ARTICLE

Helium-Oxygen Therapy for Infants With Bronchiolitis

A Randomized Controlled Trial

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Objective: To compare nebulized racemic epinephrine delivered by 70% helium and 30% oxygen or 100% oxygen followed by helium-oxygen inhalation therapy via high-flow nasal cannula (HFNC) vs oxygen inhalation via HFNC in the treatment of bronchiolitis.

Design: Prospective, randomized, controlled, single-blind trial.

Setting: This study was conducted from October 1, 2004, through May 31, 2008, in the emergency department of an urban, tertiary care children's hospital.

Patients: Infants aged 2 to 12 months with a Modified Wood's Clinical Asthma Score (M-WCAS) of 3 or higher.

Interventions: Patients initially received nebulized albuterol treatment driven by 100% oxygen. Patients were randomized to the helium-oxygen or oxygen group and received nebulized racemic epinephrine via a face mask. After nebulization, humidified helium-oxygen or oxygen was delivered by HFNC. After 60 minutes of inhalation therapy, patients with an M-WCAS of 2 or higher received a second delivery of nebulized racemic epinephrine followed by helium-oxygen or oxygen delivered by HFNC.

Main Outcome Measure: Degree of improvement of M-WCAS for 240 minutes or until emergency department discharge.

Results: Of 69 infants enrolled, 34 were randomized to the helium-oxygen group and 35 to the oxygen group. The mean change in M-WCAS from baseline to 240 minutes or emergency department discharge was 1.84 for the helium-oxygen group compared with 0.31 for the oxygen group ($P<.001$). The mean M-WCAS was significantly improved for the helium-oxygen group compared with the oxygen group at 60 minutes ($P=.005$), 120 minutes ($P<.001$), 180 minutes ($P<.001$), and 240 minutes ($P<.001$).

Conclusion: Nebulized racemic epinephrine delivered by helium-oxygen followed by helium-oxygen inhalation therapy delivered by HFNC was associated with a greater degree of clinical improvement compared with that delivered by oxygen among infants with bronchiolitis.

Trial Registration: clinicaltrials.gov Identifier: NCT00116584

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ACUTE VIRAL BRONCHIOLitis is the most common lower respiratory tract infection in the first year of life and represents a common cause of visits to the emergency department (ED) in the winter.[1] Despite recent advances in the treatment of patients with bronchiolitis, this disease continues to be associated with significant morbidity and mortality.[2] An estimated 3% to 8% of hospitalized infants develop acute respiratory failure that requires mechanical ventilation.[3] These findings highlight the continued need for new therapies targeting bronchiolitis.

Helium-oxygen inhalation is a reemerging area of interest. It has been used in the treatment of pediatric asthma exacerbations and may also be effective for bronchiolitis.[4,5] Bronchiolitis is characterized by airway obstruction and turbulent gas flow, which may be improved by helium-oxygen because helium-oxygen improves gas flow through high-resistance airways.[6,7] In contrast, many treatments for bronchiolitis have been studied, but there is a lack of evidence endorsing any specific treatment other than supportive care.[8-10]

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The study's objective was to evaluate the effectiveness of helium-oxygen compared with oxygen to deliver nebulized racemic epinephrine and as a component of

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Table 1. Modified Wood's Clinical Asthma Scores (M-WCASs)[a]

Variable	M-WCAS 0	0.5	1	2
Saturated oxygen	≥95% in room air	90%-95% in room air	90%, with F_{IO_2} >0.21	<90%, with F_{IO_2} >0.21
Inspiratory breath sounds	Normal	Slightly unequal	Markedly unequal	Decreased or absent
Expiratory wheezing	None	End expiration	Entire expiration	Inspiratory and expiration
Accessory muscles	None	Mild	Moderate	Maximal
Cerebral function	Normal	Agitated when disturbed	Depressed or agitated	Markedly depressed or coma

	Respiratory Distress Assessment Instrument, No. of Points[b] 0	1	2	3	4	Maximum Points
Wheezing						
Expiration	None	End	1-2	3-4	All	4
Inspiration	None	Part	All	NA	NA	2
Location	None	Segmental ≤2-4 lung fields	Diffuse ≥3-4 lung fields	NA	NA	2
Retractions						
Supraclavicular	None	Mild	Moderate	Marked	NA	3
Intercostal	None	Mild	Moderate	Marked	NA	3
Subcostal	None	Mild	Moderate	Marked	NA	3

Abbreviations: F_{IO_2}, fraction of inspired oxygen; NA, not applicable.
[a] Reproduced with permission from Lowell et al.[12]
[b] Within each variable the subscores are summed to give a total score. The maximum total points is 8 for wheezing and 9 for retractions.

inhalation therapy for infants with bronchiolitis. We hypothesized that infants with clinically significant bronchiolitis treated with helium-oxygen–driven nebulization followed by helium-oxygen inhalation therapy would have more clinical improvement, as assessed by clinical bronchiolitis score, than those who received conventional oxygen-driven nebulization followed by oxygen inhalation therapy.

METHODS

STUDY PARTICIPANTS

This study was conducted from October 1, 2004, through May 31, 2008, in the ED of an urban, tertiary care children's hospital. The institutional review board approved the study. The study was approved by the US Food and Drug Administration. Informed consent was obtained from the parent or guardian.

A convenience sample of infants was enrolled from October 1 through March 31 each year when bronchiolitis had a high incidence. Patients were 2 to 12 months of age with a Modified Wood's Clinical Asthma Score (M-WCAS) of 3 or higher[11] (**Table 1**). A study investigator (K.S.) assessed for the diagnostic criteria for bronchiolitis, which included the following: tachypnea, cough, prolonged expiratory phase, wheezing, rales, chest retractions, and hyperinflation of lungs on chest radiograph. Patients were excluded when any of the following conditions were present: cyanotic heart disease, lobar pneumonia on chest radiograph, croup, foreign body aspiration, preexisting chronic lung disease, underlying chronic medical conditions, supraventricular tachycardia secondary to albuterol or racemic epinephrine administration, intolerance to the use of a nonrebreather face mask, bronchodilator treatment within 2 hours of initiation of the study, use of oral or parenteral corticosteroids within the preceding 72 hours, or history of persistent airway hyperreactivity in the 3 months before the study. We defined persistent airway reactivity based on a parental or guardian history of clinical improvement after nebulized albuterol treatment before the ED visit.

STUDY PROTOCOL

The primary clinical scoring system, M-WCAS, has been previously established by Martinón-Torres et al[4] to be a useful tool for studying helium-oxygen therapy for bronchiolitis. Total scores can range from 0 to 10, with 3 to 10 signifying clinically significant bronchiolitis. Clinical significance was operationally defined based on our observations that infants with an M-WCAS of 3 or higher were being admitted to the hospital during the pilot phase. A clinically significant improvement was defined as a change of 1.5 U or more over time, as was a difference of 1.5 U or more between groups at any point in time.[4,13]

The secondary clinical scoring system, the Respiratory Distress Assessment Instrument (RDAI)[12] (Table 1), has been used extensively. It is one of the most commonly used clinical scores for bronchiolitis,[11] with established internal validity[14] and excellent interobserver reliability.[12,14-17] One advantage of the RDAI is that it does not incorporate supplemental oxygen and pulse oximetry in its scoring system.

A timeline of study flow is illustrated in **Figure 1**. A trial of inhaled β-agonists for patients with bronchiolitis was standard of care in our ED at the time of the study. During this initial albuterol nebulization, a research assistant (K.S.) identified the patient as eligible for enrollment and notified the investigator on call for the study (I.K.K.).

The investigator examined and scored the initial M-WCAS. Patients achieving an initial M-WCAS of 3 or higher and meeting all eligibility criteria were invited to participate. After informed consent, patients were randomly assigned to either the helium-oxygen or oxygen group and placed on a standardized study pathway (Figure 1). Randomization was predetermined using a random number generator and occurred in blocks of 10. Assignments were kept in sealed opaque en-

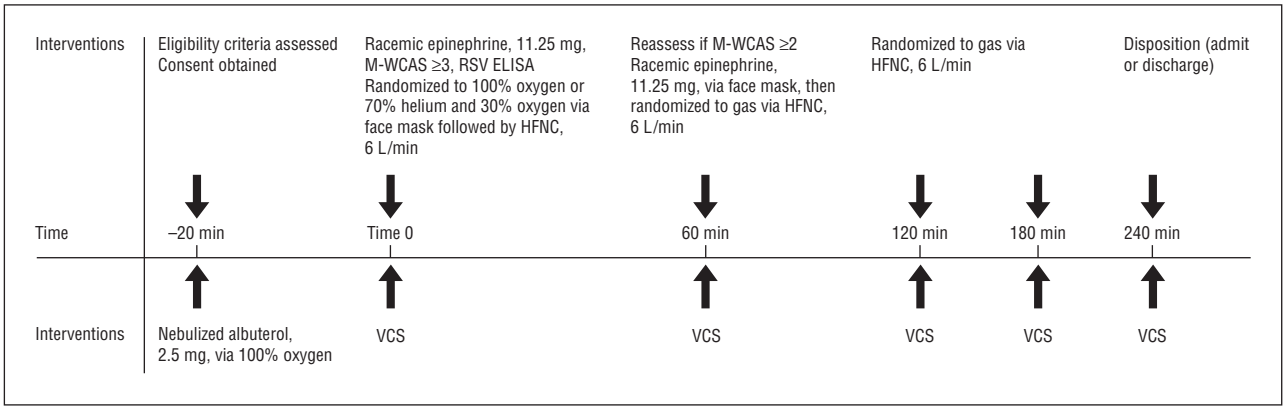


Figure 1. Timeline in the emergency department. ELISA indicates enzyme-linked immunosorbent assay; HFNC, high-flow nasal cannula; M-WCAS, Modified Wood's Clinical Asthma Score; RSV, respiratory syncytial virus; and VCS, videotaped clinical score.

velopes and opened immediately after informed consent by the study investigator.

Helium-oxygen or oxygen mixtures were administered from the nebulizer via a nonrebreathing face mask at 20°C. Helium-oxygen concentrations of 70% helium and 30% oxygen were administered via a 280 regulator (Compressed Gas Association, Chantilly, Virginia) driven by a standardized pressure of 50 pounds per square inch gauge. For nebulization, a small volume nebulizer with helium-oxygen flows of 16 L/min or oxygen flows of 10 L/min was used.[18] For inhalation via high-flow nasal cannula (HFNC), all patients were started at 6 L/min. Patients randomized to the oxygen group were started at a fraction of inspired oxygen of 100%, and patients randomized to the helium-oxygen group were started at 70% helium and 30% oxygen. Helium-oxygen flows were adjusted using a 1.6 correction factor because the flow meters were calibrated to oxygen.[18] The respiratory therapists were unmasked to the type of gas because they controlled and monitored the mixing of gases at the blender.

Similar to other studies during 2005-2006, the Vapotherm system (Vapotherm, Stevensville, Maryland) was used initially for humidified gas delivery until December 31, 2005.[19] Patients were not recruited from January 1, 2006, through September 31, 2006, while safety discussions with the Centers for Disease Control and Prevention were ongoing. Beginning October 1, 2006, the MR850 Humidification System with an MR290 Autofeed Chamber (Fisher & Paykel Healthcare Inc, Irvine, California) was used. This system was introduced because of cost analysis, ease of sterilization, and reports issued by the Centers for Disease Control and Prevention regarding possible Vapotherm system contamination with *Ralstonia* sp. There were no cases of Vapotherm-related infections in our hospital. The Vapotherm and Fisher & Paykel devices, at the time of the study, were approved by the Food and Drug Administration for pediatric use.

Percentages of inspired helium-oxygen were titrated to maintain patient oxygen saturation at 93% or higher. If necessary, patients in the helium-oxygen group were titrated to a maximum of 50% helium and 50% oxygen to maintain patient oxygen saturation at 93% or higher. Those patients who required more than 50% oxygen in the helium-oxygen group were designated as having received failed treatment. In these cases, administration of the helium-oxygen mixtures was stopped and a rescue 100% oxygen therapy was started.

Time zero was the time that helium-oxygen or oxygen was given. Clinical assessments were performed at 0, 60, 120, 180, and 240 minutes. Clinical assessments were completed using a recordable stethoscope (Simulscope II; Cardionics, Webster, Texas) and a mini-DV video camcorder (Panasonic Corp, Osaka, Japan). A standardized auscultory examination covering 4 positions on the anterior and posterior aspects of the chest (8 total) was performed for each time point. A masked scorer (E.P.) later reviewed the videotape and assigned an M-WCAS and RDAI score. A single scorer was used to eliminate interobserver variability.

Before the initiation of the study, the standardized video-recorded M-WCAS assessment was piloted and validated. During the pilot trial, Spearman rank correlations comparing the video-recorded M-WCAS to the coinvestigators' M-WCAS ranged from 0.665 to 0.975. Using intraclass correlation coefficients, observed reliabilities for each of the raters were consistently above 0.70.

Because there is no standard discharge criteria for bronchiolitis, we used the Wainwright "readiness to discharge" tool to determine length of stay: no supplemental oxygen for 10 hours, minimal or no chest retractions, and feeding adequately without the need for intravenous fluids.[20] The inpatient team determined discharge; however, they were masked to the "readiness to discharge" assessment by the study team.

Emergency department discharge was determined by an unmasked pediatric emergency medicine attending physician. Enrolled patients received telephone follow-up at 24 hours and 7 days after hospital discharge using a structured questionnaire. Letters were sent to patients without successful follow-up, and electronic medical records were reviewed for patients with return ED visits or readmissions within 7 days of discharge.

STATISTICAL ANALYSIS

The primary outcome measure was the degree of improvement of M-WCAS for 240 minutes (at 60-minute intervals) or until ED discharge (if <240 minutes). A 240-minute time frame has been shown to be useful to examine the effects of helium-oxygen therapy.[21]

Simple comparisons between groups or categorical variables were made with the χ^2 or Fisher exact test. The Mann-Whitney test was used to compare the mean changes in M-WCAS over time. Two-way analysis of variance was performed for both groups. Groups were compared using unpaired *t* tests or Mann-Whitney tests.

RESULTS

A total of 2836 patients in a convenience sample were screened for enrollment (**Figure 2**). A total of 2580 patients were ineligible due to an M-WCAS lower than 3. Eligibility criteria were met by 256 infants. Of these 256 infants, 187 met exclusion criteria. Of these 187 ex-

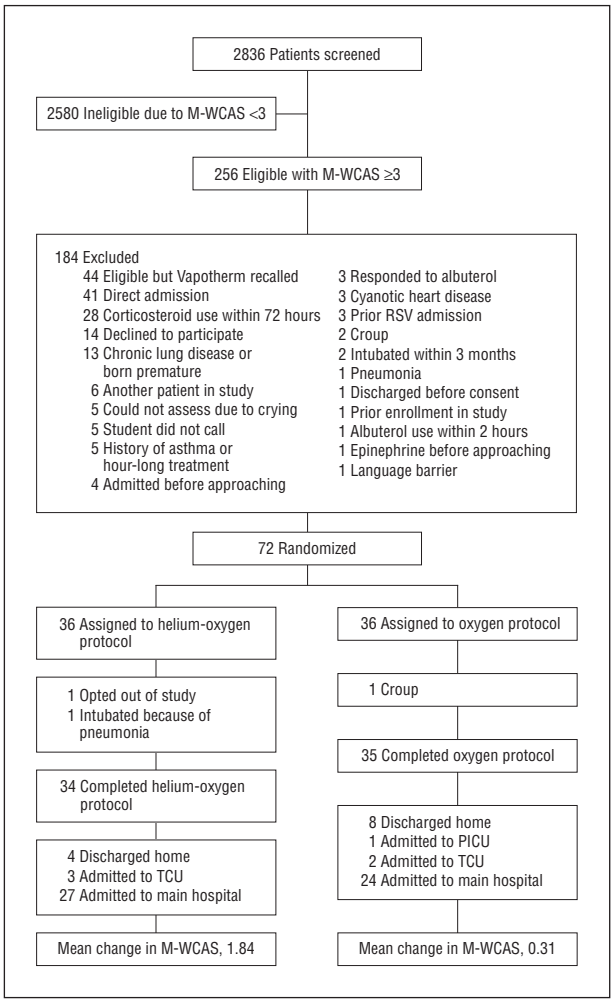


Figure 2. Flowchart of the study patients. M-WCAS indicates Modified Wood's Clinical Asthma Score; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus; and TCU, transitional intermediate intensive care unit.

cluded patients, 141 were excluded for the following criteria: Vapotherm issue (44 patients), direct admission (41 patients), corticosteroid use within 72 hours (28 patients), declined to participate (15 patients), and chronic lung disease (13 patients). The remaining 46 patients met other exclusion criteria. Thirty-four infants completed treatment with helium-oxygen therapy and 35 with oxygen therapy. Treatment failed in 1 patient in the helium-oxygen group who required more than 50% oxygen, helium-oxygen, and intubation. This patient was found to have a lobar pneumonia on chest radiograph after enrollment. There were no reported adverse events.

No significant demographic differences were found between the treatment groups with respect to sex, race, or age (**Table 2**). Duration of clinical symptoms and recent use of β_2-agonist medications were also similar between groups (Table 2). Both groups had equivalent baseline severity of illness by a comparison of initial mean M-WCAS (P=.16). Infants in the oxygen group had chest radiographs ordered more frequently by ED caretakers than infants in the helium-oxygen group (P<.001).

Mean video recorded M-WCASs assessed by the masked investigator in the first 4 hours are shown in

Table 2. Demographics of the Study Patients

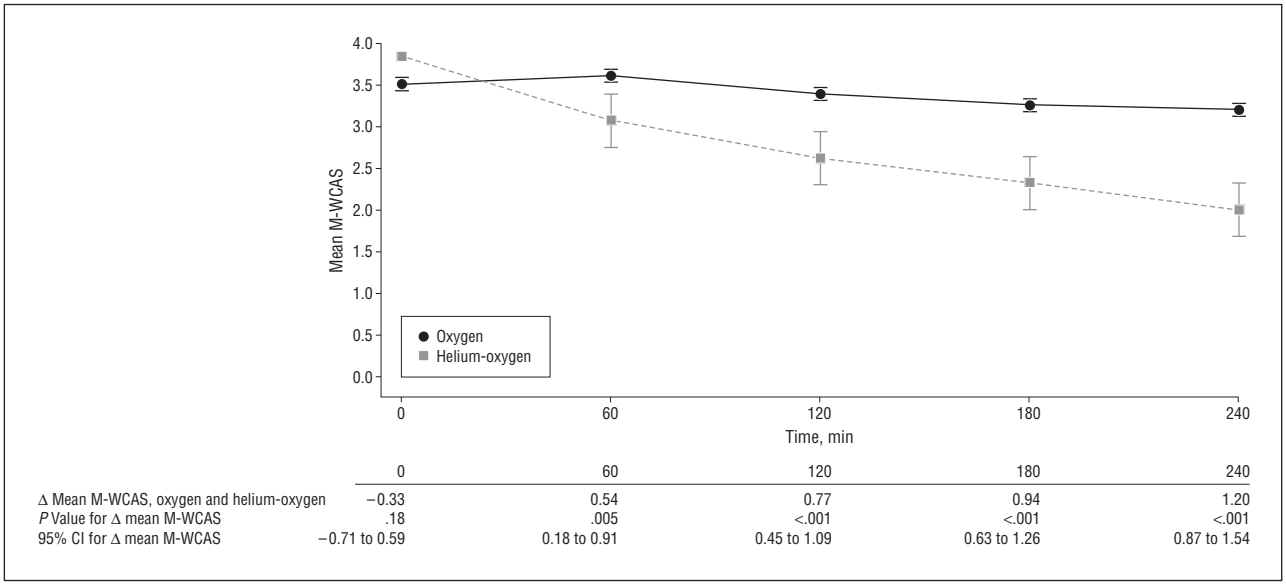
Demographic	Value[a] Helium-Oxygen (n=34)	Oxygen (n=35)
Age, mean, mo	5.09	6.11
Age, median, mo	3.78	5.03
Sex		
Female	11 (32)	11 (31)
Male	23 (68)	24 (69)
Race		
White	15 (44)	25 (71)
African American	15 (44)	8 (23)
Other	4 (12)	2 (6)
Respiratory syncytial virus status		
Negative	11 (32)	18 (51)
Positive	23 (68)	17 (49)
Chest radiography		
Not performed	14 (41)	1 (3)
Performed	20 (59)	34 (97)
Asthma, family history		
No history	17 (50)	18 (51)
History	17 (50)	17 (49)
Atopy, family history		
No history	20 (59)	26 (74)
History	14 (41)	9 (26)
Parental smoking		
No smoking	17 (50)	19 (54)
Smoking	17 (50)	16 (46)
Albuterol use within 24 hours		
No use	23 (68)	21 (60)
Use	11 (32)	14 (40)
Insurance type		
Medicaid	3 (9)	2 (6)
Medicare	20 (59)	19 (54)
Private	10 (29)	13 (37)
Self pay	1 (3)	1 (3)
Duration of symptoms (mean/median), d		
Cough	1.59 (1.50)	2.00 (2.00)
Wheezing	1.03 (1.00)	1.34 (1.00)
Runny nose	1.50 (1.50)	1.91 (2.00)

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

Figure 3. For our primary analysis, the mean change in M-WCAS from baseline to 240 minutes was 1.84 for the helium-oxygen group compared with 0.31 for the oxygen group (P<.001).

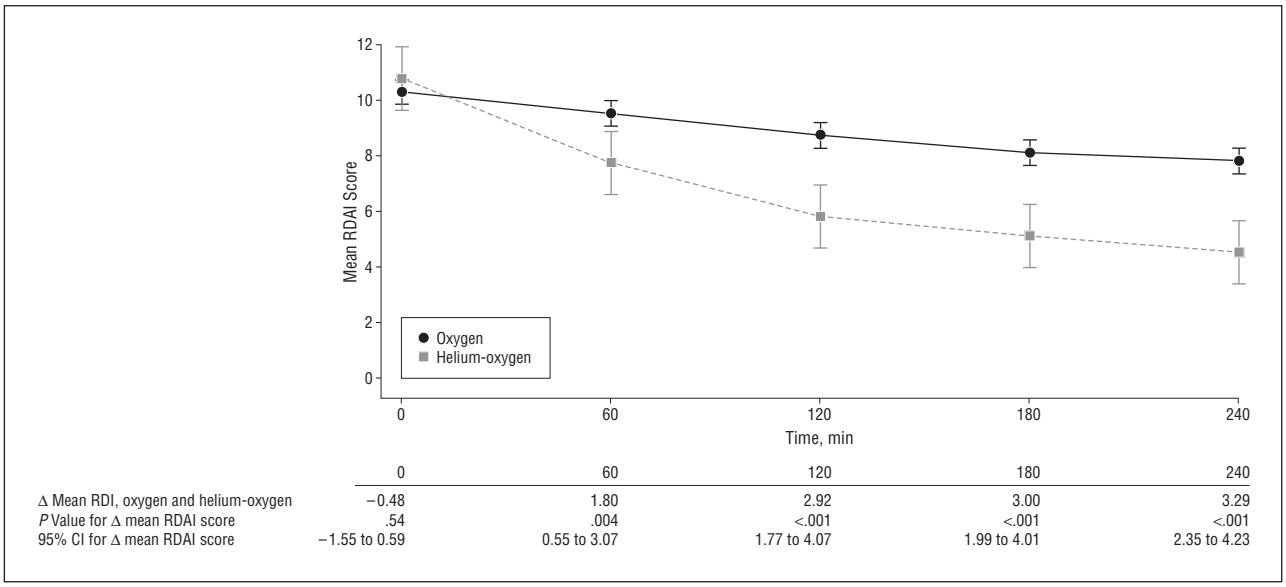
At baseline, the helium-oxygen group's mean M-WCAS was higher by 0.17 than the oxygen group's mean M-WCAS (3.84 vs 3.67, P=.16). Our analysis included this baseline difference. A significant time main effect was found (P<.001), indicating an overall decline across time, and a significant group main effect was found (P<.001), reflecting the overall lower values in the helium-oxygen group. Most important, there was an interaction between group and time, indicating a different pattern of change over time in the 2 groups.

At time 0 the helium-oxygen group was slightly worse (P=.16), but at all subsequent times it was significantly better (P=.005 at 60 minutes, then P<.001 thereafter). The 95% CIs suggest a mean difference of at least 0.5 from 120 minutes onward. At 240 minutes, the absolute mean differences in M-WCAS between groups



	0	60	120	180	240
Δ Mean M-WCAS, oxygen and helium-oxygen	−0.33	0.54	0.77	0.94	1.20
P Value for Δ mean M-WCAS	.18	.005	<.001	<.001	<.001
95% CI for Δ mean M-WCAS	−0.71 to 0.59	0.18 to 0.91	0.45 to 1.09	0.63 to 1.26	0.87 to 1.54

Figure 3. Mean Modified Wood's Clinical Asthma Scores (M-WCASs) vs time.



	0	60	120	180	240
Δ Mean RDI, oxygen and helium-oxygen	−0.48	1.80	2.92	3.00	3.29
P Value for Δ mean RDAI score	.54	.004	<.001	<.001	<.001
95% CI for Δ mean RDAI score	−1.55 to 0.59	0.55 to 3.07	1.77 to 4.07	1.99 to 4.01	2.35 to 4.23

Figure 4. Mean Respiratory Distress Assessment Instrument (RDAI) scores vs time.

was statistically significant of 1.33 ($P<.001$) but did not meet the prespecified clinically significant difference of 1.5.

Mean video-recorded RDAI scores assessed by the masked investigator in the first 4 hours are shown in **Figure 4**. The RDAI scores demonstrated similar findings to M-WCAS on time main effect, group main effect, and interaction between group and time. At 60 minutes, the helium-oxygen group showed a statistically significant absolute mean RDAI compared with the oxygen group ($P=.004$). A statistically significant difference of absolute mean RDAI scores ($P<.001$) was sustained at 120, 180, and 240 minutes. By 120 minutes the mean difference between groups (2.92) was close to our predefined clinically significant cutoff,[3] and this cutoff was exceeded by 180 and 240 minutes.

Twenty-seven patients in the helium-oxygen group (79%) were admitted compared with 24 patients in the oxygen group (69%) ($P=.56$). Three patients in the helium-oxygen group were admitted to a transitional intermediate intensive care unit. Two patients in the oxygen group were admitted to a transitional intermediate intensive care unit and 1 to a pediatric intensive care unit (PICU). No infants admitted to the intensive care unit in either group were intubated.

Mean "readiness to discharge" for admitted patients in the helium-oxygen group was 41.6 vs 43.0 hours for patients in the oxygen group ($P=.87$). After discharge, 1 child in each group returned to the ED. One return patient in the helium-oxygen group was evaluated and discharged from the ED. One return patient in the oxygen group was evaluated and readmitted to the floor. Fifty-nine of 69 patients had successful telephone follow-up.

Ten patients with unsuccessful telephone follow-up had their electronic medical records reviewed, which showed no return ED visits or admissions.

One child in the helium-oxygen group required intubation. This 4-month-old child met exclusion criteria after a chest radiograph determined a lobar pneumonia. As per protocol, we did not record clinical scores because they would not have been accurate in an intubated, paralyzed, and sedated infant. In addition, we did not record "readiness to discharge" criteria for this patient because these criteria were excluded. Most important, no statistical changes were found in length-of-stay outcome measures between groups when an intent-to-treat analysis was performed, including in this child.

COMMENT

Our randomized controlled trial examined helium-oxygen therapy for bronchiolitis in the ED setting. Among a cohort of infants in the ED with bronchiolitis, treatment with helium-oxygen resulted in a statistically significant reduction in M-WCAS and in RDAI scores compared with oxygen treatment at most time points.

The helium-oxygen group scores decreased from baseline more than our prespecified level of clinically significant change in M-WCAS (1.5) by 180 minutes and maintained that decrease at 240 minutes, whereas the oxygen group showed only a slight and irregular decrease during 240 minutes. At no point, however, was the difference between the 2 groups clinically significant ($\geq$1.5). Interestingly, we observed both a statistical and clinical significance between groups using the RDAI.

One possible explanation for these contrasting findings between 2 different scoring systems is the difference in variables. The RDAI does not include pulse oximetry as a variable. In contrast, the M-WCAS includes pulse oximetry. Because most patients were receiving supplemental oxygen during the study with helium-oxygen or oxygen, this variable may have been less discriminating between the 2 groups. As a result, the RDAI may have been able to differentiate a significant change in clinical scores more effectively than the M-WCAS.

Martinón-Torres et al[4] previously demonstrated improved M-WCASs using helium-oxygen inhalation therapy via a face mask in 40 PICU patients with bronchiolitis. A difference in baseline severity of disease between our study (3.84 in the helium-oxygen group) and the study by Martinón-Torres et al (6.68 in the helium-oxygen group) may explain why these investigators observed both statistical and clinically significant differences in M-WCASs between groups, whereas we did not.

This difference in severity of disease on enrollment may also explain the difference in our findings on length of stay. Patients in the study by Martinón-Torres et al were discharged from the PICU 1.9 days earlier than controls and discharged from the hospital more than a day earlier than controls ($P<.05$). Our ED patient population was less severe on enrollment than their PICU infants with impending respiratory failure. As a result, our patients were mostly admitted to the main hospital and not intensive care unit settings.

Similar to the study by Martinón-Torres et al, we observed an M-WCAS plateau of approximately 3 after 60 minutes of therapy. This plateau may reflect that patients have received optimal benefit from helium-oxygen therapy from both HFNC and face mask delivery systems.

Cambonie et al[22] noted that helium-oxygen inhalation therapy benefited young infants (<3 months of age) and premature infants with severe bronchiolitis. Specifically, these authors noted a sharp reduction in accessory muscle use and expiratory wheezing, which is consistent with our clinical score findings. Our RDAI findings are consistent with the findings of these authors. In contrast to the findings of Martinón-Torres et al, Cambonie et al did not find a statistical difference in PICU length of stay. This study, however, was not adequately powered to observe a difference in outcomes between PICU length of stay.

Liet et al[23] led a randomized multicenter trial that also used the approach of Cambonie et al by using a hood to deliver inhalational helium-oxygen in 39 nonintubated patients. In contrast to the findings of Cambonie et al and our findings, no difference in clinical scores was detected. In addition, these authors did not detect a difference in the need for positive pressure ventilation. The hood delivery system, however, may be a suboptimal delivery system of helium-oxygen compared with HFNC or face mask. The lower density of helium-oxygen mixtures allows helium gas to rise and separate from oxygen.[24] As a result, higher levels of helium may be attained at the high point of a hood and lower levels of helium may be present at the bedside level of the patient. Subsequently, patients may breathe lower concentrations of helium. This separation may be one possible explanation between the results of our study and this trial. In addition, any mixing of ambient room air, which can occur with hoods, would result in lower subtherapeutic helium concentrations.

The mechanism of action for helium-oxygen inhalational therapy for bronchiolitis is not clearly defined.[5] Bronchiolitis is characterized by airway obstruction and turbulent gas flow, which could be improved by helium-oxygen because helium-oxygen improves gas flow through high-resistance airways.[6,7] The mechanisms of increased flow rate or less turbulent flow may lead to deeper penetration of gases to distal alveoli.[25,26] Higher minute volumes may be attainable, resulting in improvements in ventilation.[18,25,26] In addition, helium has a high diffusion coefficient for carbon dioxide relative to oxygen. Correspondingly, this diffusion coefficient may allow an environment for increased pulmonary exhalation of trapped carbon dioxide.[27] This lower retained carbon dioxide may decrease stimulation to respiratory centers, leading to decreased work of breathing, dyspnea, and anxiety.

This study found that the administration of helium-oxygen–driven nebulized racemic epinephrine followed by helium-oxygen inhalation by HFNC to infants with bronchiolitis, early in their ED care, resulted in a substantial clinical improvement as indicated by 2 clinical scores. We did not observe a significant statistical difference in "readiness to discharge" between the helium-oxygen and oxygen groups. Although our study lacked adequate power

to evaluate this secondary outcome measure, to our knowledge, it is the largest controlled trial to date.

Our study had several limitations. First, our study was powered to detect a significant and clinically important difference in 2 clinical scores; it was not powered to detect a difference in ED discharge rates or length of stay. Second, we attempted to match the drug output rate from the nebulizers by increasing the helium-oxygen flow rates until the delivery rates were similar to those attained with oxygen. The use of small volume nebulizers likely minimized increased aerosolization by helium-oxygen.[18] No attempt was made to measure or match the size of the aerosols using radionuclide tagging. Differences in aerosol size could potentially cause differences in the deposition patterns of the aerosols. Third, there was a statistical difference in the use of chest radiography between the helium-oxygen and oxygen groups. The ED physicians were unmasked during the ED visit. Therefore, the increased use of chest radiography may reflect a conservative approach to patients treated with oxygen therapy who were not improving clinically. Fourth, clinical scores may have inherent limitations with infants. Improvement with helium-oxygen in infants with bronchiolitis may be influenced by the activity of the infant (sleeping, awake, agitated), which may result in significant changes in the score independent of treatment interventions. Finally, 100% fraction of inspired oxygen via HFNC in the oxygen group may have led to nitrogen washout, atelectasis, and worsening respiratory condition.

Our small investigation demonstrated a statistically and clinically significant short-term improvement in clinical scores among a small group of patients with bronchiolitis compared with controls. These results will require confirmation with an expanded focus on masked short-term clinical outcomes, including ED length of stay, admission rates, and complications. Our findings suggest that helium-oxygen may serve a future role as an adjunct therapy for severe bronchiolitis.

Future studies should focus on defining the role of helium-oxygen inhalation therapy in severe bronchiolitis and better determining optimal helium-oxygen mixtures, nasal continuous positive airway pressures, and delivery systems. From a practical consideration, patients with severe bronchiolitis are a challenging subset of patients to identify early and to study. Larger sample sizes may benefit future clinical trials.

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