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Using high-flow nasal cannulas for infants with bronchiolitis admitted to paediatric wards is safe and feasible

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Short title: High-flow nasal cannulas for infant bronchiolitis

ABSTRACT

Aim. Using a high-flow nasal cannula (HFNC) for infant bronchiolitis is increasingly common, but insufficiently studied. In this retrospective study, we examined the outcomes of HFNC and compared infants who did and did not respond to this oxygen delivery method.

Methods. This 2012-2015 study of six Finnish hospitals focused on 88 infants under 12 months who received HFNC: 53 on paediatric wards and 35 in paediatric intensive care units (PICUs). We reviewed patient files for underlying factors, clinical parameters and HFNC treatment. The treatment failed if the patient was transferred to another respiratory support.

Results. We found HFNC treatment was successful in 76 (86%) infants, including all 53 on the paediatric wards and 23/35 PICU patients. The responders´ heart rates were significantly lower and their oxygen saturation was significantly higher 60 minutes after HFNC treatment started, then stayed relatively constant. Their respiratory rate was only significantly lower after 360 minutes. In non-responders, the respiratory rate initially decreased but was higher at 180 and 360 minutes after the start of HFNC.

Conclusion. We found preliminary evidence that oxygen support needs and heart rate were useful early predictors of HFNC therapy success in infants hospitalised with bronchiolitis, but respiratory rate was not.

Key words: Bronchiolitis, high-flow oxygen cannula, infant, oxygen saturation, respiratory rate

Key notes

- Infants with bronchiolitis often receive oxygen delivered by high-flow nasal cannulas (HFNC), but outcome data are scarce.
- Our retrospective study of 88 infants under 12 months found that 86% responded well: 53/53 on paediatric wards and 23/35 in paediatric intensive care units.
- We found preliminary evidence that oxygen support needs and heart rate may be useful early predictors of HFNC in infants with bronchiolitis, but respiratory rate may not be.

INTRODUCTION

Bronchiolitis is the main infectious reason for hospitalisation of less than 12 months old infants when they do not have any notable underlying disease. On average, 1-3% of infants need to be treated in hospital (1) and Finnish studies have reported that 6% of hospitalised infants were treated in a paediatric intensive care unit (PICU) (2, 3). Bronchiolitis is diagnosed on a clinical basis and existing guidelines recommend that the cornerstones of bronchiolitis treatment are careful monitoring of oxygenation and fluid intake and supplementing these and providing ventilator support as necessary (4). Minimal handling is now recommended when treating bronchiolitis, which means avoiding of unnecessary manoeuvres such as drug or saline inhalations (5). Systematic reviews have showed that inhaled salbutamol and other beta-agonists (6), as well as systemic or inhaled corticosteroids

(7), are ineffective in bronchiolitis. Inhaled racemic adrenalin may also be useful in some cases (8).

Most guidelines consider that an oxygen saturation level of 92% is sufficient and recommend a threshold of 90% to 92% when supplementary oxygen needs to be started (9, 10). A multicentre, double-blind, randomised controlled trial (RCT) concluded that an oxygen saturation rate of 90% was as safe and clinically effective as 94% (11). Using of high-flow nasal cannula (HFNC) to treat infants with bronchiolitis who need supplementary oxygen is increasingly common, but insufficiently studied. If low oxygen saturations like 90% are accepted, the way that the oxygen is administered is crucial.

HFNC treatment has many potential physiological benefits. The oxygen saturation levels increase, the infants` breathing becomes easier and slower and three pilot studies reported that this resulted in improved clinical scores in infants with bronchiolitis (12-14). HFNC treatment also decreased the intubation rates recorded by two retrospective chart reviews (15, 16). Two prospective RCTs of 202 and 1472 infants showed that treatment failures were less frequent with HFNC than standard low-flow oxygenation and that more than half of the patients who failed standard low-flow therapy were successfully rescued with HFNC (17, 18). HFNC has been shown to be well tolerated and can be safely used on paediatric wards (13, 19).One pilot study reported that decreasing heart and respiratory rates during the first hour after starting HFNC treatment predicted treatment success (19).

We previously carried out a questionnaire study on using HFNC for infant bronchiolitis during the 2015-2016 respiratory syncytial virus epidemic in Finland and received replies from 17 hospitals, covering 77.5% of the infants born in Finland in 2015. This showed that most HFNC (85%) was given on paediatric wards (20). The aim of this retrospective,

multicentre study was to evaluate the real-life use of HFNC in infants with bronchiolitis, focusing on why some treatment succeeded and some failed.

MATERIAL AND METHODS

Design

We identified infants treated with HFNC for bronchiolitis at less than 12 months of age in 2012-2015 from the electronic patient files of six Finnish hospitals. This retrospective multicentre review of patient records covered two tertiary-level university hospitals (Tampere and Oulu) and four secondary-level central hospitals (Seinäjoki, Jyväskylä, Lahti and Joensuu) in Finland. We carried out the study with the permission of the chief physician of each attending hospital, and we did not contact the patients and the data was handled as coded, and the study did not require parental permission.

The population of less than 12 months old children in the six hospital districts, based on Government data, represented 33% of the children born in Finland in 2015: Tampere (5,425), Oulu (4,988), Seinäjoki (2,057), Jyväskylä (2,583), Joensuu (1,507) and Lahti (1,887). The hospitals were from different parts of Finland in order to provide a good geographic spread.

Data collection

We collected the data for this study from electronic files of each hospital, and identified infants diagnosed with bronchiolitis who received HFNC treatment, based on the notes made by medical staff. We used the International Classification of Diseases Tenth Revision codes J10-18, J20-22, J45 and J46 and included bronchiolitis cases treated on the wards or in the paediatric intensive care units (PICU) of the attending hospitals from 2012 to 2015.

Bronchiolitis was defined as the first breathing difficulty, with or without wheezing, in association with an acute lower respiratory tract infection at less than 12 months of age. Having confirmed the diagnosis we selected those patients who had been treated with HFNC during bronchiolitis hospitalisation and collected the detailed baseline and clinical data using a structured form.

The hospital and the year when the patient was in hospital was recorded and we collected data on age at admission, gender, gestational age, birth weight, length of stay in hospital and the duration of HFNC treatment. We also recorded the presence of any underlying diseases including respiratory distress syndrome of a newborn infant, and the presence of bronchopulmonary dysplasia or congenital heart disease. Any doctor-diagnosed atopic disease, such as atopic dermatitis or food allergies, any family history of asthma and the use of beta-agonists and inhaled corticosteroids were also recorded.

We recorded the flow settled in the HFNC device in L/min and L/min/kg and the percentage of oxygen concentration at the beginning of the HFNC treatment, and after 60, 180 and 360 minutes. The flow and percentage were also recorded at the time of weaning from HFNC if HFNC treatment was successful or at the time of transfer to another respiratory support if HFNC treatment was unsuccessful. We collected data on heart and respiratory rates and oxygen saturations on admission and at the same time points. Respiratory syncytial virus aetiology of bronchiolitis was recorded. All these data were collected separately for the ward and PICU stays.

Statistics

We performed the statistical analyses with the SPSS 24 Software (SPSS Inc., Chicago, IL, USA). The results were presented as medians and minimum to maximum ranges since the

variables were non-normally distributed in exploratory analyses. Mann-Whitney U test was used for continuous variables when analysing two independent samples and Wilcoxon test for continuous variables when analysing two dependent measurements. Pearson`s chi square test was used for categorised variables.

RESULTS

During the four-year surveillance period, 88 infants with bronchiolitis under 12 months of age were treated with HFNC: 53(60.2%) on the wards and 35 in the PICUs (Fig.1). The numbers of HFNC treatments given on the wards by year were six (60%) in 2013, 25 (60%) in 2014 and 22 (61%) in 2015. We found that 76 infants (86.4%) were just treated with HFNC and they were categorized as responders. The other 12 were transferred to another form of respiratory support and categorized as non-responders: two to mechanical ventilation and 10 to nasal continuous positive airway pressure (Fig.1).

The median age of the 88 infants (58.4% boys) was six (0-42) weeks, the median birth weight was 3278 (640-4800) grams and the median gestational age 38 (24-42) weeks. Both the birth weight and gestational age were significantly lower in non-responders than responders (Table 1). We found that 22 (25%) infants were preterm, born at less than 37 gestational weeks, and of those seven (31.8%) were non-responders (p=0.006 versus 7.6% in full-terms). The respiratory syncytial virus aetiology of bronchiolitis did not differ significantly between responders and non-responders (Table 1).

The median length of stay in hospital was six days in the 76 responders and eight days in the 12 non-responders, but the median duration of HFNC treatment was three days in both groups (Table 1). The median length of stay was six (2-13) days in those 53 treated on the

ward and six (2-22) days in those 35 treated in the PICU. The median duration of HFNC treatment was the same, at three (1-8) days in both groups.

Underlying illnesses and use of medication before bronchiolitis were rare (Table 2). Congenital heart disease was present in five infants and four were responders.

There were no significant differences in heart rates, respiratory rates and oxygen saturations between the responders and non-responders at the start of HFNC treatment (Table 3). As expected, the heart rates were higher and the oxygen saturation lower in non-responders than in responders at the end of HFNC treatment. Only 37-82% of the measurements were precisely recorded in the patient records and could be included in the analyses.

Likewise, there were no significant differences in the flows and oxygen concentrations settled in the HFNC device at the start of HFNC therapy between the responders and non-responders (Table 3). As expected, the required flows and oxygen concentrations were higher in non-responders than in responders at the end of HFNC treatment. The settled flows and oxygen concentrations were precisely recorded in 82-92% of the patient records.

At the start of HFNC treatment, the settled flow was $\leq$0.5 L/min/kg in three (3.4%) patients, and likewise, $\leq$2L/min in three (3.4%) patients. At the end of the HFNC therapy, the settled flow was $\leq$0.5 L/min/kg in 30 (39.5%) responders and $\leq$2L/min in 33 (43.4%) responders.

When the parameters were compared between the start and the end of HFNC therapy, the beneficial changes in heart rate, respiratory rate, oxygen saturation, and required flow rate and oxygen support were significant in responders (Table 3). In non-responders, the only non-beneficial change that was statistically significant was the required flow in the HFNC device (Table 3).

Heart rates, respiratory rates, oxygen saturations, and settled flows and oxygen concentrations were compared at different time points of zero, 60, 180 and 360 minutes from the start of the therapy (Table S1). In responders, heart rates were significantly lower and oxygen saturations significantly higher at the 60-minute point compared to the start, and both remained relatively constant after that. The responders´ respiratory rate only differed significantly from the rate at the start at the 360-minute point. In non-responders, the respiratory rate decreased at first, but was higher at 180 and 360 minutes than at the start of HFNC (Table S1).

DISCUSSION

There are four main results in this retrospective study on HFNC treatment for infant bronchiolitis in six Finnish children`s hospitals in 2012-2015. First, the overall success rate of HFNC treatment was 86.4%, and this included all 53 HFNC treatments that were given on the paediatric wards. Second, lower gestational age, lower birth weight and being born preterm were associated with failures of HFNC treatment, but having a history of respiratory distress syndrome or bronchopulmonary dysplasia were rare and did not explain the HFNC failures. Third, heart rate and oxygen saturation improved during the first 60 minutes of HFNC treatment in responders, but the improvement of respiratory rate took longer, at up to 6 hours. Finally, HFNC treatment was started with a flow of $\leq$0.5 L/min/kg in 3.4% of patients and ended up at that rate in 43.4% of cases. Such flows do not equate to high-flow treatment, and administering of low-flow treatment with an HFNC device may even be harmful.

As summarised previously (21), HFNC treatment has been shown to be effective in reducing the need (15,16,19) and duration of intensive care (15) in bronchiolitis patients compared to

historical controls. The pooled effect was so high in this review, that HFNC therapy proved cost-effective when it was compared to standard low-flow oxygenation (21). In a prospective semi-randomised pilot study (14), the median length of stay in hospital was three days shorter in 18 bronchiolitis patients treated with HFNC and the median duration of oxygen administration was two days shorter when they were compared to those treated with low-flow oxygenation. Thus far, only two RCT studies have been published on HFNC for bronchiolitis (17, 18). Kepreotes et al compared 101 infants with bronchiolitis under 24 months of age treated with HFNC and 101 age-matched controls treated with standard low-flow oxygenation on a paediatric ward in their one-hospital study (17). The treatment failure rate was lower (14% versus. 33%) in those treated with HFNC, and 61% of those with failure in the low-flow group were successfully rescued with HFNC. Franklin et al compared 739 infants with bronchiolitis under 12 months of age treated with HFNC and 733 age-matched controls treated with standard low-flow oxygenation on paediatric wards in their multicenter study (18). The treatment failure rate was lower (12% versus 23%) in those treated with HFNC, and again, 61% of those with failure in the low-flow group were successfully rescued with HFNC. However, the treatment groups did not differ with regard to the length of hospital stay or the duration of oxygen administration in either study. The results mean that 87-93% of hospitalised bronchiolitis patients who needed oxygen support could be treated using standard or HFNC treatments on paediatric wards (17, 18). The respective figure was 56% in our present study, which probably reflected how careful clinicians were when a new mode of treatment was introduced. Prior to that HFNC was just used to treat bronchiolitis in PICUs in occasional cases.

In two Finnish studies, the PICU treatment rate was 6 % among infants hospitalised for bronchiolitis at ages less than 12 months (3) or less than 6 months (2). Low birth weight, low gestational age and congenital heart disease are well-known risk factors for intensive care and

respiratory support in infants with bronchiolitis (23-28). In the present study, infants who did not respond sufficiently to HFNC treatment and needed another more effective method of respiratory support, were more likely to be born preterm, with lower gestational age and birth weight.

Physiological studies have documented the beneficial effects of HFNC treatment in bronchiolitis. One study of 27 infants found that oxygen saturation increased within one hour of starting HFNC and respiratory rate decreased within three hours (12). In a semi-randomised pilot study of 36 infants, the respiratory rate decreased during the first hour and was constant after that (14). Another study of 61 infants found that the heart rate and respiratory rate decreased rapidly in those that responded. This suggests that non-responders who need another more effective form of respiratory support, could be identified during the first hour of HFNC therapy (19). However, in the RCT study of 202 infants with bronchiolitis mentioned above, heart rates did not differ between cases and controls at four or 12 hours, but respiratory rate decreased even more in the controls than cases at four hours (17). In the responders of the present study, respiratory rate was only significantly lower at six hours than at the start of HFNC therapy, but not earlier, while the respiratory rate in non-responders fell initially before increasing. Our observations agree with those of Kepreotes et al (17) and mean that during the first few hours, the respiratory rate cannot be used to screen those infants with bronchiolitis who will not respond to HFNC.

Standard low-flow oxygen administration means that the flow rate is based on widely accepted clinical experience, which is a maximum 2L/min (17,18). Higher flow rates may cause epithelial damage in airways if air-oxygen mixture is not warmed and moistened effectively. In physiological studies, the optimal flow rates in HFNC treatment for infants

with bronchiolitis have been 2-8 L/min (29) or 0.5-2.0 L/min/kg (30). Breathing efforts decreased when the flow in the HFNC device increased from 0.5 to 1.5 L/min/kg, but did not fall further at higher rates, and HFNC treatment was more beneficial in infants weighing under 8kg than exceeding that weight (30). The nasal prongs used in HFNC treatment need to be sufficient in diameter to minimise air leakage around the cannula. Therefore, using an HFNC device for low-flow treatment may worsen the clinical condition of infants by increasing their breathing efforts. In the present study, the settled flow was <0.5 L/min/kg in about 40% of patients at the end of HFNC treatment, which means that nearly half of the infants with bronchiolitis were weaned from HFNC by using a low flow through a high-flow device. In addition to the risk of increased breathing efforts, this slow weaning exposes the patients to longer treatment times, a higher risk of harmful events and longer hospital stays. It may also increase healthcare costs.

CONCLUSION

The vast majority of infants hosiptalised with bronchiolitis can be treated with HFNC on paediatric wards when low-flow oxygenation fails and more invasive and expensive intensive care can often be avoided. We found preliminary evidence that oxygen support needs and heart rate were useful early predictors of the success of HFNC therapy in infants hospitalised with bronchiolitis, but respiratory rate was not. The present study was a retrospective chart review and there were missing data in the patient records. In addition, hospital practices and even the numbers of HFNC devices may have influenced the results. Thus, the results of this retrospective study are hypotheses generating and not hypotheses solving, which requires prospective studies.

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ABBREVIATIONS

HFNC, high-flow nasal cannula

PICU, paediatric intensive care unit

RCT, randomised controlled study

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FIGURES AND TABLES

Figure 1. Flow chart of bronchiolitis cases treated with high-flow nasal cannulas (HFNC). All the subjects were less than 12 months of age and admitted to six Finnish Children`s hospitals in 2012-2015.

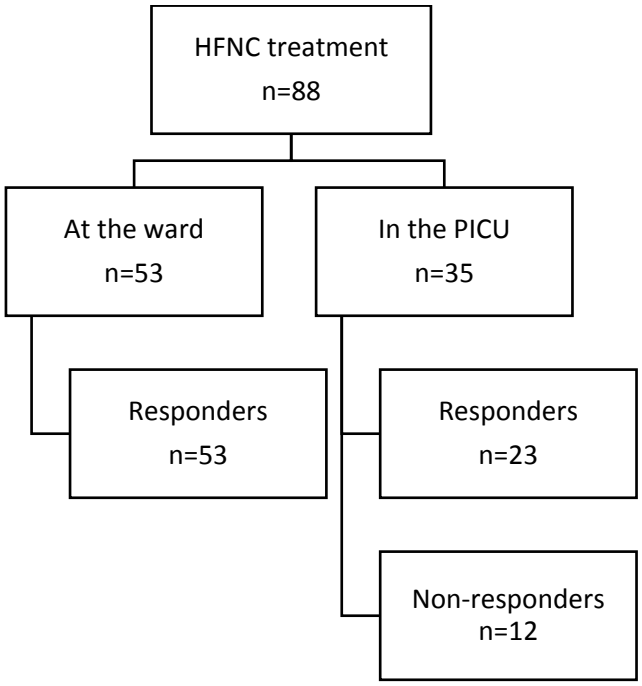

Table 1. Baseline data on infants who responded and did not respond when treated with HFNC

	All n=88	Responders n=76	Non-responders n=12	p value
Gender, boys (%)	52 (58.4)	44 (57.9)	8 (66.7)	0.566
Age on admission in weeks, median (min-max)	6 (0-42)	6 (0-42)	6.5 (2-18)	0.751
Gestational age in weeks, median (min-max)	38 (24-42)	39 (25-42)	34.5 (24-41)	0.002
Birth weight in grams, median (min-max)	3278 (640-4800)	3438 (840-4800)	2580.5 (640-3800)	0.001
RSV positive cases (%)	73 (83)	64 (84.2)	9 (75)	0.546
Length of stay in hospital in days, median (min-max)	6 (2-22)	6 (2-13)	8 (4-22)	0.014
Duration of HFNC treatment in days, median (min-max)	3 (0.06-8)	3 (0.15-8)	3 (0.06-5.5)	0.247

RSV, respiratory syncytial virus

Table 2. Underlying illnesses and pre-bronchiolitis therapies in infants treated with HFNC, presented separately for responders and non-responders

	All n=88	Responders n=76	Non-responders n=12
History of RDS	1 (1.1)	0	1 (8.3)
BPD	2 (2.3)	1 (1.3)	1 (8.3)
CHD	5 (5.7)	4 (5.3)	1 (8.3)
Atopy[1]	2 (2.3)	2 (2.6)	0
Asthma in family	1 (1.1)	1 (1.3)	0
Inhaled beta-agonists*	3 (3.4)	3 (3.9)	0
Inhaled corticosteroids^	1 (1.1)	1 (1.3)	0

RDS, respiratory distress syndrome; BPD, bronchopulmonary dysplasia; CHD, congenital heart disease. [1]Atopy in infants was defined as presence of doctor-diagnosed atopic dermatitis or food allergy, and family asthma as doctor-diagnosed asthma in parents or siblings. * Before bronchiolitis, on demand; ^ Before bronchiolitis, intermittent

Table 3. Heart and respiratory rates, oxygen saturations, and flows and oxygen concentrations settled in the HFNC device, presented separately for responders and non-responders at the start and at the end of HFNC treatment.

	Responders, start of HFNC N=76	Non-responders, start of HFNC N=12	Responders, end* of HFNC N=76	Non-responders, end^ of HFNC N=12	P between start and end p1 responders p2 non-responders
Heart rate, median (min-max)	157 (113-213) n=51	164.5 (152-180) n=8 p=0.236 vs responders	143.5 (106-194) n=48	172.5 (131-210) n=6 p=0.031 vs responders	p1=0.008 p2=0.753
Respiratory rate, median (min-max)	54 (20-100) n=37	42 (29-69) n=7 p=0.510 vs responders	40.5 (27-61) n=28	47.5 (25-61) n=6 p=0.415 vs responders	p1=0.002 p2=0.345
Oxygen saturation %, median, (min-max)	93 (72-100) n=62	91 (80-98) n=8 p=0.375 vs responders	98 (91-100) n=59	94 (91-99) n=7 p=0.032 vs responders	p1=0.000 p2=0.173
Flow L/min, median (min-max)	6 (2-15) n=70	5 (2-6) n=11 p=0.166 vs responders	2.25 (0.5-7) n=66	6 (5-10) n=10 p<0.001 vs responders	p1=0.000 p2=0.027
Flow L/min/kg, median (min-max)	1.1 (0.4-2.5) n=69	1.25 (0.5-1.9) n=11 p=0.451 vs responders	0.5 (0.1-1.8) n=62	1.6 (1.0-3.3) n=10 p<0.001 vs responders	p1=0.000 p2=0.028
Oxygen %, median (min-max)	30 (21-85) n=69	30 (21-60) n=11 p=0.736 vs responders	21 (21-25) n=66	32.5 (23-100) n=10 p<0.001 vs responders	p1=0.000 p2=0.496

* Weaning from HFNC; ^Transfer to another respiratory support