A Randomized Comparison of Helium–Oxygen Mixture (Heliox) and Racemic Epinephrine for the Treatment of Moderate to Severe Croup

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ABSTRACT. Objective. To compare the additive effect of a heliox–oxygen mixture (Heliox) or racemic epinephrine (RE) on croup scores (CSs) in children with moderate to severe croup treated with humidified oxygen and steroids.

Design. A prospective, randomized, double-blind trial.

Setting. Emergency department and pediatric intensive care unit of an urban level I trauma center.

Participants. Randomly assigned, consecutive children ages 6 months to 3 years presenting with moderate to severe croup (CS: ≥5).

Interventions. After cool humidified oxygen and 0.6 mg/kg of intramuscular dexamethasone, patients were randomized to receive either Heliox or RE. Vital signs, oxygen saturation, and CSs were recorded at regular intervals.

Outcome/Analysis. Reductions in CSs were compared using repeated-measures analysis of variance.

Results. Thirty-three patients were enrolled. Three were excluded because of protocol violations, and 1 was excluded because of lack of documentation, leaving 29 patients for final analysis. The average age was 24.2 months, 20 were male (68.8%). Both Heliox and RE were associated with improvement in CSs over time. There were no significant differences in mean CS, oxygen saturation, respiratory rate, or heart rate between groups at baseline or at the end of the treatment period.

Conclusion. In patients with moderate to severe croup, the administration of Heliox resulted in similar improvements in CS compared with patients given RE. Pediatrics 2001;107(6). URL: http://www.pediatrics.org/cgi/content/full/107/6/e96; heliox–oxygen mixture, croup.

ABBREVIATIONS. RE, racemic epinephrine; CS, croup score; ED, emergency department.

Laryngotracheobronchitis, or croup, is a common respiratory illness in children. Most cases of croup are mild and require only supportive care with humidified oxygen. However, in moderate to severe cases, aggressive therapy may be necessary to avoid exhaustion and subsequent respiratory failure. Although steroids have gained widespread acceptance as a means of attenuating subglottic edema, racemic epinephrine (RE) has long been considered the mainstay of acute therapy for moderate to severe croup.1

Helium is a biologically inert gas that possesses a very low specific gravity (density) and is one third the viscosity of air.2 These properties result in a decreased resistance to airflow (lower Reynolds number), and suggest that a helium–oxygen mixture may be a useful adjunct to improve ventilation via enhanced laminar airflow in the face of moderate to severe croup. Recently, mixtures of helium and oxygen have been used successfully in the pediatric intensive care unit setting for treatment of both refractory viral and postextubation croup.3–5

Although both Heliox (AGA Gas, Flint, MI) and RE have been independently shown to decrease the work of breathing and lower croup scores (CSs),3,4,6 no study to date has compared these modalities in the management of moderate to severe croup. Therefore, the purpose of this study was to compare the relative effect of Heliox and RE on CSs in pediatric patients with moderate to severe croup.

METHODS

This was a prospective, randomized, double-blind study conducted at an urban level I trauma center that serves as a primary teaching site for an emergency medicine residency. The study was initiated by emergency department (ED) attending physicians and continued by pediatric intensive care unit staff for children requiring admission. This study was approved by the institutional review board of the hospital; written informed consent was obtained from the parents of all participants.

Children between the ages of 6 months and 3 years with an ED diagnosis of moderate to severe croup were eligible for the study; Moderate to severe croup was defined as the presence of hoarseness, barking cough, and stridor in a patient with a preceding (<1 week) upper respiratory infection, and a corresponding Modified Taussig CS of 5 or greater (Table 1). Children with a Modified Taussig CS of ≤5 were also eligible for enrollment if they scored a 3 in any 1 of the 5 individual categories. Exclusion criteria included a history of congenital cardiac disease, tracheal stenosis, or bronchopulmonary dysplasia; signs or symptoms suggesting other causes of stridor, such as epiplottitis, bacterial tracheitis, retropharyngeal or peritonsillar abscess, reactive airway disease, tumor, or supraglottic foreign body.

Patients were randomized via a computer-generated randomization scheme to receive RE or a blend of 70% helium:30% oxygen mixture administered via facemask or tent house at a flow rate of 10 to 12 L/minute. Oxygen flowmeters (Chemtron Allied Health Care, St Louis, MO) were calibrated at 345 kPa (50 lb/in²-gauge) in...
advance to correct for the differences in physical properties of the 2 gases. Children randomized into the Heliox arm received 3 hours of continuous gas therapy, with nebulized saline administered as a placebo. Children randomized into the RE arm received 0.5 mL of RE in 2.5 mL of normal saline, with 100% oxygen for a total of 3 hours; therefore, both arms required 3 hours of therapy. Nebulized RE and saline (placebo) were powered using 100% oxygen and 70%/30% helium-oxygen mixture, respectively. Therefore, gas therapy was not interrupted at any time during the study. RE treatment was considered finished once the nebulizer cup was empty and mist was no longer visualized. If no significant improvement in symptoms was observed after 15 minutes, a second dose of either RE or an equal volume of placebo was given. Data were collected for a total of 4 hours. Enrolling physicians reserved the right to exclude patients and administer rescue medications (RE) at any time during the study.

Gas delivery was provided by size H and E cylinder tanks (AGA Gas, Flint, MI). The helium and air tanks were blinded with double cloth covers with identical standard pressure compensated flow meters exposed. Venturi ports on all nebulizers were closed, thus, ensuring no difference in sound or appearance of the setup. RE or placebo was given with small volume nebulizers (Vixone, Westmed Inc, Tuscon, AZ) and similar medication volumes. Only a respiratory therapist knew which treatment the patient was receiving. This individual was not involved in patient recruitment or data collection.

Our minimum sample size of 14 patients in each group yielded an ~80% power to detect a difference in change in CSs of 2 between groups and >90% power to detect a change in CSs of 3 between groups. The principal outcome measure was the change in CS. Secondary outcome measures included changes in oxygen saturation, respiratory rate, and heart rate. All baseline parameters were measured on room air. CSs were recorded at baseline and at 30, 60, 90, 120, 150, 180, and 240 minutes. All children received continuous cool mist and 0.6 mg/kg of intramuscular dexamethasone. A 3-hour treatment and 1-hour observation period was considered optimal to avoid compromising patient safety. This observation period is consistent with previously published data by Ledwith et al regarding safe discharge of patients after the administration of RE. Standardized CS training was conducted by the principal investigator before the beginning of the study. All investigators participated. Logistic constraints prohibited comparisons of CS between enrolling physicians during the study. However, interobserver agreement was assessed for 5 patients with moderate to severe croup before the study, with good agreement (κ = 0.76). Although a CS of 5 or greater was necessary for enrollment into this study, CSs were not used as a basis for providing or withholding treatment in enrolled patients. Patients were withdrawn from the study if their oxygen saturation was <90% after a second dose of either RE or placebo, if they could not tolerate the facemask or tent house, or if their clinical condition deteriorated at any time during the study.

All results were reported as mean ± standard deviation. Independent samples t tests were used to compare continuous variables between groups. Similarly, χ² analysis was used to compare frequency data. To compare changes in CS, heart rate and respiratory rate, and arterial oxygen saturation over the course of the study, repeated-measures analysis of variance was used. Physiologic measurements were examined first for change over time, then for differences in change over time between the 2 treatment arms. Statistical significance was set at .05, although exact P values were reported when significant. All statistical analysis was performed using SAS, Version 6.12 (SAS Institute, Cary, NC).

### RESULTS

Between September 1, 1997, and March 1, 1998, 58 patients met inclusion criteria. The parents of 14 patients declined participation. Of the remaining participants, 11 patients were not prospectively identified, and 4 patients were later excluded because of protocol violations (2 patients unable to tolerate facemask, 1 patient with reactive airway disease and pneumonia, and 1 patient with incomplete data). Two other patients who were excluded required rescue doses of RE (1 in the Heliox group and 1 in the RE group). No patients required intubation. Comparison of these individuals with the 29 patients successfully studied demonstrated no apparent enrollment bias (Table 2). In the Heliox arm, 11 patients were treated using a facemask apparatus and 3 via tent house. No differences were noted between groups when considering change in CSs, vital signs, or oxygen saturation. Four patients in the RE arm and 3 in the Heliox arm received a second dose of RE and saline placebo, respectively; outcomes for both groups were similar.

Among the patients included in the randomization, there were no significant differences at baseline between patients treated with Heliox and those treated with RE (Table 2). Initial CSs ranged from 5 to 9. Two children with an initial CS of 5 were classified as severe based on a stridor score of 3.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Enrolled (n = 29)</th>
<th>Nonenrolled <em>(n = 15)</em></th>
<th>Heliox (n = 14)</th>
<th>RE (n = 15)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mo)</td>
<td>24 ± 6</td>
<td>23 ± 7</td>
<td>24.4 ± 9</td>
<td>24.0 ± 6.7</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender</td>
<td>68.8%</td>
<td>76.8%</td>
<td>64.3%</td>
<td>73.3%</td>
<td>NS</td>
</tr>
<tr>
<td>Initial severity</td>
<td>6.7 ± 0.6</td>
<td>6.5 ± 1.1</td>
<td>6.8 ± 0.9</td>
<td>6.7 ± 0.9</td>
<td>NS</td>
</tr>
<tr>
<td>CS</td>
<td>162 ± 13</td>
<td>154 ± 24</td>
<td>159 ± 15</td>
<td>164 ± 11</td>
<td>NS</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>44 ± 9</td>
<td>40 ± 7</td>
<td>44 ± 10</td>
<td>45 ± 8</td>
<td>NS</td>
</tr>
<tr>
<td>Respiratory rate (min⁻¹)</td>
<td>95 ± 5</td>
<td>96 ± 3</td>
<td>95 ± 5</td>
<td>96 ± 2</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS indicates not significant. Results reported as mean ± standard deviation. Ninety-five percent confidence intervals calculated with independent samples t test or χ² distribution where appropriate.

* Nonenrolled patients were reported as the 11 patients not prospectively identified plus the 4 patients excluded from the study (n = 15).
Improvements in all measured parameters were seen in both treatment arms over time ($P < .01$ in each case). Although significant differences in CSs were noted between Heliox-treated and RE-treated participants at all time intervals after 90 minutes ($P < .05$), the overall results using repeat-measures analysis of variance revealed no significant differences in CSs at the end of the observation period ($P = .13$; Fig 1). In addition, there were no statistically significant differences between treatment groups in other measured severity parameters (heart rate, $P = .29$; respiratory rate, $P = .94$; arterial oxygen saturation, $P = .28$).

**DISCUSSION**

We believe that this is the first report of a double-blind, randomized study comparing the effects of RE and Heliox in children with acute viral croup. We have shown that compared with RE, Heliox results in a similar reduction in CS in pediatric ED patients with moderate to severe croup. Our results are consistent with other studies evaluating the clinical efficacy of Heliox in the treatment of acute croup. In 1979, Duncan$^3$ treated 7 patients refractory to RE with a 70% helium–oxygen mixture and noted a significant decrease in their CSs. Duncan concluded that Heliox was efficacious for the treatment of croup and that intubation was avoided in each of the 7 patients. In 1982, Nelson and McClellan$^4$ reproduced these results in 14 children with croup not responding to RE, concluding that Heliox was useful as adjunctive therapy. Unfortunately, both studies were small, nonblinded, and uncontrolled. In addition, Duncan enrolled patients with other underlying medical problems (teratoma, tetralogy of Fallot, pneumonia), making the cause of airway obstruction less clear. Finally, the need for intubation was not defined or intended as an outcome measure in either study. Therefore, the suggestion that the administration of Heliox obviated the need for intubation in these patients is based only on the opinion of the author.

In a recent prospective, double-blind study comparing Heliox with humidified oxygen in children with acute viral croup, Terregino et al$^8$ found no statistically significant difference in CSs between the 2 groups. However, in this study, patients ill enough to require RE were excluded. Because most cases of mild croup will respond to humidified oxygen alone, this study population was less likely to benefit from Heliox.

Several study limitations merit discussion. Because of the relatively small numbers of participants, the study was not powered to detect small differences between groups. Although we did not include a control arm of patients who received only cool mist and steroids, all enrolled children were sufficiently ill to require aggressive treatment. Thus, it was most appropriate that all patients received either RE or Heliox. This study was sufficiently large to detect differential improvements in the CS over time. However, because a control arm was not studied, we cannot exclude the possibility that the incremental improvement noted in the Heliox arm after 90 minutes was not attributable, at least in part, to cool mist and oxygen. Furthermore, the relevance of this improvement is unknown, because outcomes such as admission rates and hospital length of stay were not specifically measured.

CSs are a helpful research tool used to standardize disease severity at an arbitrary point, and a decreasing score provides an objective measure of clinical improvement. However, CSs are poor predictors of respiratory failure and none have been universally accepted as the gold standard. We chose the Modified Taussig CS because it weighs patient color, anxiety, retractions, stridor, and level of consciousness equally, yet classifies disease as severe if a maximal score is present in any 1 category (Table 1). This is particularly important when grading stridor and re-
tractions, because both have been fluoroscopically shown to inversely correlate with the diameter of the trachea.9

Twenty-five patients who were eligible for the study were not enrolled, and it is possible that this group may have responded differently to treatment. However, initial CSs of study patients were similar to those children who were not enrolled because of parental refusal.

Although helium–oxygen mixtures are considered safe, hypoxia has been previously reported with use in preterm infants with a history of bronchopulmonary dysplasia and subglottic stenosis.10 In our study, 3 patients with an initial oxygen saturation of ≤90% received Heliox. All 3 responded promptly with normal oximetry, and none experienced any serious sequelae. Oxygen saturation did not differ between the study groups, and no patients required exclusion because of sustained hypoxia. Finally, it is possible that observer bias influenced the reporting of CSs. However, previously mentioned measures to ensure blinding were adhered to meticulously.

CONCLUSION

Our data suggest that the administration of Heliox results in a similar reduction in CSs compared with RE in children with moderate to severe croup. Larger studies examining the utility and cost-effectiveness of Heliox seem warranted. Future studies should consider the usefulness of Heliox alone or as an adjunct to RE, when evaluating outcomes, such as hospital admission rates and length of stay.

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REFERENCES

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