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REGULAR ARTICLE

Using a high-flow nasal cannula provided superior results to low-flow oxygen delivery in moderate to severe bronchiolitis

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ABSTRACT

Aim: An observational study was carried out on infants with moderate to severe bronchiolitis to compare the clinical outcomes following treatment with a high-flow nasal cannula (HFNC) or standard low-flow oxygen.

Methods: We enrolled subjects below 12 months of age who were affected by their first bronchiolitis episode. Non-formal randomisation, based on HFNC availability, was used to assign subjects to either the HFNC or standard oxygen groups. Respiratory rate, respiratory effort and the ability to feed were compared between the two groups at enrolment and at regular time points. The oxygen requirements and the length of hospital stay were also analysed.

Results: Overall, 36 of the 40 enrolled infants completed the study: 18 treated with HFNC (mean age 3.2 months, range 1.2–5.4 months) and 18 with low-flow oxygen delivery (mean age 3.6 months, range 1.3–5.0 months). Improvements in the respiratory rate, respiratory effort and ability to feed were significantly faster in the HFNC group than the low-flow oxygen group. The HNFC group needed oxygen supplementation for two days less than the other group and hospital stays were three days shorter.

Conclusion: HFNC provided superior clinical outcomes for infants under 12 months with moderate-to-severe bronchiolitis compared to low-flow oxygen.

INTRODUCTION

Bronchiolitis is the most common lower respiratory tract infection during the first year of life and one of the main reasons for hospitalisation (1,2). To date, there is no specific treatment for bronchiolitis, and the mainstays of therapy are maintaining an adequate hydration status and oxygen supplementation (3–5).

The use of a high-flow nasal cannula (HFNC) is one of the most recent non-invasive ventilation support modalities, and it has been advocated as a promising approach for bronchiolitis management (6–8). HFNC provides humidified and heated oxygen, flushes the dead space of the nasopharyngeal cavity, develops a minimal continuous positive airway pressure, reduces inspiratory resistance and improves airways conductance and pulmonary compliance (6–8). Preliminary studies have suggested that the use of high-flow heated and humidified oxygen may rapidly improve oxygen saturation in infants suffering from bronchiolitis (8,9). Another advantage of this respiratory support technique lies in the fact that it may be used in both paediatric wards and paediatric intensive care units (PICU) (10).

Several guidelines on bronchiolitis management have indicated the need for prospective studies to compare HFNC and low-flow oxygen delivery strategies (3,4).

The aim of this study was to compare the clinical outcomes of infants with their first episode of moderate-to-severe

Abbreviations
HFNC, high-flow nasal cannula; PICU, paediatric intensive care unit; RSV, respiratory syncytial virus; SpO_2, peripheral oxygen saturation.

Key notes

- We compared the clinical outcomes of 36 infants with moderate to severe bronchiolitis who received oxygen treatment with a high-flow nasal cannula (HFNC) or standard low-flow oxygen.
- Improvements in the respiratory rate, respiratory effort and ability to feed were significantly faster in the HFNC group than the low-flow oxygen group.
- The HNFC group needed oxygen supplementation for two days less than the other group and hospital stay was three days shorter.

bronchiolitis, who were treated with either HFNC or standard low-flow oxygen delivery strategies in a paediatric ward.

PATIENTS AND METHODS

Study protocol

A prospective study was conducted from January 2014 to March 2014 in the Paediatric Emergency Department of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. The criteria for inclusion were admission for a diagnosis of moderate or severe bronchiolitis, the need for oxygen supplementation (peripheral oxygen saturation <92% in room air), aged below 12 months, gestational age >34 weeks, the absence of an underlying disease or any condition at risk for bronchiolitis complications and written informed consent signed by the parents. Bronchiolitis was defined as the acute onset of respiratory distress with cough and diffuse crackles on auscultation (1,11). On admission, a severity score was assigned according to our standard procedure (Table S1): a score of four or more identified moderate-to-severe bronchiolitis. The exclusion criteria included a gestational age ≤34 weeks, admission to a neonatal intensive care unit at birth, a history of previous bronchiolitis or wheezing episodes, chronic respiratory disease, congenital airway anomalies, craniofacial malformations, haemodynamically significant heart disease, underlying neurological disease or admission to the PICU according to previously defined criteria (3,4,12). An education plan, focused on identifying the inclusion and exclusion criteria, adherence to the study protocol and the correct use of HFNC devices, was performed for medical and nursing staff of the emergency department prior to the study enrolment.

A formal randomised control trial was denied by the Institutional Ethics Committee, as there was already retrospective data that supported the use of HFNC for infants admitted for bronchiolitis (3,4,8–10). However, an observational study with HFNC usage was considered acceptable. Two high-flow nasal cannula devices were available at our institution, and they were used on a non-formal randomisation basis, which depended on their availability, as previously described by Aminalai et al. (13). If no HFNC device was available, then standard low-flow oxygen delivery treatment was provided. In subjects treated with HFNC, oxygen supplementation was delivered by AIRVO2 (Fisher and Paykel Healthcare, Auckland, New Zealand) through appropriately sized nasal cannulae with a humidified and heated flow (L/min = 8 mL/kg × respiratory rate × 0.3) (14,15). In infants treated with low-flow oxygen delivery, oxygen supplementation was provided by standard nasal prongs. The oxygen supplementation volumes were chosen to achieve peripheral oxygen saturation (SpO_2) ≥94% (16).

Measurements

The respiratory rate, the respiratory effort and the ability to feed were assessed according to previously described criteria (3,17) and recorded at regular time points (Table S2). The whole duration of oxygen supplementation and hospital length of stay were also analysed.

Adverse events and failed treatments, including admission to PICU, were recorded. Admission to the PICU implied the withdrawal from the study. However, the difference in the respiratory rate and effort, and of the ability to feed between the two groups, was also analysed including data of withdrawn subjects obtained before PICU admission. Prerequisites for discharge were as follows: a stable condition, 12 hours of oxygen supplementation, milk intake above 50% of the expected volume and the possibility of adequate monitoring by caregivers at home. The study was concluded at the patient's discharge.

Statistical analysis

Fisher's exact test was used to analyse dichotomous variables, and normality was tested using the Shapiro–Wilk test. A random-intercept linear regression model was used to compare the trends of respiratory rate over time in the two groups, while taking into account intrapatient correlation (18). In particular, we fitted a model containing the following covariates: baseline respiratory rate, group, time and seven group–time interaction terms. We simultaneously tested all interaction terms using a global Wald test. The log-rank test was used to compare the time to get SpO_2 to 92% or more in room air and the time for discharge in the two groups. $p < 0.05$ was considered statistically significant. The primary outcome was the respiratory rate modification at 24 hours compared with the respiratory rate upon enrolment and a sample size of 17 patients per group was deemed sufficient to detect one standard deviation difference between the two treatments, with an α error of 0.05 and 80% power. Taking into account some variability and the risk of needing intensive care, we anticipated a possible dropout rate of 15-20%, which meant that we aimed to enrol 20 patients per group. The statistical analysis was performed with Stata Statistical Software, release 13 (StataCorp LP, College Station, Texas, USA).

RESULTS

The population admitted to the emergency department for bronchiolitis during the study period is reported in Figure S1. A total of 40 infants with moderate-to-severe bronchiolitis were enrolled in the study: 20 were treated by HFNC and 20 with standard low-flow oxygen delivery. No significant differences for demographic, clinical, laboratory and treatment data at enrolment were found (Table 1). Four of the 40 enrolled subjects, two per group, required PICU admission. Therefore, detailed results from 36 infants who completed the study were available for further analysis.

The respiratory rate dropped significantly at 30 minutes and at one, three, eight and 72 hours in the HFNC group compared to the infants treated with standard low-flow oxygen delivery (Fig. 1). Accordingly, the change in respiratory rate indicated a significant different trend between the groups over time ($p = 0.026$). Results were not modified

Table 1 Demographic, clinical, laboratory and treatment characteristics at enrolment of 40 subjects who entered the study

	Standard low-flow oxygen delivery treatment (n = 20)	High-flow nasal cannula treatment (n = 20)
Male, n	12	9
Age (months)	3.6 (1.3-5.0)*	3.2 (1.2-5.4)*
RSV-positive, n	16	14
Respiratory rate (breaths/min)	59.2 (7.8)	58.1 (12.4)
SpO_2 in ambient air (%)	88 (2)	87 (2)
Heart rate (beats/min)	151 (16)	147 (16)
Gestational age at birth (weeks)	38.1 (1.4)	37.9 (1.2)
Birth weight (Kg)	3.070 (0.523)	3.045 (0.610)
Breastfeeding (exclusive or predominant), n	17	16
Bronchiolitis severity score		
4–6 (moderate), n	12	11
7–8 (severe), n	8	9
Need for intravenous fluid replacement, n	4	3
Subjects in treatment with bronchodilators, n	6	7
Subjects in treatment with antibiotics, n	4	6
White blood count (G/L)	11930 (3250)	10360 (4780)
Neutrophils (%)	38.5 (15.5)	38.8 (14.8)
C-reactive protein (mg/L)	8.5 (2.9)	9.1 (2.0)

SpO_2, peripheral oxygen saturation.
Values are shown as frequency or as mean and standard deviation. No significant difference was observed at the enrolment between the two groups.
*mean and ranges.

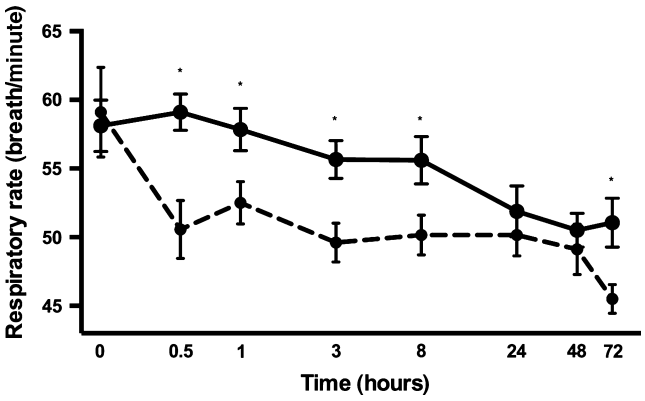

Figure 1 Respiratory rate (breaths/minute) in infants managed with high-flow nasal cannula or standard low-flow oxygen delivery treatment. Mean respiratory rate at enrolment, 0.5, 1, 3, 8, 24, 48 and 72 hours in infants treated with high-flow nasal cannula (dashed line) and with standard low-flow oxygen delivery (continuous line). Dots indicate the mean values and vertical lines the 95% confidence intervals. Time values on the horizontal line are expressed as logarithmic values. *$p < 0.05$.

after including the two subjects per group requiring PICU admission (p value for interaction terms 0.048).

The results of respiratory effort, ability to feed, duration of oxygen supplementation and length of hospital stay are summarised in Table 2. After the admission, a significant higher percentage of subjects in HFNC group presented a normalised respiratory effort at all time points compared to the low-flow oxygen delivery group (Table 2).

Table 2 Clinical outcomes in 36 subjects who completed the study

	Standard low-flow oxygen delivery treatment (n = 18)	High-flow nasal cannula treatment (n = 18)
Age, months	3.9 (1.5–5.0)*	3.5 (1.4–5.5)*
Male, n	10	8
Subjects with abnormal Respiratory effort, n (%)		
0.5 hour	18 (100)†	13 (72)
One hour	18 (100)†	13 (72)
24 hours	17 (94)†	9 (50)
72 hours	11 (61)‡	0 (0)
Subjects with impaired ability to feed, n (%)		
24 hours	7 (39)	5 (28)
48 hours	5 (28)†	0 (0)
Duration of oxygen supplementation, days	6 (5–7)‡	4 (3–5)
Length of hospital stay, days	9 (8–10)‡	6 (5–7)

The Table reports the respiratory rate, respiratory effort, ability to feed, duration of oxygen supplementation and length of hospital stay in the two groups at different time points of the study. The results are given either as median and interquartile or as relative frequency (with percentage). Significance of respiratory effort and ability to feed difference between the two groups was not modified even including subjects admitted to PICU.
*mean and ranges.
†$p < 0.05$.
‡$p < 0.005$.

During the first 24 hours after admission, infants in the HFNC and standard low-flow oxygen delivery treatment group had a similar ability to feed. At 72 hours, all infants in the HFNC group reached a normal ability to feed, compared to only 13 in the standard low-flow oxygen delivery treatment group ($p = 0.045$). Time to get normal oxygen saturation in ambient air was significantly lower ($p = 0.006$) in infants receiving treatment with HFNC compared with infants receiving treatment with standard low-flow oxygen delivery (Fig. 2). Similarly, the time to discharge was significantly shorter ($p = 0.002$) in the HFNC group than in the low-flow oxygen delivery group (Fig. 3).

No patient had any treatment-related adverse events, and all of the infants tolerated the treatments.

DISCUSSION

This study shows managing infants hospitalised for moderate to severe bronchiolitis with HFNC, compared to the standard low-flow oxygen delivery strategy, appeared more efficacious for the improvement of respiratory rate, respiratory effort, ability to feed and the duration of oxygen supplementation, with a reduction in the length of hospitalisation.

Others have shown the effectiveness of HFNC treatment in infants with bronchiolitis hospitalised in a paediatric

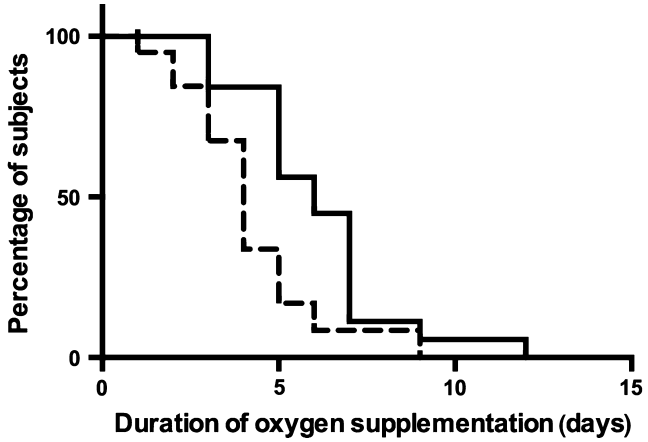

Figure 2 Duration of oxygen supplementation in infants managed with high-flow nasal cannula or standard low-flow oxygen delivery treatment. Percentage of subjects requiring oxygen supplementation in high-flow nasal cannula (dashed line) and in standard low-flow oxygen delivery (continuous line) group over the study.

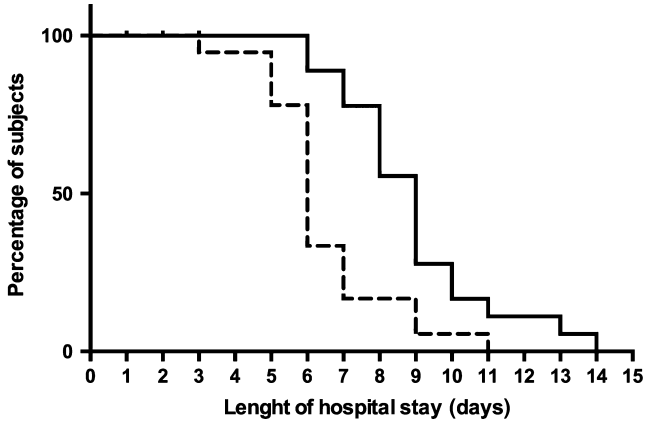

Figure 3 Length of hospital stay in infants managed with high-flow nasal cannula or standard low-flow oxygen delivery treatment. Percentage of inpatients in high-flow nasal cannula (dashed line) and in standard low-flow oxygen delivery (continuous line) group over the study.

ward, with regard to reducing the respiratory rate (8,16). In agreement with these results, we observed a lower respiratory rate in the first eight hours, after 72 hours and, overall, during the whole study period, in infants treated with HFNC in comparison with those treated with standard low-flow oxygen delivery. Similarly, subjects treated with HFNC normalised sooner than those treated with low-flow oxygen delivery. In a pioneering electrophysiology study, a significant reduction of diaphragm activity in 14 infants affected with bronchiolitis was found after the introduction of HFNC (18). The potential mechanisms include that HFNC devices deliver higher concentrations of oxygen and produce positive pressure, reducing the work of respiratory muscles and respiratory distress (19). The reduction of diaphragm activity and other respiratory muscles results in an overall decrease in oxygen consumption (18). Moreover, warmed and humidified oxygen might also thin secretions and reduce mucus plugging (19). These factors are likely to improve respiratory gas exchange and explain the reduced need for oxygen supplementation in patients managed with HFNC.

Nutritional state plays a key role in infants with respiratory infections, influencing metabolism, the immune response and, consequently, the clinical course (3,17). In addition, it is well known that respiratory effort tends to reduce the ability to feed. The interplay between the improvement of respiratory outcomes and rapid recovery on the ability to feed can explain the short length of hospitalisation in infants managed with HFNC, who were discharged an average of three days before those treated with standard low-flow oxygen delivery. However, this finding should be cautiously considered, as the adequacy of caregivers might have influenced the discharge decision in some cases.

No difference in PICU admissions was found between the HFNC and low-flow oxygen delivery groups. The number of subjects treated with HFNC and requiring PICU admission was similar to that of a study conducted on 25 infants with moderate-to-severe bronchiolitis (19). It is possible that a difference in PICU admissions may be found in a larger study population. Nevertheless, our experience confirms that HFNC is usually safe and well tolerated by infants (20).

Contrasting results have been reported regarding the use of HFNC in infants hospitalised in the PICU for bronchiolitis. In a retrospective study on 115 infants with bronchiolitis, HFNC reduced the intubation rate by 68% and the PICU stay by two days compared with other respiratory support options (21). However, in a retrospective study of 19 infants managed with nasal continuous positive airway pressure and 15 infants managed with HFNC, no difference was found between the two groups with regard to the respiratory rate or intubation rate (22). We speculate that the prompt use of HFNC in infants admitted for moderate to severe bronchiolitis in the emergency department may have resulted in more favourable outcomes than the use of HFNC in infants with worsening conditions admitted to PICU.

This study had some limitations. The first is that it was limited to a single institution with a rather small number of enrolled infants who did not have underlying disease at risk for bronchiolitis complications. However, the study supports conclusions in favour of HFNC as suggested by the published guidelines on bronchiolitis management (3,4). Second, the assignment of subjects to either HFNC or low-flow oxygen delivery treatment was not formally performed. However, this non optimal randomisation technique allowed us to generate two homogeneous treatment groups. Third, monitoring was performed by different physicians or nurses because of the regular turnover of the staff members. Finally, preterm infants and subjects with a severe underlying disease were excluded. This implies that our results cannot be generalised to all infants affected by bronchiolitis. The strength of this study is that we prospectively compared HFNC and low-flow oxygen delivery treatments in two different groups of infants in a general paediatric ward.

Multicentre randomised controlled trials comparing HFNC with other oxygen delivery strategies in infants with bronchiolitis may help to identify infants who would find HFNC treatment particularly effective. These should include patients with diseases of different severity as well as those with comorbidities and also analyse the pharmacoeconomic differences in the cost of care and long-term outcomes in terms of respiratory recurrences.

CONCLUSION

This study of otherwise healthy infants under the age of 12 months being treated for their first episode of moderate to severe bronchiolitis in a paediatric ward found that HFNC was superior to low-flow oxygen delivery treatment for producing a favourable clinical outcome.

FUNDING

No funding was received to perform this study.

CONFLICTS OF INTEREST

The authors have no conflict of interests to disclose.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1 Patient flow chart from the Paediatric Emergency Department.
Table S1 Bronchiolitis severity score.
Table S2 Monitoring of respiratory rate, respiratory effort and ability to feed during study.

