, location, RSV and other organisms, patient demographics, risk factors, withdrawals).
3. Interventions (fraction of inspired helium, duration of therapy, route of delivery, mechanical ventilation, intubation).
4. Control; concurrent treatments.
5. Outcomes. We extracted the results based upon the ITT population.

Assessment of risk of bias in included studies

Two review authors (JML, GC) assessed the methodological quality of the included trials. Each study was assessed for validity with The Cochrane Collaboration's tool for assessing risk of bias (Higgins 2008). We classified five features from grade A to grade C: generation of allocation sequence, allocation concealment, blinding, ITT, analysis, and loss to follow up. High quality trials were defined as those with adequate allocation concealment (grade A) and adequate blinding of investigators, participants and outcome assessors (grade A). We resolved any disagreement between the two review authors by discussion.

Measures of treatment effect

We compared treatment with inhaled heliox to a placebo (oxygen or air) for primary and secondary outcomes. For endpoints with dichotomous measures (for example, mortality, need for endotracheal intubation), we measured effect size using the risk ratio (RR) and 95% confidence interval (CI). We calculated the mean difference (MD) and 95% CI for numerical outcomes.

Unit of analysis issues

We analysed studies with non-standard designs, such as cross-over trials, according to particular biases. The main concerns over risk of bias in cross-over trials are whether the cross-over design is suitable, whether there is a carry-over effect, whether only first trial period data are available, incorrect analysis and comparability of results with those from parallel-group trials. Since helium is an inert gas with no intrinsic bronchodilatory or anti-inflammatory properties, and could be useful only by improving gas flow, there is unlikely to be carry-over of treatment effect across trial periods.

Dealing with missing data

In case of missing values, we contacted the original trial authors to request missing data. Otherwise, data are assumed to be missing at random. We also addressed the potential impact of missing data on the findings of the review in the Discussion section.

Assessment of heterogeneity

We assessed heterogeneity between studies by using the I^2 statistic (Higgins 2003). Heterogeneity was considered weak when the I^2 statistic was less than 0.25.

Assessment of reporting biases

We assessed publication bias by funnel plots. Publication bias need not lead to asymmetry in funnel plots. In the absence of any intervention effect, selective publication based on the P value alone will lead to a symmetrical funnel plot in which studies on the extreme left or right are more likely to be published than those in the middle. This could bias the estimated between-study heterogeneity variance.

Data synthesis

We used a fixed-effect model when studies were homogenous or a random-effects model when studies were heterogeneous.

Subgroup analysis and investigation of heterogeneity

We used Review Manager to perform statistical analysis of extracted data. Planned subgroup analyses included infants younger than 12 months of age still hospitalised but not receiving mechanical ventilation, and infants under 12 months of age recruited under mechanical ventilation. The main endpoint in the first subgroup was the need for mechanical ventilation, and in the second subgroup the change in oxygenation index one hour after heliox administration. These were not undertaken because of the limited number of included trials.

Sensitivity analysis

We planned sensitivity analyses. This was not undertaken because of the limited number of included trials.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

The MEDLINE search retrieved 227 citations, CENTRAL 273 citations, EMBASE 209 and LILACS a total of 41 citations. The ClinicalTrials.gov search retrieved one ongoing study about heliox/helium in bronchiolitis (but in this study heliox was only used to drive racaemic epinephrine nebulisation). We contacted trial authors of the included studies and they allowed us to locate two other studies currently in progress.

Included studies

Four trials met the criteria for study selection for this review (see Characteristics of included studies table). Two studies were parallel-group trials (Cambonie 2006; Liet 2005) and two studies used a cross-over design (Holmann 1998; Martinon-Torres 2008). One study was a multi-centre trial involving three hospitals in Canada and one hospital in France (Liet 2005). The other studies were conducted in France (Cambonie 2006), in the USA (Holmann 1998) and in Spain (Martinon-Torres 2008). In one trial (Holmann 1998) not all infants were randomised, but it was possible to recover data from the randomised infants separately. We only extracted these data for this review.

The four trials included only non-intubated children. One other recent trial (unblinded, cross-over design) (Kneyber 2009) has included 13 mechanically ventilated, sedated and paralysed infants. Results of this quasi-RCT are mentioned solely in the Discussion.

Participants

All patients were recruited in a paediatric intensive care unit (PICU). They were all admitted with respiratory syncytial virus (RSV) bronchiolitis. All children were under two years of age; they were all under nine months in two trials (Cambonie 2006; Liet 2005) and all under three months in one trial (Cambonie 2006).

Interventions

All infants were treated with inhaled heliox versus a placebo (oxygen or air). Different protocols were used: inhalation of either heliox or air-oxygen for one hour under an oxy hood (Cambonie 2006), inhalation in a random order of heliox and air-oxygen by non-rebreather reservoir mask for two 20-minute study periods (Holmann 1998), inhalation of either heliox or air-oxygen under an inflatable head hood continuously (until ventilation or weaning after at least 24 hours of therapy) (Liet 2005) and inhalation in a random order of heliox and air-oxygen by non-invasive ventilation equipment (nasal continuous positive airway pressure) for two 30-minute study periods (Martinon-Torres 2008). In the four trials all available data about heliox concerned non-intubated children.

Outcome measures

In three trials the primary outcome measure was the effect on respiratory distress using a clinical scoring system, the modified Wood clinical asthma score (mWCAS) (Cambonie 2006; Holmann 1998; Martinon-Torres 2008). The mWCAS initially described by Wood (Wood 1972) grades cyanosis, inspiratory breath sounds, accessory muscles used, expiratory wheezing and cerebral function from 0 to 2, with increased severity receiving a higher score. In the other study (Liet 2005), the primary outcome measure was the rate of initiation of positive pressure, with a clinical score using the respiratory distress assessment instrument (RDAI). The RDAI was first described by Lowell (Lowell 1987) and grades wheezing and retractions with the maximum total points for wheezing being eight and for retractions nine.
Side effects associated with heliox inhalation were reported in all four trials.

Excluded studies

We excluded 10 publications about heliox therapy in children because they were case reports with no control groups (Duncan 1979; Gross 2000; Gupta 2004; Iglesias-Fernandez 2007; Kneyber 2006; Martinon-Torres 2005; Martinon-Torres 2006; Tobias 1999; Ulhoa 2000; Williams 2004). We also excluded paediatric publications reporting the effects of heliox therapy for conditions other than bronchiolitis (Abd-Allah 2003; Dieperink 2007; Elleau 1993; Tobias 1997; Winters 2000). One study was not blinded and had an inadequate method of randomisation (alternate inclusion) (Martinon-Torres 2002).

Risk of bias in included studies

Allocation

Three of the four trials described adequate allocation concealment (Cambonie 2006; Holmann 1998; Liet 2005). The method of randomisation was explicitly described and considered to be adequate in two trials (Holmann 1998; Liet 2005). In one another trial (Cambonie 2006), the authors were requested to provide details regarding the method of randomisation and upon review this study was judged adequate. In the remaining trial (Martinon-Torres 2008), after assessing information provided by the trial authors, the method of randomisation and allocation concealment were judged adequate only for the first infant (coin tossing only for the first infant, then alternate inclusion in the treatment group or control group for the first cross-over study period). This trial was classified as a quasi-RCTs and was kept in the review because of its cross-over design and other research methodologies.

Blinding

The methods for double-blinding were considered appropriate in three trials (Cambonie 2006; Holmann 1998; Liet 2005). The other trial was not blinded (Martinon-Torres 2008). This point is of concern as the main significant retrieved effect of heliox therapy is a respiratory score based on a clinical observation. Nevertheless, this trial was kept because of the sparse data available for this meta-analysis.

Incomplete outcome data

We extracted all available data from the four studies.

Selective reporting

All outcomes were available in the included studies. We cannot be certain that selective reporting did not occur, but have no reason to suspect this potential bias.

Other potential sources of bias

Two trials (Holmann 1998; Martinon-Torres 2008) included infants under two years of age whether or not it was their first episode of acute bronchiolitis. Using this criterion, the inclusion of asthmatic infants was possible in these trials. Moreover, it is quite confusing to collect together results from infants less than one month old (often born prematurely) and results from older children.
The flow rate of heliox delivery should always be higher than the inspiratory peak flow rate of the infant to avoid dilution by room air. As inspiratory peak flow rate can be very high for a brief time, the inclusion of a large reservoir device is suggested for any investigation using a medical nebuliser driven by heliox to prevent the dilution of the gas by the room air (Corcoran 2004). Thus, the four different protocols used for delivering heliox (see above) could represent a potential bias.
The Liet trial (Liet 2005) used an inflatable head hood with a gas flow rate of 9 to 15 L/min. As there was no collapse of the non-rigid plastic head hood, one can assume there was no room air dilution. This argument is not valid for Cambonie 2006 as a classic rigid head hood with a gas flow rate of 7 L/min was used. A reservoir device was used in one trial (Holmann 1998). However, significant dilution by room air has recently been well documented during heliox administration via a standard high-concentration reservoir mask (Standley 2008).
Although the Holmann trial demonstrated a reduction in the clinical respiratory distress score following heliox inhalation (Holmann 1998), the benefit was lower compared to the two other trials that used the same score to assess respiratory distress (Cambonie 2006; Martinon-Torres 2008). The Martinon-Torres trial (Martinon-Torres 2008) was performed with a device routinely used in neonatal units for non-invasive ventilation, with specific nasal equipment. A room air dilution of helium could theoretically occur if the

infant breathes by the mouth. Nevertheless this device, equipped with a heated humidifier, delivered a flow rate of 10 to 15 L/min which limited this risk. Moreover, the humidifier included a reservoir system large enough to accommodate the increased tidal volumes that would be expected with heliox inhalation (Corcoran 2004).

Another concern is the dispatching of the gases in the hood. The lower density of helium relative to oxygen and nitrogen means that helium tends to concentrate at the top of the hood, which potentially increases the density of the mixture inhaled by the infant (Stillwell 1989). However, this concern can be alleviated. Firstly, infants subjected to the hood were in a supine position to allow the respiratory distress evaluation, thus placing mouth and nose at least in a median position relative to the top and bottom of the hood. Secondly, some clinical studies (Weber 2001) show the efficacy of helium-oxygen mixtures administered by hood in patients with upper airways obstruction, suggesting that the activity of a dyspnoeic infant under the hood probably modifies the distribution of gases in the device. Thirdly, in one trial (Cambonie 2006) oxymetry was continuously monitored at the top of the hood and did not show any difference between the prescribed and the measured concentrations of oxygen in the hood.

Effects of interventions

See: **Summary of findings for the main comparison** Mortality; **Summary of findings 2** Need for mechanical ventilation; **Summary of findings 3** Rate of intubation; **Summary of findings 4** Length of PICU stay; **Summary of findings 5** Change in clinical respiratory scores within the first hour after starting heliox treatment; **Summary of findings 6** Change in CO2 within the first hour after starting heliox treatment; **Summary of findings 7** Change in O2 needs after 1 hour of heliox treatment; **Summary of findings 8** Change in SpO2 in the first hour after starting heliox treatment; **Summary of findings 9** Change in clinical score after 24 hours of heliox treatment; **Summary of findings 10** Change in O2 needs after 24 hours of heliox treatment; **Summary of findings 11** Change in CO2 after 24 hours of heliox treatment

Four randomised controlled trials involving 84 infants with respiratory syncytial virus (RSV) bronchiolitis compared heliox inhalation to air or oxygen inhalation. The following clinical outcomes are representative of subgroups of these 84 participants.

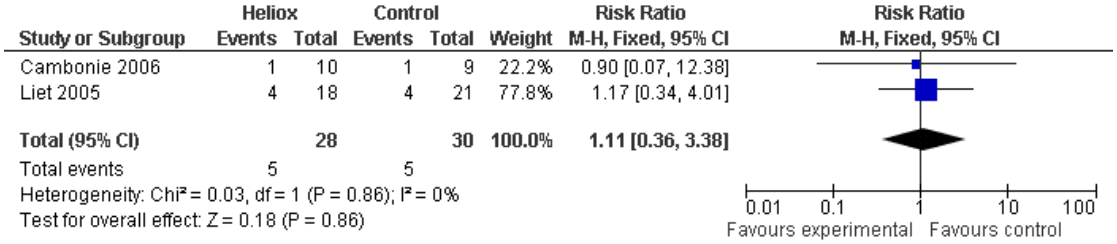
1. Mortality

Mortality was reported in two trials (Cambonie 2006; Liet 2005). One child died in the experimental group due to irreversible respiratory failure 34 days after stopping helium treatment (Liet 2005).

2. Need for mechanical ventilation

Two trials used the need for mechanical ventilation (invasive or not) as an outcome measure (Cambonie 2006; Liet 2005). These trials failed to demonstrate a reduction in the need for mechanical ventilation with heliox (RR 1.11, 95% CI 0.36 to 3.38, P = 0.86) (Figure 1).

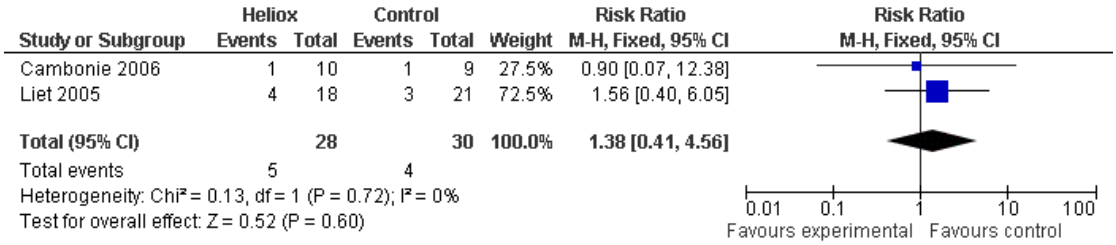
Figure 1. Forest plot of comparison: 1 Heliox inhalation versus air or oxygen inhalation, outcome: 1.2 Need for mechanical ventilation.



3. Rate of intubation

Two trials used the rate of intubation as an outcome measure (Cambonie 2006; Liet 2005). These trials failed to demonstrate a reduction in the rate of intubation with heliox use (RR 1.38, 95% CI 0.41 to 4.56, P = 0.60) (Figure 2).

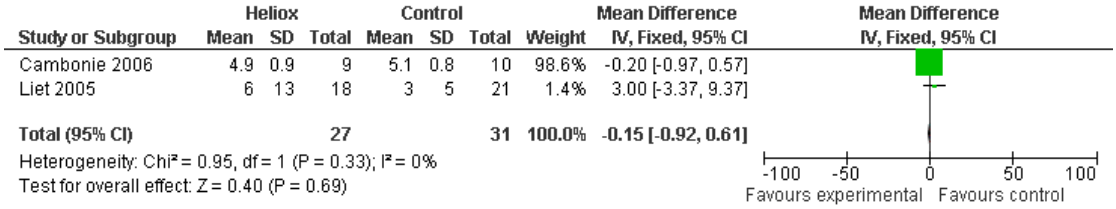
Figure 2. Forest plot of comparison: 1 Heliox inhalation versus air or oxygen inhalation, outcome: 1.3 Rate of intubation.



4. Length of paediatric intensive care unit (PICU) stay

Two trials used PICU length of stay as an outcome measure (Cambonie 2006; Liet 2005). These trials failed to demonstrate a reduction in the length of PICU stay with heliox use (MD -0.15 days, 95% CI -0.92 to 0.61, P = 0.69) (Figure 3).

Figure 3. Forest plot of comparison: 1 Heliox inhalation versus air or oxygen inhalation, outcome: 1.4 Length of PICU stay.

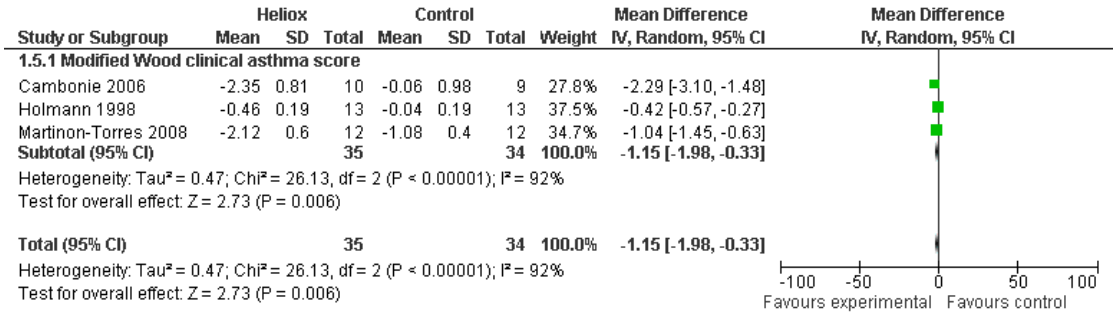


In one trial (Liet 2005), a child included in the heliox group had contracted both RSV and adenoviral respiratory tract infection. He died 38 days after the beginning of mechanical ventilation due to irreversible respiratory failure. The weight of the results of this trial is only 1.4% for this item, and does not cause a significant difference.

5. Change in clinical respiratory scores within the first hour after starting heliox treatment

Three trials (Cambonie 2006: Holmann 1998: Martinon-Torres 2008) used a clinical respiratory score as an outcome measure (the modified Wood clinical asthma score). All three trials, with a total of 69 infants, demonstrated a benefit of heliox inhalation in reducing clinical respiratory scores. The pooled results demonstrate that infants treated with heliox inhalation had a statistically significant reduction in clinical respiratory scores (MD = -1.15, 95% CI -1.98 to -0.33, P = 0.006) (Figure 4). According to these data, the addition of heliox therapy represents a 11.5% reduction in the clinical respiratory score.

Figure 4. Forest plot of comparison: 1 Heliox inhalation versus air or oxygen inhalation, outcome: 1.5 Change in Clinical respiratory scores in the first hour after starting heliox treatment.



If only trials where room air dilution of heliox is less probable are included (Cambonie 2006; Martinon-Torres 2008), the pooled data show a statistically significant reduction in clinical respiratory scores (MD -1.61, 95% CI -2.83 to -0.39, P = 0.001, n = 43).

6. Change in CO_2 within the first hour after starting heliox treatment

Two trials used change in CO_2 within the first hour after starting treatment as an outcome measure (Cambonie 2006; Martinon-Torres 2008). These studies failed to demonstrate a reduction in change in CO_2 within the first hour after starting heliox treatment (MD -2.09 mmHg, 95% CI -6.20 to 2.02, P = 0.32).

7. Change in O_2 needs after one hour of heliox treatment

One trial used change in O_2 needs after one hour of heliox treatment as an outcome measure (Cambonie 2006). This trial failed to demonstrate a reduction in change in O_2 needs after one hour of heliox treatment (MD 2.06%, 95% CI -2.86 to 6.98, P = 0.41).

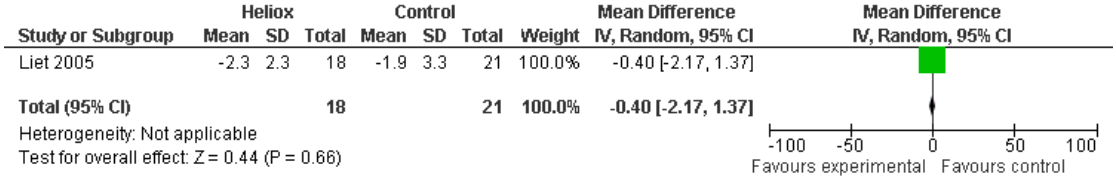
8. Change in SpO_2 within the first hour after starting heliox treatment

One trial used change in oxygen saturation on pulse oximetry (SpO_2) within the first hour after starting heliox treatment as an outcome measure (Martinon-Torres 2008). This trial failed to demonstrate a reduction in change in SpO_2 in the first hour after starting heliox treatment (MD 1.10%, 95% CI -1.90 to 4.10, P = 0.47).

9. Change in clinical score after 24 hours of heliox treatment

One trial used change in clinical score after 24 hours of heliox treatment as an outcome measure (Liet 2005). This trial failed to demonstrate a reduction in clinical score after 24 hours of heliox treatment (MD -0.40, 95% CI -2.17 to 1.37, P = 0.66) (Figure 5).

Figure 5. Forest plot of comparison: 1 Heliox inhalation versus air or oxygen inhalation, outcome: 1.9 Change in clinical score after 24 hours of heliox treatment.



10. Change in O_2 needs after 24 hours of heliox treatment

One trial used change in need for O_2 after 24 hours of heliox treatment as an outcome measure (Liet 2005). This trial failed to demonstrate a reduction in O_2 needs after 24 hours of heliox treatment (MD -2%, 95% CI -13.40 to 9.40, P = 0.73).

11. Change in CO_2 after 24 hours of heliox treatment

One trial used change in CO_2 after 24 hours of heliox treatment as an outcome measure (Liet 2005). This trial failed to demonstrate a reduction in change in CO_2 after 24 hours of heliox treatment (MD 3 mmHg, 95% CI 0.17 to 5.83, P = 0.04).

12. Adverse events

There were no adverse effects reported related to heliox inhalation (Cambonie 2006; Holmann 1998; Liet 2005; Martinon-Torres 2008).

One child included in the heliox group (Liet 2005) contracted both RSV and adenoviral respiratory tract infection, and died 38 days after the beginning of mechanical ventilation due to irreversible respiratory failure. Helium therapy was discontinued four days after randomisation.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

	Experimental events	Experimental total	Control events	Control total
Cambonie 2006	1	10	1	9
Liet 2005	4	18	4	21

	Experimental events	Experimental total	Control events	Control total
Cambonie 2006	1	10	1	9
Liet 2005	4	18	3	21

	Experimental n	Experimental days (SD)	Control n	Control days (SD)
Cambonie 2006	9	4.9 (0.9)	10	5.1 (0.8)
Liet 2005	18	6 (13)	21	3 (5)

SD = standard deviation

	Experimental n	Experimental mean (SD)	Control n	Control mean (SD)
Cambonie 2006	10	-2.35 (0.81)	9	-0.06 (0.98)
Holmann 1998	13	-0.46 (0.19)	13	-0.04 (0.19)
Martinon-Torres 2008	12	-2.12 (0.6)	12	-1.08 (0.4)

SD = standard deviation

	Experimental n	Experimental mmHg (SD)	Control n	Control mmHg (SD)
Cambonie 2006	10	-2.2 (0.78)	9	-2.1 (0.93)

Martinon-Torres 2008	12	-9.7 (3.3)	12	-5.4 (1.6)

SD = standard deviation

	Experimental n	Experimental mean (SD)	Control n	Control mean (SD)
Cambonie 2006	10	+0.5 (3.98)	9	-1.56 (6.52)

	Experimental n	Experimental mean (SD)	Control n	Control mean (SD)
Martinon-Torres 2008	12	8.0 (3.8)	12	6.9 (3.7)

	Experimental n	Experimental mean (SD)	Control n	Control mean (SD)
Liet 2005	18	-2.3 (2.3)	21	-1.9 (3.3)

SD = standard deviation

	Experimental n	Experimental mean (SD)	Control n	Control mean (SD)
Liet 2005	18	-2 (21)	21	0 (14)

SD = standard deviation

	Experimental n	Experimental mean (SD)	Control n	Control mean (SD)
Liet 2005	18	-4 (4)	21	-7 (5)

SD = standard deviation

DISCUSSION

Summary of main results

In this review we retrieved four trials which objectively assessed the effect of the addition of heliox to standard medical care on the course of acute bronchiolitis in infants who were hospitalised in paediatric intensive care units (PICUs) and still not intubated.

We examined four primary outcomes. Two trials used the need for mechanical ventilation (invasive or not), the rate of intubation and the length of stay in PICU as outcomes (Cambonie 2006; Liet 2005). The pooled results from these two trials failed to demonstrate a reduction in the need for mechanical ventilation, the rate of intubation or the length of stay in PICU. There were no adverse effects reported related to heliox inhalation in any of the four trials included in this review.

Secondary outcomes incorporated gas exchange effects and variation in clinical respiratory scores. Three trials used changes in modified Wood clinical asthma scores as outcomes (Cambonie 2006; Holmann 1998; Martinon-Torres 2008). This score, initially described by Wood (Wood 1972), grades cyanosis, inspiratory breath sounds, accessory muscles used, expiratory wheezing and cerebral function from 0 to 2, with increased severity receiving a higher score. All three trials, with a total of 69 infants, demonstrated a benefit of heliox inhalation in reducing clinical respiratory scores. The pooled results show that infants treated with heliox inhalation had a statistically significant reduction in clinical respiratory scores (MD = -1.15, 95% CI -1.98 to -0.33, P = 0.006). This represents an 11.5% reduction in the clinical respiratory score. This benefit of heliox inhalation on clinical scores in the first hour after starting heliox treatment was not associated with any significant change in gas exchange: no reduction in CO_2, need for oxygen, or SpO_2. Only one trial assessed changes after 24 hours of heliox treatment in clinical score, in need for oxygen and in CO_2 data. This trial failed to demonstrate any significant reduction in these outcome measures.

A recent trial (Kneyber 2009) assessed the effect of the addition of heliox in 13 mechanically-ventilated, sedated and paralysed infants. Mechanical ventilation significantly decreased respiratory system resistance. This was not accompanied by an improved CO_2 elimination, or a reduced air-trapping.

The available data suggest that heliox inhalation could be useful in addition to standard medical care in the management of acute bronchiolitis in infants who are hospitalised in paediatric critical care units and still not intubated. Of note, this benefit is observed on clinical score only during the first hour after starting heliox therapy, and is not confirmed by gas exchange effects. No benefits were observed in terms of need for mechanical ventilation, rate of intubation or in the length of stay in the PICU.

The method of delivering heliox might alter the validity and the relevancy of these results. Four different protocols for delivering heliox were used: inhalation of either heliox or air-oxygen for one hour under an oxy hood (Cambonie 2006), inhalation in a random order of heliox and air-oxygen by non-rebreather reservoir mask for two 20-minute study periods (Holmann 1998), inhalation of either heliox or air-oxygen under an inflatable head hood (Liet 2005) and inhalation in a random order of heliox and air-oxygen by non-invasive ventilation equipment (nasal continuous positive airway pressure) for two 30-minute study periods (Martinon-Torres 2008). When removing the trial that used non-rebreather reservoir mask (a method of delivery where there is a proven room air dilution), the benefit of heliox administration observed in clinical score only during the first hour after starting heliox therapy is higher. Nevertheless, all these trials provide consistent results.

Overall completeness and applicability of evidence

One trial (Martinon-Torres 2008) was considered a quasi-RCTs (where there is alternate allocation to treatment and control groups) but kept in the review because of its cross-over design with brief periods. Data from this trial affect the results of the effects of heliox inhalation in clinical respiratory scores in the first hour after starting heliox treatment but the provided data were similar to those of the two other integrated trials with a comparable weight (34.7%).

The sample size of this review is relatively small and its statistical power might be sufficient for some outcome measures but not for others.

Quality of the evidence

The only outcome for which a benefit of heliox therapy in bronchiolitis was demonstrated (change in clinical respiratory scores within the first hour after starting heliox treatment) was found to have statistical heterogeneity (Analysis 1.5). This statistical heterogeneity remains even after removing the study using a standard high-concentration reservoir mask.

Potential biases in the review process

The funnel plots performed are symmetric on the median line (Figure 6; Figure 7; Figure 8). Nevertheless, very few studies were included in this review.

Figure 6. Funnel plot of comparison: 1 Heliox inhalation versus air or oxygen inhalation, outcome: 1.5 Change in clinical respiratory scores within the first hour after starting heliox treatment.

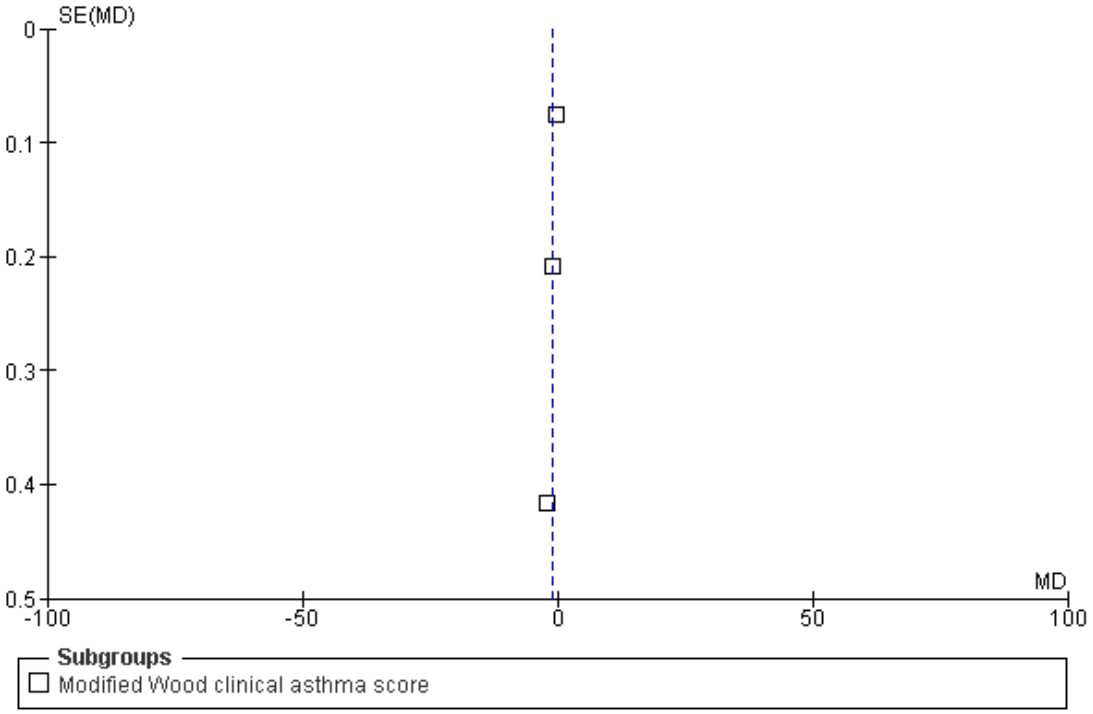


Figure 7. Funnel plot of comparison: 1 Heliox inhalation versus air or oxygen inhalation, outcome: 1.2 Need for mechanical ventilation.

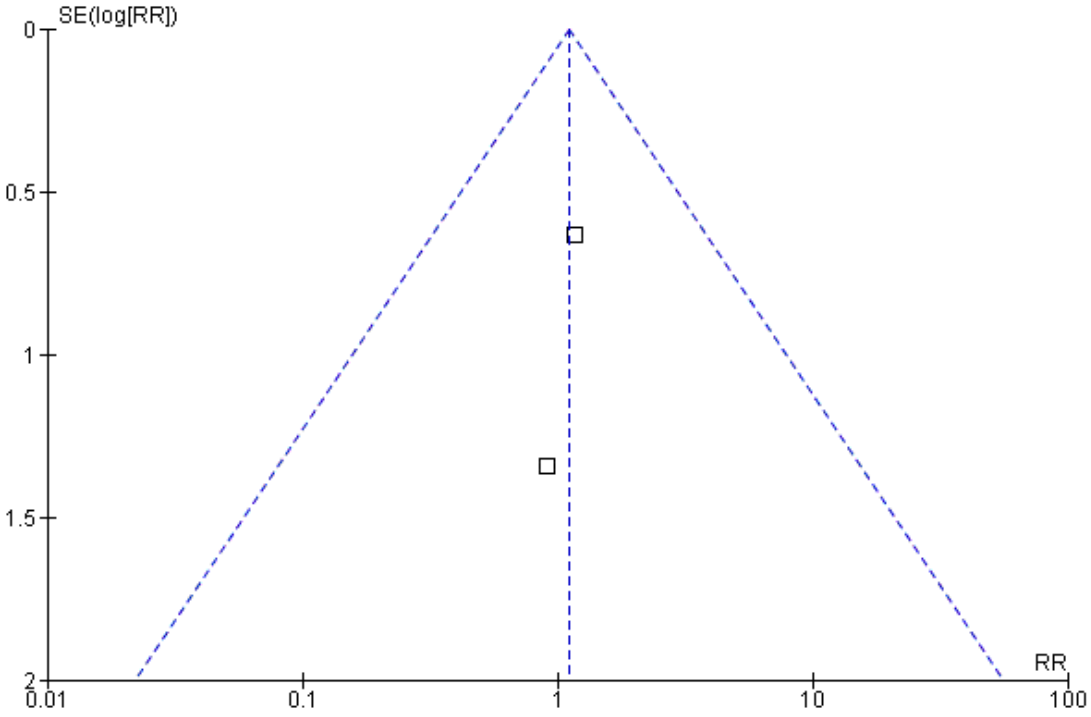
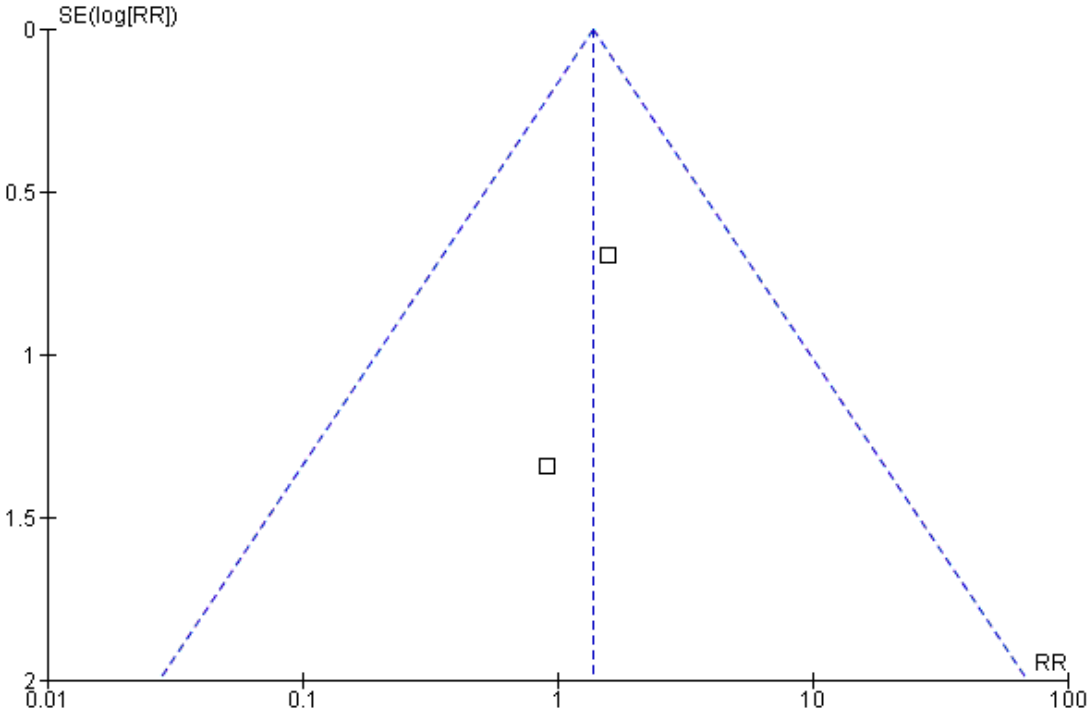


Figure 8. Funnel plot of comparison: 1 Heliox inhalation versus air or oxygen inhalation, outcome: 1.3 Rate of intubation.



Agreements and disagreements with other studies or reviews

No disagreements were found between the few included studies.

AUTHORS' CONCLUSIONS

Implications for practice

Heliox inhalation produces an 11.5% reduction in the clinical respiratory score in infants hospitalised in a paediatric intensive care unit (PICU) for acute bronchiolitis and not intubated. Nevertheless, this therapy does not reduce the need for mechanical ventilation, intubation or the length of stay in the PICU. Given the good safety profile, heliox therapy could be used in addition to standard medical care to treat infants who are hospitalised in PICUs for acute bronchiolitis and not yet intubated.

Implications for research

Further large randomised controlled trials, preferably multi-centered, are still required to evaluate the effectiveness of heliox inhalation in infants with acute bronchiolitis. An additional consideration would be the potential benefit of heliox therapy in association with continuous positive airway pressure (CPAP), to reduce the need for intubation and the length of stay in PICU. To be adequately blinded such studies would have to compare the use of CPAP with heliox and CPAP with air/oxygen, bearing in mind that vocalisation and the different sound made by a CPAP device using helium may alert the investigators to the study gas.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cambonie 2006

Methods	Prospective, randomised, double-blind study
Participants	20 infants (all < 3 months old) admitted to the PICU with moderate-to-severe RSV bronchiolitis
Interventions	Inhalation of either heliox or air-oxygen for 1 hour under an oxy hood
Outcomes	Primary goal: assess effect on respiratory distress evaluated using the modified Wood clinical asthma score (m-WCAS) at H1 Need for mechanical ventilation, rate of intubation, length of mechanical ventilation, length of stay in PICU, mortality Wheezing score evaluated at H1 and H24, pCO2 at H1, respiratory rate at H1
Notes	Score BABAA After request: score AABAA

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computerised random listing
Allocation concealment?	Yes	Sealed envelopes
Blinding? All outcomes	Yes	One investigator was not blinded: the physiologist

Holmann 1998

Methods	Randomised, double-blind, controlled, cross-over study
Participants	13 infants (3 weeks to 23 months old) admitted to the PICU with RSV bronchiolitis
Interventions	Inhalation in a random order of heliox and air-oxygen by non-rebreather reservoir mask for two 20-minute study periods
Outcomes	Clinical asthma score at 20 minutes
Notes	Score AABAA

Risk of bias

Item	Authors' judgement	Description

Holmann 1998 (*Continued*)

Adequate sequence generation?	Yes	Coin-tossing
Allocation concealment?	Yes	
Blinding? All outcomes	Yes	One investigator was not blinded: the respiratory therapists; blinding was maintained by covering the on-off valves to the air and helium sources with tape

Kneyber 2009

Methods	Prospective, cross-over study
Participants	13 infants (4 weeks to 23 weeks old; 3 born prematurely) admitted to PICU with RSV bronchiolitis, and mechanically ventilated (AVEA® ventilator, Cardinal Health), sedated and paralysed
Interventions	Three 30-minute periods: data collected at t0 and t60 (ventilation with nitrox), and at t30 and t90 (ventilation with heliox)
Outcomes	Respiratory system resistance, peak expiratory flow rate, lung resistance, static compliance, change in end-expiratory lung volume Response to heliox (electrical impedance tomography measurements: EIT) Oxygenation index, alveolo-arterial oxygen gradient, ventilation index, dead-space/tidal volume ratio
Notes	CCCAA

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	No	No randomisation
Allocation concealment?	No	
Blinding? All outcomes	No	Unblinded study

Liet 2005

Methods	Multi-centre, randomised, double-blind, placebo-controlled trial
Participants	39 infants (all < 9 months old) admitted to the PICU with first episode of severe RSV bronchiolitis
Interventions	Inhalation of either heliox or air-oxygen under an inflatable head hood

Liet 2005 (*Continued*)

Outcomes	Primary outcome was initiation of positive pressure ventilation Need for mechanical ventilation, rate of intubation, length of mechanical ventilation, length of stay in PICU, mortality FiO_2 at H24, pCO_2 at H24, respiratory distress assessment instrument (RDAI) at H24
Notes	Score AABAA

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computerised random listing with stratification by centre
Allocation concealment?	Yes	Sealed envelopes
Blinding? All outcomes	Yes	One investigator was not blinded: the respiratory therapists; identical tanks at the bedside of all patients and gas flow meters covered with opaque bags to hide the dials

Martinon-Torres 2008

Methods	Prospective, interventional, single-centre, cross-over study
Participants	12 infants (< 2 years old) admitted to the PICU with RSV bronchiolitis
Interventions	Inhalation in a random order of heliox and air-oxygen by noninvasive ventilation equipment (nasal continuous positive airway pressure) for 2 30-minute study periods
Outcomes	Main outcome measures: modified Wood clinical asthma score (m-WCAS) measured, SpO_2 and pCO_2 at 30 minutes Rate of intubation, length of mechanical ventilation, length of stay in PICU, mortality mWCAS at H24 and H48, pCO_2 at H24
Notes	Score ACCAA After request: score CCCAA

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	No	Coin tossing only for the first infant; then alternately
Allocation concealment?	No	

Blinding? All outcomes	No	

H1: first hour
H24: twenty-fourth hour
m-WCAS: modified Wood clinical asthma score
pCO_2: carbon dioxide pressure
PICU: paediatric intensive care unit
RDAI: respiratory distress assessment instrument
RSV: respiratory syncytial virus
SpO_2: oxygen saturation on pulse oximetry
Scores mentioned in the *Notes* are related to five items assessed for each study and classified in descending order from grade A to grade C: generation of allocation sequence, allocation concealment, blinding, intention-to-treat (ITT) analysis and loss to follow up (see Assessment of risk of bias in included studies).

Characteristics of excluded studies *[ordered by study ID]*

Abd-Allah 2003	No infant, no bronchiolitis
Dieperink 2007	No bronchiolitis
Duncan 1979	Case report
Elleau 1993	No infants, no bronchiolitis
Gross 2000	Series of case reports
Grosz 2001	Series of case reports
Gupta 2004	Case report
Iglesias-Fernandez 2007	Series of case reports
Isakov 1970	No bronchiolitis
Kneyber 2006	Case report
Martinon-Torres 2002	Inadequate method of randomisation (alternate inclusion), unblinded study
Martinon-Torres 2005	Case report
Martinon-Torres 2006	Series of case reports
Paret 1996	Case report

(*Continued*)

Tobias 1997	Not about bronchiolitis
Tobias 1999	Case report
Ulhoa 2000	Series of case reports
Williams 2004	Series of case reports
Winters 2000	No bronchiolitis

Characteristics of ongoing studies *[ordered by study ID]*

BREATHE trial

Trial name or title	-
Methods	
Participants	
Interventions	-
Outcomes	-
Starting date	-
Contact information	Dr Parviz Habibi PhD FRCP FRCPCH Reader and Consultant Paediatric Intensive Care & Respiratory Medicine - Department of Paediatrics, Wright Fleming Institute, St. Mary's Campus, Imperial College Norfolk Place, London W2 1PG
Notes	First results will be presented at ATS conference in May 2010

DATA AND ANALYSES

Comparison 1. Heliox inhalation versus air or oxygen inhalation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	2	58	Risk Difference (M-H, Fixed, 95% CI)	0.04 [-0.08, 0.15]
2 Need for mechanical ventilation	2	58	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.36, 3.38]
3 Rate of intubation	2	58	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.41, 4.56]
4 Length of PICU stay	2	58	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.92, 0.61]
5 Change in clinical respiratory scores within the first hour after starting heliox treatment	3	69	Mean Difference (IV, Random, 95% CI)	-1.15 [-1.98, -0.33]
5.1 Modified Wood clinical asthma score	3	69	Mean Difference (IV, Random, 95% CI)	-1.15 [-1.98, -0.33]
6 Change in CO2 in the 1st hour after starting treatment	2	43	Mean Difference (IV, Random, 95% CI)	-2.09 [-6.20, 2.02]
7 Change in O2 needs after 1 hour of heliox treatment	1	19	Mean Difference (IV, Random, 95% CI)	2.06 [-2.86, 6.98]
8 Change in SpO2 within the first hour after starting heliox treatment	1	24	Mean Difference (IV, Random, 95% CI)	1.10 [-1.90, 4.10]
9 Change in clinical score after 24 hours of heliox treatment	1	39	Mean Difference (IV, Random, 95% CI)	-0.40 [-2.17, 1.37]
10 Change in O2 needs after 24 hours of heliox treatment	1	39	Mean Difference (IV, Random, 95% CI)	-2.0 [-13.40, 9.40]
11 Change in CO2 after 24 hours of heliox treatment	1	39	Mean Difference (IV, Random, 95% CI)	3.0 [0.17, 5.83]

Analysis 1.1. Comparison 1 Heliox inhalation versus air or oxygen inhalation, Outcome 1 Mortality.

Review: Heliox inhalation therapy for bronchiolitis in infants

Comparison: 1 Heliox inhalation versus air or oxygen inhalation

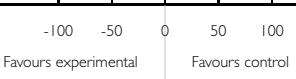
Outcome: 1 Mortality

Study or subgroup	Heliox n/N	Control n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Cambonie 2006	0/10	0/9		32.8 %	0.0 [-0.18, 0.18]
Liet 2005	1/18	0/21		67.2 %	0.06 [-0.08, 0.19]
Total (95% CI)	**28**	**30**		**100.0 %**	**0.04 [-0.08, 0.15]**

Total events: 1 (Heliox), 0 (Control)

Heterogeneity: $Chi^2 = 0.23$, df = 1 (P = 0.63); $I^2 = 0.0\%$

Test for overall effect: Z = 0.63 (P = 0.53)



Analysis 1.2. Comparison 1 Heliox inhalation versus air or oxygen inhalation, Outcome 2 Need for mechanical ventilation.

Review: Heliox inhalation therapy for bronchiolitis in infants

Comparison: 1 Heliox inhalation versus air or oxygen inhalation

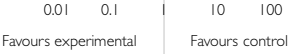
Outcome: 2 Need for mechanical ventilation

Study or subgroup	Heliox n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cambonie 2006	1/10	1/9		22.2 %	0.90 [0.07, 12.38]
Liet 2005	4/18	4/21		77.8 %	1.17 [0.34, 4.01]
Total (95% CI)	**28**	**30**		**100.0 %**	**1.11 [0.36, 3.38]**

Total events: 5 (Heliox), 5 (Control)

Heterogeneity: $Chi^2 = 0.03$, df = 1 (P = 0.86); $I^2 = 0.0\%$

Test for overall effect: Z = 0.18 (P = 0.86)



Analysis 1.3. Comparison 1 Heliox inhalation versus air or oxygen inhalation, Outcome 3 Rate of intubation.

Review: Heliox inhalation therapy for bronchiolitis in infants

Comparison: 1 Heliox inhalation versus air or oxygen inhalation

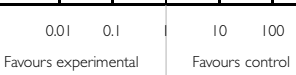
Outcome: 3 Rate of intubation

Study or subgroup	Heliox n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Cambonie 2006	1/10	1/9		27.5 %	0.90 [0.07, 12.38]
Liet 2005	4/18	3/21		72.5 %	1.56 [0.40, 6.05]
Total (95% CI)	**28**	**30**		**100.0 %**	**1.38 [0.41, 4.56]**

Total events: 5 (Heliox), 4 (Control)

Heterogeneity: $Chi^2 = 0.13$, df = 1 (P = 0.72); $I^2 = 0.0\%$

Test for overall effect: Z = 0.52 (P = 0.60)



Analysis 1.4. Comparison 1 Heliox inhalation versus air or oxygen inhalation, Outcome 4 Length of PICU stay.

Review: Heliox inhalation therapy for bronchiolitis in infants

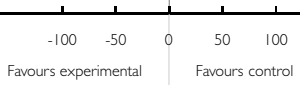
Comparison: 1 Heliox inhalation versus air or oxygen inhalation

Outcome: 4 Length of PICU stay

Study or subgroup	Heliox N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Cambonie 2006	9	4.9 (0.9)	10	5.1 (0.8)		98.6 %	-0.20 [-0.97, 0.57]
Liet 2005	18	6 (13)	21	3 (5)		1.4 %	3.00 [-3.37, 9.37]
Total (95% CI)	**27**		**31**			**100.0 %**	**-0.15 [-0.92, 0.61]**

Heterogeneity: Chi^2 = 0.95, df = 1 (P = 0.33); I^2 =0.0%

Test for overall effect: Z = 0.40 (P = 0.69)



Analysis 1.5. Comparison 1 Heliox inhalation versus air or oxygen inhalation, Outcome 5 Change in clinical respiratory scores within the first hour after starting heliox treatment.

Review: Heliox inhalation therapy for bronchiolitis in infants

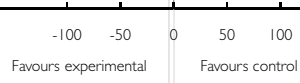
Comparison: 1 Heliox inhalation versus air or oxygen inhalation

Outcome: 5 Change in clinical respiratory scores within the first hour after starting heliox treatment

Study or subgroup	Heliox N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Modified Wood clinical asthma score							
Cambonie 2006	10	-2.35 (0.81)	9	-0.06 (0.98)		27.8 %	-2.29 [-3.10, -1.48]
Holmann 1998	13	-0.46 (0.19)	13	-0.04 (0.19)		37.5 %	-0.42 [-0.57, -0.27]
Martinon-Torres 2008	12	-2.12 (0.6)	12	-1.08 (0.4)		34.7 %	-1.04 [-1.45, -0.63]
Total (95% CI)	**35**		**34**			**100.0 %**	**-1.15 [-1.98, -0.33]**

Heterogeneity: Tau^2 = 0.47; Chi^2 = 26.13, df = 2 (P<0.00001); I^2 =92%

Test for overall effect: Z = 2.73 (P = 0.0064)



Analysis 1.6. Comparison 1 Heliox inhalation versus air or oxygen inhalation, Outcome 6 Change in CO2 in the 1st hour after starting treatment.

Review: Heliox inhalation therapy for bronchiolitis in infants

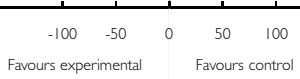
Comparison: 1 Heliox inhalation versus air or oxygen inhalation

Outcome: 6 Change in CO2 in the 1st hour after starting treatment

Study or subgroup	Heliox N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Cambonie 2006	10	-2.2 (0.78)	9	-2.1 (0.93)		52.7 %	-0.10 [-0.88, 0.68]
Martinon-Torres 2008	12	-9.7 (3.3)	12	-5.4 (1.6)		47.3 %	-4.30 [-6.38, -2.22]
Total (95% CI)	**22**		**21**			**100.0 %**	**-2.09 [-6.20, 2.02]**

Heterogeneity: $Tau^2 = 8.18$; $Chi^2 = 13.81$, df = 1 (P = 0.00020); $I^2 = 93\%$

Test for overall effect: Z = 0.99 (P = 0.32)



Analysis 1.7. Comparison 1 Heliox inhalation versus air or oxygen inhalation, Outcome 7 Change in O2 needs after 1 hour of heliox treatment.

Review: Heliox inhalation therapy for bronchiolitis in infants

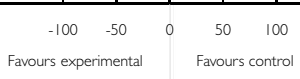
Comparison: 1 Heliox inhalation versus air or oxygen inhalation

Outcome: 7 Change in O2 needs after 1 hour of heliox treatment

Study or subgroup	Heliox N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Cambonie 2006	10	0.5 (3.98)	9	-1.56 (6.52)		100.0 %	2.06 [-2.86, 6.98]
Total (95% CI)	**10**		**9**			**100.0 %**	**2.06 [-2.86, 6.98]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.82 (P = 0.41)



Analysis 1.8. Comparison 1 Heliox inhalation versus air or oxygen inhalation, Outcome 8 Change in SpO2 within the first hour after starting heliox treatment.

Review: Heliox inhalation therapy for bronchiolitis in infants

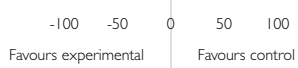
Comparison: 1 Heliox inhalation versus air or oxygen inhalation

Outcome: 8 Change in SpO2 within the first hour after starting heliox treatment

Study or subgroup	Heliox N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Martinon-Torres 2008	12	8 (3.8)	12	6.9 (3.7)		100.0 %	1.10 [-1.90, 4.10]
Total (95% CI)	**12**		**12**			**100.0 %**	**1.10 [-1.90, 4.10]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.72 (P = 0.47)



Analysis 1.9. Comparison 1 Heliox inhalation versus air or oxygen inhalation, Outcome 9 Change in clinical score after 24 hours of heliox treatment.

Review: Heliox inhalation therapy for bronchiolitis in infants

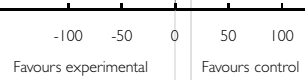
Comparison: 1 Heliox inhalation versus air or oxygen inhalation

Outcome: 9 Change in clinical score after 24 hours of heliox treatment

Study or subgroup	Heliox N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Liet 2005	18	-2.3 (2.3)	21	-1.9 (3.3)		100.0 %	-0.40 [-2.17, 1.37]
Total (95% CI)	**18**		**21**			**100.0 %**	**-0.40 [-2.17, 1.37]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.44 (P = 0.66)



Analysis 1.10. Comparison 1 Heliox inhalation versus air or oxygen inhalation, Outcome 10 Change in O2 needs after 24 hours of heliox treatment.

Review: Heliox inhalation therapy for bronchiolitis in infants

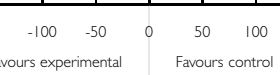
Comparison: 1 Heliox inhalation versus air or oxygen inhalation

Outcome: 10 Change in O2 needs after 24 hours of heliox treatment

Study or subgroup	Heliox N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Liet 2005	18	-2 (21)	21	0 (14)		100.0 %	-2.00 [-13.40, 9.40]
Total (95% CI)	**18**		**21**			**100.0 %**	**-2.00 [-13.40, 9.40]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.34 (P = 0.73)



Analysis 1.11. Comparison 1 Heliox inhalation versus air or oxygen inhalation, Outcome 11 Change in CO2 after 24 hours of heliox treatment.

Review: Heliox inhalation therapy for bronchiolitis in infants

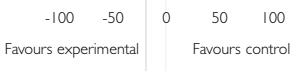
Comparison: 1 Heliox inhalation versus air or oxygen inhalation

Outcome: 11 Change in CO2 after 24 hours of heliox treatment

Study or subgroup	Heliox N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Liet 2005	18	-4 (4)	21	-7 (5)		100.0 %	3.00 [0.17, 5.83]
Total (95% CI)	**18**		**21**			**100.0 %**	**3.00 [0.17, 5.83]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.08 (P = 0.037)



APPENDICES

Appendix 1. EMBASE search strategy

1. 'helium'/exp
2. helium:ti,ab OR heliox:ti,ab OR heo2:ti,ab OR 'he-o2':ti,ab
3. #1 OR #2
4. random*:ti,ab OR placebo:ti,ab,de OR 'double blind':ti,ab
5. #3 AND #4

Appendix 2. LILACS search strategy

The **LILACS** search (heliox OR helium) retrieved a total of 41 citations.
1. 'helium'/exp
2. helium:ti,ab OR heliox:ti,ab OR heo2:ti,ab OR 'he-o2':ti,ab
3. #1 OR #2
4. random*:ti,ab OR placebo:ti,ab,de OR 'double blind':ti,ab
5. #3 AND #4

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 4, 2010

14 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Dr. Jean-Michel Liet (JML) had primary responsibility for protocol development and wrote the draft protocol and review. Dr. Gilles Cambonie (GC) participated in the development of the protocol, was responsible for study selection, quality assessment and data collection. Dr. Vineet Gupta (VG) contacted trial authors of all studies to locate other unpublished or in progress studies, and provided input for writing the protocol and review. Dr. Thierry Ducruet (TD) read the protocol and the review, and checked the statistical aspects. The final version of the review was approved by all review authors.

DECLARATIONS OF INTEREST

Jean-Michel Liet and Gilles Cambonie were investigators in two trials, both supported by Air Liquide Santé International. Air Liquide provided the heliox and air tanks, set up the study equipment and was involved in the study design. In both trials, Air Liquide Santé had no role in data management, data analysis or data interpretation, or writing of the report and decision to submit it for publication. The review authors have no financial relationship with Air Liquide Santé.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Not only first episodes of acute bronchiolitis were included. Not all infants were under 12 months of age.