A Randomized Controlled Trial to Compare Heated Humidified High-Flow Nasal Cannulae with Nasal Continuous Positive Airway Pressure Postextubation in Premature Infants

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Objective To determine whether postextubation respiratory support via heated, humidified, high-flow nasal cannulae (HHHFNC) results in a greater proportion of infants younger than 32 weeks' gestation being successfully extubated after a period of endotracheal positive pressure ventilation compared with conventional nasal continuous positive airway pressure (NCPAP).

Study design We randomly assigned preterm ventilated infants to Vapotherm HHHFNC or NCPAP after extubation. The primary outcome, extubation failure, was defined by prespecified failure criteria in the 7 days after extubation.

Results A total of 132 ventilated infants younger than 32 weeks' gestation were randomized to receive either HHHFNC (n = 67) or NCPAP (n = 65). Extubation failure occurred in 15 (22%) of the HHHFNC group compared with 22 (34%) of the NCPAP group. There was no difference in the number of infants reintubated in the first week. Treatment with HHHFNC reduced the nasal trauma score 3.1 (SD 7.2) versus NCPAP 11.8 (SD 10.7), $P < .001$.

Conclusions HHHFNC and NCPAP produced similar rates of extubation failure. *(J Pediatr 2013;162:949-54)*.

Nasal continuous positive airway pressure (NCPAP) improves the rate of successful extubation in premature infants. Extubation failure rates vary with gestation, birth weight, and mode of NCPAP.[1] The most effective way of providing NCPAP is with short binasal prongs that fit snugly in an infant's nose to minimize air leakage.[2] The pressure within the continuous positive airway pressure circuit is regulated directly and transmits positive distending pressure to the upper airway.[3] Several NCPAP devices are available, but all can cause nasal trauma. Damage to the skin often is mild and resolves with the cessation of NCPAP but can result in permanent disfigurement and long-term functional sequelae.[4,5]

Heated, humidified, high-flow nasal cannulae (HHHFNC) deliver blended gas at flow rates (>1 L/min) through nasal cannulae smaller than those of NCPAP. HHHFNC prongs usually are smaller than 1 cm in length, with a narrow diameter that taper towards the ends. The prongs are positioned to sit just inside the nares and do not provide a seal. The circuit flow is adjusted according to clinical variables. There is a pressure relief valve in the circuit but pressures are not routinely measured in clinical practice. HHHFNC transmit a positive end distending pressure to the infant's upper airway.[6-11]

HHHFNC seem to be well tolerated in patients and easy to apply, leading to increased use around the world. In a number of reports, authors describe the use of HHHFNC as a mode of respiratory support in premature infants[12-15]; however, these are a heterogeneous group of studies with respect to study design, sample size, and flow rates used, which makes it difficult to draw meaningful clinical conclusions. A 2011 Cochrane review of respiratory support via nasal cannula at >1 L/min in preterm infants found insufficient evidence to establish their safety or efficacy in the preterm population.[16] We undertook this study to determine whether postextubation respiratory support via HHHFNC would result in comparable rates of successful extubation when compared with NCPAP.

Methods

Infants were eligible for the study if they were born at less than 32 weeks' gestation, required endotracheal intubation and positive pressure ventilation, and were considered ready for extubation by the clinical team. Infants with suspected upper airway obstruction, congenital airway malformations, or major cardiopulmonary

BPD	Bronchopulmonary dysplasia
FiO_2	Fraction of inspired oxygen
HHHFNC	Heated, humidified, high-flow nasal cannulae
NCPAP	Nasal continuous positive airway pressure
NIMV	Nasal intermittent mandatory ventilation
PEEP	Positive end-expiratory pressure

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malformations were excluded. The study was approved by the Institutional Human Research Ethics Committee of Mercy Hospital for Women, Melbourne, Australia. The trial was not registered because it was approved in 2007, prior to the requirement for trial registration in Australia. Informed written consent was obtained from parents. Infants were randomized to receive HHHFNC via Vapotherm with 1.5-mm external diameter nasal cannulae (Vapotherm Inc, Stevensville, Maryland) or NCPAP via Hudson binasal prongs, 3.7-4.6 mm external diameter (Hudson Respiratory Care Inc, Temecula, California). The same fixation method was used for both nasal interfaces (Sticky Whiskers Beevers Manufacturing & Supply, McMinville, Oregon). A random number sequence was generated with STATA Statistical Software (Release 10.0, 2001; Stata Corp, College Station, Texas). The randomization sequence was stratified by gestational age into less than 28 weeks' gestation and 28.0-31.6 weeks' gestation. A variable block size was used for treatment allocation. Allocation was matched by the use of sequentially numbered, sealed opaque envelopes that were opened immediately before the subjects were extubated.

All infants received a loading dose of 20 mg/kg caffeine citrate before extubation and a maintenance dose of 10 mg/kg/day until 34 completed weeks of gestation. The decision to extubate was at the discretion of the treating physician; no mandatory extubation variables were set. Infants allocated to NCPAP were extubated to a positive end-expiratory pressure (PEEP) of 8 cm H_2O if the fraction of inspired oxygen (FiO_2) > 0.3 or a PEEP of 7 cm H_2O if FiO_2 <0.3. Oxygen saturation targets were 85%-92%. PEEP was weaned to a minimum of 5 cm H_2O. Infants allocated to Vapotherm HHHFNC were extubated to a flow rate of 8 L/min. Oxygen saturation targets were 85%-92%. Flow rate was weaned to a minimum of 4 L/min.

Clinicians used the FiO_2 and level of respiratory distress to wean therapy in both groups. All infants stayed on their assigned mode of respiratory support until they were able to manage without respiratory support or changed to unhumidified low flow subnasal oxygen ≤0.2 L/min. The primary outcome of extubation failure in the 7 days after extubation was defined a priori. Individual failure criteria were not mutually exclusive and were defined as follows: apnea (respiratory pause >20 seconds), more than 6 episodes in 6 hours or 1 requiring intermittent positive pressure ventilation; acidosis, pH <7.25 and PCO_2 >66 mmHg and >15% sustained increase in FiO_2 from extubation. Extubation failure was deemed to have occurred if any single criterion was met in any one of the 7 days after extubation. The decision to reintubate an infant remained with the treating physician.

A nasal trauma score was adapted from Kaufman et al,[17] and nasal trauma scores were recorded 3 times daily for the 7 days after extubation. The sum of these 21 scores was used as the summary measure of nasal trauma (**Appendix**; available at www.jpeds.com). The duration of respiratory support and supplemental oxygen requirement were recorded. Bronchopulmonary dysplasia (BPD) was defined as the need for respiratory support or supplemental oxygen at 36 weeks postmenstrual age. Cranial ultrasounds were performed on days 3, 14, 28, and 42 if the infant remained hospitalized in the study center. Scans were reported by a single radiologist blinded to study allocation using the Papile classification. Necrotizing enterocolitis was defined at surgery, or by radiographic evidence of pneumatosis intestinalis, hepatobiliary gas, or free peritoneal air. Infants were deemed to have achieved full enteral feeds 120 mL/kg/day was sustained for 3 consecutive days. Incidence of postextubation pneumothoraces was recorded.

Statistical Analyses

Review of data from the study center over a 2-year period (2004-2006) revealed 50% of infants <32 weeks' gestation who required mechanical ventilation met the study extubation failure criteria in the 7 days after extubation with a reintubation rate of 35%. A sample size of 130 provided 80% power to detect a reduction in extubation failure from 50% to 25% (alpha = 0.05). Analysis was by intention to treat. Mean values and proportions between groups were analyzed by Student *t* test or 2-sample test of proportions, respectively. All statistical analyses were performed using STATA Statistical Software: (Release 10.0. Stata Corp).

Results

The numbers of infants who were eligible for the study and the numbers who were randomly assigned to either Vapotherm HHHFNC or NCPAP are shown in **Figure 1**. A total of 132 infants were enrolled between January 1, 2009, and July 31, 2011. All infants were followed for the first 7 days after extubation, and 121 infants were followed until their discharge home.

The baseline demographic and ventilation characteristics of enrolled infants are shown in **Table I**, and, with the exception of sex, were similar. There were more males in the NCPAP group n = 41 (63%) compared with n = 33 (49%) of those assigned HHHFNC. There was no interaction of sex with the primary outcome variable of extubation failure ($P = .5$).

Primary outcomes overall and by subgroup are shown in **Table II**, and secondary outcomes are in **Table III** (available at www.jpeds.com). There were no differences in rates of extubation failure or BPD between the 2 groups. There were no differences in extubation failure rates in either gestational age stratum. Infants assigned to HHHFNC had significantly less nasal trauma than those assigned to NCPAP ($P < .001$).

The flowchart for infants in each group is shown in **Figure 2**. Seven infants assigned to HHHFNC and 8 in the NCPAP group were reintubated in the first week after extubation, having met the failure criteria. Two infants assigned to HHHFNC and 7 assigned to NCPAP were changed to nasal intermittent mandatory ventilation (NIMV), having met the failure criteria. At parental request, one infant's therapy was changed from NCPAP to HHHFNC; consent was retained for the use of primary outcome data.

A total of 13 (20%) of infants assigned to NCPAP were changed to HHHFNC as the result of nasal trauma in the first