RESEARCH PAPER

Heated Humidified High Flow Nasal Cannula *versus* Nasal Continuous Positive Airway Pressure as Primary Mode of Respiratory Support for Respiratory Distress in Preterm Infants

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Objective: To compare the outcomes of preterm infants with respiratory distress initiated on either Heated Humidified High Flow Nasal Cannula or Nasal Continuous Positive Airway Pressure as a primary mode of respiratory support.

Study Design: Prospective observational cohort study

Setting : Tertiary care level III neonatal intensive care unit

Participants : 88 preterm infants between 28 to 34 weeks of gestation with mild to moderate respiratory distress within 6 hours of birth.

Intervention: Eligible infants were treated either with Heated Humidified High Flow Nasal Cannula (*n*=46) or Nasal Continuous Positive Airway Pressure (*n*=42).

Primary outcome : Need for mechanical ventilation within 72 hrs of initiating support.

Results: Baseline demographic characteristics were comparable between the two groups. There was no difference in the requirement of mechanical ventilation between Heated Humidified High Flow Nasal Cannula (19.5%) and Nasal Continuous Positive Airway Pressure (26.2%) groups [RD – 0.74 (95% CI 0.34-1.62; *P* =0.46)]. Moderate or severe nasal trauma occurred less frequently with Heated Humidified High Flow Nasal Cannula (10.9%) in comparison to Nasal Continuous Positive Airway Pressure (40.5%) (*P*= 0.004).

Conclusion: Heated Humidified High Flow Nasal Cannula was comparable to Nasal Continuous Positive Airway Pressure as a primary respiratory support for preterm infants with respiratory distress, with lesser incidence of nasal trauma.

Keywords: *Mechanical ventilation, Nasal trauma, Non- invasive ventilation.*

Non-invasive ventilatory strategies, such as nasal continuous positive airway pressure (NCPAP) and early surfactant is known to reduce the lung inflammation and injury associated with mechanical ventilation (MV) and decreases the incidence of bronchopulmonary dysplasia (BPD) [1]. Avoidance of intubation and the increased use of NCPAP has become the primary mode of therapy for respiratory problems in preterm neonates [2,3]. However, there are problems with the use of NCPAP like difficulties in maintaining the nasal prongs in the nostrils, granulation, ulceration, necrosis, nasal vestibular stenosis, nasal deformities, poor tolerance of the infant to the apparatus, and difficulties in positioning the neonate [4,5].

Heated humidified high flow nasal cannula (HHHFNC) delivers positive distending pressure without the clinical limitations mentioned above [6]. The use of HHHFNC has increased in many neonatal intensive care units (NICUs) across the world over the past several years [7,8]. The exact role of HHHFNC has been somewhat loosely defined, but it has become increasingly popular as a support modality where NCPAP might traditionally have been used [6]. The increasing use of HHHFNC instead of CPAP is, in part, due to its greater ease of use, improved patient tolerance and similar efficacy to NCPAP [6-9]. However, evidence in support of HHFNC as a primary mode of non-invasive respiratory support is scarce [10]. The aim of present study was to investigate whether HHHFNC is as effective as NCPAP as a primary mode of respiratory support for mild to moderate respiratory distress in preterm infants.

METHODS

This prospective observational study was conducted at a level III Neonatal intensive care unit (NICU) of a tertiary hospital from January 2013 to December 2013. The study was approved by the Institutional ethics committee. Preterm infants between 28 and 34 weeks of gestation, with mild to moderate respiratory distress within 6 hours of birth, were included. Infants with 5 minute Apgar scores

<5, nasopharyngeal pathology (*e.g*., choanal atresia, cleft lip or palate), major congenital malformations and those with antenatally diagnosed congenital heart disease were excluded from the study. Written informed consent was obtained from the parents of enrolled neonates. We had two HHHFNC and two Bubble NCPAP systems in our unit. Eligible infants were allocated to either of the device (HHHFNC or NCPAP) depending on the availability of the device. If both the devices were available at the time of allocation, the infant was allocated to NCPAP. Mild to moderate respiratory distress was defined as: Silverman-Anderson score (SAS) of 3-6, FiO_2 requirement ≤60% at initiation to maintain SpO_2 between 88-93%, and an arterial pH >7.2 and $PaCO_2$ <60 mmHg.

HHHFNC therapy was administered using RT329 Infant oxygen therapy Breathing Circuit and MR850 Humidifier (Fisher and Paykel Healthcare, Inc.) using short binasal prongs. The size of the nasal prongs did not exceed more than 50% of the size of the nares. HHHFNC was initiated at a flow of 3 L/min with a FiO_2 titrated to a maximum of 60% to maintain SpO_2 between 88-93%. Changes in flow was made by increments of 1L/min to a maximum flow of 6 L/min if distress persisted. Weaning was done by stepwise reduction of FiO_2 to 21% and flow to 1 L/min, followed by removal of HHHFNC at 1 L/min and 21% oxygen.

NCPAP was delivered by bubble CPAP system (BC 151, Fisher and Paykel Healthcare, Inc.) with MR850 humidifier using short binasal prongs as interface (Hudson RCI Infant Nasal Prong CPAP cannula system). NCPAP was initiated at 5 cm H_2O and a flow of 6L/min with FiO_2 to maintain SpO_2 between 88-93 %. CPAP pressure and FiO_2 were titrated to a maximum of 7 cmH_2O and 60%, respectively. A maximum of 8L/min of flow was allowed to ensure adequate bubbling in the water chamber. The criteria for weaning were: absence of respiratory distress (minimal or no retractions; SAS score: 0-1) and respiratory rate between 40 and 60 per minute), and SpO_2 > 90% on FiO_2 <30% and PEEP <5 cm H_2O. Weaning from CPAP used stepwise reduction of FiO_2 by 5% to 21% and CPAP to 4 cm H_2O, followed by removal of CPAP prongs. Infants were diagnosed to have failed HHHFNC or NCPAP and were started on MV when they: (*a*) remained hypoxic, *i.e*. SpO_2 <88% despite FiO_2 > 60%, and flow rate >6L/min for HHHFNC group and PEEP >7 cm H_2O for NCPAP group; (*b*) SAS score >6 despite the maximum settings; (*c*) had recurrent apnea (>3 episodes within 24 hours) or any episode of apnea requiring bag and mask ventilation; (*d*) had pH<7.2, or $PaCO_2$ >60 mmHg; or (*e*) required inotropic support.

Surfactant (Survanta) was administered in a dose of 100 mg/kg in 3 aliquots by the INSURE technique (Intubate, Surfactant and rapid Extubation) if FiO_2 was ≥40% within 2 hr of starting NCPAP or HHHFNC. Infants considered to have HHHFNC/NCPAP failure were managed by intubation and MV.

The primary outcome was MV within 72 hr of starting either HHHFNC or NCPAP support. The secondary outcomes were: the duration of non invasive ventilation (NIV), duration of oxygen, frequency of air leaks, and BPD (oxygen treatment at 36 weeks). Other outcomes were: frequency of patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH) grades 3 and 4, retinopathy of prematurity (ROP) ≥ stage 3, time to full feeds, feeding intolerance, gastrointestinal perforation, clinical and culture proven Early onset sepsis (EOS) and Late onset sepsis (LOS), length of hospital stay, mortality, and nasal trauma. An independent observer from the nursing staff, blinded to the intervention, examined the nose for injury. The clinical examination was done 12 hourly and regular nasal toilet was provided. Nasal trauma was classified as mild (erythema and tenderness), moderate (indentation over nasal septum/excoriation) and severe (columella necrosis/bleeding). Repositioning of the interface and external massage was given for mild nasal trauma. Mupirocin ointment and occlusive plastic dressing was applied for moderate/severe trauma to prevent it from further worsening. Nasal trauma was recorded at the point of removal of NCPAP and HHHFNC. For the purpose of the study, infants were assessed for these outcomes till discharge from the hospital.

Infants were monitored as per standard nursing protocols. All infants on NCPAP/HHHFNC had an appropriate sized gastric tube placed, open to the atmosphere, to reduce distension of the stomach.

Data collection of maternal variables included maternal complications, mode of delivery and antenatal steroids. Gestational age was calculated based on mothers last menstrual period and/or early pregnancy ultrasound scan or New Ballard score [11]. Infant variables evaluated included birth weight, gestational age, presence of Intra Uterine Growth Retardation (weight <10th on Lubchenco percentile) [12], resuscitation, *X*-ray chest, arterial blood gas, FiO_2 requirement and SAS score at 30 min of starting non invasive ventilation.

BPD was defined according to the National Institutes of Health consensus definition [13]. PDA was confirmed by bedside echocardiography, and IVH was defined by using the Papile classification [14]. NEC was classified according to Bell's classification, as modified by Kliegman and Walsh, at stage II or greater [15]. ROP was defined according to the International classification of retinopathy

of prematurity [16]. Full feeds were defined as feeds that reached 150 mL/kg per day.

Based on the observation in our unit, the failure rate for primary outcome was estimated to be 40% in CPAP group. We hypothesized that the failure rate of primary outcome with HHHFNC group would be 15%. With a two sided α error of 0.05 and power 80%, the estimated sample size was 90 (45 in each group). To compare the baseline and outcome variables on a continuous scale two sample *t* tests or Mann Whitney *U* test were used as appropriate. To compare the baseline and outcome variables on nominal type of data Chi Square test or Fisher Exact test were used as appropriate. A two sided p value <0.05 was considered significant. Statistical analysis was performed using SPSS Statistics Version 17.0 for Windows (SPSS, Chicago, IL, USA)

RESULTS

We assessed 103 infants for eligibility and 15 were excluded. Six were excluded because of clinical conditions that did not meet the eligibility criteria and nine parents refused consent. Out of 88 preterm infants enrolled in the study, 42 received NCPAP and 46 received HHHFNC. Baseline demographic characteristics were comparable between the two groups (***Table* I**). There was no significant difference in the primary outcome of early failure rate, *i.e*. MV rate within 72 hours of starting treatment. The failure rate in HHHFNC group was 19.5% and the failure rate in NCPAP group was 26.2% (*P*=0.46). There were no significant differences between the two groups for duration of non-invasive ventilation (NIV), duration of ventilator days, duration of oxygen requirement, incidence of air leaks, BPD, PDA, NEC, IVH > grade 3 and 4, ROP ≥stage 3, time to full feeds, feeding intolerance, clinical and culture proven EOS and LOS, duration of hospital stay, and mortality (***Table* II**).

None of the infants in either group developed pneumothorax or gastrointestinal perforation. Moderate or severe nasal trauma occurred significantly less frequently with HHHFNC (10.9%) in comparison to NCPAP (40.5%) (*P*= 0.003) (***Table* II**).

DISCUSSION

In this prospective observational study, we found no significant difference between HHHFNC and NCPAP as a primary mode of respiratory support in the primary outcome of intubation and MV within 72 hours of initiating support. No differences were seen for the secondary variables.

In a subgroup of a multicentre trial by Yoder, *et al*. [10], HHHFNC was similar in efficacy to NCPAP when used as primary support in respiratory distress. However, infants managed on NCPAP had fewer days of any positive pressure support (ventilator, NCPAP, HHHFNC) as well

TABLE I COMPARISON OF BASELINE CHARACTERISTICS IN THE TWO GROUPS

Baseline Characteristics	*HHHFNC (n=46)*	*NCPAP (n=42)*	*P value*
Gestational age (wk)*	31.1 (2.3)	31.4 (2.3)	0.22
Birthweight (g)*	1313 (211)	1353 (208)	0.07
Male gender#	25 (54%)	18 (43%)	0.30
Intra Uterine Growth Retardation#	7 (15%)	8 (19%)	0.77
Steroids#			
No steroids	19 (41%)	19 (45%)	
Inadequate steroids	14 (30%)	10 (24%)	0.78
Adequate steroids	13 (28%)	13 (31%)	
Vaginal delivery#	28 (61%)	33 (78%)	0.07
Resuscitated at birth#	15 (33%)	14 (33%)	0.94
APGAR Score at 5 minute**	8 (7,8)	8 (7,8)	0.35
Silverman Anderson Score**	4 (4,5)	5 (4,5)	0.08
FiO_2 at initiation*	41.2 (8.7)	39.7 (9.4)	0.11
Surfactant#	25 (54%)	30 (71%)	0.12
Age at receiving surfactant (h)*	2.46 (2.5)	2.83 (2.26)	0.46
Age at starting respiratory support (h) *	2.33 (1.09)	1.82 (1.25)	0.05

*Values in *mean (SD), **median (IQR) or # No.(%). HHHFNC- Heated Humidified High Flow Nasal Cannula, NCPAP- Nasal Continuous Positive Airway Pressure.*

TABLE II PRIMARY AND SECONDARY OUTCOMES IN TWO STUDY GROUPS

No	*HHHFNC (n=46)(%)*	*NCPAP (n=42)(%)*	*Relative risk/Mean difference (95 % CI)*	*P value*
Failure	9 (19.5%)	11 (26.2%)	0.74 (0.34-1.62)	0.46
Duration of support (h)*	67.15 (40.69)	66.9 (36.1)	0.25 (-15.79 to 16.29)	0.98
Ventilator days*	2.0 (0.81)	1.75 (0.86)	0.25 (-0.10 to 0.60)	0.16
Duration of oxygen requirement (d)*	3.76 (2.6)	3.5 (2.2)	0.26 (-0.74 to 1.26)	0.62
Bronchopulmonary dysplasia	2 (4.3%)	1 (2.3%)	1.82 (0.17-19.4)	0.61
Patent ductus arteriosus	12 (26%)	10 (24%)	1.09 (0.52- 2.60)	0.80
Feed intolerance	10 (22%)	9 (21%)	1.01 (0.45-2.25)	0.71
Necrotizing enterocolitis	3 (6.5%)	2 (4.7%)	1.36 (0.24-7.80)	0.72
Intraventricular hemorrhage (> grade 2)	3 (6.5%)	2 (4.7%)	1.36 (0.24-7.80)	0.72
Retinopathy of prematurity > stage 3	2 (4.3%)	2 (4.7%)	0.91 (0.13-6.19)	0.92
Early onset sepsis (EOS)				
Clinical	13 (28%)	9 (21%)	1.31 (0.62-2.76)	0.46
Culture positive	6 (13%)	5 (12%)	0.09 (0.36-3.32)	0.87
Late onset sepsis (LOS)				
Clinical	9 (20%)	11 (26%)	0.74 (0.34-1.62)	0.46
Culture positive	5 (11%)	7 (17%)	0.65 (0.22-1.89)	0.43
Pulmonary interstitial emphysema	5 (11%)	7 (17%)	0.65 (0.22-1.89)	0.43
Mortality	6 (13%)	6 (14%)	0.91 (0.31-2.61)	0.86
Nasal Trauma[#]				
Mild	14 (30%)	9 (21%)	1.42 (0.68 to 2.93)	0.34
Moderate	4 (9%)	13 (31%)	0.28 (0.09 to 0.79)	0.01
Severe	1 (2%)	4 (10%)	0.25 (0.02 to 2.14)	0.01
Moderate or severe	5 (11%)	17 (41%)	0.26 (0.12 to 0.47)	0.004
Time to reach full feeds (d)*	9.46 (3.65)	10.6 (6.13)	-1.14 (-3.27 to 0.99)	0.29
Duration of hospitalization (d)*	19.5 (14.4)	19.3 (9.3)	0.20 (-4.82 to 5.22)	0.94

*Values in No (%) or * mean (SD),HHHFNC- Heated Humidified High Flow Nasal Cannula, NCPAP- Nasal Continuous Positive Airway Pressure. 95% CI =95% confidence interval.*

as shorter duration of study mode support than infants managed by HHHFNC. The change of the nasal interface and/or use of protective nasal dressings did not seem to decrease the nasal trauma for infants on NCPAP [17,18]. Recent trials reported a significantly lesser nasal trauma in the HHHFNC group [18,19]. Apart from cosmetic distortion, a breach of mucocutaneous barrier may act as an avenue for infection, especially by gram-negative bacteria [20]. Despite concerns of unregulated pressure delivery during HHHFNC support, no difference in the occurrence in any form of air leak has been found in several studies which compared HHHFNC with NCPAP [10,21]. The concerns of over inflation or under recruitment of alveoli by HHHFNC stemmed from some earlier studies [22-24]. Recent studies have clearly shown that HHHFNC is as efficient as NCPAP as a post-extubation respiratory support in preterm infants [9,10,19]. Clinically important pressures are now generated after the introduction of better designed systems which provide optimal heating and humidification [24,25].

In conclusion, HHHFNC appears to have similar efficacy and safety to NCPAP when applied as a primary mode of respiratory support to preterm infants between 28 and 34 weeks of gestation with mild to moderate respiratory distress. HHHFNC causes less nasal trauma than NCPAP. The use of HHHFNC as a primary therapy for respiratory distress from birth requires further research in form of well-designed randomized controlled trials with adequate sample size.

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WHAT IS ALREADY KNOWN?

- Headed humidified high-flow nasal cannula (HHHFNC) is comparable to nasal CPAP in efficacy as a post-extubation respiratory support.

WHAT THIS STUDY ADDS?

- HHHFNC is similar in efficacy to nasal CPAP as a primary mode of respiratory support in preterm infants.

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