High-flow nasal cannula oxygen therapy for infants with bronchiolitis: Pilot study

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Aim: To obtain data on the safety and clinical impact of managing infants with bronchiolitis on the ward with high-flow nasal cannula (HFNC) treatment.

Methods: A prospective pilot study was conducted of 61 infants aged <12 months with bronchiolitis and oxygen requirement presenting to the emergency department. HFNC was commenced at 2 L/kg/min, and fraction of inspired oxygen was titrated to oxygen saturation > 94%. A standard-treatment group (n = 33) managed with standard low-flow subnasal oxygen during the same time period was retrospectively identified.

Results: Admission demographics, heart rate (HR) and respiratory rate (RR) were similar in test and standard-treatment groups. Responders and non-responders to HFNC were identified within 60 min of treatment. Non-responders to HFNC requiring paediatric intensive care unit (PICU) admission showed no change in HR and RR, whereas responders showed decreases in HR and RR (P < 0.02). Patients receiving HFNC were four times less likely to need PICU admission than the standard treatment group (OR 4.086, 95%CI 1.0–8.2; P = 0.043). No adverse events such as pneumothorax, bradycardia, bradypnoea, emergency intubation or cardiopulmonary resuscitation were observed. No patients admitted to the PICU required intubation.

Conclusions: HFNC treatment in the paediatric ward is safe. Non-responders requiring PICU admission can be identified within the first hour of HFNC treatment by monitoring HR and RR. It is feasible to undertake a randomised controlled trial based on this pilot with the aim of decreasing PICU admissions.

Key words: bronchiolitis; high-flow nasal cannula; infant.

What is already known on this topic

1 High-flow nasal cannula (HFNC) treatment is in use throughout many neonatal, adult and paediatric intensive care units (ICUs).
2 It is thought to provide incidental continuous positive airway pressure and reduce intubation rates.
3 There is potential for its use outside the ICU environment.

What this paper adds

1 Evidence is presented to guide a larger randomised controlled trial for the safety and feasibility of HFNC treatment use in the paediatric ward environment for the management of bronchiolitis.
2 HFNC treatment on the ward is safe.
3 Non-responders to HFNC can be identified early.

Bronchiolitis in infants is the most common reason for non-elective hospital admissions. Within Australia it accounts for an estimated 8000–9000 admissions per year. In 2011 the Australian and New Zealand Paediatric Intensive Care Registry reported 858 admissions of bronchiolitis to paediatric intensive care units (PICUs), reflecting approximately 10% of all bronchiolitis hospital admissions.1 There is a general trend in bronchiolitis management towards reduced intubation and ventilation and an increased use of non-invasive ventilation (NIV).2 The latest addition to the respiratory management of bronchiolitis is the use of high-flow nasal cannula (HFNC) therapy. Studies in neonates and recently in infants have shown that HFNC therapy delivers inadvertent continuous positive airway pressure (CPAP)3 and improves work of breathing (WOB).4–6 Since the introduction of HFNC treatment, a significant reduction in the need for mechanical respiratory support other than HFNC has been demonstrated.5,6,11 The striking advantage and efficacy of HFNC may be based on its simple application and minimal interference with patient comfort. However, the uptake of HFNC treatment in paediatrics has been sporadic. This is, in part, due to a lack of guidelines on ‘best practice’.

For the purpose of gaining some clinical data on the safety and clinical impact of HFNC use in a regular paediatric ward, we performed a case control study in infants with bronchiolitis aged less than 12 months of age. Secondary outcomes of this pilot study were to demonstrate a proof of concept for a future...
randomised controlled trial (RCT) and to present data on the decreased prevalence of respiratory deterioration and requirement for PICU admission.

**Methods**

**Study design**

A prospective pilot study was conducted, investigating the use of HFNC treatment in a paediatric ward setting. The use of an RCT design for this study was denied by the institutional ethics board, as there are no convincing data yet available for safety of HFNC use in regular ward settings. Inclusion of case controls who were admitted during the same period was retrospectively allowed by the ethics board for the purpose of comparison. These patients received standard oxygen therapy and are referred to as the standard-treatment group.

**Study protocol**

Prior to the study, staff education on the protocol and equipment was implemented utilising a structured education plan. The plan targeted both medical and nursing staff in the emergency department (ED) and paediatric ward. ED staff education focused on recognition and identification of candidates meeting inclusion and exclusion criteria, adherence to study protocol, notification to study investigator, understanding correct selection and application of equipment, commencement of HFNC treatment and ongoing assessment of the patient. Ward staff education focused on ongoing respiratory care, adherence to the study protocol, and understanding and recognition of deteriorating and improving infants.

Patients were screened from July 2011 to May 2012 in the ED of Mater Children’s Hospital, Brisbane, Queensland, Australia, for the following inclusion criteria: age <12 months, clinical diagnosis of bronchiolitis and oxygen requirement ($S\_O\_2 < 94\%$ in room air). Exclusion criteria were the following: craniofacial malformation, upper airway obstruction (stridor), and impending PICU admission based on severity of illness (impending intubation, NIV, low level of consciousness, apnoea) or transfer elsewhere. Informed consent to the study was obtained for all patients receiving HFNC treatment.

Patients for the standard-treatment group were identified retrospectively through chart review and included all infants with the same inclusion and exclusion criteria as the study patients who were admitted during the same time period to the same paediatric ward. Informed consent was waived for this group.

**HFNC intervention**

After consent was provided by the parents or guardians, the infants had the appropriate-sized nasal cannula applied, and flow was commenced through a circuit (RT329, BC3780 and BC2745; Fisher & Paykel Healthcare, Auckland, New Zealand) at 2 L/kg/min to a maximum of 10 L/min. Fraction of inspired oxygen ($F_O\_2$) was titrated (Bird Air–Oxygen Blender, CareFusion, Yorba Linda, CA, USA) to maintain oxygen saturation between 94% and 98%, and the humidifier (Fisher & Paykel Healthcare MR850) was auto-set at 37°C. All other areas of nursing and medical management for bronchiolitis remained unchanged for the study purpose according to standard hospital protocol and consultant directive. Patients were transferred to the paediatric ward after commencement of HFNC treatment. Once $F_O\_2$ could be reduced to 0.21, and oxygen saturations remained at 94% or higher, flow was turned off. If $S\_O\_2$ dropped below 94%, flow returned at the same rate. If $S\_O\_2$ did not improve, then $F_O\_2$ was increased and titrated to achieve $S\_O\_2$ of 94% or higher. This weaning procedure was repeated until the patient was able to remain off HFNC treatment.

**Measures**

Physiological parameters including heart rate (HR), respiratory rate (RR), $S\_O\_2$, temperature and a respiratory score for WOB were documented (from no distress to severe distress in three levels). Observations were recorded on admission and at regular time points until discharge. Hospital length of stay (LOS) and length of treatment (LOT) of either HFNC treatment or low-flow subnasal oxygen treatment were measured. Demographic data and comorbidities such as prematurity, chromosomal abnormality and repaired/unrepaired cardiac anomaly were recorded. Serious adverse events, as a measure of safety, were defined as cardiopulmonary arrest, pneumothorax, bradypnoea, bradycardia, requirement for CPR or emergency intubation in the ward/PICU. Criteria for admission to PICU were the following: requirement for escalation of care, including cases of $S\_O\_2 < 92\%$ despite 2 L/min $O\_2$ in the control group or $F_O\_2 > 60\%$ in the HFNC group; inability to manage the patient on the ward (nursing); and deterioration in physiological parameters (persistent tachypnoea (>60 breaths/min) and tachycardia (>180 beats/min)). PICU admission in such cases was discussed and determined between the paediatric consultant and PICU registrar/consultant after patient review.

**Statistical analysis**

Demographic and clinical data, the number of adverse events and the number of PICU admissions were compared between the HFNC and standard-treatment groups using Fisher’s exact test and the independent-samples t-test where appropriate. For the relationship between physiological data and time among the different groups, a generalised linear model (GLM) was used. To describe the change of physiological data over time, an ANOVA for repeated measurements with Bonferroni correction was used (SPSS 15.0, SPSS Inc, Chicago, IL, USA). Data are presented as mean and 95% confidence interval (CI), and a $P$ value < 0.05 was considered significant.

**Results**

A total of 1111 patients were screened in the ED between July 2011 and May 2012, and 61 patients were enrolled for HFNC treatment. Subsequently, 33 patients were identified retrospectively as meeting the inclusion criteria and included in the standard-treatment group (Fig. 1). There were no statistically significant differences in the demographic and physiological characteristics of patients in the HFNC and standard-treatment groups on admission (Table 1).
There were no serious adverse events observed during the study in either group, and importantly, no emergency procedures such as intubation and mechanical ventilation were required.

Overall, among the four patient groups, there was a significant difference in the change of HR over time ($P < 0.001$, GLM) from admission (Fig. 2). The HR in patients remaining in the paediatric ward for both HFNC and standard-treatment groups dropped significantly within the first 60 min (responders). In patients requiring PICU admission, the HR remained unchanged and even increased after admission (non-responders). Responders to care could be identified by their HR dropping by 15 beats (or 15–20%) from their baseline at admission. In the responders in the HFNC group, mean HR changed significantly within 60 min from 158 beats/min (95% CI 154–164) to 144 beats/min (95% CI 138–150), whereas the mean HR of the non-responders increased slightly from 159 beats/min (95% CI 144–173) to 162 beats/min (95% CI 152–171) ($P = 0.02$).

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Fig. 1 Screening flow chart from the emergency department (ED). †Patients were eligible but not approached, as ED staff did not alert study staff. HFNC, high-flow nasal cannula; PICU, paediatric intensive care unit.

Table 1 Demographic and physiological characteristics of high-flow nasal cannula and standard-treatment groups at admission

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HFNC group (n = 61)</th>
<th>Standard-treatment group (n = 33)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>39 (64)</td>
<td>19 (58)</td>
<td>0.66</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>22 (36)</td>
<td>14 (42)</td>
<td>0.66</td>
</tr>
<tr>
<td>Age (days), mean (95% CI)</td>
<td>157 (128–187)</td>
<td>146 (104–188)</td>
<td>0.66</td>
</tr>
<tr>
<td>Weight (kg), mean (95% CI)</td>
<td>6.8 (6.1–7.5)</td>
<td>6.6 (5.6–7.7)</td>
<td>0.78</td>
</tr>
<tr>
<td>Ex-prematurity (&lt;37 weeks gestation), n (%)</td>
<td>19 (31)</td>
<td>6 (18)</td>
<td>0.23</td>
</tr>
<tr>
<td>Other comorbidity, n (%)†</td>
<td>3 (5)</td>
<td>2 (6)</td>
<td>0.58</td>
</tr>
<tr>
<td>NPA-positive, n (%)‡</td>
<td>55 (95)</td>
<td>32 (97)</td>
<td>0.54</td>
</tr>
<tr>
<td>Heart rate (beats/min), mean (95% CI)</td>
<td>158 (153–163)</td>
<td>159 (152–166)</td>
<td>0.75</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min), mean (95% CI)</td>
<td>54 (51–57)</td>
<td>53 (50–57)</td>
<td>0.78</td>
</tr>
<tr>
<td>$\text{S}_\text{O}_2$ (%, mean (95% CI)</td>
<td>89 (88–90)</td>
<td>90 (89–92)</td>
<td>0.17</td>
</tr>
<tr>
<td>Hospital length of stay (h), median (IQR)</td>
<td>92 (59–141)</td>
<td>92 (48–124)</td>
<td>0.60</td>
</tr>
<tr>
<td>Salbutamol therapy, n (%)</td>
<td>16 (26)</td>
<td>8 (24)</td>
<td>0.83</td>
</tr>
<tr>
<td>Steroid therapy, n (%)</td>
<td>7 (12)</td>
<td>4 (12)</td>
<td>0.93</td>
</tr>
<tr>
<td>Antibiotic therapy, n (%)</td>
<td>12 (20)</td>
<td>8 (24)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

†Includes trisomy 21, repaired and unrepaired cardiac anomaly, and tracheomalacia. ‡Viruses including respiratory syncytial virus, influenza, rhinovirus, enterovirus, adenovirus and human metapneumovirus. Fisher’s exact test and independent-samples t-test have been used as appropriate. CI, confidence interval; HFNC, high-flow nasal cannula; NPA, nasopharyngeal aspirate.
Fig. 2 Changes in heart rate (HR) in intervention and comparison groups after inclusion in the study. For both the standard-treatment responders and the high-flow nasal cannula (HFNC) responders, the HR decreased significantly (**p < 0.001, ANOVA). HR remained high and did not change significantly for the patients requiring paediatric intensive care unit admission (the HFNC and standard-treatment non-responders). Values are shown as mean and 95% CI.

Fig. 3 Changes in respiratory rate (RR) in intervention and comparison groups after inclusion in the study. For both the HFNC responders and standard-treatment responders, the RR decreased, but the decrease was significant only for the standard-treatment responders (**p < 0.05, ANOVA). RR remained high in HFNC non-responders and decreased in the standard-treatment non-responders. Values are shown as mean and 95% CI.

Similarly, the change in RR after admission was significantly different between the groups over time (p = 0.05, GLM) (Fig. 3). The RR decreased significantly for both the HFNC responders and the standard-treatment responders after admission. The RR in the HFNC non-responder group remained high, but in the standard-treatment non-responders it decreased after admission. In the responders in the HFNC group, RR dropped from 54 breaths/min (95% CI 51–57) to 51 breaths/min (95% CI 48–54), with that of the non-responders increasing from 54 breaths/min (95% CI 48–60) to 58 breaths/min (95% CI 48–69) (p = 0.07) at 60 min. However, the differences in RR became significant at 180 min (p < 0.05).

Of the 61 patients in the HFNC group, 8 (13%) were admitted to the PICU (HFNC non-responders) compared with 53 (87%) who remained on the paediatric ward (HFNC responders). In the standard-treatment group, 10 patients (31%) required PICU admission (standard-treatment non-responders), and 23 (69%) remained on the paediatric ward (standard-treatment responders) (OR 4.086, 95% CI 1.0–8.2; p = 0.043). Between the responders and non-responders in both groups (HFNC and standard treatment) there were no physiological and demographic differences on admission (Table 2). Of those patients admitted to the PICU, one patient in the HFNC group and three in the standard-treatment group required a period of NIV. The remaining patients referred to the PICU received HFNC treatment only at 2 L/kg/min. No patients were intubated.

Hospital LOS was similar between the two groups (p = 0.56), with the median time being 92 h for both the HFNC and standard-treatment groups (95% CI 52–140). LOT was similar for patients admitted to the PICU and those who remained on the paediatric ward in the standard-treatment group as well as the HFNC group (p = 0.07 and p = 0.32, respectively).

Discussion

The data from our study show that HFNC treatment can safely be used in a regular paediatric ward with a 1:4 nursing ratio, as no serious adverse event was observed. We determined that the safety of HFNC treatment can be monitored using clinical indicators such as HR and RR, providing a safe boundary for HFNC use in the ward. Responders and non-responders to HFNC treatment can be identified and described using HR and RR within 60 min of application. It is reasonable to anticipate that a future larger RCT may make similar findings of reduced PICU admission rates (4 times less likely) by following our protocol.

This pilot study was tested in a ‘real-world’ environment where standard care was not changed, only the oxygen delivery device. This approach allowed separation of oxygen delivery-specific aspects of the treatment and identification of responders and non-responders, which was important to demonstrate as a safety aspect of HFNC treatment. Infants responding to HFNC treatment showed decreased HR within the first hour of initiation. The RR also dropped in the responders, but with a slight delay at 180 min. The non-responders to HFNC showed no change in HR and RR within the first 60 min of observation. Non-responders to HFNC warrant medical review for potential PICU admission. A similar pattern was also observed in the standard-treatment group, in which responders and non-responders to standard treatment could be identified within 60 min. Interestingly, in the standard-treatment group the RR in the non-responders dropped within the first 60 min compared with the responders, but the differences were not statistically significant. This drop in RR may have been due to a mild degree of hypoxaemia or may be explainable by the low number of patients in the study. This concept of certain parameters differentiating responders from non-responders has been identified in other studies. One limitation of the study design is that the repeated measurement of HR and RR were robust descriptors but not necessarily predictors of response or non-response for both the intervention and comparison groups. Real predictors such as prematurity, heart disease and pre-existing...
Table 2  Demographic and physiological characteristics of responders and non-responders in high-flow nasal cannula and standard-treatment groups at admission

<table>
<thead>
<tr>
<th></th>
<th>HFNC responders (n = 8)</th>
<th>Standard-treatment non-responders (n = 10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (days), mean (95% CI)</td>
<td>170 (70–270)</td>
<td>6.9 (4.8–9.0)</td>
<td>0.34</td>
</tr>
<tr>
<td>Weight (kg), mean (95% CI)</td>
<td>6.9 (4.8–9.0)</td>
<td>6.1 (4.0–8.6)</td>
<td>0.70</td>
</tr>
<tr>
<td>Ex-prematurity (%)</td>
<td>11 (12)</td>
<td>6.1 (4.0–8.6)</td>
<td>0.34</td>
</tr>
<tr>
<td>NPA-positive (%)</td>
<td>10 (12)</td>
<td>11 (12)</td>
<td>0.70</td>
</tr>
<tr>
<td>Respiratory rate (breaths/min), mean (95% CI)</td>
<td>34 (27–41)</td>
<td>38 (28–48)</td>
<td>0.34</td>
</tr>
<tr>
<td>Length of treatment (h), median (IQR)</td>
<td>7 (5–8)</td>
<td>9 (5–8)</td>
<td>0.34</td>
</tr>
</tbody>
</table>

- HFNC: high-flow nasal cannula
- NPA: nasopharyngeal aspirate
- NIV: non-invasive ventilation

High-flow nasal cannula in bronchiolitis
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No patients subsequently admitted to the PICU needed intubation, and all continued either on HFNC or NIV. This low intubation rate is consistent with our and others’ previously reported use of HFNC in bronchiolitis.9,11 The early use of HFNC in a paediatric ward reduced the number of PICU admissions without any serious adverse events having been observed. We speculate that the early application of HFNC treatment is the key element, preventing further progression of airway obstruction and reversing some of the atelectasis. A recent uncontrolled study comparing HFNC with nasal CPAP showed that HFNC may be associated with a similar efficacy and even a trend towards a reduction in need for sedation.13 This experience is aligned with the trend towards use of early NIV in general.2 However, HFNC treatment did not shorten hospital LOS overall, and its associated physiological effect does not modulate the course of the underlying viral illness.

While hospital LOS was not shortened during the study, there are fiscal implications for reducing PICU admissions. The current cost for a 92-h combined PICU and ward admission in our hospital is estimated at A$15 517 per patient. The costs for the same patient on the paediatric ward are estimated at A$4992 per patient. It is predicted that the annual cost saving for our 19-bed PICU with 1400 admissions annually would be approximately A$1.2 million.

For a future RCT, the definition of high flow needs to be discussed. The original idea of delivering higher flow rates at >2 L/min originated from a need for better humidification of the delivered oxygen. In the past, this was achieved using higher flow rates. These higher flow rates created inadvertent CPAP. Previously published papers have explained some of the physiological effect of high flow with inadvertent CPAP.3,5,14,15 A study by Milesi et al.3 showed that flow rates of approximately 1.5–2 L/kg/min created a positive pharyngeal pressure during the entire respiratory cycle. Interestingly, a recent study by Mundel et al.16 in healthy adults has shown that during the inspiratory phase little or no positive pressure is delivered, and only during the expiratory phase is positive pressure observed. Further detailed physiological studies measuring changes on high flow, particularly of the intrathoracic pressures, are needed.

Generally, flow rates > 2 L/min subnasally in infants are regarded as ‘high flows’ with a maximal limit of 8–10 L/min. This maximum of 10 L/min using our HFNC device was not based on any clinical or physiological rationale but solely on the decision of the device manufacturer. For this study, flow was titrated at 2 L/kg/min with a maximal flow of 10 L/min. In infants with a high RR, relatively high-flow rates are needed to match the maximal inspiratory flow of the patient. The choice of 2 L/kg/min is based on the fact that in the past with the older generation of continuous-bias-flow ventilators, the bias flow was set at 2 L/kg/min to match the high inspiratory flows.17

Another finding was that we were able to wean the HFNC to room air (21% O2) before the HFNC was switched off, and no weaning of the flow rate was allowed. The oxygen in the control group was weaned from 2 L/min to off according to S0. This approach followed a shift in paradigm that considers that an early oxygen requirement can be treated with CPAP by recruiting previously collapsed lung regions. The weaning approach did not prolong the time of respiratory support or hospital LOS.
Limitations

This study may be criticised because of its non-randomised design. Our ethics review board denied us permission to perform a RCT and requested a pilot study investigating the safety of HFNC treatment first. After completion of the study, we were allowed to retrospectively analyse a case control group (standard oxygen therapy) of all infants with bronchiolitis who were admitted within the same time frame and fulfilled the inclusion criteria but were not enrolled in the study (due to the study investigator not being contacted). This group matched the study group in their demographic and physiological data on admission and were treated in the same paediatric ward using the same 1:4 nursing ratio and hospital bronchiolitis management protocol. The small number of patients in the study does not allow for a strong conclusion, and only a RCT will address the question of the effects of HFNC treatment in the ward environment.

Conclusion

This pilot study produced interesting results on the safety of HFNC treatment in a ward environment. It gives guidelines as to how a larger RCT may be conducted. Physiological parameters such as HR and RR correlate well with the response to treatment and hence potential PICU admission. With viral bronchiolitis being the most common reason for non-elective admissions to PICUs in Australia, using HFNC treatment in paediatric wards may result in substantial cost savings without impact on safety of patient care. It would be worthwhile to undertake a RCT and investigate the fiscal implications of reducing PICU admissions by utilising this treatment in the ward environment.

Acknowledgements

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References


