RESEARCH BRIEF

Nasal Intermittent Positive Pressure Ventilation with Heliox in Premature Infants with Respiratory Distress Syndrome: *A Randomized Controlled Trial*

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Objective: To assess the efficacy of nasal intermittent positive pressure ventilation with heliox in preterm infants with respiratory distress syndrome.

Methods: Premature infants with mild respiratory distress syndrome requiring non-invasive respiratory support were eligible. Infants were randomly assigned to heliox or air-oxygen group. The main outcome was the length of ventilation.

Results: Heliox significantly decreased the length of ventilation. The length of ventilation was positively correlated with interleukin-6 at baseline. Carbon dioxide elimination was better in the heliox group.

Conclusion: Heliox delivered with nasal intermittent positive pressure ventilation may be effective in reducing length of ventilation and increasing carbon dioxide elimination.

Keywords: *Helium, Oxygen, Prematurity, Ventilation.*

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The use of heliox for neonatal ventilation has gained interest in recent years [1]. Its beneficial effect lies in the lower density compared to air-oxygen mixture (airox) [2], thereby reducing the driving pressure needed under turbulent flow conditions and promoting laminar flow in areas of airway narrowing [3]. These physical properties have been reported to be beneficial in different neonatal diseases [4]. To the best of our knowledge, there have been no reports about nasal intermittent positive pressure ventilation (NIPPV) with heliox in neonates. The aim of our study was to assess the efficacy of NIPPV with heliox on length of ventilation and lung inflammation cytokines in preterm infants with respiratory distress syndrome (RDS).

METHODS

Neonates <37 weeks of gestation with a diagnosis of RDS who required a fraction of inspired oxygen (FiO_2) ≥0.3 to maintain PaO_2 >50 mmHg in the first hour after birth were eligible for enrolment in this randomized controlled trial. The diagnosis of RDS was based on clinical manifestations and chest radiograph findings. All the neonates had bedside chest *X*-ray done by the same machine after admission to neonatal intensive care unit (NICU). Infants were excluded from this study if they met any of the following criteria: pneumonia, meconium aspiration, major congenital anomalies, intubation in the delivery room, transient tachypnea without radiological evidence of RDS, consent not provided or refused, or severe respiratory failure requiring intubation.

Participants were randomly assigned to receive helium-oxygen (heliox) or air-oxygen (airox) mixture using a sealed-envelope method. Heliox group was treated with NIPPV for 3 hours with heliox (70% helium and 30% oxygen) delivered from cylinders followed by airox until NIPPV was no longer needed. The airox group received NIPPV with (30% oxygen and 70% air). The main outcome measures were length of ventilation (time taken to successful extubation from ventilation), and maintaining oxygen saturation >90%. The physicians were unmasked as heliox was delivered by special cylinders. Infants were considered for weaning from nasal respiratory support when peak inspiratory pressure was below 20 cmH_2O and FiO_2 was below 25%. Infants were intubated when pH <7.2, PaO_2 >50 mmHg with FiO_2 >0.5, $PaCO_2$ >60 mmHg or having frequent episodes of apnea. The secondary outcomes were changes in transcutaneous pressure of oxygen and carbon dioxide ($TcPO_2$ and $TcPCO_2$), lung inflammation cytokines, intubation rate and complications.

All the data were analyzed using SPSS 17 software. Fisher's exact test, 2-way analysis of variance with repeated measures, multiple linear regression, correlation analysis and independent-samples *t* test were used to analyze the data.

The study was approved by the ethics committee of Daping Hospital. Informed consent was obtained from parents before enrolment of their children into the study. The sample size of 32 participants was calculated to detect a reduction of 0.8-day in the length of ventilation with 80% power for a 2-sided α of 0.05.

RESULTS

Thirty-six neonates were included; 19 were randomized to heliox group and 17 to control group. The clinical characteristics are compared in ***Table* I**.

Heliox significantly reduced mean (SD) length of ventilation in comparison to airox. Length of ventilation was significantly and positively correlated with IL-6 at baseline (r=0.474, *P*=0.006). Three infants required intubation in the airox group, while none required it in the heliox group. Both $TcPO_2$ and $TcPCO_2$ improved after 3 hours in each group ($P<0.001$); the difference was not statistically significant at each time point (***Fig*. 1**). Carbon dioxide elimination was better in the heliox group (10.4 mmHg *vs*. 6.0 mmHg, *P*=0.03) (***Fig*. 1**).

Cytokines were not significantly different between the two groups, except for IL-6, a reduction that was lower in the heliox group (***Table* II**). Seven patients in the heliox group and five in the control group were diagnosed with patent ductus arteriosus (PDA), while 3 patients in the heliox group and 1 patient in the control group were diagnosed with necrotizing enterocolitis (NEC). After 3 hours, there was no statistically significant differences of peak inspiratory pressure, mean airway pressure, oxygen saturation and respiratory rate in the two groups.

TABLE I BASELINE CHARACTERISTICS OF INFANTS IN THE STUDY

	Heliox (*n*=19)	*Airox* (*n*=17)
Males, *n* (%)	13 (68.4)	10 (58.8)
Birth weight, mean (SD), kg	2.15 (0.47)	2.19 (0.44)
Gestational age, mean (SD), wk	34.2 (1.8)	34.3 (1.8)
Cesarean delivery, *n* (%)	13 (68.4)	14 (82.4)
Antenatal steroids, *n* (%)	11(57.9)	9 (52.9)
Apgar 1 min, median (range)	9 (6-10)	9 (7-10)
Stage of *X*-ray chest, median (range)	1.4 (1-3)	1.8 (1-3)
	7 (36.8)	8 (47.1)
Need of surfactant, *n* (%)	2 (10.5)	2 (11.8)
Birth weight <1500g, *n* (%)	2 (11.1)	2 (11.8)

TABLE II COMPARISON OF OUTCOMES BETWEEN NEONATES RECEIVING HELIOX or Airox for Ventilation

	Heliox (n=19)	*Controls (n=17)*	*P*
Length of ventilation, *h*	39.3 (15.1)	57.8 (25.0)	0.02
Interleukin-6, u/mL	48.4 (48.3)	146.4 (51.2)	0.17
*Malonyldialdehyde	6.4 (2.8)	5.1 (3.6)	0.25
#Tumor necrosis factor-α	347.4 (340.7)	296.5 (281.9)	0.67
Myeloperoxidase, IU/L	235.9 (233.9)	168.9 (166.9)	0.38
Inducible nitric oxide synthase, IU/mL	10.7 (7.9)	9.6 (7.4)	0.70

*Interleukin-6 was collected at baseline and 3 hours of the administration, while others were collected at 3 hours of the administration. All data in mean (SD); *μg/mL; # ng/L.*

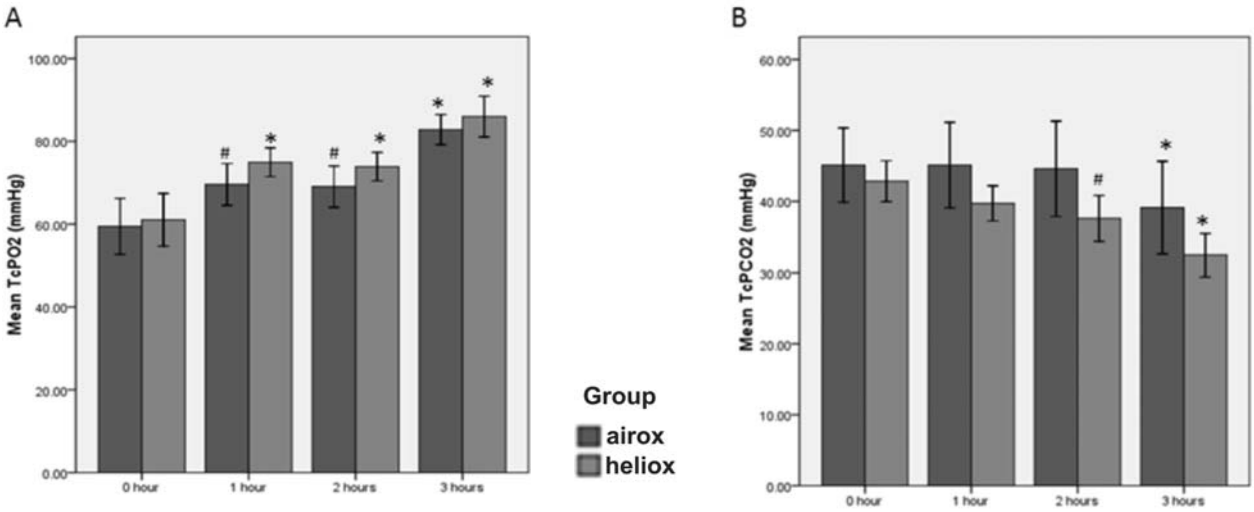

FIG. 1 *Comparion of transcutaneous pressure of oxygen ($TcPO_2$) and carbon dioxide ($Tc\,PCO_2$) in neonates receiving Heliox or Airox.*

WHAT THIS STUDY ADDS?

- NIPPV with heliox reduces length of ventilation and increases the carbon dioxide elimination in preterm infants with mild respiratory distress syndrome.

DISCUSSION

In our study, heliox decreased length of ventilation in comparion to airox. Both $TcPO_2$ and $TcPCO_2$ improved after 3 hours, and carbon dioxide elimination was better in the heliox group. Analysis of lung inflammation cytokines showed no statistically significance between the two groups, but the values of IL-6 showed a noticeable reduction in the heliox group.

The technique was well tolerated in all infants. The small sample size, short time frame of heliox ventilation and unmasked assignement were the main limitations of this study. Our study findings of reduction in lenth of ventilation were similar to those by Elleau, *et al*. [6]. However, Colnaghi, *et al*. [7] found heliox failed to reduce length of ventilation when combined with nasal CPAP. The delivery method of heliox is crucial to its efficacy [8]. NIPPV might have increased the efficacy of heliox as compared with nasal CPAP. Helium might have anti-inflammatory effects [9,10]; heliox with NIPPV might have alleviated inflammation reaction in the acute phase of RDS. Heliox group in our study showed a better elimination of carbon dioxide, which is in agreement with previous reports [11,12]. This might be attributed to the better carbon dioxide diffusion in heliox [13,14].

We conclude that heliox delivered with NIPPV may be effective in reducing length of ventilation and increasing carbon dioxide elimination in preterm neonates with mild RDS. Large, double-blind, randomized controlled trials are needed to assess further benefits of heliox therapy in preterm infants.

Contributors: XL, LI: conceptualized and designed the study, drafted the initial manuscript, and approved the final manuscript as submitted; JS: designed the data collection instruments, and coordinated and supervised data collection, critically reviewed the manuscript; JZ: carried out the initial analyses, reviewed and revised the manuscript and approved the final manuscript as submitted; ST: carried out the initial analyses, reviewed and revised the manuscript and approved the final manuscript as submitted; YS: instructed the designation and implementation of the study, reviewed and revised the manuscript and approved the final manuscript as submitted.
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