Heliox Therapy in Bronchiolitis: Phase III Multicenter Double-Blind Randomized Controlled Trial

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ABSTRACT

Determination of the therapeutic role of Heliox in bronchiolitis remains a mainstay of therapy in bronchiolitis. Earlier studies suggest that helium-oxygen therapy may be beneficial, but evidence is limited. We aimed to compare efficacy of 2 treatment gases, Heliox and Airox (21% oxygen + 79% helium or nitrogen, respectively), on length of hospital treatment for bronchiolitis.

METHODS: This was a multicenter randomized blinded controlled trial of 319 bronchiolitic infant subjects randomly assigned to either gas; 281 subjects completed the study (140 Heliox, 141 Airox), whose data was analyzed. Treatment was delivered via facemask (nasal cannula, if the facemask intolerant) ± continuous positive airway pressure (CPAP). Severe bronchiolitics received CPAP from the start. Primary end point was length of treatment (LoT) required to alleviate hypoxia and respiratory distress. Secondary end points were proportion of subjects needing CPAP; CPAP (LoT); and change in respiratory distress score.

RESULTS: Analysis by intention to treat (all subjects); median LoT (interquartile range, days): Heliox 1.90 (1.08–3.17), Airox 1.87 (1.11–3.34), P = .41. Facemask tolerant subgroup: Heliox 1.46 (0.85–1.95), Airox 2.01 (0.93–2.86), P = .03. Nasal cannula subgroup: Heliox 2.51 (1.21–4.32), Airox 2.81 (1.45–4.78), P = .53. Subgroup started on CPAP: Heliox 1.55 (1.38–2.01), Airox 2.26 (1.84–2.73), P = .02. Proportion of subjects needing CPAP: Heliox 17%, Airox 19%, O.R. 0.87 (0.47–1.60), P = .76. Heliox reduced respiratory distress score after 8 hours (mixed models estimate, 0.1298; P < .001). The effect was greater for facemask than nasal cannula (mixed models estimate, 0.085; P = .04).

CONCLUSIONS: Heliox therapy does not reduce LoT unless given via a tight-fitting facemask or CPAP. Nasal cannula heliox therapy is ineffective. Pediatrics 2013;131:661–669

WHAT’S KNOWN ON THIS SUBJECT: Bronchiolitis, a leading cause of infant hospitalization, has few proven treatments. A few small studies have reported the beneficial effects of a mixture of 21% oxygen + 79% helium (Heliox). The 2010 Cochrane Review concluded that additional large randomized controlled trials were needed to determine the therapeutic role of Heliox in bronchiolitis.

WHAT THIS STUDY ADDS: The Bronchiolitis Randomized Controlled Trial Emergency-Assisted Therapy with Heliox—An Evaluation (BREATHE) trial is the largest multicenter randomized controlled trial to date to investigate the efficacy of Heliox in acute bronchiolitis. The delivery method for Heliox therapy was found to be crucial to its efficacy.
Acute viral bronchiolitis is a leading cause of infant hospitalization, with a rising incidence and health-economic burden in developed countries. In the United States, ∼75,000 respiratory syncytial virus (RSV)-positive bronchiolitic infants are hospitalized each year. Stang et al estimated the annual cost burden of this to be between US$385 and $585 million. Although there are many treatments, few have a strong evidence base or have demonstrated a reduced length of hospital stay or need for respiratory support, with oxygen being the mainstay of therapy. A mixture of 21% oxygen + 79% helium (Heliox) is lighter than air or oxygen, promoting laminar flow in areas of turbulence or airway narrowing and thus may improve respiratory distress and wheezing. Heliox also reduces respiratory system resistance, has a higher binary diffusion coefficient for CO2 and O2 and therefore may enhance alveolar gas exchange and lung recruitment, and is an inert gas with an excellent safety profile. Heliox may therefore be a useful therapy in bronchiolitis that is associated with small airway inflammation causing increased respiratory system resistance and increased work of breathing. Since 1996 when Paret et al successfully treated a bronchiolitic infant in respiratory failure with Heliox, 9 studies (combined total of 172 infants) have investigated Heliox treatment in bronchiolitis. Six of these studies reported various clinical benefits, including improvement of hypercapnea and respiratory distress. These studies had small sample sizes, used different delivery methods for Heliox, and were not always blinded, and only 1 study assessed the effect of Heliox on length of treatment (LoT) or hospital stay. Furthermore, regardless of clinical efficacy, heliox must be cost-effective. The cost of a single bed day on a pediatric ward is $1947. Even reducing the hospital LoT by 0.5 days would save $974, which is equivalent to 14 cylinders of Heliox at a cost of $70 each. In our experience, only 3 to 5 cylinders per day are consumed during Heliox therapy, thus supporting our hypothesis that Heliox may be cost-effective if it reduces duration of hospital treatment. The 2010 Cochrane Review concluded that additional large randomized controlled trials (RCTs) were needed to investigate the delivery system for Heliox and determine its therapeutic role in bronchiolitis. We therefore report the largest phase III RCT, called Bronchiolitis Randomized Controlled Trial Emergency-Assisted Therapy with Heliox—An Evaluation (BREATHE). Results of this work have been previously published as an abstract.

**METHODS**

**Setting**

A prospective, double-blind RCT was carried out in the bronchiolitis seasons during 2005 to 2008 across 4 centers in the United Kingdom and Australia.

**Participants**

Pediatricians in the emergency departments or pediatric wards of participating hospitals, independent of the BREATHE study, assessed infants (or 12-month corrected age if premature). They clinically determined if the infants had a diagnosis of bronchiolitis (history of upper respiratory tract infection followed by wheezing, coughing, breathing difficulty, or chest crackles on auscultation) and if they needed hospitalization for respiratory distress or hypoxia (percutaneous oxygen saturation [SpO2] < 93% in room air). Exclusion criteria were as follows: imminent intubation; SpO2 < 93% despite 15 L/minute O2 via nonrebreathing facemask (FM); tracheostomy; participation in another study in the previous 4 weeks; salbutamol, epinephrine, or ipratropium therapy within 1 hour or systemic steroids within 4 hours of entry into the study; and bronchiolitis readmission within 24 hours of exit from BREATHE. An independent data committee monitored safe conduct throughout the study. The trial was registered internationally and had independent ethics committee approval.

**Interventions**

Heliox or a mixture of 21% oxygen + 79% nitrogen (Airox), labeled as gas A or B, was the treatment or control intervention with additional oxygen titrated via Y-connection tubing, resulting in 2 gas mixes: A or B ± additional oxygen. Gas delivery was by a tight-fitting 3-valve, nonrebreathing facemask (FM; 1192; Intersurgical) or a nasal cannula (NC; BC 2745-20; Fisher & Paykel Healthcare) if the subject was FM intolerant. Gas A or B drove the continuous positive airway pressure (CPAP) device (EME infant flow driver; CareFusion).

**Outcome Measures**

The primary end point was the total LoT to alleviate hypoxia (SpO2 ≥ 93% in room air) and respiratory distress (minimal work of breathing). LoT was calculated from the start to successful stop of the trial gas, as defined by clinical stability (minimal work of breathing and SpO2 ≥ 93%) for 1 hour breathing room air. Minimal work of breathing was qualified as having a normal respiratory rate, no cyanosis, no nasal flaring, no tracheal tug or grunting, no head bobbing, and no use of accessory muscles except for mild intercostal recessions. Secondary end points were proportion of each treatment group needing CPAP and the change in respiratory distress over time measured by the Modified Wood’s Clinical Asthma Score (Table 1). We used a scoring tool to assess change in respiratory distress over time, similar to that used in previous heliox studies. The scoring tool was a modified version of the original Wood’s Clinical Asthma Score.
TABLE 1 Modified Wood’s Clinical Asthma Score

<table>
<thead>
<tr>
<th>SCORE</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulse oximetry</td>
<td>SpO₂ &gt; 93%: Room Air</td>
<td>SpO₂ &lt; 94%: Room Air</td>
<td>SpO₂ &lt; 94%: 40% FiO₂</td>
</tr>
<tr>
<td>Accessory muscle use</td>
<td>NONE of:</td>
<td>ANY one of:</td>
<td>ALL four of:</td>
</tr>
<tr>
<td></td>
<td>• Recessions</td>
<td>• Recessions</td>
<td>• Recessions</td>
</tr>
<tr>
<td></td>
<td>• Head bobbing</td>
<td>• Head bobbing</td>
<td>• Head bobbing</td>
</tr>
<tr>
<td></td>
<td>• Nasal flaring</td>
<td>• Nasal flaring</td>
<td>• Nasal flaring</td>
</tr>
<tr>
<td></td>
<td>• Tracheal tug</td>
<td>• Tracheal tug</td>
<td>• Tracheal tug</td>
</tr>
<tr>
<td>Cyanosis</td>
<td>No</td>
<td>Yes – In room air</td>
<td>Yes – In 40% FiO₂</td>
</tr>
<tr>
<td>Cerebral function</td>
<td>Normal</td>
<td>Depressed or Agitated</td>
<td>Coma</td>
</tr>
<tr>
<td>Breath sounds</td>
<td>Normal</td>
<td>Unequal</td>
<td>Decreased or absent</td>
</tr>
<tr>
<td>Expiratory wheezing</td>
<td>None</td>
<td>Yes</td>
<td></td>
</tr>
</tbody>
</table>

Maximum score = 11.

At each assessment period, the type of delivery (FM or NC) and FM tolerance was prospectively recorded on the trial clinical report forms to allow analysis of LoT in the FM and NC subgroups. We also recorded the duration of CPAP therapy (CPAP LoT) in a group of severe bronchiolitic subjects who were commenced on CPAP from the beginning of treatment to compare the impact of Heliox versus Airox on duration of CPAP. Management of bronchiolitis was standardized to a strict protocol across trial centers: gas A or B ± oxygen humidified via MR850 (Fisher & Paykel Healthcare), minimal handling, attention to hydration status, and careful airway toilet/suction. Intravenous fluids were preferred over nasogastric feeding in subjects with severe respiratory distress. Bronchodilator, epinephrine, or steroid use constituted protocol violations. A team of BREATHE trial nurses ensured adherence to these standards and the trial protocol. The BREATHE treatment protocol is shown in Fig 1. Subjects had FM therapy for 30 minutes. If they were FM intolerant, the NC protocol was used. If subjects were hypoxic despite FM/NC, the CPAP protocol was started. FM tolerance was recorded at each assessment period, and FM tolerance was strictly defined as mask on all of the time except for oronasal suction and feeding. FM intolerance was defined as increasing agitation, distress, shaking head from side to side, and pulling the FM off the face for 30 minutes. NC was started in subjects who remained FM intolerant for 30 minutes. The optimum flow rate for trial gas was based on titration against oxygen to achieve SpO₂ ≥ 93% using the minimum flow of additional oxygen. For FM therapy, the maximum combined flow rate (gas A/B + oxygen) was 10 L/minute and for NC therapy it was 3 L/minute based on consensus of practice. CPAP was started if subjects were hypoxic (SpO₂ < 93%) despite oxygen >4 L/minute via FM or >2 L/minute via NC. CPAP was discontinued once subjects were weaned to 1 to 2 cmH₂O pressure and were no longer hypoxic in fraction of inspired oxygen (FiO₂) < 0.4 for 1 hour. CPAP failure was defined as hypoxia (SpO₂ < 93%) despite 9 cmH₂O pressure and FiO₂ 0.6, whereupon subjects exited the trial. Those subjects with severe bronchiolitis at presentation, who required immediate commencement of CPAP driven by gas A or B, followed the CPAP protocol (Fig 1).

Sample Size

Sample size calculation (using nQuery Advisor v4.0) was based on an unpaired t test with 80% power for a 2-sided α of 5% to detect a 0.75-day LoT reduction. A baseline mean LoT for bronchiolitis of 2.7 days (SD = 2.3 days) was assumed. The calculation showed that 298 subjects would be needed to achieve a 0.75-day LoT reduction in a center that treats 100 infants would save 75 bed-days and was considered a positive impact on health economics.

Randomization and Blinding

After written informed consent was obtained from parents, patients were enrolled and allocated to Gas A or B by telephone using computer-stratified block-randomization. Parents/legal guardians and clinical/study personnel were blinded to randomization sequence and allocation. Randomization codes remained secure until the end of the trial. For blinding, identical cylinders marked Gas A or B and identical equipment and connections were used. The CPAP oxygen dial was blanked off and FiO₂ was regulated by the LED display. The air inlet to the CPAP device was modified to deliver Gas A or B using identical connectors.

Statistical Methods

The primary endpoint (LoT) was analysed blind, for all subjects, based on intention to treat, in order to determine any difference in LoT between treatment groups known as gas A and gas B. Subgroup LoT data was analyzed for FM, NC subjects and for CPAP subjects who were severe enough to warrant CPAP from the start. The Mann-Whitney test was used to compare LoT between treatment groups (as data was skewed), with results summarized as medians with interquartile ranges.
FIGURE 1
BREATHE treatment protocol.
(IQR). Fisher’s exact test was used to compare proportions progressing to CPAP in the two groups. All analyses were two tailed with an alpha level set at 0.05. STATA 10 and SPSS 17 were used for analysis. Change in respiratory distress over time measured by MWCAS was analyzed for all subjects as well FM and RSV positive (RSV+) subgroups. Mixed Models methodology was used since it takes into account correlated measures (gas type, gender, birth gestation, age, weight, virus status, temperature, heart rate, respiratory rate, SpO2). Due to the nature of the data, the square root transformation of MWCAS was used as the dependant variable for the modelling. The modelling and estimation of the effects of interest was carried out by the PROC MIXED routine in SPSS version 17, with a significance level set at 5%.

RESULTS

Participant Flow, Recruitment, Baseline Characteristics, and Numbers Analyzed

Infants presenting with any respiratory signs or symptoms were screened between the period of 2005 to 2008. A total of 361 patients with clinically diagnosed bronchiolitis were considered for eligibility. Consent was obtained for 319 subjects who were randomized and enrolled into the study. The consort flowchart (Fig 2) shows that 3 subjects were excluded (2 withdrawal of consent and 1 screening failure); therefore, 316 subjects were allocated to treatments. An additional 35 subjects were excluded because of protocol violation, consent withdrawal, screening failure, hospital clinician’s decision, or premature disruption of therapy. Thus,
281 subjects (140 Heliox and 141 Airox) with similar baseline characteristics (Table 2) completed the study, and their data was analyzed. The results are summarized in Table 3. There were no hospital readmissions for subjects who had completed or exited the trial.

**Length of Treatment**

Analysis of data from all 281 subjects showed no difference in median LoT between treatment groups [Heliox 1.90 days (interquartile range 1.08–3.17) compared to Airox 1.87 days (interquartile range 1.11–3.34), \( P = .41 \)]. However, LoT was significantly reduced in favor of Heliox for FM-tolerant subjects [Heliox, 1.46 days (interquartile range 0.85–1.95); Airox, 2.01 days (interquartile range 0.93–2.86) \( P = .03 \)]. A more notable reduction in LoT was seen in RSV+ subjects [Heliox, 1.31 days (interquartile range 0.61–1.91); Airox, 2.18 days (interquartile range 1.40–2.95) \( P = .004 \)]. There was no difference in LoT for NC subjects [Heliox 2.51 days (interquartile range 1.21–4.32), Airox 2.81 days (interquartile range 1.45–4.78) \( P = .53 \)].

**Averting Need for CPAP**

Analysis of data from all 281 subjects showed no reduction in proportion of cases progressing to CPAP [24 of 140 Heliox subjects (17%) vs 27 of 141 Airox subjects (19%); odds ratio 0.87 (0.47–1.60), \( P = .76 \)]. However, for FM-tolerant RSV+ subjects there was a 66% reduction in proportions requiring CPAP in favor of Heliox, at borderline significance [3 of 27 Heliox subjects (11%) vs 10 of 31 Airox subjects (32%); odds ratio 0.26 (0.07–1.02), \( P = .76 \)].

**Impact on CPAP Efficacy**

Heliox significantly reduced median LoT for severe bronchiolitic subjects who were started directly onto CPAP [Heliox 1.55 days (interquartile range 1.38–2.01), Airox 2.26 days (interquartile range 1.84–2.73); \( P = .02 \)].

**Impact on Respiratory Distress**

Heliox reduced respiratory distress in all 281 subjects across all time points and statistically significant at 8 hours onwards. MWCAS (mixed models estimate \( = −0.1298, 95\% \) confidence interval \( = −0.202 \) to \( = −0.057, P < .001 \)). Regardless of gas type, FM was more effective than NC (mixed models estimate \( = 0.093, 95\% \) confidence interval \( = 0.005 \) to 0.181, \( P = .04 \)).

**Adverse Events**

Six subjects required intubation for different reasons. In one case there was CPAP equipment malfunction which precipitated emergency
Heliox shortened the length of hospital stay. Because many other variables can affect the length of hospital stay, we chose to measure total LoT as the primary end point, because it is directly linked to therapy. We found Heliox conferred no benefit over oxygen when delivered by NC at flow rates of ≤3 L/minute. We believe the difference in efficacy between FM and NC is caused by several factors. A tight-fitting FM is used in clinical situations when the highest FiO₂ needs to be delivered with minimal air entrainment. Delivering a high concentration of helium must also be very important for Heliox therapy, and our previous findings also provide support for the statistically significant finding of a 0.75-day reduction in LoT (0.87 day).

The BREATHE study was powered to detect a 0.55-day reduction in LoT; however, the observed 66% reduction only reached borderline statistical significance, which may be because of the relatively small number of CPAP patients (n = 58). Martinon-Torres et al 17 in their Heliox-CPAP study demonstrated a reduction in work of breathing and improved CO₂ clearance. The BREATHE study also enabled assessment of the impact of Heliox on CPAP efficacy. We analyzed data for subjects who were started on CPAP from the beginning of the trial because their pathophysiology had not yet been altered by previous therapy. We found that CPAP duration was significantly reduced if Heliox was the driving gas for CPAP. The numbers of subjects totaled only 21, so we cannot draw any strong conclusions. However, if the finding of reduced treatment time was to be replicated in a larger CPAP study, this would represent a significant health-economic benefit for using Heliox to drive CPAP in cases of severe bronchiolitis.

We did not select patients based on clinical severity but screened consecutive infants presenting with any respiratory signs or symptoms and found 361 patients with clinically diagnosed bronchiolitis. We could not rule out the possibility that some patients may have had asthma. However, any cases of asthma-bronchiolitis overlap would have been balanced out between the 2 treatment groups through the process of randomization. Virus detection from nasopharyngeal aspirate was carried out by the hospitals on 281 of the enrolled patients. We found 227 of 281 (≈80%) were virus positive, with RSV accounting for the vast majority. The centers routinely assayed only for RSV, para-influenza, adenovirus, Flu A/B, and rhinovirus. Therefore, the 80% virus positive rate (Table 2) was most likely an underestimate and we are confident that our clinical selection criteria captured mostly viral bronchiolitis.

The BREATHE study is the largest phase III, multicenter, double-blinded RCT of Heliox in bronchiolitis. It attempted to resolve the challenges of blinding. The use of special hosing material, identical in appearance for Heliox and Airox ensured that there was no difference in sound generation that could have alerted the investigator to identify the study gas. The BREATHE study linked efficacy to the mode of delivery: CPAP or tight-fitting nonrebreathing FM. However, the large number of subjects treated by NC meant that the positive findings in favor of Heliox were limited to only 84 subjects who tolerated the FM. Although the use of the FM was a major limitation of this study...
used a bonnet to allow a tighter-fitting 3-valve, nonrebreathing FM to deliver the highest concentration of oxygen and helium. However, FMs are generally poorly tolerated in young children, and this was also our experience. To maximize FM compliance in their study, Martinón-Torres et al. used swaddling to comfortably restrain subjects with the FM held against the face by soft elasticized tube netting applied over the head. We used a bonnet to allow a tighter-fitting FM and help prevent the elastic band from slipping down, used swaddling, and encouraged staff and mothers to maximize compliance. Despite our best efforts, many subjects did not tolerate the FM, and it proved impossible to apply it continuously. Mask intolerance was highlighted after recruitment of the first few subjects into the trial when we found nursing staff wishing to use an NC, the commonly used mode of oxygen delivery for infants. It was considered unethical to withhold a trial gas treatment if subjects had already started to improve. We therefore considered delivery of trial gas via NC because Williams et al. successfully used NC with Heliox in infants, and oxygen is already conventionally administered via NC. Therefore, NC was included as a protocol amendment for subjects who were FM intolerant.

We prospectively studied a cohort of clinically diagnosed bronchiolitic infants, regardless of severity and viral etiology, enabling us to identify a treatment for bronchiolitis that can be used across different modalities (FM and CPAP) and points of care (emergency department, ward, and PICU). Nonetheless, this approach to recruitment resulted in a smaller proportion of severe cases, making it difficult to conclusively study outcomes such as CPAP. The latter is very important because CPAP compared with standard treatment has been shown to improve ventilation, with a reduction in hypercapnea, with growing consensus that CPAP therapy prevents deterioration and need for mechanical ventilation.

We did not collate data on length of stay but rather focused on length of treatment. The study was powered for the latter because LoT was a clear and definitive endpoint in the disease process.

The BREATHE study was not powered to investigate intubation rates, which would also have been informative. Only 8 of 316 (2.5%) needed intubation. Therefore, a much larger sample size or a moderate number of a more selected severe group of patients would be needed to investigate the impact of Heliox on intubation rates. The BREATHE protocol (part B, not yet carried out) had originally been designed to investigate intubation rate in a more severe subgroup of bronchiolitics (defined as already requiring CPAP). A baseline figure of 35% was assumed for the bronchiolitis intubation rate (defined as CPAP failure) derived from data for our PICU at St Mary’s hospital. The power calculation showed that a total of 86 severe bronchiolitics on CPAP would need to be recruited to detect a reduction in the intubation rate from 35% to 10% with 80% power.

The BREATHE study has highlighted the need to review our approach to respiratory care in general: use of FM has tolerance issues, and NC (at conventional flow rates) has limited efficacy. Although NC delivery of Heliox at flow rates <3 L/minute was ineffective, we theorize that at higher flow rates (tolerated based on our anecdotal experience), Heliox therapy by nasal cannula may be effective. A well-designed RCT comparing 3-valve nonrebreathing FM versus high-flow NC therapy is needed to identify the optimal method of delivery. Furthermore, a sufficiently powered RCT of Heliox-driven versus conventional Airox-driven CPAP would determine whether Heliox reduces the need for mechanical ventilation.

In the meantime, the clinical practice recommendations arising from the BREATHE study findings are as follows:

- Heliox therapy should be started for bronchiolitic infants who require hospital admission for treatment of hypoxemia or respiratory distress.
- If the use of Heliox therapy needs to be rationalized, it could be targeted to those who are RSV positive.
- Heliox therapy should only be delivered via a tight-fitting nonrebreathing FM or CPAP, as per the protocol outlined in the BREATHE study.

CONCLUSIONS

The BREATHE study showed that the delivery method of Heliox is critical to its efficacy. Heliox is effective if delivered via a tight-fitting nonrebreathing FM or CPAP but not via a NC at conventional flow rates. With effective delivery, Heliox reduces the LoT, alleviates respiratory distress, improves CPAP efficacy, and may reduce the need for CPAP. A more acceptable patient interface for effective delivery remains the challenge for industry if Heliox is to be more widely used in pediatric respiratory care.

ACKNOWLEDGMENTS

We thank the patients, families, and nursing, medical, and other healthcare staff across all the hospitals, whose cooperation and support allowed us to undertake the BREATHE trial. We especially thank the BREATHE team members whose meticulous attention to trial conduct ensured the rigor of this study.
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