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[Intervention Review]

Heliox for croup in children

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ABSTRACT

Background

Croup is an acute viral respiratory infection with upper airway mucosal inflammation that may cause respiratory distress. Most cases are mild. Moderate to severe croup may require treatment with corticosteroids (from which benefits are often delayed) and nebulised epinephrine (adrenaline) (which may be short-lived and can cause dose-related adverse effects including tachycardia, arrhythmias, and hypertension). Rarely, croup results in respiratory failure necessitating emergency intubation and ventilation.

A mixture of helium and oxygen (heliox) may prevent morbidity and mortality in ventilated neonates by reducing the viscosity of the inhaled air. It is currently used during emergency transport of children with severe croup. Anecdotal evidence suggests that it relieves respiratory distress.

This review updates versions published in 2010 and 2013.

Objectives

To examine the effect of heliox compared to oxygen or other active interventions, placebo, or no treatment, on relieving signs and symptoms in children with croup as determined by a croup score and rates of admission and intubation.

Search methods

We searched CENTRAL, which includes the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE; Embase; CINAHL; Web of Science; and LILACS in January and February 2018. We also searched the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/) and ClinicalTrials.gov (clinicaltrials.gov) on 8 February 2018. We contacted British Oxygen Company, a leading supplier of heliox (BOC Australia 2017).

Selection criteria

Randomised controlled trials (RCTs) and quasi-RCTs comparing the effect of heliox in comparison with placebo or any active intervention(s) in children with croup.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. We reported data that could not be pooled for statistical analysis descriptively.

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Main results

We included 3 RCTs with 91 children aged between 6 months and 4 years. Study duration was from 7 to 16 months; all studies were conducted in emergency departments in the USA (two studies) and Spain. Heliox was administered as a mixture of 70% heliox and 30% oxygen. Risk of bias was low in two studies and high in one study due to an open-label design. We added no new trials for this update.

One study of 15 children with mild croup compared heliox with 30% humidified oxygen administered for 20 minutes. There may be no difference in croup score changes between groups at 20 minutes (mean difference (MD) -0.83, 95% confidence interval (CI) -2.36 to 0.70). The mean croup score at 20 minutes postintervention may not differ between groups (MD -0.57, 95% CI -1.46 to 0.32). There may be no difference between groups in mean respiratory rate (MD 6.40, 95% CI -1.38 to 14.18) and mean heart rate (MD 14.50, 95% CI -8.49 to 37.49) at 20 minutes. The evidence for all outcomes in this comparison was of low quality, downgraded for serious imprecision. All children were discharged, but information on hospitalisation, intubation, or re-presenting to emergency departments was not reported.

In another study, 47 children with moderate croup received one dose of oral dexamethasone (0.3 mg/kg) with either heliox for 60 minutes or no treatment. Heliox may slightly improve croup scores at 60 minutes postintervention (MD -1.10, 95% CI -1.96 to -0.24), but there may be no difference between groups at 120 minutes (MD -0.70, 95% CI -4.86 to 3.46). Children treated with heliox may have lower mean Taussig croup scores at 60 minutes (MD -1.11, 95% CI -2.05 to -0.17) but not at 120 minutes (MD -0.71, 95% CI -1.72 to 0.30). Children treated with heliox may have lower mean respiratory rates at 60 minutes (MD -4.94, 95% CI -9.66 to -0.22), but there may be no difference at 120 minutes (MD -3.17, 95% CI -7.83 to 1.49). There may be no difference in hospitalisation rates between groups (OR 0.46, 95% CI 0.04 to 5.41). We assessed the evidence for all outcomes in this comparison as of low quality, downgraded due to imprecision and high risk of bias related to open-label design. Information on heart rate and intubation was not reported.

In the third study, 29 children with moderate to severe croup received intramuscular dexamethasone (0.6 mg/kg) and either heliox with one to two doses of nebulised saline, or 100% oxygen with one to two doses of adrenaline for three hours. Heliox may slightly improve croup scores at 90 minutes postintervention, but may have little or no difference overall using repeated measures analysis. We assessed the evidence for all outcomes in this comparison as of low quality, downgraded due to high risk of bias related to inadequate reporting. Information on hospitalisation or re-presenting to the emergency department was not reported.

The included studies did not report on adverse events, intensive care admissions, or parental anxiety.

We could not pool the available data because each comparison included data from only one study.

Authors' conclusions

Due to very limited evidence, uncertainty remains about the effectiveness and safety of heliox. Heliox may not be more effective than 30% humidified oxygen for children with mild croup, but may be beneficial in the short term for children with moderate to severe croup treated with dexamethasone. The effect may be similar to 100% oxygen given with one or two doses of adrenaline. Adverse events were not reported, and it is unclear if these were monitored in the included studies. Adequately powered RCTs comparing heliox with standard treatments are needed to further assess the role of heliox in the treatment of children with moderate to severe croup.

PLAIN LANGUAGE SUMMARY

Helium-oxygen (heliox) treatment for children with croup

Review question

We assessed whether inhaling heliox is safe and beneficial in treating children with croup compared with fake treatment (placebo) or other therapies such as 30% humidified oxygen, or 100% oxygen with epinephrine (adrenaline, a drug that helps open airways).

Background

Croup is a short-term illness that causes upper airways blockages. Croup is common among children aged up to six years, and is triggered by viral infections; it is more frequent in autumn and winter. Symptoms include barking cough, hoarseness, abnormal breathing sounds, and chest wall retractions.

Corticosteroid drugs are standard treatment for children with croup, but a limitation of this treatment is that time is needed for the drug to take effect. Children with severe croup may need additional emergency treatments such as a breathing tube or mechanical breathing support. Children with severe croup may need oxygen and adrenaline inhaled as a fine mist (nebulised). Adrenaline is generally safe, but can cause side effects such as fast heart rate and anxiety. Identifying a safe, effective, and fast-acting treatment is important for children and their families.

Heliox (a combination of helium and oxygen) gas may improve airflow and relieve breathing distress. Some studies have shown benefits from heliox for children with croup.

This review updates versions published in 2010 and 2013.

Search date

8 February 2018.

Study characteristics

We did not include any new trials in this update.

We included three randomised controlled trials (studies in which participants are allocated by chance to receive a treatment) involving a total of 91 children with croup aged from 6 months to 4 years. Studies ran for between 7 and 16 months; two were conducted in the USA and one in Spain. In one study children with mild croup received either heliox with 30% oxygen; in another study children with moderate croup received oral dexamethasone (a type of corticosteroid) and either heliox or no treatment; and in the third study children with moderate to severe croup received injected dexamethasone and either heliox or 100% oxygen with adrenaline.

Key results

Heliox may be no more effective than 30% oxygen for children with mild croup; as effective as 100% oxygen given with one or two doses of adrenaline; and slightly more effective than no treatment for children with moderate to severe croup. None of the studies reported adverse events.

Quality of evidence

The quality of the evidence was low as the trials included few children, and in one trial children, their families, and the physicians knew which treatment was given.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Heliox compared to oxygen 30% for croup in children

Heliox compared to oxygen 30% for croup in children

Patient or population: children with croup

Setting: emergency department

Intervention: heliox

Comparison: oxygen 30%

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with oxygen 30%	Risk with heliox				
Change in croup score at 20 minutes	The mean croup score at 20 minutes was 1.57 (0.7 to 2.44).	MD 0.83 lower (2.36 lower to 0.7 higher)	-	15 (1 RCT)	⊕⊕⊕⊕ LOW ¹	Measured at 20 minutes after the intervention using a modified Westley croup score; scale range 0 to 16 (Terregino 1998)
Change in respiratory rate at 20 minutes	The mean respiratory rate at 20 minutes was 27.4 (SD 5.6).	MD 6.4 higher (1.38 lower to 14.18 higher)	-	15 (1 RCT)	⊕⊕⊕⊕ LOW ¹	Terregino 1998 did not report change in respiratory rate between pre- and postintervention, therefore we have reported the mean respiratory rate at endpoint 20 minutes. Reported respiratory rate range: 25.4 to 37.5 breaths/min
Change in heart rate at 20 minutes	The mean heart rate at 20 minutes was 137.9 (SD 12.2).	MD 14.5 higher (8.49 lower to 37.49 higher)	-	15 (1 RCT)	⊕⊕⊕⊕ LOW ¹	Terregino 1998 did not report change in heart rate between pre- and postintervention, therefore we have reported the mean heart rate at endpoint 20 minutes. Reported heart rate range: 137.4 to 158.1 beats/min
Proportion of children hospitalised and duration of hospitalisation - not reported	-	-	-	-	-	Terregino 1998 reported that all children were discharged.
Proportion and duration of intubation - not reported	-	-	-	-	-	Terregino 1998 reported that no child required administration of racemic epinephrine and that there were no complications. Proportion of children intubated was not reported.

Proportion of children representing for medical care for ongoing croup symptoms - not reported	-	-	-	-	-	
Adverse events - not reported	-	-	-	-	-	Terregino 1998 reported that there were no complications.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial; **SD:** standard deviation

GRADE Working Group grades of evidence

High quality : We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality : We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

¹We downgraded the evidence two levels due to very small participant numbers in the single included study.

Summary of findings 2. Heliox compared to placebo or no treatment for croup in children

Heliox compared to placebo or no treatment for croup in children

Patient or population: children with croup

Setting: emergency department

Intervention: heliox

Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo or no treatment	Risk with heliox				
Change in croup score at 60 minutes	The mean change in croup score at 60 min-	MD 1.1 lower (1.96 lower to 0.24 lower)	-	47 (1 RCT)	⊕⊕⊕⊕ LOW 1, 2	Pardillo 2009 measured change in croup score at 60 minutes after the intervention using a modified Taussig croup score; scale range 0 to 15. This

	utes was 3.74 (SD 1.6).					outcome refers to change in scores from pre- to postintervention.
Change in respiratory rate at 60 minutes	The mean change in respiratory rate was 35.61 (SD 9.15).	MD 4.94 lower (9.66 lower to 0.22 lower)	-	47 (1 RCT)	⊕⊕⊕⊕ LOW 1, 2	Pardillo 2009 did not report change in respiratory rate between pre- and postintervention, therefore we have reported the mean respiratory rate at endpoint 60 minutes. Reported range of respiratory rate: 30.67 to 39.13 breaths/min
Change in heart rate at 60 minutes - not reported	-	-	-	-	-	
Proportion of children hospitalised and duration of hospitalisation	Study population		OR 0.46 (0.04 to 5.41)	47 (1 RCT)	⊕⊕⊕⊕ LOW 1, 2	This outcome was only reported as number of children hospitalised. 1 child in the heliox group and 2 children in the control group were admitted to hospital (Pardillo 2009). Duration of hospitalisation was not reported.
	87 per 1000	42 per 1000 (4 to 340)				
Proportion and duration of intubation - not reported	-	-	-	-	-	Pardillo 2009 reported that 5 children in the control group and 1 child in the heliox group required rescue adrenaline. Proportion of children Intubated was not reported.
Proportion of children re-presenting for medical care for ongoing croup symptoms (return to care)	Study population		OR 0.95 (0.12 to 7.41)	47 (1 RCT)	⊕⊕⊕⊕ LOW 1, 2	2 children in each group returned for care within 72 hours (Pardillo 2009).
	87 per 1000	83 per 1000 (11 to 414)				
Adverse events - not reported	-	-	-	-	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomised controlled trial; **SD:** standard deviation

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

- ¹We downgraded the evidence one level due to the open-label design of the study.
- ²We downgraded the evidence one level due to the small number of participants.

BACKGROUND

Description of the condition

Croup, also known as viral laryngotracheobronchitis or laryngotracheitis, is a common respiratory syndrome in children that may progress to an acute respiratory obstruction. Croup is characterised by a barking cough, hoarseness, varying degrees of inspiratory stridor, and chest wall retractions. Symptoms tend to be worse when the child is agitated, and at night, especially in the early hours of the morning (Bjornson 2013), possibly due to lower serum levels of endogenous cortisol (Bjornson 2008). Croup is usually preceded by a one- to three-day period of viral upper respiratory tract infection symptoms. The barking cough resolves within 48 hours in 60% of affected children (Bjornson 2013). Croup commonly affects children aged six months to three years (Bjornson 2013), with the highest incidence in the second year of life (Bjornson 2008); it is more common in boys (1.5:1 boys:girls) (Searing 2014). A seasonal variation in the occurrence of croup, with a peak in autumn and winter, has been reported (Bjornson 2008; Segal 2005). Two commonly used methods for assessing the severity of croup are the Westley and Taussig Croup Scales (Taussig 1975; Westley 1978). The croup score is assigned based on the following five observed parameters: level of consciousness, stridor, air entry, retractions, and colour (ranging from normal to cyanotic). The Westley croup score has numerical values ranging from 0 to 17. Values less than four correspond to mild croup, four to six to moderate croup, and more than six to severe croup (Westley 1978). Modifications of this score have been used in the literature, for instance one ranging from 0 to 16 (Terregino 1998). The Taussig scale has numerical values ranging from 0 to 14. A score of less than four corresponds to mild croup, four to seven to moderate croup, and more than seven to severe croup (Taussig 1975). Also modified versions have been used in studies, for instance a modified Taussig croup scale ranging from 0 to 15 (Weber 2001).

Croup is thought to be triggered by a viral infection, most commonly by human parainfluenza virus (HPIV), particularly HPIV types 1 and 3, influenza A and B viruses, respiratory syncytial virus, rhinoviruses, and adenoviruses (Lee 2016). A strong association between human metapneumovirus and coronavirus HCoV-NL63 has also been identified (Bjornson 2008). Occasionally croup is triggered by a bacterial infection, most commonly *Mycoplasma pneumoniae* (Marx 1997; Segal 2005). Measles and diphtheria remain causes of croup in unimmunised populations (Bjornson 2008). Bacterial superinfection may also occur, most commonly with *Staphylococcus aureus* or *Streptococcus* species (Searing 2014). In a recent series of children requiring intubation for severe croup, antibiotics were prescribed in 51% of children (Gelbart 2016). Viral invasion of the glottic and subglottic mucosa causes inflammation and oedema, followed by epithelial necrosis and shedding, leading to narrowing of the upper airway (Bjornson 2008). Parainfluenza virus is also believed to activate chloride secretion and inhibit sodium absorption across the tracheal epithelium, contributing to upper airway oedema (Bjornson 2008). As this narrowing progresses, the pressure gradient necessary to move air through the upper airway becomes greater, leading to an increased effort in breathing. This may result in fatigue of the respiratory muscles and subsequently lead to respiratory failure, requiring emergency intubation.

Children with two or more episodes of croup before the age of four have a high incidence of asthma, allergies, and gastroesophageal

reflux, and may have an underlying anatomic abnormality or other cause of airway narrowing (Hiebert 2016). Systemic, oral, or nebulised corticosteroids are the currently accepted treatments for moderate to severe croup, supplemented in more severe cases by nebulised epinephrine and oxygen (Bjornson 2013a). Antibiotics do not normally play a role in the treatment of acute croup.

Corticosteroids have been shown to improve symptoms of croup, but it takes time for the full effect to be achieved (Russell 2011). An oral dose of 0.15 mg/kg dexamethasone has shown a significant benefit of 30 minutes compared to placebo (Dobrovolic 2012). Nebulised budesonide has been shown to have a beneficial effect as early as one to two hours after administration (Fitzgerald 1996; Klassen 1998). However, in the meantime the child remains at risk of deterioration and of developing respiratory failure, requiring emergency intubation and ventilation.

Description of the intervention

Helium is a biologically inert, colourless, odourless, and non-combustible gas that was first discovered in 1868 by Janssen and Lockyer. In the early 1930s, Barach pioneered the successful use of a helium-oxygen mixture (heliox) in the treatment of adults and children with asthma and upper airway obstruction (Barach 1935; Barach 1936). However, it was not until the 1980s that helium-oxygen mixtures regained popularity, possibly due to the rising mortality from asthma (Robin 1988). This led to an increase in clinical trials assessing the effect of heliox in the management of acute upper and lower airway obstructive disorders in children (Cambonie 2006; Grozs 2001; Hollman 1998; Martín-Torres 2002). Heliox is used in concentrations of helium:oxygen at 80:20, 70:30, or 60:40.

How the intervention might work

Heliox has a similar viscosity to and a substantial seven-fold lower density than air, and when combined with oxygen results in heliox, a gas mixture with an up to three-fold (heliox 80/20) lower density than air (Papamoschou 1995). The density of a gas mixture is proportional to the Reynolds number (Re), a dimensionless ratio of the inertial to the viscous force, and will thus have an effect on the type of gas flow present in the airway. It is known that turbulent flow occurs when Re is greater than 3000, and laminar flow occurs when Re is lower than 2000 (Glauser 1969). Pathological narrowing of the airway, as seen in croup, will lead to increased turbulence and higher gas flow resistance, resulting in an increased breathing effort. In theory, a gas of low density, such as heliox, should create a less turbulent or even laminar flow by reducing the Reynolds number, leading to a decrease in resistance to gas flow and the work of breathing (Houck 1990). Heliox is also believed to improve gas exchange, due to a delivery of increased tidal volume as a result of lowering the resistive forces within the airway (Katz 2001; Katz 2003). A Cochrane Review investigating the role of heliox inhalation therapy in infants with acute respiratory syncytial virus bronchiolitis concluded that the addition of heliox therapy to standard medical care may significantly reduce a clinical score evaluating respiratory distress in the first hour after starting treatment (Liet 2015). In a Cochrane Review on acute asthma in non-intubated participants, evidence did not support routine use of heliox in acute asthma, but the authors suggest that heliox may have beneficial effects in children or adults with more severe obstruction (Rodrigo 2006).

Heliox for croup in children (Review)

Why it is important to do this review

Croup can cause anxiety and distress to affected children and their parents. In mild cases, supportive treatment may suffice, but in moderate to severe cases, more aggressive therapy may be required to prevent exhaustion and respiratory failure. The available treatment options for croup are limited. Corticosteroids take time for clinical effects to be achieved. Nebulised epinephrine (adrenaline) is widely used. Adrenaline has rapid onset and short-lived benefit, but can be associated with dose-related side effects such as tachycardia, hypertension, and arrhythmias. Treatment of croup with heliox has demonstrated a beneficial effect, albeit in small numbers of children (Beckmann 2000; DiCecco 2004; Duncan 1979; Nelson 1982; Smith 1999). The benefit of heliox appeared not to differ from that of nebulised epinephrine in one study (Weber 2001). No significant evidence of benefit was reported in a previous version of this review (Vorwerk 2010), but data from a Spanish randomised controlled trial suggested that heliox, when added to corticosteroids, clinically improves moderate croup (Pardillo 2009). A published retrospective cohort study indicated that heliox, when added to standard treatment for transporting critically ill children with croup, provides rapid and sustained improvement in croup scores with no extension of length of stay in the intensive care unit (Kline-Krammes 2012).

This review update aimed to assess the current evidence regarding the role of heliox in children with croup in order to guide clinical practice.

OBJECTIVES

To examine the effect of heliox compared to oxygen or other active interventions, placebo, or no treatment, on relieving signs and symptoms in children with croup as determined by a croup score and rates of admission and intubation.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs comparing the effect of helium-oxygen mixtures with placebo, or no treatment or any active interventions.

Types of participants

Children with a clinical diagnosis of croup or laryngotracheobronchitis. We excluded other upper airway obstruction conditions such as epiglottitis, foreign body inhalation, or peritonsillar abscess.

Types of interventions

Heliox was compared to placebo or any active interventions, and where similar routes of administration were used for both groups.

Types of outcome measures

Primary outcomes

1. Change in croup score.
 - a. Change in croup score between pre- and postintervention.
 - b. Croup score postintervention.

Secondary outcomes

1. Change in respiratory rate (change between pre- and postintervention and scores postintervention).
2. Change in oxygen requirements (change pre- and postintervention and scores postintervention).
3. Change in heart rate (change between pre- and postintervention and scores postintervention).
4. Proportion of children hospitalised.
5. Duration of hospitalisation.
6. Proportion of children intubated.
7. Duration of intubation.
8. Proportion of children admitted to paediatric intensive care units.
9. Duration of admission to paediatric intensive care units.
10. Return to medical care for ongoing croup symptoms.
11. Parental anxiety.
12. Adverse events.
13. Other reported outcomes.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2018, Issue 1), part of the Cochrane Library (www.cochranelibrary.com/), (accessed 8 February 2018), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (Ovid, 1950 to 8 February 2018); Embase (Elsevier, 1974 to 8 February 2018); CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCO, 1981 to 8 February 2018); Web of Science (Clarivate Analytics, 1955 to 8 February 2018); and LILACS (Latin American and Caribbean Health Science Information database) (BIREME, 1982 to 8 February 2018). Details of the previous search are presented in [Appendix 1](#).

We searched MEDLINE and CENTRAL using the strategy in [Appendix 2](#). The search terms were adapted for Embase ([Appendix 3](#)), CINAHL ([Appendix 4](#)), Web of Science ([Appendix 5](#)), and LILACS ([Appendix 6](#)).

There were no language or publication restrictions.

Searching other resources

We searched two international clinical trials registries for ongoing or unpublished trials to 8 February 2018: the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (www.who.int/ictpr/en/) and the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov). We also screened the reference lists of included studies and systematic reviews for other potentially eligible studies. We contacted the authors of included studies and the regulatory affairs department of British Oxygen Company, a leading medical gas supplier, in December 2017 to ask if the manufacturer was aware of any additional published or unpublished trials involving heliox in children with croup between 2013 and 2017 (BOC Australia [pers comm]).

Data collection and analysis

Selection of studies

Two review authors (IM, NS) independently assessed titles and abstracts of all retrieved citations to identify potentially relevant reports. All review authors assessed the list of potentially relevant reports retrieved in full-text to determine whether they fulfilled the inclusion criteria. Two review authors (IM, NS) subsequently assessed the full-text reports. We reached agreement about trial inclusion by consensus.

Data extraction and management

Two review authors (IM, NS) independently extracted and reviewed data on:

1. design (description of randomisation, use of blinding, allocation concealment, handling of study withdrawals);
2. participants (total number, setting, age, exclusions);
3. intervention (type of helium-oxygen mixture, route of intervention, control group intervention, study duration); and
4. outcomes (primary, secondary, outcome analysis).

We used a standard data extraction form and reached agreement by consensus.

Assessment of risk of bias in included studies

Two review authors (IM, MVD) assessed the risk of bias of included studies using Cochrane's 'Risk of bias' tool, addressing the following domains ([Higgins 2011](#)).

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel; blinding of outcome assessment.
4. Incomplete outcome data.
5. Selective reporting.
6. Other sources of bias.

Measures of treatment effect

We analysed dichotomous data, such as proportion of hospital admissions, as odds ratio (OR) with 95% confidence intervals (CI) and continuous data, such as change in croup score, as mean difference (MD) with 95% CI.

Unit of analysis issues

We analysed outcomes for individual children. In studies where the unit of analysis (individual children) was not the same as the unit of randomisation, such as in cluster-randomised trials or cross-over trials, we planned to use the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* to adjust for the effect of clustering ([Higgins 2011](#)). Where measures were repeated over time (such as measurement of croup scores at different time points after receiving the intervention), we planned to select a single time point and meta-analyse only data at this time for studies in which data were presented ([Higgins 2011](#)). We planned to select a short-term time point because this was clinically relevant for studies comparing heliox and other treatments for children with croup.

Dealing with missing data

We planned to contact investigators or study sponsors to verify key study characteristics and obtain missing numerical data where possible (e.g. when a study was identified as abstract only). Where this was not possible and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results by a sensitivity analysis.

If numerical outcome data such as standard deviations or correlation coefficients were missing and could not be obtained from the authors, we calculated them from other available statistics such as P values according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

We contacted study authors to obtain missing data.

Assessment of heterogeneity

We assessed the included studies for clinical and methodological heterogeneity. We planned to assess statistical heterogeneity by calculating the P value of the Chi² test and the I² statistic. We considered an I² statistic of 50% or more as significant heterogeneity.

Assessment of reporting biases

We planned that if we were able to pool more than 10 trials, we would create and examine a funnel plot to explore possible small-study and publication biases.

Data synthesis

Where pooled studies reported a different croup score at the same time points, we planned to combine the outcomes by using the standardised mean difference (SMD) with 95% CI. We planned to use the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* to calculate the SMD ([Higgins 2011](#)).

If standard deviations or confidence intervals (required for calculating the SMD) were not available from the study reports, we used the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* to impute the missing standard deviations from the standard error of the mean by multiplying by the square root of the sample size or from CIs from the mean, whichever was provided in the report ([Higgins 2011](#)).

We planned to pool data using both fixed-effect and random-effects models as described in the *Cochrane Handbook for Systematic Reviews of Interventions* and to explore the impact of each on the overall treatment effect estimate ([Higgins 2011](#)).

GRADE and 'Summary of findings' table

We created 'Summary of findings' tables comparing heliox to 30% oxygen ([Summary of findings for the main comparison](#)) and to placebo ([Summary of findings 2](#)) for the primary outcome change in croup score, and for the secondary outcomes as available from the studies: change in respiratory rate; change in heart rate; proportion of children hospitalised and duration of hospitalisation; proportion of children intubated and duration of intubation; rate of return to medical care for ongoing croup symptoms; and adverse events.

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of evidence as it related to the studies that contributed data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro GDT 2015). We justified all decisions to downgrade the quality of studies in footnotes, and made comments to aid readers' understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses based on:

1. type of control (placebo or no treatment, humidified oxygen, nebulised epinephrine);
2. severity of disease (mild, moderate, severe); and

3. duration of treatment effects.

Sensitivity analysis

We planned to investigate the impact of heterogeneity on the overall estimated effect of the intervention.

RESULTS

Description of studies

Results of the search

Our search on 8 February 2018 identified 22 trial reports, of which one was a duplicate report. None of the 21 reports met our inclusion criteria after title and abstract review. Previous searches in November 2013 identified 86 trial reports, of which 21 were excluded after preliminary screening and 65 were considered to be potentially eligible. Sixty-two studies did not meet the inclusion criteria and were excluded after abstract review. Three studies met our inclusion criteria (Figure 1).

Figure 1. Flow diagram of study selection.

Included studies

We added no new trials for this 2018 update.

We included three RCTs involving a total of 91 children (Pardillo 2009; Terregino 1998; Weber 2001). Two studies were published in English, Terregino 1998; Weber 2001, and one in Spanish (Pardillo 2009).

Design

All included studies were RCTs; two were double-blinded (Terregino 1998; Weber 2001), and one was a prospective, randomised, open clinical trial (Pardillo 2009).

Population

The studies included a total of 91 children (Pardillo 2009, N = 47; Terregino 1998, N = 15; Weber 2001, N = 29). All children in the included studies shared similar characteristics in terms of age.

Setting

Two studies were conducted in emergency departments, one in Madrid, Spain (Pardillo 2009), and one in New Jersey, USA (Terregino 1998). Weber 2001, conducted in Michigan, USA, recruited children via the emergency department. Children who were admitted to paediatric intensive care unit were followed up (Weber 2001).

Participants

Pardillo 2009 enrolled 47 children aged between 6 and 36 months. There were 18 males and 6 females in the treatment group and 19 males and 4 females in the control group. All children had moderate croup (defined as (modified) Taussig score between 5 and 8). Children who had congenital or acquired cardiac conditions, bronchopulmonary dysplasia, stenosis or malformations of the trachea, bronchospasm at diagnosis, intolerance of oral dexamethasone, or who had received corticosteroids in the previous two weeks were excluded (Pardillo 2009).

Terregino 1998 enrolled 15 children aged between 9 months and 4 years (gender not reported) with mild croup using a modified Westley croup scoring system with a maximum value of 16. Children who had a presumed diagnosis of epiglottitis, history of chronic upper airway obstruction, were in severe respiratory distress or their oxygen requirements exceeded 2 L/min to maintain an oxygen saturation of at least 95% were excluded (Terregino 1998).

Weber 2001 included 29 children aged between 6 months and 3 years with moderate to severe croup, defined as a modified Taussig croup score ≥ 5 or a score of 3 in any of the 5 categories (Taussig 1975). There were 9 males and 5 females in the treatment group and 11 males and 4 females in the control group. Children were excluded if they had known congenital cardiac or tracheo-broncho-pulmonary disease or if they had other causes of stridor such as epiglottitis, bacterial tracheitis, retropharyngeal or peritonsillar abscess, reactive airway disease, tumour, or supraglottic foreign body.

Interventions

Pardillo 2009 administered a single dose of 0.3 mg/kg dexamethasone orally to all 47 children in the study. Heliox was administered to 24 children via a mask with a reservoir to prevent re-inhalation for a period of one hour; 23 children received no treatment unless their oxygen saturations fell below 92% during the study, in which case oxygen was administered by nasal prongs.

Terregino 1998 (N = 15) randomised eight children to receive humidified heliox and seven to 30% humidified oxygen. Both were delivered via a tight-fitting mask for 20 minutes. Children received no additional treatments.

All 29 children in Weber 2001 received continuous cool mist and 0.6 mg/kg intramuscular dexamethasone. Children were then randomised to receive heliox (14 children) or 100% oxygen plus one to two doses of nebulised racemic epinephrine (15 children). Gas therapy was administered via a face mask or tent house continuously for three hours followed by a further 60-minute observation period.

Outcomes

Pardillo 2009 assessed changes in Taussig croup score and respiratory rate, which were measured at 60 and 120 minutes. Secondary outcome measures were need for nebulised rescue epinephrine, admission rate, and reconsultation within the following 72 hours.

Terregino 1998 assessed change in Westley croup score at 20 minutes (Westley 1978). The authors used a numerical modification of the Westley score with a maximum score of 16; the different parameters were level of consciousness, colour, stridor, air entry, and retractions. Other outcomes were measured at 5-minute intervals for a total of 20 minutes including heart rate, respiratory rate, and oxygen saturation.

Weber 2001 assessed change in croup score over time (at 30, 60, 90, 120, 150, 180, and 240 minutes). Secondary outcomes were changes in oxygen saturation, respiratory rate, and heart rate.

Excluded studies

We excluded a total of 86 studies in previous versions of this review. The search conducted in 2018 identified 21 records. None of these were found to be RCTs and eligible for inclusion after title and abstract review (Excluded studies).

Risk of bias in included studies

Overall, we assessed risk of bias as low for two studies (Terregino 1998; Weber 2001). We assessed Pardillo 2009 as at high risk of bias overall due to the open-label study design. (See Figure 2, Figure 3, and Characteristics of included studies tables.)

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Pardillo 2009						
Terregino 1998						
Weber 2001						

Allocation

We assessed two trials as at low risk of bias for this domain as allocation was adequately concealed (Terregino 1998; Weber 2001). Terregino 1998 used sequentially numbered, sealed envelopes, and Weber 2001 used computer-randomised allocation. Pardillo 2009 did not describe the concealment method, but used a computer program for randomisation. We assessed the risk of bias for this study as unclear.

Blinding

We assessed two trials in which both children and outcome assessors were blinded, and only respiratory therapists were not blinded to treatment allocation, as at low risk of bias for this domain (Terregino 1998; Weber 2001). We assessed one study in which neither participants nor assessors were blinded to treatment as at high risk of bias (Pardillo 2009).

Incomplete outcome data

There was no evidence of missing outcome data, and no participants were lost to follow-up in all three included studies (Pardillo 2009; Terregino 1998; Weber 2001). We assessed the studies as at low risk of attrition bias.

Selective reporting

We assessed one study that reported all expected outcomes as at low risk of reporting bias (Terregino 1998). We assessed two studies as at high risk of reporting bias (Pardillo 2009; Weber 2001): Weber 2001 did not present study outcomes at any predefined time points, and although Pardillo 2009 reported predefined major outcome data, they did not indicate if any participants required supplementary oxygen.

Other potential sources of bias

We assessed all studies as at unclear risk for other sources of bias. Terregino 1998 used a convenience sample of consecutive children presenting to an emergency department. The children were not randomly selected, which carries a potential risk of bias. There was the potential for risk of bias in Weber 2001 due to lack of outcome data.

None of the studies disclosed funding sources or study authors' potential conflicts of interest.

Effects of interventions

See: [Summary of findings for the main comparison Heliox compared to oxygen 30% for croup in children](#); [Summary of findings 2 Heliox compared to placebo or no treatment for croup in children](#)

Comparison 1: Heliox versus humidified 30% oxygen

Only Terregino 1998 (15 children) compared heliox (given as a mixture of 70% helium and 30% oxygen) with 30% humidified oxygen and provided data for analysis ([Summary of findings for the main comparison](#) and [Table 1](#)).

Primary outcome

Change in croup score

The effect of heliox on symptoms and signs of croup was presented as a modified Westley croup score before the intervention and

20 minutes after the intervention, as well as the mean change in croup score between pre- and postintervention (Terregino 1998). There may be no difference in croup score between pre- and postintervention at 20 minutes; the mean difference (MD) between groups of the change (pre- and postintervention) in croup scores was -0.83 (95% confidence interval (CI) -2.36 to 0.70; participants = 15; studies = 1; [Analysis 1.1](#); low-quality evidence).

Croup scores measured at 20 minutes after administration may not differ between groups (MD -0.57, 95% CI -1.46 to 0.32; participants = 15; studies = 1; [Analysis 1.2](#); low-quality evidence).

We downgraded the quality of the evidence for both outcomes two levels due to serious imprecision (very small sample size).

Secondary outcomes

1. Change in respiratory rate

Terregino 1998 did not report the change in respiratory rate but reported the mean respiratory rate in each group at the endpoint of 20 minutes postintervention. Overall, there may be no difference between groups in mean respiratory rate but the difference between the two groups at this time point favoured oxygen (MD 6.40, 95% CI -1.38 to 14.18; participants = 15; studies = 1; [Analysis 1.3](#); low-quality evidence). We downgraded the quality of the evidence for this outcome two levels due to serious imprecision (very small sample size). (Note: the effect size as reported by the study authors is MD 6.3, 95% CI -2.2 to 14.8.)

2. Change in oxygen requirements

The need for oxygen was not reported, however Terregino 1998 mentions that mean oxygen saturation was stable over time in both groups. There may be no difference between the groups in arterial oxygen saturation (oxygen saturation 99.4% in the oxygen group versus 99.0% in the heliox group; MD -0.40, 95% CI -1.68 to 0.88; participants = 15; studies = 1; [Analysis 1.4](#); low-quality evidence). We downgraded the quality of the evidence for this outcome two levels due to serious imprecision (very small sample size).

3. Change in heart rate

Terregino 1998 did not report the change in heart rate but reported the mean heart rate in each group at the endpoint of 20 minutes postintervention. There may be no difference between the two groups (MD 14.50, 95% CI -8.49 to 37.49; participants = 15; studies = 1; [Analysis 1.5](#); low-quality evidence). We downgraded the quality of the evidence for this outcome two levels due to serious imprecision (very small sample size). (Note: the effect size as reported by the study authors is MD 14.5, 95% CI -5.4 to 34.5.)

4 and 5. Proportion and duration of hospitalisation

This outcome was not reported, but the authors mention that "all children were discharged" (Terregino 1998).

6 and 7. Proportion and duration of intubation

This outcome was not reported (Terregino 1998).

8 and 9. Proportion and duration of admission to paediatric intensive care units

This outcome was not reported, but the authors mention that "all patients were discharged" (Terregino 1998).

10. Return to medical care for ongoing croup symptoms

This outcome was not reported (Terregino 1998).

11. Parental anxiety

This outcome was not reported (Terregino 1998).

12. Adverse events

Terregino 1998 mentioned there was "no recorded complication". Adverse events were not reported.

13. Other reported outcomes

Terregino 1998 reported that no children required administration of racemic epinephrine.

Comparison 2: Heliox versus placebo or no treatment

Pardillo 2009 (47 children) contributed data for the analysis of heliox (given as a mixture of 70% helium and 30% oxygen) compared with placebo or no treatment (Summary of findings 2 and Table 2).

Primary outcome

Change in croup score

Pardillo 2009 did not report the change in croup scores with a standard deviation (SD) for each of the two groups. The effect of heliox on symptoms and signs of croup was presented as croup scores measured pre- (time 0) and at two time points postintervention (at 60 and 120 minutes after administering the intervention) (Pardillo 2009). Using the SD of the difference estimate from the Terregino 1998 study (an SD value of 1.5), we calculated a standard error for the mean difference (0.31) that we imputed for the analyses of change in croup score between pre- and postintervention.

The mean change between start of treatment and 60 minutes postintervention (outcome 'change in croup score at 60 minutes') may favour heliox (MD -1.10, 95% CI -1.96 to -0.24; participants = 47; studies = 1; Analysis 2.1; low-quality evidence).

The mean change between start of treatment and 120 minutes postintervention (outcome 'change in croup score at 120 minutes') may not be different between the heliox and control group (MD -0.70, 95% CI -1.56 to 0.16; participants = 47; studies = 1; Analysis 2.2; low-quality evidence).

The Taussig croup scores at the endpoints of 60 and 120 minutes postintervention were also reported for both groups. The difference in Taussig scores between the groups at endpoint 60 minutes postintervention may favour heliox (MD -1.11, 95% CI -2.05 to -0.17; participants = 47; studies = 1; Analysis 2.3; low-quality evidence); at endpoint 120 minutes postintervention there may be no difference between groups (MD -0.71, 95% CI -1.72 lower to 0.3 higher; participants = 47; studies = 1; Analysis 2.4; low-quality evidence).

We downgraded the quality of the evidence for all croup score outcomes two levels due to imprecision (small sample size with wide confidence intervals) and risk of bias (open-label study).

Pardillo 2009 also compared changes in croup scores in children with a Taussig score 5 to 6 and those with a Taussig score 7 to 8 (range for moderate croup is 5 to 8 on the Taussig scale).

For children with a croup score 5 to 6 (30 participants), the scores at 60 minutes postintervention were 2.53 (SD 1.76) in the heliox group and 2.93 (0.8) in the control group. The scores at 120 minutes postintervention were 1.53 (1.4) in the heliox group and 1.87 (1.84) in the control group.

For children with a croup score 7 to 8 (17 participants), the scores at 60 minutes postintervention were 2.78 (1.64) in the heliox group and 5.25 (1.7) in the control group. The scores at 120 minutes postintervention were 1.33 (1.0) in the heliox group and 2.75 (2.71) in the control group.

The authors reported that the mean croup score at 60 minutes postintervention was lower in the group with scores 5 to 6 compared with the group with scores 7 to 8, but this difference was only statistically significant in the control group ($P = 0.001$), and not in the heliox group ($P = 0.696$).

The mean croup score at 120 minutes was lower in the group with scores 5 to 6 compared with the group with scores 7 to 8, but this difference was not statistically significant ($P = 0.609$ in the control group). The mean croup score at 120 minutes postintervention in the heliox group was lower in children with croup scores 7 to 8 compared with those with croup scores 5 to 6, but this difference was also not statistically significant ($P = 0.107$).

As information about the number of children in each group (i.e. how many children with moderate croup were in the heliox or control group) was not reported, it was not possible to calculate the MD between the heliox and the control group at 60 or 120 minutes postintervention.

Secondary outcomes

1. Change in respiratory rate

Pardillo 2009 did not report the mean change in respiratory rates between pre- and postintervention (with SD) in the two groups, but instead reported the mean respiratory rates in each group at different time points. We were unable to impute an SD as there were no other studies available from which to derive this SD. We have therefore reported the effect on respiratory rate as a difference between groups at a specific time point. There may be a greater reduction in respiratory rate in children who received heliox compared with children in the control group at 60 minutes postintervention (MD -4.94, 95% CI -9.66 to -0.22; participants = 47; studies = 1; Analysis 2.5; low-quality evidence) but not at 120 minutes postintervention (MD -3.17, 95% CI -7.83 to 1.49; participants = 47; studies = 1; Analysis 2.6; low-quality evidence) (Pardillo 2009). We downgraded the quality of the evidence two levels due to imprecision (small sample size with wide confidence intervals) and risk of bias (open-label study).

2. Change in oxygen requirements

Pardillo 2009 did not report this outcome.

3. Change in heart rate

Pardillo 2009 did not report this outcome.

4 and 5. Proportion and duration of hospital admission

Pardillo 2009 reported that two children in the control group and one in the treatment group were hospitalised ($P = 0.609$). Overall, there may be a difference in the proportion of hospitalised

children between groups; the odds ratio (OR) for the proportion of children who were admitted was 0.46 (OR 0.46, 95% CI 0.04 to 5.41; participants = 47; studies = 1; [Analysis 2.7](#); low-quality evidence). We downgraded the quality of the evidence two levels due to imprecision (small sample size with wide confidence intervals) and risk of bias (open-label study).

6 and 7. Proportion and duration of intubation

[Pardillo 2009](#) did not report this outcome.

8 and 9. Proportion and duration of admission to paediatric intensive care units

[Pardillo 2009](#) did not report this outcome.

10. Return to medical care for ongoing croup symptoms

[Pardillo 2009](#) reported that two children each in the heliox (8.3%) and control groups (8.7%) re-presented at the emergency department within 72 hours of first presentation ($P = 1.0$). Overall, there may be no difference in re-presentation to the emergency department; the OR for the proportion of children who re-presented to hospital in the 72 hours following the intervention was 0.95 (OR 0.95, 95% CI 0.12 to 7.41; participants = 47; studies = 1; [Analysis 2.8](#); low-quality evidence). We downgraded the quality of the evidence two levels due to imprecision (small sample size with wide confidence intervals) and risk of bias (open-label study).

11. Parental anxiety

[Pardillo 2009](#) did not report this outcome.

12. Adverse events

[Pardillo 2009](#) did not report this outcome.

13. Other reported outcomes

In [Pardillo 2009](#), one child in the heliox group and five in the control group required rescue nebulised epinephrine ($P = 0.0097$), but there may be no difference between groups (OR 0.16 in favour of heliox, 95% CI 0.02 to 1.46; participants = 47; studies = 1; [Analysis 2.9](#); low-quality evidence). We downgraded the quality of the evidence two levels due to imprecision (small sample size with wide confidence intervals) and risk of bias (open-label study).

Comparison 3: Heliox versus 100% oxygen plus nebulised epinephrine (adrenaline)

[Weber 2001](#) (29 children) contributed data for this analysis comparing heliox (given as a mixture of 70% helium and 30% oxygen) plus one to two doses of nebulised saline versus 100% oxygen plus nebulised epinephrine. All data for the primary outcome (change in croup score) were presented only in a graph. Results of analyses for other outcomes were only reported as P values. Attempts to obtain numerical data from the study authors were unsuccessful.

Primary outcome

Change in croup score

Croup scores were measured at 30, 60, 90, 120, 150, 180, and 240 minutes after the interventions ([Weber 2001](#)). No raw croup scores were presented at the measured time points, but data estimates could be extracted from the graph.

- 30 minutes: heliox 5.2 and control 5.3

- 60 minutes: heliox 4.5 and control 4.9
- 90 minutes: heliox 3.9 and control 4.3
- 120 minutes: heliox 3.3 and control 4.0
- 180 minutes: heliox 2.9 and control 3.8
- 240 minutes: heliox 2.2 and control 3.2

The authors reported that the differences were statistically significant at all time intervals after 90 minutes, but the overall results were not statistically significant using repeat-measures analysis. We downgraded the quality of the evidence two levels due to high risk of bias (inadequate reporting).

Secondary outcomes

1. Change in respiratory rate

[Weber 2001](#) reported no statistically significant differences between treatment groups in respiratory rate ($P = 0.94$) (no absolute numbers reported).

2. Change in oxygen requirements

[Weber 2001](#) reported no statistically significant differences between treatment groups in arterial oxygen saturation ($P = 0.28$) (no absolute numbers reported).

3. Change in heart rate

[Weber 2001](#) reported no statistically significant differences between treatment groups in heart rate ($P = 0.29$) (no absolute numbers reported).

4 and 5. Proportion and duration of hospital admission

[Weber 2001](#) did not report this outcome.

6 and 7. Proportion and duration of intubation

[Weber 2001](#) reported that "no patients required intubation".

8 and 9. Proportion and duration of admission to paediatric intensive care units

[Weber 2001](#) did not report this outcome.

10. Return to medical care for ongoing croup symptoms

[Weber 2001](#) did not report this outcome.

11. Parental anxiety

[Weber 2001](#) did not report this outcome.

12. Adverse events

[Weber 2001](#) did not report this outcome.

13. Other reported outcomes

[Weber 2001](#) reported that "four patients in the epinephrine arm and three in the heliox arm received a second dose of racemic epinephrine and saline placebo, respectively. Outcomes for both groups were similar" (p. 2).

Subgroup analyses

We did not conduct subgroup analyses as there were insufficient studies and data available. However, we reported the effect of treatments on subgroups of included children, and at different time points, where reported in the individual studies.

DISCUSSION

Summary of main results

We included three RCTs with a total of 91 participants that assessed the effect of heliox inhalation to treat children with croup ([Pardillo 2009](#); [Terregino 1998](#); [Weber 2001](#)).

[Terregino 1998](#) compared helium-oxygen (70:30) inhalation with humidified oxygen (30%) in children with mild croup. [Weber 2001](#) compared helium-oxygen (70:30) inhalation with oxygen (100%) plus nebulised racemic epinephrine. [Pardillo 2009](#) compared helium-oxygen (70:30) inhalation with no treatment in children with moderate croup. Overall, there maybe a greater improvement in croup scores from pre- to postintervention with heliox than with the comparator interventions. This improvement in croup scores did not reach statistical significance in the two studies ([Terregino 1998](#); [Weber 2001](#)). There were no significant changes in heart rate, respiratory rates, or oxygen saturation between the intervention and comparison groups.

Adverse events were not reported as an outcome, and none of the studies reported on the need for intubation. Some children were admitted to hospital, and some re-presented to the emergency department in the [Pardillo 2009](#) study. [Weber 2001](#) lacked numerical data for outcomes relevant to this review, and we were unable to obtain these data from the study authors. Our interpretation of findings for [Weber 2001](#) was therefore limited.

Overall completeness and applicability of evidence

We were unable to make a robust conclusion based on the data from the included studies about the efficacy of heliox to relieve symptoms and signs of croup in children, or on rates of admission or intubation in these children. All included studies reported changes in croup scores, however other review outcomes were not consistently reported.

The included studies represented different severities of croup ([Pardillo 2009](#); [Terregino 1998](#); [Weber 2001](#)): children in [Terregino 1998](#) had mild croup; in [Weber 2001](#) moderate to severe croup; and in [Pardillo 2009](#) moderate croup. [Terregino 1998](#) excluded children with severe croup who may have benefited from heliox, and no children received corticosteroids or epinephrine, which is contrary to current standard practice and makes it difficult to apply results to current clinical practice. [Weber 2001](#) excluded children from analyses who required rescue nebulised epinephrine, who could not tolerate the gas delivery system, or for whom outcome data were incomplete. [Weber 2001](#) presented incomplete outcome data, which limited the quality of the evidence available for interpretation.

Duration of heliox administration varied among the included studies. It has been reported that clinical assessment of heliox benefit requires at least an hour of therapy ([Martín-Torres 2002](#)). The chosen duration of 20 minutes in [Terregino 1998](#) may have been too short to demonstrate a significant benefit, particularly as [Pardillo 2009](#) and [Weber 2001](#) reported statistically significant differences in improvement in children who received heliox after 60 and 90 minutes of treatment, respectively.

[Weber 2001](#) used tent houses to deliver heliox for some children. Tent houses are considered to be suboptimal for heliox delivery; helium accumulates at the top of the tent, so the helium

concentration reaching the child's upper airway is markedly reduced ([Martín-Torres 2003](#); [Stillwell 1989](#)).

Children in two studies received corticosteroid therapy, which reflects clinical practice for the treatment of croup ([Pardillo 2009](#); [Weber 2001](#)).

Only [Pardillo 2009](#) reported data for other outcomes that are relevant to clinical practice such as numbers of children requiring rescue epinephrine and children re-presenting to hospital for treatment. None of the studies reported data relevant to all review outcomes.

The results of the included studies indicate that heliox has a positive effect in reducing the severity of signs and symptoms of croup as observed from change in croup score and may be beneficial as part of initial treatment while waiting for the action of corticosteroids to take effect. There is also evidence that heliox may be useful during transport of children with severe croup.

Quality of the evidence

The quality of the evidence was low ([Summary of findings for the main comparison](#); [Summary of findings 2](#); [Table 1](#); [Table 2](#)).

All three studies reported the primary outcome, change in croup score, although scoring systems differed. [Terregino 1998](#) used a modified Westley croup scoring scale, and [Pardillo 2009](#) and [Weber 2001](#) used the Taussig croup scoring scale. Data from [Weber 2001](#) for change in croup score and other outcomes were not available for analysis. Most of the secondary outcomes predefined in the review were not reported by the included studies. Furthermore, secondary outcomes in the studies differed. [Terregino 1998](#) reported change in heart rate data but did not report oxygen requirement data. The study authors stated that mean arterial oxygen saturation was stable and identical in both groups of children ([Terregino 1998](#)). [Pardillo 2009](#) did not report this outcome or change in heart rate.

We downgraded the quality of the evidence by two levels. Two studies had very small sample sizes: [Terregino 1998](#) included 15 children, and [Weber 2001](#) included 29 children; and serious imprecision. One study (including 47 children) compared heliox to no heliox (control), and represented about half of all participants in this review ([Pardillo 2009](#)). We downgraded the quality of the evidence for outcomes comparing heliox and no heliox by two levels to low due to imprecision (small sample size) and risk of bias due to the open-label design ([Pardillo 2009](#)).

Potential biases in the review process

We used a systematic and comprehensive search strategy in several databases. We also contacted a leading medical gas supplier to enquire about any unpublished studies ([BOC Australia \[pers comm\]](#)). It is possible that we missed studies despite this thorough search. However, given the paucity of evidence and that heliox is not a widely used treatment, other data may not change our conclusions.

We contacted authors to obtain additional data because reporting in the published papers was limited. We were unable to obtain missing data from the authors of two studies, and this may have introduced bias ([Pardillo 2009](#); [Weber 2001](#)).

In order to calculate our primary outcome, change in croup score, for comparison 2 (Pardillo 2009), we imputed an SD derived from the Terregino 1998 study. However, Terregino 1998 used the modified Westley croup score (total score of 16), whereas Pardillo 2009 used a modified Taussig croup score (total score of 15). Although both scoring systems are very close, this may have introduced some bias in the calculation for Pardillo 2009, and any inferences about how both studies compare must therefore be made with caution.

Agreements and disagreements with other studies or reviews

A case series described seven children (aged from newborn to three years) with severe airway obstruction due to postintubation or infectious croup who were given heliox as a carrier for oxygen. Although most children had underlying medical problems, helium-oxygen inhalation was found to significantly reduce respiratory distress, as measured by a croup score, and prevented the need for tracheal intubation (Duncan 1979). A further case series of 14 children (aged from 3 months to 21 months) with viral croup were referred for possible tracheal intubation or tracheostomy (Nelson 1982). These children were commenced on helium-oxygen inhalation and a subsequent improvement in respiratory distress was observed; no children required intubation. Both case series included a heterogeneous study population and lacked a control group, which made it very difficult to comment on the contribution of heliox mixtures to the observed clinical outcomes.

Anecdotal evidence of heliox benefit is further supported by Smith 1999, who reported dramatic relief of respiratory distress in three children with croup who were commenced on heliox therapy. A retrospective chart review included 35 children (17 were treated with heliox and 18 did not receive heliox treatment), who were transported by air and admitted to a paediatric intensive care unit (PICU) (Kline-Krammes 2012). Children treated with heliox had higher baseline croup scores compared to children in the control group. The improvement in croup scores in the heliox group was more rapid, and there was no difference in numbers of children requiring nebulised racemic epinephrine during transport. The length of stay in the PICU was similar for the children who had received heliox and those who had not received heliox treatment during transport to the PICU.

There are currently no other systematic reviews assessing the use of heliox for croup, and the three studies included in this review are the only RCTs assessing the use of heliox for children with croup.

AUTHORS' CONCLUSIONS

Implications for practice

We found some low-quality evidence to suggest a short-term benefit of heliox inhalation in the treatment of moderate to severe croup in children who have been administered oral or intramuscular dexamethasone. The benefit of heliox appears to be no different from 100% oxygen combined with one to two doses of nebulised racemic epinephrine (adrenaline) (Weber 2001). Pardillo 2009 reported that heliox appeared slightly more beneficial than no treatment. The difference in croup score (Taussig score) between children who were administered heliox and those without additional treatment was around one point on the croup scale, which was in the moderate range after 60 minutes. The clinical significance of this difference is not clear. In children with mild croup, the benefit of humidified heliox appeared to be equivalent to 30% humidified oxygen, suggesting that heliox is not indicated in these children provided that 30% oxygen is available (Terregino 1998).

Implications for research

Adequately powered randomised controlled trials that compare heliox with standard treatments are needed to establish the role of heliox therapy in the management of children with moderate to severe croup. Trials also need to incorporate clinical outcomes with health and economic relevance such as rate and duration of admission to paediatric intensive care units, rate and duration of intubation, rate of return to medical care for ongoing croup symptoms, rate and duration of hospital admission, parental anxiety, and side effects.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Pardillo 2009

Methods	Prospective, randomised, open clinical trial Study duration: 13 months
Participants	Inclusion criteria <ul style="list-style-type: none"> • Setting: emergency department • Country: Spain • Health status: moderate croup (Taussig croup score between 5 and 8) • Number: treatment = 24; control = 23 • Age: range = 6 months to 3 years • Sex (m/f): treatment 18/6; control 19/4 Exclusion criteria <p>Children with congenital or acquired cardiac conditions, bronchopulmonary dysplasia or stenosis or malformations of the trachea, bronchospasm at diagnosis, intolerance of oral dexamethasone, or children treated with corticosteroids in the previous 2 weeks were excluded.</p>
Interventions	<p>All children received oral dexamethasone 0.3 mg/kg to max of 10 mg. Rescue treatment was nebulised epinephrine and oxygen via nasal route if saturation fell below 92%.</p> <p>Intervention group: heliox 70%/30% via a mask with a reservoir to prevent re-inhalation; flow rate of 10 L/min for 1 hour</p> <p>Control group: no treatment</p>
Outcomes	<p>Primary outcomes: change in croup score and respiratory rate at 60 and 120 minutes</p> <p>Secondary outcomes: need for nebulised rescue epinephrine, admission rate, reconsultation within the following 72 hours</p>
Notes	<p>No information on funding source or authors' potential conflicts of interest provided.</p> <p>We only used data available from the publications; we could obtain no additional data from the study authors.</p>

Risk of bias

Heliox for croup in children (Review)

Pardillo 2009 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of a computer-generated randomisation scheme
Allocation concealment (selection bias)	Unclear risk	Not described, concealment could not be assessed
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label study; assessors knew to which study arms participants belonged
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up
Selective reporting (reporting bias)	High risk	Results for the children who required rescue epinephrine reported, but outcomes for those who were admitted or who re-presented at 72 hours were not reported.
Other bias	Unclear risk	Assessors may have influenced overall outcomes due to the lack of blinding.

Terregino 1998

Methods	Randomised controlled trial Study duration: 16 months
Participants	Inclusion criteria <ul style="list-style-type: none"> Setting: emergency department Country: USA Health status: features of mild croup Number: treatment = 8; control = 7 Age: range = 9 months to 4 years Sex (m/f): study did not report participants' gender. Exclusion criteria Children were excluded if in severe respiratory distress, oxygen saturation < 95% on 2 L/min oxygen, or other causes of upper airway obstruction.
Interventions	Intervention group: humidified helium-oxygen mixture (70:30) for 20 minutes Control group: humidified oxygen (30%) for 20 minutes
Outcomes	Primary: change in croup score at 20 minutes Secondary: change in heart rate, respiratory rate, oxygen saturation at 20 minutes post-treatment
Notes	No information on funding source or authors' potential conflicts provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Heliox for croup in children (Review)

Terregino 1998 (Continued)

Random sequence generation (selection bias)	Low risk	Use of sequentially numbered, sealed envelopes available only to the respiratory therapist
Allocation concealment (selection bias)	Low risk	Allocation was adequately concealed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No evidence of missing outcome data
Selective reporting (reporting bias)	Low risk	All expected study outcomes were reported.
Other bias	Unclear risk	Convenience sample used.

Weber 2001

Methods	Randomised controlled trial Study duration: 7 months
Participants	Inclusion criteria <ul style="list-style-type: none"> • Setting: emergency department • Country: USA • Health status: features of moderate to severe croup (corresponding to a modified Taussig croup score ≥ 5) • Number: treatment = 14; control = 15 • Age: range = 6 months to 3 years • Sex (m/f): treatment 9/5; control 11/4 Exclusion criteria Children were excluded if known congenital cardiac or tracheo-broncho-pulmonary disease or if other causes of stridor such as epiglottitis, bacterial tracheitis, retropharyngeal or peritonsillar abscess, reactive airway disease, tumour, or supraglottic foreign body.
Interventions	All children received intramuscular dexamethasone 0.6 mg/kg. Intervention group: heliox (70%/30%) and up to 2 doses of nebulised normal saline over 3 hours Control group: oxygen (100%) and up to 2 doses of nebulised racemic epinephrine over 3 hours
Outcomes	Primary: change in croup score at 30, 60, 90, 120, 150, 180, 240 minutes Secondary: change in heart rate, respiratory rate, oxygen saturation at 30, 60, 90, 120, 180, and 240 minutes
Notes	"This study was funded, in part, by the Hurley Respiratory Therapy Department, Hurley Medical Center." No information on authors' potential conflicts of interest provided.

Heliox for croup in children (Review)

Weber 2001 (Continued)

We contacted study authors to request additional data but received no response.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Use of computer-generated randomisation scheme
Allocation concealment (selection bias)	Low risk	Allocation was adequately concealed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up
Selective reporting (reporting bias)	High risk	Lack of reporting of some of the expected outcome data
Other bias	Unclear risk	Given the described participant selection process, there may be other potential sources of bias.

m/f: male/female

L/min: litres per minute

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aliaga Simões De Souza 2014	Retrospective descriptive-exploratory study (from 2018 search)
Barnes 2016	Case report (from 2018 search)
Beckmann 2000	Case report (2009 and 2013 searches)
Berganza 2013	Case report (2018 search)
Bjornson 2013	Literature review (from 2018 search)
Brown 2002	Review (from 2013 search)
Canares 2014	Literature review (from 2018 search)
Choi 2012	Review (from 2013 search)
Cutrera 2017	Literature review (from 2018 search)
DiCecco 2004	Case report
Duncan 1979	Case series (2009 and 2013 searches)

Study	Reason for exclusion
Frazier 2010	Review (from 2013 search)
Gupta 2005	Review
Hashemian 2016	Literature review (from 2018 search)
Iglesias Fernández 2007	Cohort study
Johnson 2014	Systematic review (from 2018 search)
Johnson 2016	Literature review (from 2018 search)
Kaditis 1998	Not RCT (from 2013 search)
Khemani 2013	Not heliox or croup related (from 2018 search)
Kline-Krammes 2012	Review (from 2013 search)
Makepeace 2014	Literature review not on croup or heliox (from 2018 search)
Miller 2013	Case study (from 2018 search)
Myers 2004	Review
Myers 2006	Review (2009 and 2013 searches)
Nelson 1982	Case series
Nicolai 2012	Review (from 2013 search)
Rosekrans 1998	Not RCT (from 2013 search)
Rudinsky 2015	Not RCT (from 2018 search)
Smith 1999	Case reports
Verma 2013	Literature review on bronchiolitis (from 2018 search)
Virbalas 2015	Literature review (from 2018 search)
Wald 2010	Not RCT (from 2013 search)
Wright 2005	Not RCT (from 2013 search)
Wright 2016	Literature review (from 2018 search)

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Heliox versus humidified 30% oxygen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in croup score	1	15	Mean Difference (IV, Fixed, 95% CI)	-0.83 [-2.36, 0.70]
2 Mean croup score at 20 minutes	1	15	Mean Difference (IV, Fixed, 95% CI)	-0.57 [-1.46, 0.32]
3 Mean respiratory rate at 20 minutes	1	15	Mean Difference (IV, Fixed, 95% CI)	6.40 [-1.38, 14.18]
4 Mean oxygen saturation at 20 minutes	1	15	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.68, 0.88]
5 Mean heart rate at 20 minutes	1	15	Mean Difference (IV, Fixed, 95% CI)	14.5 [-8.49, 37.49]

Analysis 1.1. Comparison 1 Heliox versus humidified 30% oxygen, Outcome 1 Change in croup score.

Analysis 1.2. Comparison 1 Heliox versus humidified 30% oxygen, Outcome 2 Mean croup score at 20 minutes.

Analysis 1.3. Comparison 1 Heliox versus humidified 30% oxygen, Outcome 3 Mean respiratory rate at 20 minutes.

Analysis 1.4. Comparison 1 Heliox versus humidified 30% oxygen, Outcome 4 Mean oxygen saturation at 20 minutes.

Analysis 1.5. Comparison 1 Heliox versus humidified 30% oxygen, Outcome 5 Mean heart rate at 20 minutes.

Comparison 2. Heliox versus placebo or no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in croup score at 60 minutes	1	47	Mean Difference (IV, Fixed, 95% CI)	-1.1 [-1.96, -0.24]
2 Change in croup score at 120 minutes	1	47	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-1.56, 0.16]
3 Mean Taussig croup score at 60 minutes	1	47	Mean Difference (IV, Fixed, 95% CI)	-1.11 [-2.05, -0.17]
4 Mean Taussig croup score at 120 minutes	1	47	Mean Difference (IV, Fixed, 95% CI)	-0.71 [-1.72, 0.30]
5 Mean respiratory rate at 60 minutes	1	47	Mean Difference (IV, Fixed, 95% CI)	-4.94 [-9.66, -0.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Mean respiratory rate at 120 minutes	1	47	Mean Difference (IV, Fixed, 95% CI)	-3.17 [-7.83, 1.49]
7 Proportion of children hospitalised	1	47	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.04, 5.41]
8 Proportion of re-presentations to emergency department	1	47	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.12, 7.41]
9 Need for rescue adrenaline	1	47	Odds Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.46]

Analysis 2.1. Comparison 2 Heliox versus placebo or no treatment, Outcome 1 Change in croup score at 60 minutes.

Analysis 2.2. Comparison 2 Heliox versus placebo or no treatment, Outcome 2 Change in croup score at 120 minutes.

Analysis 2.3. Comparison 2 Heliox versus placebo or no treatment, Outcome 3 Mean Taussig croup score at 60 minutes.

Analysis 2.4. Comparison 2 Heliox versus placebo or no treatment, Outcome 4 Mean Taussig croup score at 120 minutes.

Analysis 2.5. Comparison 2 Heliox versus placebo or no treatment, Outcome 5 Mean respiratory rate at 60 minutes.

Analysis 2.6. Comparison 2 Heliox versus placebo or no treatment, Outcome 6 Mean respiratory rate at 120 minutes.

Analysis 2.7. Comparison 2 Heliox versus placebo or no treatment, Outcome 7 Proportion of children hospitalised.

Analysis 2.8. Comparison 2 Heliox versus placebo or no treatment, Outcome 8 Proportion of re-presentations to emergency department.

Analysis 2.9. Comparison 2 Heliox versus placebo or no treatment, Outcome 9 Need for rescue adrenaline.

ADDITIONAL TABLES

Table 1. Additional analyses for heliox compared to 30% oxygen for croup in children

Additional analyses for heliox compared to 30% oxygen for croup in children					
Patient or population: children with croup					
Setting: emergency department					
Intervention: heliox					
Comparison: 30% oxygen					
Outcomes	Anticipated absolute ef- fects* (95% CI)	Relative effect (95% CI)	Nº of par- ticipants (studies)	Quality of the evi- dence	Comments

Table 1. Additional analyses for heliox compared to 30% oxygen for croup in children (Continued)

	30% oxygen	Heliox			(GRADE)	
Change in croup score	The mean change in croup score was 1.42 lower (SD 1.27).	MD 0.83 lower (2.36 lower to 0.7 higher)	-	15 (1 RCT)	⊕⊕⊕⊕ LOW ¹	Terregino 1998 used a modified Westley croup score; scale range: 0 to 16.
Mean croup score at 20 minutes	The mean croup score at 20 minutes was 1.57 (SD 0.97).	MD 0.57 lower (1.46 lower to 0.32 higher)	-	15 (1 RCT)	⊕⊕⊕⊕ LOW ¹	Terregino 1998 used a modified Westley croup score; scale range: 0 to 16.
Mean respiratory rate at 20 minutes	The mean respiratory rate at 20 minutes was 27.4 (SD 5.6).	MD 6.4 higher (1.38 lower to 14.18 higher)	-	15 (1 RCT)	⊕⊕⊕⊕ LOW ¹	Terregino 1998 did not report change in respiratory rate between pre- and postintervention, therefore we have reported the mean respiratory rate at endpoint 20 minutes. Reported respiratory rate range: 25.4 to 37.5 breaths/min
Mean heart rate at 20 minutes	The mean heart rate at 20 minutes was 137.9 (SD 12.2).	MD 14.5 higher (8.49 lower to 37.49 higher)	-	15 (1 RCT)	⊕⊕⊕⊕ LOW ¹	Terregino 1998 did not report change in heart rate between pre- and postintervention, therefore we have reported the mean heart rate at endpoint 20 minutes. Reported heart rate range: 137.4 to 158.1 beats/min
Proportion and duration of hospitalisation	-	-	-	-	-	Terregino 1998 reported that all children were discharged.
Proportion and duration of intubation - not reported	-	-	-	-	-	Terregino 1998 reported that no child required administration of racemic epinephrine and that there were no complications. Proportion of children intubated was not reported.
Proportion of children representing for medical care for ongoing croup symptoms - not reported	-	-	-	-	-	
Adverse events - not reported	-	-	-	-	-	Terregino 1998 reported that there were no complications.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RCT:** randomised controlled trial; **SD:** standard deviation

GRADE Working Group grades of evidence

Heliox for croup in children (Review)

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Table 1. Additional analyses for heliox compared to 30% oxygen for croup in children (Continued)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

¹We downgraded the evidence two levels due to the very small numbers of participants.

Table 2. Additional analyses for heliox compared to placebo or no treatment for croup in children

Additional analyses for heliox compared to placebo or no treatment for croup in children

Patient or population: children with croup

Setting: emergency department

Intervention: heliox

Comparison: placebo or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Quality of the evidence (GRADE)	Comments
	Placebo or no treatment	Heliox				
Change in croup score at 60 minutes	The mean change in croup score at 60 minutes was 2.48 lower (SD 1.49).	MD 1.1 lower (1.96 lower to 0.24 lower)	-	47 (1 RCT)	⊕⊕⊕⊕ LOW 1 2	Pardillo 2009 used a modified Taussig croup score; scale range 0 to 15. This outcome refers to change in scores from pre- to postintervention.
Change in croup score at 120 minutes	The mean change in croup score at 120 minutes was 4.05 lower (SD 1.49).	MD 0.7 lower (1.56 lower to 0.16 higher)	-	47 (1 RCT)	⊕⊕⊕⊕ LOW 1 2	Pardillo 2009 used the Taussig croup score; scale range 0 to 15. This outcome refers to change in scores from pre- to postintervention.
Mean croup score at 60 minutes	The mean croup score at 60 minutes was 3.74 (SD 1.6).	MD 1.11 lower (2.05 lower to 0.17 lower)	-	47 (1 RCT)	⊕⊕⊕⊕ LOW 1 2	Pardillo 2009 used the Taussig croup score; scale range 0 to 15. This outcome refers to the mean scores at 60 minutes postintervention.
Mean croup score at 120 minutes	The mean croup score at 120 minutes was 2.17 (SD 2.16).	MD 0.71 lower (1.72 lower to 0.3 higher)	-	47 (1 RCT)	⊕⊕⊕⊕ LOW 1 2	Pardillo 2009 used the Taussig croup score; scale range 0 to 15. This outcome refers to the mean scores at 120 minutes postintervention.
Mean respiratory rate at 60 minutes	The mean respiratory rate at 60 minutes was 35.61 (SD 9.15).	MD 4.94 lower (9.66 lower to 0.22 lower)	-	47 (1 RCT)	⊕⊕⊕⊕ LOW 1 2	Pardillo 2009 did not report change in respiratory rate between pre- and postintervention, therefore we have reported the mean respiratory rate at endpoint 60 minutes. Reported range of respiratory rate: 30.67 to 39.13 breaths/min

Table 2. Additional analyses for heliox compared to placebo or no treatment for croup in children (Continued)

Proportion of children hospitalised	Study population		OR 0.46 (0.04 to 5.41)	47 (1 RCT)	⊕⊕○○ LOW ^{1 2}	This outcome is only reported as number of children hospitalised. 1 child in the heliox group and 2 children in the control group were admitted to hospital (Pardillo 2009). Duration of hospitalisation was not reported.
	87 per 1000	42 per 1000 (4 to 340)				
Adverse events - not reported	-	-	-	-	-	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RCT:** randomised controlled trial; **SD:** standard deviation

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

¹We downgraded the evidence one level due to the open-label design of the study.

²We downgraded the evidence one level due to the small number of participants.

APPENDICES

Appendix 1. Details of previous search

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library 2013, Issue 10), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (1950 to October week 5 2013); Embase (1974 to November 2013); and CINAHL (1982 to November 2013).

We searched MEDLINE and CENTRAL using the following terms. The search terms were adapted for Embase and CINAHL.

MEDLINE (Ovid)

- 1 exp Croup/
- 2 laryngotracheit*.mp.
- 3 laryngotracheo*.mp.
- 4 "laryngo tracheo bronchit*".mp.
- 5 croup.mp.
- 6 helium.mp.
- 7 heliox.mp.
- 8 "he-O2".mp.
- 9 heO2.mp.
- 10 "he O2".mp.
- 11 exp Helium/
- 12 "young adult".mp.
- 13 (infant* or baby or babies or newborn* or paediatric* or pediatric* or child* or teen* or neonat* or adolescen*).mp.
- 14 1 or 2 or 3 or 4 or 5
- 15 6 or 7 or 8 or 9 or 10 or 11
- 16 12 or 13
- 17 14 and 15 and 16

Embase (Ovid) 1980 to November 2013

```

1 exp Croup/
2 croup.mp.
3 laryngotracheit*.mp.
4 "laryngo tracheo bronchit*".mp.
5 laryngotracheo*.mp.
6 exp Helium/
7 exp Heliox/
8 helium.mp.
9 heliox.mpl
10 "He-O2".mp.
11 HeO2.mp.
12 "young adult*".mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (31526)
13 (infant* or baby or babies or newborn* or paediatric* or pediatric* or child* or teen* or neonat* or adolescen*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1308855)
14 1 or 2 or 3 or 4 or 5
15 6 or 7 or 8 or 9 or 10 or 11
16 12 or 13
17 14 and 15 and 16

```

CINAHL (NHS Healthcare Databases Advanced Search) 1981 to November 2013

```

1. CROUP/
2. laryngotracheo*.af.
3. croup.af.
4. laryngotracheit*.af.
5. "laryngo trachea bronchit*".af.
6. HELIUM/
7. helium.af.
8. heliox.af.
9. "he-O2".af.
10. "he O2".af.
11. heO2.af.
12. (infant* OR baby OR babies OR newborn* OR pediatric* OR paediatric* OR child* OR teen* OR neonat* OR adolescen*).af.
13. "young adult*".af.
14. 1 OR 2 OR 3 OR 4 OR 5
15. 6 OR 7 OR 8 OR 9 OR 10 OR 11
16. 12 OR 13
17. 14 AND 15 AND 16

```

Appendix 2. MEDLINE (Ovid) search strategy

```

1 Croup/
2 croup.tw.
3 laryngotracheit*.tw.
4 laryngotracheo*.tw.
5 laryngo tracheo bronchit*.tw.
6 Parainfluenza Virus 2, Human/ or parainfluenza virus 1, human/ or parainfluenza virus 3, human/
7 parainfluenza*.tw.
8 or/1-7
9 Helium/
10 helium*.tw,nm.
11 heliox.tw,nm.
12 (heo2 or he-o2 or he o2).tw,nm.
13 or/9-12
14 8 and 13

```

Appendix 3. Embase (Elsevier) search strategy

```

#13 #7 AND #12
#12 #8 OR #9 OR #10 OR #11
#11 heo2:ab,ti OR 'he-o2':ab,ti OR 'he o2':ab,ti

```

```
#10 helium*:ab,ti OR heliox:ab,ti
#9 'heliox'/de
#8 'helium'/de
#7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
#6 parainfluenza*:ab,ti
#5 'parainfluenza virus 1'/de OR 'parainfluenza virus 2'/de OR 'parainfluenza virus'/de
#4 laryngotracheo*:ab,ti OR laryngotracheit*:ab,ti OR 'laryngo tracheo bronchitis':ab,ti OR 'laryngo-tracheo-bronchitis':ab,ti
#3 'laryngotracheobronchitis'/de
#2 croup:ab,ti
#1 'croup'/de
```

Appendix 4. CINAHL (EBSCO) search strategy

```
S11 S4 and S10
S10 S5 or S6 or S7 or S8 or S9
S9 TI helium N1 oxygen OR AB helium N1 oxygen
S8 TI ( heo2 or "he o2" or "he-o2" ) OR AB ( heo2 or "he o2" or "he-o2" )
S7 TI heliox OR AB heliox
S6 TI helium* OR AB helium*
S5 (MH "Helium")
S4 S1 or S2 or S3
S3 TI (laryngotracheit* or laryngotracheo* or "laryngo tracheo bronchitis" or "laryngo-tracheo-bronchitis") OR AB (laryngotracheit* or laryngotracheo* or "laryngo tracheo bronchitis" or "laryngo-tracheo-bronchitis")
S2 TI croup OR AB croup OR TI parainfluenza* OR AB parainfluenza*
S1 (MH "Croup")
```

Appendix 5. Web of Science (Clarivate Analytics) search strategy

Topic=(croup or laryngotracheit* or laryngotracheo* or laryngotracheobronchit* or laryngo-tracheo-bronchit* or parainfluenza*) AND Topic=(helium* or heliox or heo2 or he-o2 or "he o2")

Time span = All Years. Databases = SCI-EXPANDED, CPCI-S.

Appendix 6. LILACS (BIREME) search strategy

(mh:croup OR croup OR crup OR crupe OR mh:"Parainfluenza Virus 1, Human" OR mh:"Parainfluenza Virus 2, Human" OR mh:"Parainfluenza Virus 3, Human" OR parainfluenza* OR laryngotracheobronchit* OR laryngotracheit* OR "laryngo tracheo bronchitis" OR "laryngo-tracheo-bronchitis" OR "Virus de la Laringotraqueobronquitis Aguda" OR "Virus Crup-Asociado" OR "Virus da Laringotraqueobronquite Aguda" OR "Virus Asociado a Crupe") AND (mh:helium OR helium* OR helio OR hélio OR heliox OR heo2 OR "he o2" OR "he-o2") AND db:(LILACS)

WHAT'S NEW

Date	Event	Description
8 February 2018	New citation required but conclusions have not changed	'Summary of findings' tables added and integrated into the text of the review. Conclusions remain unchanged.
8 February 2018	New search has been performed	Searches updated. We did not identify any new trials for inclusion.

HISTORY

Protocol first published: Issue 4, 2007
Review first published: Issue 2, 2010

Date	Event	Description
12 November 2013	New citation required and conclusions have changed	One new trial added to the evidence in favour of using heliox in children with moderate to severe croup.
12 November 2013	New search has been performed	Updated searches
7 September 2012	Amended	Withdrawn
8 July 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

This review is based on the withdrawn review by C Vorwerk and TJ Coats ([Vorwerk 2010](#)). The current author team updated the searches and made considerable changes to the text.

IM led the review team. IM and NS drafted the review; MLVD provided methodological support; and TM provided content expertise. All authors contributed to the draft and interpretation of the findings and to the writing of the review and approved the final version of the review.

DECLARATIONS OF INTEREST

Irene Moraa: None known.

Nancy Sturman: None known.

Treasure M McGuire: None known.

Mieke L van Driel: None known.

SOURCES OF SUPPORT

Internal sources

- Funding, Other.

None

External sources

- Funding, Other.

None

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added a GRADE assessment of outcomes and 'Summary of findings' tables for the 2018 update, consistent with current Cochrane methods and reporting requirements. For the primary outcome of change in croup score, we have presented the data in two ways: change in the score pre- and postintervention, and the score at endpoints. For the secondary outcomes, three outcomes had rate and duration combined as one outcome. We have now separated and relabeled these outcomes as proportion of children (previously rate), while duration remains as duration. The number of secondary outcomes has therefore increased to 13 from 10 in the previous review.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [therapeutic use]; Airway Obstruction [etiology] [*therapy]; Airway Resistance [drug effects]; Bronchodilator Agents [therapeutic use]; Croup [*complications]; Dexamethasone [therapeutic use]; Epinephrine [therapeutic use]; Helium [*administration & dosage]; Oxygen [*administration & dosage]; Oxygen Inhalation Therapy [methods]; Randomized Controlled Trials as Topic

MeSH check words

Child, Preschool; Humans; Infant