High-Flow Nasal Cannula Oxygen in Children with Bronchiolitis: A Randomized Controlled Trial

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Abstract

Objective: To determine whether high-flow nasal cannula oxygen (HFNCO) provided enhanced respiratory support in bronchiolitis than low-flow oxygen (LFO). Methods: We conducted a prospective, randomized controlled trial in children between 1-24 months diagnosed with moderate-to-severe bronchiolitis requiring oxygen therapy. Participants received LFO via face mask (6-10 L/min) or HFNCO (2 L*kg/min). Primary outcomes were the time that heart rate (HR) and respiratory rate (RR) return to their normal range for age and the time that baseline clinical respiratory score (CRS) regress to a lower severity score. Secondary outcomes were changes in HR, RR, and CRS over time, length of stay (LOS), duration of oxygen requirement, treatment failure, and adverse event (AE). Results: Eighty-seven children were enrolled (48 in LFO; 39 in HFNCO). The time that HR and RR baseline values reached their normal range for age was shorter in HFNCO therapy (2.0h [1.0-4.0] vs. 12.0h [2.0-24.0] and 4.0 h [2.0-12.0] vs. 24.0 h [4.0-48.0], respectively; P< .001); additionally, the improvement in CRS emerged more quickly in children treated with HFNCO (2.0 h [1.0-4.0] vs. 4.0 h [2.0-24.0]; P = .003). While the duration of oxygen requirement (19.0 h [4.0-30.0] vs. 29.5 h [14.0-45.7]; P = .009) and treatment failure (3% vs. 21%) was statistically lower in children who received HFNCO, there were no differences in LOS and AE between groups. Conclusion: HFNCO may provide enhanced respiratory support with a notable improvement in HR, RR, and CRS than LFO. Comprehensive studies are needed to assess the clinical efficacy of HFNCO therapy.

1-INTRODUCTION

Acute bronchiolitis is a common disease characterized by inflammation, edema, and necrosis in the lower respiratory airways. It continues a substantial health burden for infants and young children worldwide.[1] In the United States of America (USA), approximately 2-3% of children younger than 12 months of age (accounts for 57.000-120.000 hospitalizations annually) are hospitalized with respiratory syncytial virus-related bronchiolitis.[2–5]The total estimated inpatient charges exceed $1.7 billion annually in the USA.[6] Similarly, from 2002 through 2014 in Australia and New Zealand, increasing the admission to the intensive care unit (ICU) due to bronchiolitis has raised health care costs.[7] The treatment of this frequent and costly condition is mainly supportive, including hydration, oxygen supplementation, and respiratory support.[8] On the other hand, high-flow nasal cannula oxygen (HFNCO) becomes an essential and promising treatment modality for bronchiolitis.[1,8]

Initial observational and physiological studies using HFNCO determined improved gas exchange, decreased respiratory effort, and reduced mechanical ventilation (MV) rates.[9,10] Milani et al.[11] showed that HFNCO

was efficacious not only in improving respiratory rate (RR) and respiratory effort but also in reducing the duration of oxygen therapy and length of hospital stay (LOS). In contrast, two recent randomized, controlled trials[12,13] comparing the effects of HFNCO and LFO in infants with bronchiolitis found no statistically changes in heart rate (HR), RR, duration of oxygen therapy, and LOS. Similar to these results, there have been controversial reports regarding bronchiolitis severity scores. While Ballestero et al.[14] found that pulmonary score decreased in more patients with HFNCO (53%) compared to those with conventional oxygen therapy (28%), Chen et al.[15]did not show a significant decrease in respiratory distress assessment instrument over time between HFNCO and standard dry oxygen. A 2014 Cochrane review[16] proposed that there has been insufficient evidence to identify the effectiveness of HFNCO. Similarly, the American Academy of Pediatrics (AAP) Bronchiolitis Guideline[17] concluded that not enough randomized clinical trials have been present to recommend its routine use despite the promising. We aimed to examine whether HFNCO provided enhanced respiratory support, evidenced by a notable improvement in HR, RR, and clinical respiratory score (CRS), in infants with bronchiolitis and hypoxemia admitted to the general pediatric ward.

2-METHODS

2.1-Study design, participants, and definitions

From March 2017 through March 2020, we conducted a prospective, randomized, controlled study comparing the effect of HFNCO and LFO therapy on children diagnosed with bronchiolitis and requiring oxygen supplementation in Ege University Medical Faculty Children Hospital. The trial performed followed the recommendations of the Consolidated Standards of Reporting Trials statement of 2010.[18]

Participants eligible for the study were children aged between 1-24 months with clinical-diagnosed moderate to severe bronchiolitis, hypoxia, and admission to the general pediatric ward. Exclusion criteria included admission to ICU for MV, receiving LFO or HFNCO therapy at other facilities before arrival, an underlying medical condition (e.g., congenital heart disease, chronic lung disease, neuromuscular disease, metabolic disease, or immunodeficiency), a craniofacial malformation, upper airway obstruction, pneumothorax, or nasal trauma. Bronchiolitis was diagnosed based on the 2014 AAP Clinical Practice Guideline.[17] The severity of the disease was considered using CRS involving RR, retraction, dyspnea/consciousness status, and wheezing (Supplemental Table 1; p1-2).[19]Each parameter in CRS ranges from 0 to 3 points. The higher total score is the worst presentation clinically. Participants with CRS between 5 and 8 points are considered moderate bronchiolitis, and those with CRS between 9 and 12 points are defined as severe bronchiolitis. Hypoxia was defined as peripheral capillary oxygen saturation (SpO_2) <92% while breathing room air.[17]

2.2-Interventions

Participants who met inclusion criteria were invited to participate in the study, and written informed consent was obtained from the parent/guardian. Then, enrolled participants were assigned to either LFO or HFNCO by using simple randomization. On even-numbered days, patients received LFO, while on odd-numbered days received HFNCO. Masking of the treatment was not possible because of the visual difference between the two interventions.

Participants on LFO received supplemental oxygen via a simple face mask at a range of 6-10 L/min to maintain a SpO_2 level between 92%-98%. Oxygen therapy weaned off when the patient sustained the SpO_2 above 92% in the ambient oxygen concentration (21%). Participants on HFNCO received supplemental oxygen via Airvo 2 high-flow system (Fisher and Paykel Healthcare), using an age-appropriate Optiflow Junior cannula, at a 2 L*kg/min (between 8 L/min and 25 L/min). The fraction of inspired oxygen (FiO_2) was set at 40%. Then, the $FiO_2$was adjusted to obtain the SpO_2 levels between 92%-98%. After the starting flow rate continued for a minimum of 4 h, it was decreased by 0.5 L*kg/min per hour according to the patient's clinical response. When the FiO_2 was equal to the ambient oxygen concentration (21%), and the flow rate was decreased to 0.5 L*kg/min, HFNCO was stopped. Our hospital did not have a standardized protocol for weaning off HFNCO therapy at the study time. Therefore, the lead investigator and other researchers created a new protocol to reduce any bias on wean off oxygen (Supplemental p3-7). Treatment failure was considered at 4 h when at least three of the following five criteria were present: i) An increase or no

changes in HR relative to baseline; ii) An increase or no changes in RR relative to baseline; iii) Persistence of low SpO_2 (<92%) in the three near and independent measurements despite receiving FiO_2 >40% (HFNCO) and at a maximum 10 L/min (LFO); iv) An increase or no changes in CRS relative to baseline; v) Arterial blood partial pressure of carbon dioxide [?]60 mm/Hg. Children who failed on HFNCO were transferred to the ICU. Those who deteriorated on LFO were trialed HFNCO (at 2 L*kg/min) as a rescue treatment in the general ward. The patients who did not respond to HFNCO were transferred to the ICU. Fifteen days after discharge, we carried out follow-up phone interviews with parents or caregivers (Supplement Table 2; p8,9).

Participants were followed with a cardiorespiratory monitor and pulse oximetry. The baseline assessments including HR, RR (measured by counting one minute; and corrected according to age and body temperature[20,21]), SpO_2 (determined by the value of pulse oximetry with an appropriate waveform sustaining for 3 s), CRS, blood pressure, and body temperature were performed in room air. Those measurements were recorded at the 1, 2, 4, 12, and 24 h; then were evaluated once a day until discharge. In addition, venous blood gas was obtained at baseline and 4 h. The multiplex real-time polymerase chain reaction was performed on nasopharyngeal swab specimens at admission to show the viral pathogens (respiratory syncytial virus-A and -B, rhinovirus, parainfluenza virus [1-4], influenza A, B, and A(H1N1)pdm09, human metapneumovirus, adenovirus, coronavirus [OC43, 229E, NL63, and HKU1], human bocavirus, and enterovirus).

The primary outcome was the time that HR and RR returned to the normal range for age and the time that CRS took to regress from severe to moderate bronchiolitis or from moderate to mild bronchiolitis. Secondary outcomes included changes in HR, RR, and CRS from randomization to an average of 96 h. We also analyzed the duration of oxygen therapy, LOS, treatment failure, ICU admission, and adverse events (AEs).

2.3-Power calculation

Several randomized, controlled studies comparing HFNCO and LFO have assessed changes in HR, RR, and CRS over time in children with bronchiolitis. However, we could not find a study comparing the time that HR and RR returned to the normal range for age and, similarly, the time for our CRS outcome mentioned. Therefore, we made a preliminary analysis and sample calculation by evaluating the data of 24 patients who met the study criteria. Sample size calculations were done using a t-test on primary outcomes to obtain a power of 90% and an alpha of .05. The sample size for HR and RR yielded 39 patients in each group, while the sample size for CRS yielded 50 subjects. Unfortunately, we did not reach the number of participants calculated with the power analysis because of the financial problem. So instead, we figured the effect sizes r of primary outcomes with the Mann-Whitney-U test interpreted as 0.1 small, 0.3 medium, and 0.5 large, according to the r = z/[?]n formula.[22,23] The effect size for each of the primary outcomes was presented below the table.

2.4-Statistical analysis

Patient characteristics were presented as frequencies and percentages for categorical data and means (SD) or medians (IQR) for continuous data. The primary analysis of all outcomes followed the intention-to-treat (ITT) principle. Between groups, we used the Mann-Whitney-U test for comparing the time of success for HR, RR, and CRS (SPSS Inc., version 25.0, Chicago, IL, USA). The longitudinal analysis part of the study was performed non-parametrically with the Brunner-Langer model for CRS conducted with a linear mixed model in a parametric way for HR and RR. The Brunner-Langer model (F1-LD-F1) was applied using web-based software (R software, version 3.5.2, package: nparLD, R Foundation for Statistical Computing, Vienna, Austria;*http://r-project.org*). The PROC MIXED procedure in the SAS software was used (Version 9.3; SAS Institute, Cary, NC, USA) to perform linear mixed models in which subjects were included as random effects. When there was a significant interaction effect in the longitudinal analysis ($P < .1$), the time effect was analyzed in each group, and groups were compared at baseline and following time points (the baseline was subtracted from these time points). The proportions of the treatment failure, rescued patient, ICU admission, and AE were analyzed using Fisher's Exact test and, given with odds ratios (ORs) and 95% Confidence Intervals (CIs). A 2-sided $P < .05$ defined statistical significance.

3-RESULTS

We assessed 5643 patients for eligibility, and 5556 subjects were excluded because of mild bronchiolitis, no desaturation, comorbidity, and the presence of respiratory illness other than bronchiolitis. Of 472 eligible patients, 134 were missed opportunities, and 251 parents declined to participate in the study. Eighty-seven participants (48 in LFO vs. 39 in HFNCO) were included in the study. Ten patients in LFO therapy and one in HFNCO therapy ($P = .02$) needed an escalation of care at 4 h (Figure 1). Baseline demographic and clinical characteristics of patients were presented in Table 1.

3.1-Primary outcome measures

Compared with LFO, the time that HR and RR baseline values reached their normal range for age was shorter in HFNCO therapy (2.0 h [1.0-4.0] vs. 12.0 h [2.0-24.0] and 4.0 h [2.0-12.0] vs. 24.0 h [4.0-48.0], respectively; $P< .001$); additionally, the improvement in CRS emerged more quickly in children treated with HFNCO (2.0 h [1.0-4.0] vs. 4.0 h [2.0-24.0]; $P = .003$; Table 2). The cumulative number of patients with normal HR and RR for age over time and those whose CRS regressed to a lower severity score was presented in Figure 2-4, respectively.

3.2-Secondary outcome measures

Our results showed that HR, RR, and CRS significantly decreased over time relative to the baseline values within both therapy groups. In the comparison of groups, the mean difference (MD) in the reduction of HR and RR were the greatest at 4 h (MD -19.75 [95% CI, -28.57 to -10.92] and MD -10.61 [95% CI, -14.10 to -7.12], respectively; both $P < .001$; Table 2; Supplement Table 3; p10-12). The decrease in CRS relative to baseline over time was significantly higher in children treated with HFNCO than those treated with LFO (Table 2; Supplement Table 4; p13,14). The longitudinal analyses for HR, RR, and CRS were given in Supplement Table 5,6; p15-20.

While we found a shorter duration of oxygen therapy in children who received HFNCO (19.0 h [4.0-30.0]; $P = .009$), there was no significant difference in LOS between the groups (HFNCO; 5.0 d [4.0-7.0]; $P = .22$; Table 2]. The proportion of treatment failure was present in one patient on HFNCO and ten patients on LFO (3% vs. 21%; $P = 0.02$; Supplement Table 7; p21,22). First, HFNCO was performed on all ten patients. Two patients were transferred to the ICU after further deterioration. Eight patients had a clinical improvement. We did not observe severe AEs, such as pneumothorax, pressure injuries, or child death. Transient bradycardia was seen in both groups (three in HFNCO vs. one in LFO). Epistaxis was found in two patients who received HFNCO therapy (Table 2).

4-DISCUSSION

This randomized controlled study involving children aged between 1 and 24 months diagnosed with moderate and severe bronchiolitis requiring supplemental oxygen determined that HFNCO therapy provided a notable improvement in HR, RR, and CRS over time compared with LFO therapy. This treatment modality offers a heated, humidified, and high-flow oxygen concentration regardless of the patient's effort;[24] additionally, it optimizes the gas exchange by decreasing dead space volume and maintaining mean airway pressure.[24,25] The improvement in mucociliary clearance,[25] with increased alveolar ventilation, could positively affect high HR and RR baseline values at admission. Assessing the disease severity is essential for the clinical management of patients and clinical research. Although many scoring scales exist in the literature, there are conflicting results regarding the effect of HFNCO therapy on CRS.[11,14,15] Those contradictory outcomes might be associated with variable clinical score systems used in studies. Because of the presence of many care providers for these patients, we used the CRS reported by Liu et al.,[19] an excellent inter-rater agreement (82-88%), to minimize evaluation bias. However, comprehensive studies focusing on valid and reliable clinical tools involving objective parameters are needed.

A recent study conducted in children with moderate-to-severe bronchiolitis found no notable difference in the length of oxygen requirement and LOS between therapy groups, suggesting that early use of HFNCO does not modify the underlying disease process.[13] Another randomized, controlled study demonstrated a lower rate for

escalation of care in HFNCO therapy but no evidence for shorter LOS and the length of oxygen requirement.[12] Similar to these studies, our secondary results showed a comparable LOS and a lower rate for escalation of care in HFNCO therapy. Surprisingly, we determined that HFNCO therapy might shorten the length of oxygen requirement. While many studies showed no differences in the length of oxygen requirement,[12,13,27] a study conducted in the ICU suggested that children treated with HFNCO had a shorter duration of oxygen than those treated with LFO.[28] Besides, we note that secondary results of trials should be assessed carefully because of the power analysis calculated for primary outcomes. In our study, we administered HFNCO, at a flow rate of 2 L*kg/min, to the patients admitted to the general ward and did not identify any severe AEs. Although recently published reports did not determine any severe AEs,[10-13,26,28] critical air leak syndrome has been described in children treated with HFNCO.[29] Therefore, HFNCO therapy, a relatively new mode of respiratory support and increasingly being used, may be performed by closely monitoring the patients' clinical status.

This study had some limitations. First, it was performed in a single center, and we could not reach the number of participants calculated with the power analysis because of the financial support problem. Although we used effect size for each of the primary outcomes, the generalizability of the recommendations reduced. Second, we did not blind the allocation of oxygen therapies to introduce the risk of performance bias. Finally, the patients were not allocated to receive therapy in a ratio of 1:1. Therefore, the results may have been affected by this diversity.

One of our trial's strengths was using a clinical scoring system for children with bronchiolitis, a valuable tool for monitoring the clinical severity of bronchiolitis. Although there may be a potential bias in any clinical scoring system, CRS used in this study has been identified to have an excellent inter-observer agreement. Second, we performed the parent interview questionnaire by contacting parents 15 days after discharge to increase the accuracy of the results for each treatment arm.

In conclusion, HFNCO may provide enhanced respiratory support with a notable improvement in HR, RR, and CRS than LFO. Comprehensive studies are needed to assess the clinical efficacy of HFNCO therapy.

Acknowledgments

Contributors' Statement Page

Dr. Eşki conceptualized and designed the study, coordinated and supervised data collection, participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript;

Dr. Öztürk helped with the design of the study and acquisition of data and reviewed the manuscript critically;

Dr. Turan contributed to study design, analysis, and interpretation of data and critically reviewed the manuscript;

Dr. Özgül was involved in the analysis and interpretation of the data, and drafting and revising the manuscript;

Dr. Gülen contributed to study conceptualization and design and critically reviewed the manuscript;

Dr. Demir conceptualized and designed the study; coordinated and supervised data collection, participated in the acquisition, analysis, and interpretation of the data; reviewed and revised the manuscript; all authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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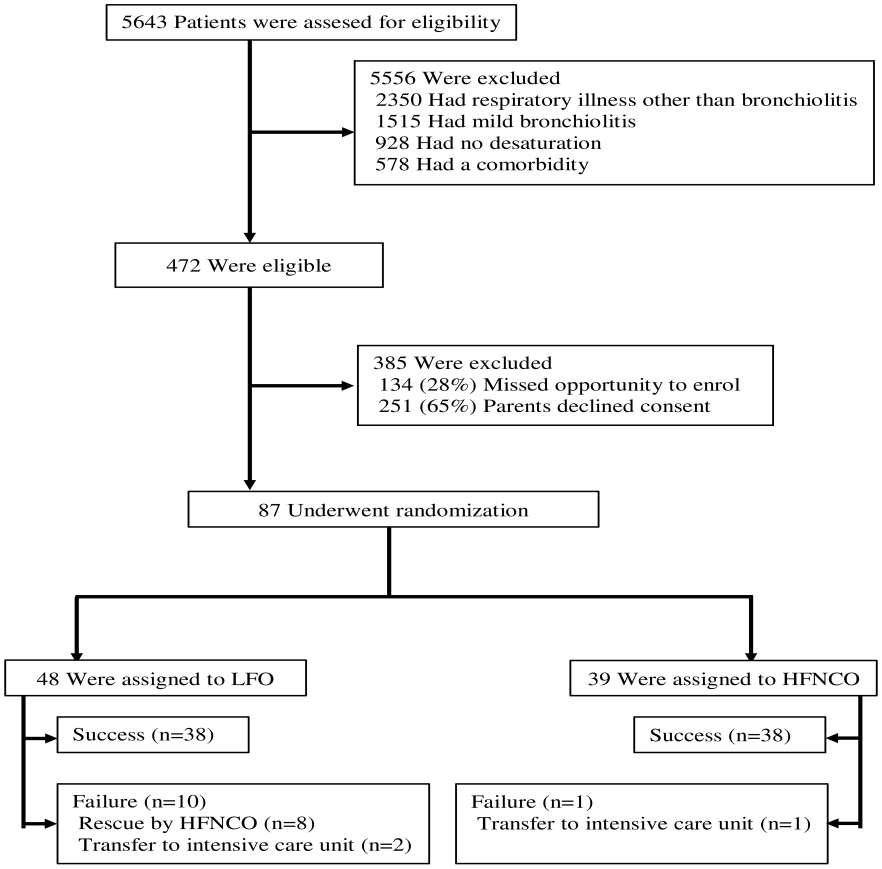

HFNCO, high-flow nasal canula oxygen; LFO, low-flow oxygen.