High Flow Nasal Cannulae Therapy in Infants with Bronchiolitis

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Objectives To determine whether the introduction of heated humidified high-flow nasal cannulae (HFNC) therapy was associated with decreased rates of intubation for infants <24 months old with bronchiolitis admitted to a pediatric intensive care unit (PICU).

Study design A retrospective chart review of infants with bronchiolitis admitted before and in the season after introduction of HFNC.

Results In the season after the introduction of HFNC, only 9% of infants admitted to the PICU with bronchiolitis required intubation, compared with 23% in the prior season (*P*=.043). This 68% decrease in need for intubation persisted in a logistic regression model controlling for age, weight, and RSV status. HFNC therapy resulted in a greater decrease in respiratory rate compared with other forms of respiratory support, and those infants with the greatest decrease in respiratory rate were least likely to be intubated. In addition, median PICU length of stay for children with bronchiolitis decreased from 6 to 4 days after the introduction of HFNC.

Discussion We hypothesize that HFNC decreases rates of intubation in infants with bronchiolitis by decreasing the respiratory rate and work of breathing by providing a comfortable and well-tolerated means of noninvasive ventilatory support. *(J Pediatr 2010;156:634-8)*.

Viral bronchiolitis is a common cause of lower respiratory tract infection in infants and often requires hospitalization in children younger than 2 years of age. It is characterized by wheezing and mucous plugging, resulting in airway obstruction. Monitoring and supportive therapy are the mainstays of treatment because no specific medical therapy is of proven benefit.

Respiratory support in infants with severe bronchiolitis has historically been provided by supplemental oxygen. Nasal continuous positive airway pressure (NCPAP) has been shown to improve clinical scores, decrease respiratory rate (RR), and improve ventilation in infants admitted to a pediatric intensive care unit (PICU) with bronchiolitis.[1-4] However, NCPAP is cumbersome and typically poorly tolerated by infants and young children.[5] Infants with more significant respiratory distress or with apnea require endotracheal intubation and mechanical ventilation to support oxygenation and ventilation. These therapies, however, may result in barotrauma or volutrauma to the lungs, trauma to the airways, or ventilator-associated pneumonia.[5]

Heated, humidified, high-flow nasal cannulae (HFNC) is a relatively new therapy that allows the delivery of high inspired gas flows (1-8 L/min in infants) with or without an increased oxygen concentration.[6-8] Ideally, these devices should deliver flow greater than the patient's peak inspiratory demand to fully supply a patient's minute ventilation. In addition to providing heated and humidified gases, HFNC provides some level of continuous positive airway pressure (CPAP), although the exact level cannot always be predicted. Neonatal studies show that the amount of CPAP generated depends on the flow delivered relative to the size of the patient and on the leak around the nasal cannulae.[9-11] Flows of 3 to 5 L/min in term and preterm infants with the Fisher & Paykel system (Fisher & Paykel Healthcare, Irvine, California) with Salter brand infant-size cannulae (Salter Labs, Arvin, California) have been shown to generate CPAP measured as intrapharyngeal pressure of 1.7 to 4.8 cm H_2O.[12]

A randomized study of HFNC versus NCPAP used after extubation to prevent reintubation in preterm infants <1250 g showed that HFNC "failed to maintain extubation status" as effectively as NCPAP.[13] A subsequent study, however, with HFNC and an early extubation protocol in preterm infants 25 to 29 weeks gestation showed that infants could safely be extubated from higher ventilator settings and thus had fewer ventilator days compared with historical control subjects.[14] In addition, a retrospective study of two tertiary care hospitals after the introduction of HFNC demonstrated that with the increase in use of HFNC compared with NCPAP in historical control subjects, overall ventilator days per patient decreased from 19.4 to 9.9 with no associated increase in other adverse outcomes.[15]

CPAP	Continuous positive airway pressure
HFNC	Heated humidified high flow nasal cannulae
LOS	Length of stay
NCPAP	Nasal continuous positive airway pressure
PICU	Pediatric Intensive Care Unit
RR	Respiratory rate
RSV	Respiratory syncytial virus

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No studies to date have addressed the use of HFNC to support infants with bronchiolitis. The primary goal of this retrospective study was to determine whether the availability of HFNC was associated with a decreased need for intubation for infants with bronchiolitis admitted to a PICU. The secondary goals were to describe the changes in respiratory measurements in infants treated with HFNC and to determine whether certain subgroups of infants showed a greater benefit.

Methods

The Fisher Paykel heated HFNC system (MR850 humidification system; Fisher & Paykel Healthcare) became available at our institution in September 2006. Low-resistance nasal cannulae available included the infant cannulae with a maximum flow rate of 7 L/min and the pediatric cannulae with a maximum flow rate of 8 L/min. Most of the infants in this study were admitted to the PICU from the emergency department or were transferred to the PICU from the general pediatrics unit. HFNC oxygen therapy was not available in those locations at the time of this study. The decision to use the HFNC was at the discretion of the attending physician in the PICU. No specific protocol was in place for use of the cannulae; however, the size of the cannulae was chosen to fit the child's nares without occlusion. Flow rate was usually started at the maximum flow rate for the particular size of cannula. A retrospective chart review was conducted to compare infants admitted from January 2005 to May 2006, before the introduction of HFNC, to infants admitted the following season from October 2006 to May 2007. No cases of bronchiolitis were seen in the summer from May 2006 to October 2006 between the seasons, nor from April to October 2005 during the first period of data collection.

All infants age <24 months who were admitted to the PICU with a diagnosis of bronchiolitis (respiratory syncytial virus [RSV] positive, RSV negative, or not specified), respiratory distress, or respiratory failure were included in our chart review. Infants were excluded if their primary diagnosis was not bronchiolitis (eg, reactive airway disease or pneumonia), or if they had a preexisting tracheostomy or were intubated in the prehospital setting, because these infants were not potential candidates for HFNC therapy. Infants were classified into 2 groups on the basis of whether HFNC was available for use. Infants admitted from January 2005 to May 2006, when HFNC was not available, were classified as HFNC-NA. Infants admitted from October 2006 to May 2007, when HFNC was available for use, constituted the HFNC-A group. All admitted patients with clinical bronchiolitis were included, whether they received HFNC or another means of respiratory support, and the groups were analyzed by the dates of their admission unless specifically noted otherwise.

Data collected included sex, age, weight, gestational age, respiratory rate, oxygen saturation at PICU presentation, the respiratory intervention received (eg, blow-by oxygen), changes in the vital signs 1 hour after that intervention, whether endotracheal intubation was required, RSV status, any complications of therapies administered, and PICU length of stay. Full term was considered to be 40 weeks gestational age for data analysis. Prematurity was defined as a gestational age of less than 37 weeks.

Intubation criteria were based on overall clinical status including RR and work of breathing (retractions, flaring, grunting) and ability to maintain that respiratory effort. In addition, poor neurologic status (tiring or lethargy), cyanosis, mottling, poor perfusion, apnea, or inability to maintain adequate oxygen saturation were indications for intubation. Rarely were blood gases obtained as a criterion.

For an infant to be discharged from PICU, he or she could have blow-by or standard nasal cannulae oxygen, but neither mechanical ventilation nor high-flow nasal cannulae could be used on the general pediatric wards during these seasons. The patient also had to be off all continuous intravenous sedative drips but could still be on a sedative wean (intravenous or oral). Apnea/bradycardia monitors were available on the general pediatric unit; however, true cardiac rhythm monitoring and oxygen saturation monitoring were available only in the PICU. Additionally, the infant could require interventions (vital signs, suctioning, etc) no more frequently than every 4 hours to be transferred from the PICU to the general pediatric unit.

Data analysis

For preliminary analyses, study groups were compared by use of the Fisher exact test for categorical variables and are presented with percentages. For continuous variables, the Wilcoxon rank-sum test was used because many exhibited skewed distributions. These data are presented with medians and minimums and maximums. Differences between the study groups in risk for selected clinical variables were computed as odds ratios and are reported with exact 95% confidence intervals. Logistic regression was used to estimate differences between the groups in risk, after controlling for possible confounding factors. Results from the logistic models are expressed as adjusted odds ratios with exact 95% confidence intervals. All data were analyzed with Stata (version 10.1; StataCorp, College Station, Texas).

Results

One hundred fifteen infants met all of the inclusion and none of the exclusion criteria and were included in the analysis, 57 from before the introduction of HFNC (2005–2006, HFNC-NA group) and 58 from the season after the introduction of HFNC (2006–2007, HFNC-A group). The age, weight, gestational age, sex, RSV status, and Pediatric Index of Mortality 2[16] score were similar between the two groups (**Table I**). More children in the HFNC-NA group had a history of prematurity, defined as a gestational age <37weeks (40% vs 19%), but the mean and median gestational ages were not significantly different (mean 36.7 weeks vs 38.4 weeks). History of chronic lung disease was similar between groups. No children in the HFNC-NA group had a history of congenital heart disease, but 1 infant in the HFNC-A group had a history of Down's syndrome after atrioventricular canal repair. The 2

Table I. Patient characteristics, vital signs and initial respiratory support in PICU in the 2005–2006 group, before the introduction of HFNC and in the 2006–2007 group after introduction of the HFNC

Characteristic	2005–2006 (HFNC-NA) (n = 57)	2006–2007 (HFNC-A) (n = 58)	*P* value
Age (mos) (median)	3.0 (0.5-19.0)	2.0 (0.25-24.0)	.09
Weight (kg) (median)	5.8 (2.5-12.3)	5.2 (2.6-14.6)	.25
Gestational age (wks) (median)	40 (24-40)	40 (23-40)	
Admission RR (breaths/min) (median)	47 (21-85)	61 (24-120)	<.001
Admission O_2 saturation (median)	97 (68-100)	95 (56-100)	.18
Pediatric Index of Mortality 2 (median)	0.40 (0.2-1.8)	0.40 (0.2-1.2)	.39
Sex (% male) (median)	32 (56.1%)	37 (63.7%)	.45
RSV positive (median)	29 (50.9%)	40 (69.0%)	.06
Respiratory support			<.001
Room air	9 (15.8%)	1 (1.7%)	
Blow-by oxygen	9 (15.8%)	1 (1.7%)	
Nasal cannula	33 (57.9%)	5 (8.6%)	
Simple face mask	1 (1.8%)	0	
Non- rebreather mask	2 (3.5%)	0	
Nasal CPAP	3 (5.3%)	0	
HFNC	0	51 (87.9%)	

groups had similar oxygen saturation levels at time of PICU admission; however, the median admitting respiratory rate was significantly higher in the HFNC-A group.

In the season before introduction of HFNC, most infants admitted with bronchiolitis received nasal cannula oxygen as their primary means of respiratory support (57.9%), with a smaller number treated with other therapies (Table I). During the 2006–2007 season, 51 (87.9%) of the 58 infants admitted with bronchiolitis received HFNC oxygen as supportive therapy.

In the season before the introduction of HFNC, 13 (23%) of the 57 infants who presented with bronchiolitis required intubation as compared with 5 (9%) of the 58 infants who presented the following season when HFNC was available as a treatment option ($P = .043$). Thus the availability of HFNC resulted in a 14% absolute risk reduction in the need for intubation, yielding a number needed to treat of 7. In this unadjusted logistic regression analysis, the availability of HFNC reduced the need for intubation in infants < 24 months of age presenting to a PICU with bronchiolitis by 68%. Controlling for age, weight, and RSV status, the results remained essentially unchanged (Table II), with a 68% decrease in the risk of requiring intubation in the season that HFNC was available. Controlling for gestational age in addition to the above, the influence of the availability of HFNC attenuated somewhat, resulting in a risk reduction of 65%.

A subgroup analysis with multivariate logistic regression did not demonstrate a group that showed particular benefit from HFNC when comparing RSV positive versus negative, or by age, weight, or gestational age. The small numbers of patients analyzed may have precluded us from finding a difference. The data suggests that infants with a history of prematurity may have greater benefit from HFNC therapy, with 8 of 23 (34.8%) formerly premature infants intubated in the HFNC-NA group as compared with only 1 of 11 (9%) formerly premature infants intubated in the HFNC-A group, but numbers were too small confirm this statistically ($P = .21$).

In addition, the infants who actually received HFNC therapy (n = 51) were compared with those who did not receive HFNC (from both seasons) for differences in response to the therapy received. Initial oxygen saturation was not different between groups and changes in oxygen saturation after initiation of therapy were not statistically different. However, infants who were treated with HFNC had a decrease in RR 1 hour after initiation of therapy of 18 ± 16 breaths/min compared with 6 ± 14 breaths/min in those who did not receive HFNC therapy (difference 12 breaths/min, $P < .001$). This effect persisted in a logistic regression model controlling for age, weight, gestational age and whether the infant required intubation (difference 11 breaths/min, $P < .0005$, 95% confidence interval: −17, −5).

Additionally, those infants who did not experience a clinically significant change in respiratory rate after HFNC were more likely to be intubated. Infants who were intubated experienced a decrease of 1 ± 17 breaths/min in RR 1 hour after initiation of HFNC therapy. Infants who did not require intubation had a 14 ± 15 breaths/min decrease in RR after initiation HFNC ($P < .003$). Of the infants who were not treated with HFNC, the change in respiratory rate 1 hour after initiation of respiratory support was the same for infants who

Table II. Results of logistic regression analyses of rates of intubation in the season after the introduction of HFNC therapy

Logistic model	OR	95% CI	*P* value
Unadjusted			
HFNC-NA	1.0	(reference)	
HFNC-A	.32	0.11-0.97	.043
Adjusted for age, weight, and RSV status:			
HFNC-NA	1.0	(reference)	
HFNC-A	.32	0.10-0.99	.049
Adjusting for age, weight, RSV status, and gestational age			
HFNC-NA	1.0	(reference)	
HFNC-A	0.35	0.11-1.14	.072

were intubated (3 ± 19 breaths/min) versus those who were not (7 ± 13 breaths/min, $P = .39$).

PICU length of stay (LOS) decreased from a median of 6 days in the HFNC-NA group to 4 days in the HFNC-A group ($P = .0058$). This was accounted for primarily by the infants who required intubation, who had a significantly longer LOS (median 13 days, min-max 5-40 days) than those not intubated (median 5 days, min-max 1-20 days). The infants who were intubated remained so for an average of 7.8 days.

HFNC was well tolerated by infants, and no complications of the therapy were seen, including nasal or facial trauma from the application of the therapy. There were no deaths in either group of patients. One patient in each group, both of whom were intubated and mechanically ventilated, had development of pneumothoraces as a complication of this therapy. Infants tolerated nasogastric feeds well with HFNC therapy, and some were eventually able to tolerate oral feeds with the HFNC in place.

Discussion

In this retrospective chart review, infants < 24 months of age who presented to the PICU with bronchiolitis demonstrated a 68% decrease in need for intubation with the introduction of HFNC therapy. This difference is unlikely to be explained by other patient characteristics, because the groups were similar at baseline. In addition, the difference persisted in a logistic regression controlling for age, weight, RSV status, and gestational age. External factors other than the introduction of HFNC were also unlikely to account for the difference seen, because admission criteria for the PICU did not change, nor did the attending staff who ultimately decided which patients required intubation. There was minimal change in the respiratory therapy or nursing staff (<10% turnover) who cared for these patients between seasons. There was no other significant change in the standard of care for bronchiolitis between these 2 seasons, including use of nebulized medications, steroids for specific indications, or suctioning.

Infants who were treated with HFNC experienced a significant decrease in respiratory rate within 1 hour after initiation of the therapy that was not observed in infants receiving other forms of oxygen and respiratory support. Not surprisingly, those who experienced the greatest decrease in RR with HFNC were the least likely to be intubated. This supports the hypothesis that HFNC decreases work of breathing and prevents need for intubation by delivering CPAP. The relatively immediate effect of HFNC therapy also supports this hypothesis. If an alternate mechanism, such as thinning of secretions were responsible, the effect would take several hours to reach its peak.

Nasal CPAP with[1] and without[2-4] heliox has been shown to decrease RR, pCO_2, and potentially prevent intubation in infants with bronchiolitis. However, it is often poorly tolerated by infants beyond the newborn period because of the need to snugly affix the relatively large prongs in the infants nose and the tubing to the face. HFNC, by providing CPAP with a less obtrusive device, may result in the same benefits as NCPAP with improved comfort and tolerance for the patient. Work of breathing in 18 preterm neonates (< 2 kg) as measured by esophageal balloon catheter was no different in infants on 3 L/min, 4 L/min, or 5 L/min of HFNC compared with nasal CPAP 6.[17] Tidal volumes and respiratory rates were similar on these flows as compared with nasal CPAP 6. Adults supported with 5 to 40 L/min HFNC showed a decrease in respiratory rate and work of breathing with no reported discomfort from the therapy.[18] We hypothesize that HFNC decreases rates of intubation in infants with bronchiolitis by decreasing the RR and work of breathing by providing a comfortable and well tolerated means of noninvasive ventilatory support. A prospective randomized trial of HFNC therapy with objective measures of work of breathing could test this hypothesis.

The longer PICU LOS in the HFNC-NA is accounted for by the greater number of intubated infants in that group. By decreasing the need for intubation in this group of infants admitted to a PICU with clinical bronchiolitis, HFNC decreased the median PICU LOS.

In conclusion, we propose that HFNC provides a well-tolerated means of ventilatory support in infants with bronchiolitis. HFNC decreases RR and may decrease the work of breathing in infants with bronchiolitis and thereby may prevent the need for intubation and mechanical ventilation. ■

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