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SHORT COMMUNICATION

Nasal continuous positive airway pressure with heliox in infants with acute bronchiolitis

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Summary This is the first study aiming to assess the effects of heliox in combination with nasal continuous positive airway pressure (Hx-nCPAP) as a rescue treatment in infants with refractory acute bronchiolitis.

Fifteen out of 78 infants with acute bronchiolitis consecutively admitted to PICU fulfilled the inclusion criteria: clinical score $\geqslant 5$ or arterial oxygen saturation ($SatO_2$) $\leqslant 92\%$ or $PCO_2 > 50$ mmHg, despite supportive therapy, nebulized L-epinephrine, and heliox therapy through non-rebreathing reservoir facemask. Hx-nCPAP was added as a rescue treatment. Baseline mean (standard deviation) values were: clinical score of 7.4 (1.2) points; PCO_2 of 63.8 (12) mmHg; respiratory rate (RR) of 66.4 (9.9); and $SatO_2$ of 88.6 (4.7)%.

Clinical score, PCO_2, RR and $SatO_2$ improved during the study time ($P < 0.05$). After 1 h the mean clinical score decreased by 1.5 points, with a total average decrease of 3.5 points at the end of the study period. The mean PCO_2 diminished by 9 and 25 mmHg, after 1 and 48 h, respectively. The mean RR decreased 13 rpm after 1 h and 30 rpm after 48 h. The Hx-nCPAP total duration ranged from 2 to 14 days. Only one patient required endotracheal intubation. No adverse effects were detected. All patients recovered fully.

In conclusion, Hx-nCPAP improved the clinical score, decreased the tachypnea and enhanced the CO_2 elimination of infants with refractory acute bronchiolitis within 1 h of administration, in a safe and non-invasive manner. Hx-nCPAP might reduce the need for endotracheal intubation. Further studies are needed.

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Introduction

Bronchiolitis is a major reason for hospitalization in infants.[1,2] It can lead to respiratory insufficiency in more than 50% of those patients admitted to the pediatric intensive care unit (PICU).[1,2] Although several therapeutic interventions have been assessed, no proven successful treatment has been achieved.[2–4]

It has been recently suggested that heliox therapy could be useful in the treatment of infants with bronchiolitis.[5,6] It has also been indicated that non-invasive ventilation (NIV), and specifically, nasal continuous positive pressure (nCPAP), may improve the respiratory status of children with hypoxemic respiratory failure.[7,8] Extrapolating from the existing data for adult patients,[9,10] and considering the theoretical fundamentals of both therapies,[5–8,11] the combination of heliox and NIV might be useful in pediatric patients. To our knowledge no data on the combined use of NIV and heliox in bronchiolitis patients have been previously reported.

The aim of this exploratory study was to assess the effects on ventilation, respiratory rate and clinical score, of administering heliox (Hx) with nCPAP (Hx-nCPAP) as a rescue treatment in infants with refractory acute bronchiolitis.

Materials and methods

Study design

A preliminary prospective, clinical, interventional, observational, single-center, uncontrolled study was planned. The study was approved by the Institutional Review Board, and written informed parental consent was obtained in all cases before enrollment.

Study subjects

Infants 1 month to 1 year old, admitted to the PICU from January 2002 to February 2004, with respiratory syncytial virus (RSV) bronchiolitis and:

- Modified Wood's Clinical Asthma Score (M-WCAS) $\geqslant 5$,[6] or
- arterial oxygen saturation $\leqslant 92\%$, or
- $PCO_2 > 50$ mmHg

despite optimized supportive therapy, nebulized L-epinephrine and heliox therapy through non-rebreathing reservoir facemask for at least 1 h, were eligible for the study. Patients with underlying chronic lung disease were not suitable.

Diagnostic criteria of bronchiolitis included tachypnea, cough, prolonged expiratory time, wheezing, rales, chest retractions, and hyperinflation of the lungs on chest radiographs.[6] RSV infection was confirmed by enzyme-linked immunoadsorbent assay of nasal secretions. Moderate-to-severe respiratory distress was defined as a M-WCAS of 5 or greater.[6]

During the study period, 78 infants with severe acute bronchiolitis were admitted to our PICU. Fifteen of them, 8 males and 7 females, fulfilled the inclusion criteria and were enrolled in the study. A mean of 8.1 (9.8) h have elapsed since they were admitted to PICU. Their median age was 2 (range 1–7) months. One patient had underlying heart disease, and 3 patients had suffered from bronchiolitis in the preceding 2 months.

All patients received one dose of nebulized epinephrine at the start of the study; it was then administered at 2–6 h intervals at the discretion of one of the three physicians responsible for the study. No patient received any nebulized medications other than epinephrine or systemic corticosteroids, before enrollment or during the study. No patient required sedation in order to tolerate Hx-nCPAP.

Definitions

Nebulized L-epinephrine: 3 mg/dose each 2–6 h, as needed.

Heliox therapy[11]: helium-70%/oxygen-30% mixture, warmed and humidified was administered at 10–15 lpm through non-rebreathing reservoir facemask. A central wall-supply of dry heliox with a prefixed concentration (70%-He and 30%-O_2) was used (Air Liquide Medicinal®, Madrid, Spain).

Intervention: H-nCPAP logistics

Those patients who fulfilled the inclusion criteria received nCPAP with heliox (70%-helium and 30%-oxygen) (Hx-nCPAP). The heliox source was directly connected to the air inlet of a non-invasive positive pressure ventilator (Infant Flow Advance®, Electromedical Medicine, United Kingdom). The ventilator was settled in CPAP mode without backup rate and with a starting pressure of 5 cm H_2O. The heliox flow was adjusted for the desired initial CPAP pressure using the air–oxygen flow meter of the device. The actual heliox flow was calculated by applying standard conversion factors.[11] The heliox mixture was delivered to the patient previously

warmed and humidified by means of a conventional device (MR730 Humidification system®; Fisher & Paykel Healthcare Spain, Madrid, Spain). Either nasal prongs or nasal mask were selected for Hx-nCPAP delivery, according to patient's size and comfort, and at the physician's discretion. CPAP pressure and FiO_2 were adjusted to maintain $SatO_2$ above 94% with the minimum FiO_2 possible, in order to deliver the highest amount of helium to the patient. When the FiO_2 needed was higher than 0.4, the pressure was increased in 1 cm H_2O increments. When $FiO_2 \leqslant 0.3$, $PCO_2 \leqslant 50$ mmHg and a clinical score <5 were maintained for 6 h, the Hx-nCPAP treatment was withdrawn.

Hx-nCPAP treatment was considered a failure when, $SatO_2$ was below 92% with CPAP above 10 cm H_2O and FiO_2 was above 0.6, or PCO_2 was persistently above 60 mmHg, or when the patient did not tolerate the technique, or if the patients' clinical condition acutely deteriorated at any time during the study. In these circumstances patients were returned to conventional therapy, re-evaluated and considered for endotracheal intubation and invasive mechanical ventilation.

Measurements and outcomes

M-WCAS, PCO_2, $SatO_2$, and respiratory rate (RR) values were recorded at baseline, then at 1 h intervals for 6 h, and afterwards, at 8 h intervals, until Hx-nCPAP therapy was discontinued. Data obtained during the first 48 h were analyzed. Demographic data, duration of heliox therapy, need for endotracheal intubation, and administration of concurrent therapies were collected for each patient.

The principal outcome measures were the change in M-WCAS, RR and PCO_2 levels. For clinical scoring, we followed a previously applied methodology.[6] The PCO_2 was continuously monitored by means of earlobe transcutaneous technique (Tosca®, Linde Medical Sensors, Switzerland) and checked at recording points by blood gas analysis. The $SatO_2$ was continuously monitored using pulse oximetry (Radical®, Massimo SET pulse oximeter, California, USA). Any adverse event potentially related to the Hx-nCPAP treatment was registered. Patient tolerance of the technique was assessed primarily by the investigator and afterwards by the nurse in attendance. Any eventual need of sedation was also recorded. All patients were followed up for at least 6 months after discharge.

Statistical analysis

The distributions of trial variables were assessed by means of Shapiro–Wilk test. Friedman's one-way analysis of variance was used to assess changes in variables over the course of the study. The differences between each measurement interval were assessed by post hoc analysis with Wilcoxon matched-pairs signed-ranks test, employing a Bonferroni correction. Statistical significance was indicated by $P<0.05$. Data are presented as mean (standard deviation) unless otherwise indicated. All statistical analyses were performed using SPSS software 12.0 version (Chicago, IL).

Results

Clinical score, $SatO_2$, RR and PCO_2 improved over the course of the study ($P<0.05$) (Table 1). At baseline, mean clinical score was 7.4 (1) points. After 1 h the mean clinical score had decreased by 1.5 points ($P<0.05$). The score continued to improve, with a total average decrease of 3.5 points at the end of the study period ($P<0.05$).

The initial mean PCO_2 was 63.8 (12) mmHg. After 1 h, an average decrease of 9 mmHg was achieved

Table 1 Summary of patient's data during the first 48 h of therapy with Hx-nCPAP.[a]

	Basal	1 h	6 h	24 h	48 h	
M-WCAS	7.4 (1.2)	6.0 (0.8)	5.5 (0.9)	4.6 (1.0)	3.9 (0.7)	$P<0.05$
RR (rpm)	66.4 (9.9)	52.7 (5.4)	43.6 (5.6)	36.2 (3.4)	31.5 (3.5)	$P<0.05$
PCO_2 (mmHg)	63.8 (12.0)	54.8 (9.5)	50.1 (10.2)	43.2 (7.9)	38.2 (6.4)	$P<0.05$
$SatO_2$ (%)	88.6 (4.7)	95.3 (2.4)	95.6 (2.8)	97.6 (1.8)	97.6 (2.0)	$P<0.05$
FiO_2	36 (6.1)	35 (5.6)	32 (4.1)	30 (2.1)	30 (1.5)	
CPAP (cmH_2O)	7.4 (1.2)	7.2 (1.1)	6 (1)	5.4 (0.5)	5.1 (0.3)	

M-WCAS, Modified-Wood clinical asthma score; $SatO_2$, arterial oxygen saturation; RR, respiratory rate; rpm, respirations per minute; CPAP, continuous positive airway pressure.

[a]Data are expressed as mean (standard deviation). Differences in measured parameters over time were assessed by means of Friedman one-way analysis of variance.

($P<0.05$). The PCO_2 levels continued to improve significantly at all the time intervals, with a total average decrease of 25 mmHg at the end of the observation period ($P<0.05$).

Mean RR was 66.4 (10) rpm at the beginning of the study, diminished by 13 rpm after 1 h, with a final average decrease of 30 rpm ($P<0.05$).

Baseline mean $SatO_2$ was 88.6 (4)%, and had improved by 7% to 95.3 (2.4)% during the first hour ($P<0.05$). A mean of 7.4 (1.2) cmH_2O of CPAP and 36 (6.1)% of FiO_2 were initially required to elevate $SatO_2$ above 94%. Mean $SatO_2$ remained stable above 94% for the rest of the observation period, with a final average increase of 9% ($P<0.05$).

Total Hx-nCPAP duration ranged from 2 to 14 days (6.1 (3.3) days). No adverse effects attributable to Hx-nCPAP were detected. All patients tolerate the technique without sedation. One patient with an initial positive response to Hx-nCPAP, worsened after 3 days due to *Escherichia coli* superinfection and secondary septic shock. He required endotracheal intubation and mechanical ventilation for 3 days, being weaned without incident. All the patients fully recovered and continued to do well after between 8 and 28 months follow-up. No patient required PICU re-admission after being discharged.

Discussion

Our results suggest heliox therapy in combination with nasal continuous positive pressure is a safe and effective option for the management of infants with unresponsive acute bronchiolitis. The use of Hx-nCPAP reduced respiratory distress, demonstrated by both the improvement in clinical score and the reduction in tachypnea. Ventilation also improved, reflected by the marked reduction seen in CO_2 levels.

Hx-nCPAP may have also helped avoid endotracheal intubation and mechanical ventilation in some patients. According to their baseline data, all of our patients treated with Hx-nCPAP fulfilled the usual criteria for endotracheal intubation and assisted ventilation[12]; however, with the application of Hx-nCPAP intubation was prevented in all but one case. A literature search reveals that 25–60% of those infants with bronchiolitis admitted to PICU may eventually need intubation and invasive ventilatory support.[1,2,13–17] Even accepting the influence of other factors different to Hx-nCPAP treatment, including distinct PICU admission policies or particular intubation criteria, in our series only 1 out of 78 (1.3%) of cases required invasive mechanical ventilation (95% exact confidence interval = 0.2–6.9%), a figure strikingly lower than previously reported.[1,2,13–17]

Only three studies to date have tried to assess the role of heliox in a bronchiolitis setting: two with facemask in spontaneously breathing infants[5,6] and another one in mechanically ventilated patients.[18] The majority of the literature concerning Hx-nCPAP concentrates on adults with acute exacerbations of chronic pulmonary obstructive disease.[9,10] Similarly to the effects found in our children, these studies suggest that Hx-nCPAP can safely improve gas exchange and reduce symptoms in such patients.[9,10]

From our preliminary clinical experience, we could postulate that Hx-nCPAP noticeably has manifold complementary, if not synergistic, effects. It is possible that nCPAP could contribute to a decrease in the workload on the inspiratory muscles, prevent or relieve atelectasis, avoid airway collapse and promote heliox distribution. Heliox could further alleviate respiratory work, enhance carbon dioxide elimination, and increase expiratory flow. Applying nCPAP may reduce the needed FiO_2 in these children, augmenting the actual helium concentration delivered to the patient.

There are limitations to our study including: its small sample size, open observational design, lack of control group, and the use of changes in the clinical score as one of the primary outcome measures. Despite their known limitations, clinical scores are often used as a research tool and this particular scoring system has been previously validated.[6] The study design did not allow us to determine the exact contribution of either heliox or nCPAP to the final effect; however, this was not its purpose. Our study shows a potential beneficial effect of Hx-nCPAP in these patients, along with good patient safety and tolerability. We believe that our results justify moving on to randomized clinical trials involving Hx-nCPAP. Apart from the need to estimate treatment effects, other issues need addressing such as the optimal time of intervention, ideal starting and maintenance parameters, the duration of treatment, and the detection of non-responders.

In conclusion, the combination of heliox and nCPAP may be effective in infants with acute severe bronchiolitis, within the first hour of its administration and, in a safe and non-invasive manner. Hx-nCPAP may provide time for other therapeutic agents to work or for the disease to resolve naturally, avoiding more aggressive interventions. Further prospective studies are now needed to ascertain the role of this therapy in the

management of bronchiolitis and to determine the precise contribution of either heliox or nCPAP to this beneficial response.

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