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High-flow nasal cannulas versus standard oxygen therapy for moderate bronchiolitis: a quasi-experimental analysis

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Abstract

Background: In the last decades none of the medical therapies investigated have shown clear efficacy in the treatment of bronchiolitis, and literature agrees on a general de-implementation of pharmacological therapies, recognizing an effective role only to nutritional support and oxygen therapy. High-flow nasal cannulas (HFNC) has become increasingly popular in the last decade, despite its lack of clear efficacy. Recent randomized controlled trials (RCT) comparing standard oxygen therapy (SOT) and HFNC did not demonstrate significant benefit of HFNC. To acquire more clinical data on HFNC efficacy we performed a retrospective, quasi-experimental analysis of patients admitted for bronchiolitis in the epidemic seasons 2021–2022 and 2022–2023.

Methods: To assess the efficacy of SOT and HFNC we used a pragmatic approach, a fuzzy regression discontinuity design, which is a quasi-experimental test. Unlike RCTs, this process is not a true randomization, but may be interpreted as quasi-randomization in an observational setting.

Results: HFNC did not reduce length of oxygen therapy (LOO) nor length of hospitalization (LOS) (respectively, p: 0.383 and p: 0.454). Treatment failure was not significantly different in the treatment groups (p: 0.354).

Conclusions: It is crucial to perform additional RCTs with uniform protocols to determine the efficacy of HFNC more accurately in the treatment of bronchiolitis. HFNC does not reduce LOO, suggesting that early use of HFNC does not change the course of disease in moderate bronchiolitis. In view of the greater complexity and higher cost, HFNC should not be routinely used as first-line treatment in children with moderate respiratory distress and mild hypoxemia.

KEYWORDS

bronchiolitis, high-flow nasal cannulas, RSV, standard oxygen therapy

1 | BACKGROUND

Bronchiolitis is an acute viral infection of the lower respiratory tract and it is the main responsible for nonelective hospital admissions in infants.[1,2] Estimates suggest that between 2% and 3% of all children younger than 12 months are hospitalized for bronchiolitis, which accounts for 57,000–172,000 hospitalizations annually in the United States. The most common pathogen is the respiratory syncytial virus (RSV), which accounts for 50%–80% of bronchiolitis presentations in infants and is also the most aggressive. Symptoms are driven by inflammation, edema, and necrosis in the lower respiratory airways, resulting in hypoxemia, hypercarbia and increased work of breathing.[3]

In the last decades many trials have been carried out to define which are the best therapies, both pharmacological and nonpharmacological. None of the medical therapies investigated have shown clear efficacy, and the latest clinical guidelines advice against routinary administration of corticosteroids, bronchodilators and other medications.[4–6] Consequently, literature is agreeing on a general de-implementation of pharmacological therapies, recognizing an effective role only to nutritional support and oxygen therapy in the management of bronchiolitis.[3,7]

High-flow nasal cannulas (HFNC) has become more and more popular in the last decade, and its use is spreading also outside the Pediatric Intensive Care Units (PICU) despite its lack of clear efficacy.[8–10] HFNC delivers a warmed and humidified mix of air and oxygen at a flow higher than the patient's inspiratory flow, and it has been variably defined. In general, it refers to a flow rate of up to 2–3 L/kg per min with a ceiling fraction of inspired oxygen (FiO2) of 40%–60%.[7] Even with different protocols of delivery, physiological effects of HFNC include decreased airways resistance and reduced work of breathing, with a certain degree of positive airway pressure and washout of the dead space.[11]

Initial studies on small cohorts supported the use of HFNC.[12–14] More recent randomized controlled trials (RCT) comparing standard oxygen therapy (SOT) and HFNC did not demonstrate with HFNC any significant reduction in length of oxygen therapy, in length of hospital stay and in transfers to PICU.[8,10,15,16]

HFNC has an estimated cost up to 16 times that of SOT[10] and requires specific training, it is therefore crucial to clearly define the efficacy of the treatment to better manage health care resources. Other issues regarding HFNC include the potential rapid deterioration of the patient, which requires preferably the presence of an in-site ICU.

To acquire more clinical data on HFNC safety and efficacy we performed a retrospective, quasi-experimental analysis of the patients admitted for bronchiolitis in the last two epidemic seasons, that is, 2021–2022 and 2022–2023.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

We retrospectively reviewed the medical records of children hospitalized with diagnosis of moderate bronchiolitis at the Emergency and General Pediatric Unit of Bambino Gesù Children's Hospital (OPBG), Rome, Italy between October 1st to 31 March of the last two epidemic seasons 2021–2022 and 2022–2023. In-site PICU was present.

Children <12 months of age were enrolled in the study. Bronchiolitis was diagnosed on the basis of anamnestic report and physical examination.[4]

Exclusion criteria were: gestational age <37 weeks; comorbidities such as heart, pulmonary or neuromuscular diseases; pneumothorax at chest x-ray; mild bronchiolitis requiring <24 h of oxygen therapy and severe bronchiolitis requiring immediate continuous positive airway pressure (CPAP) or invasive mechanical ventilation (IMV). We also excluded patients who had previously received a diagnosis of bronchiolitis and those requiring prolonged hospitalization for concomitant diseases not related to bronchiolitis.

Data extracted from medical records included age, sex, perinatal history, siblings, breastfeeding and length of hospitalization (LOS), in addition to data regarding length of oxygen therapy (LOO) and modality of respiratory support.

The study protocol was approved by the Institutional Review Board and Ethics Committee of our institution (Protocol 2053-OPBG). In view of the observational and retrospective nature of the study and given that the data are aggregated, written informed consent was exempted.

Patients' biographical, clinical and microbiological data were retrospectively extracted from medical records and tabulated anonymously using "Microsoft Excel" software.

2.2 | Procedures

All children had a nasopharyngeal aspirate collected at admission and laboratory assays were able to detect the following viruses: Influenza virus, Respiratory Syncytial virus, Adenovirus, Enterovirus, Parainfluenza virus, Metapneumovirus, Bocavirus, Rhinovirus, and Coronavirus. In addition, in the Emergency Department, all patients were screened for SARS-CoV-2 infection by nasopharyngeal swab.

According to the OPBG bronchiolitis protocol, patients with peripheral capillary oxygen saturation (SpO_2) < 92% were started on SOT. Children with $PaCO_2$ > 55 mmHg or SpO_2 persistently <90%, with increased work of breathing and respiratory rate (RR) > 50 breaths per min were started on or crossed to HFNC with a flow starting from 1 L/kg/min +1 to a maximum of 2 L/kg/min. Fraction of inspired oxygen (FiO_2) was titrated up to 40% to maintain SpO_2 > 92% and satisfactory work of breathing.

HFNC was delivered via age- appropriate Optiflow nasal cannulas and a Airvo 2 humidifier.

All patients were continuously monitored for heart rate (HR) and SpO_2. RR, HR and SpO_2 were registered at the beginning of oxygen therapy and after 4 and 24 h.

Weaning off oxygen was started as soon as possible at clinical and vital parameter stability. In accordance with the OPBG protocol, weaning from HFNCs was carried out by gradually reducing FiO_2 up to 21% and suspending flows later on.

Failure of oxygen therapy (treatment failure, TF) was defined as altered vital parameters despite the ongoing maximal therapy, assessed by the Bedside Pediatric Early Warning Score (PEWS), and by the physician's clinical decision. The PEWS, calculated at regular, score-dependent, intervals throughout the hospital stay and adjusted for the patient's age, is a score that includes heart rate, blood pressure, capillary refill time, respiratory rate, respiratory effort, oxygen saturation and oxygen therapy.

Patients who failed SOT had a trial with HFNC as second-line therapy. In case of further failure of this therapy, depending on the clinical condition, ventilatory support was provided by helmet-CPAP (HCPAP) or IMV in the intensive or sub-intensive care area.

2.3 | Outcomes

The primary outcome was time to weaning off oxygen therapy. Secondary outcomes of the study were: comparison of LOS in the SOT and HFNC groups; definition of timing of failure of SOT and HFNC; definition of the incidence of TF and assessment of any adverse effect and tolerability of SOT and HFNC.

2.4 | Statistical analysis

Categorical variables are presented as frequencies and percentages, and distributions were compared using the $\chi 2$ test. Continuous variables are presented as means (±standard deviation) or medians (interquartile range), depending on the normality analysis of the data. Mann–Whitney tests, two-tailed Student's *t*-test for independent samples or Friedman's test with Bonferroni correction were used to make direct comparisons, depending on appropriateness.

As a retrospective study, we used a fuzzy regression discontinuity design (RDD),[17] which is a quasi-experimental test, to assess the efficacy of SOT and HFNC comparing the LOO and LOS in the two patients' groups. RDD is a pragmatic approach for estimating the effectiveness of a treatment and is based on the principle that patients whose assignment variables are around the set threshold belong to the same population. Under this assumption, the threshold represents the random intervention that assigns the treatment for that population "just above" or "just below" the threshold. Unlike RCTs, this process is not a true randomization, but may be interpreted as quasi-randomization in an observational setting. It is possible to use RDD in scenarios where the treatment rule is not followed strictly, which is why the allocation variable provides a reasonable indication of the treatment received. For these reasons, RDD can be used to estimate the effect of a specific treatment on a particular outcome.[18]

Predictors of oxygen therapy failure were analyzed by multivariate regressions.

Statistical analysis was performed using SPSS 26.0 and r 4.3.1 software.

The level of statistical significance was set at 0.05.

3 | RESULTS

From 1 October to 31 March of the epidemic seasons 2021–2022 and 2022–2023, 296 patients admitted with diagnosis of bronchiolitis were assessed for eligibility. Among them, 125 patients were excluded because they met the exclusion criteria, while 171 patients were included (Figure 1).

According to clinical conditions, 116 patients were started on SOT and 55 patients received HFNC. There were no statistically significant differences in the demographic characteristics of patients in the HFNC and SOT groups at admission (Table 1).

Patients who were started on HFNC needed oxygen therapy for a significantly longer time than patients who received SOT (LOO 5.95 ± 2.47 days and 4.25 ± 2.22 days, *p*: <0.001). To avoid the selection bias given by the greater respiratory distress of patients in the HFNC group (Table 1), we decided to perform a quasi-experimental analysis with HR as the covariate and RR at 50 breaths per minute as threshold. The RDD showed that HFNC did not reduce the duration of oxygen therapy (*p*: 0.383, coeff. 0.907).

Similar findings came out from the analysis of length of hospital stay: mean LOS was significantly higher in patients who were started on HFNC (8.18 ± 3.63 days vs. 6.89 ± 2.77 days SOT, *p*: 0.011) but RDD did not show any efficacy of HFNC in reducing LOS (*p*: 0.454 coeff. 5.818, Figure 2).

In the group of patients who had treatment failure (non-responders), the interval between initiation of oxygen therapy and escalation of respiratory support was not significantly different between the two groups (15 h SOT vs. 17 h HFNC, *p*: 0.696,

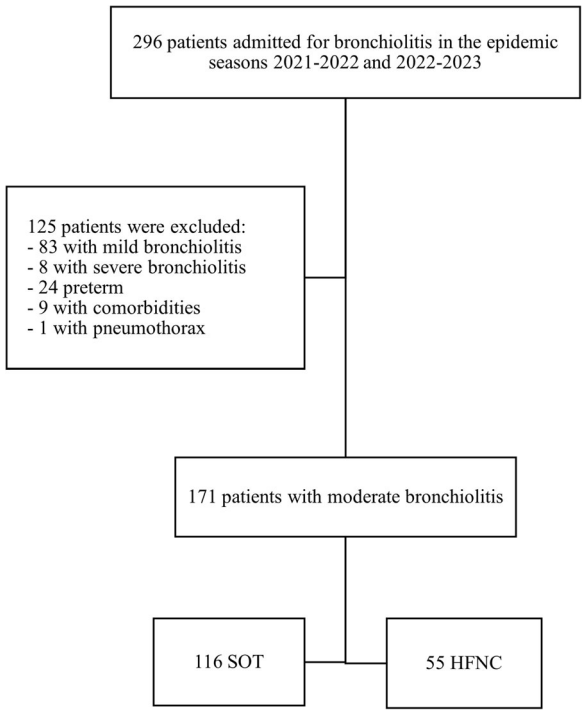

FIGURE 1 Screening flow chart for patients' enrollment. HFNC, High-flow nasal cannulas; SOT, standard oxygen therapy.

TABLE 1 Clinical and demographic characteristics of the study cohort.

	SOT *n* = 116	HFNC *n* = 55	*P*-value
Males	55 (47.4)	26 (47.2)	0.986
Age (days)	55 (41-90)	50 (30-90)	0.170
Weight at birth (g)	3349 (±413.4)	3341 (±461.4)	0.906
Weight at admission (g)	5075 (4300–5810)	4885 (4170–6000)	0.845
Breastfeeding	95 (81.9)	44 (80)	0.766
Siblings	84 (77.6)	42 (82.3)	0.446
Vital signs at admission			
SpO2 (%)	92 (90–96)	93 (90–95)	0.342
RR	35 (30–40)	50 (41–55)	<0.001
HR	139 (130–151)	160 (142–170)	<0.001
Viral isolates			0.668
0	1 (0.9)	0 (0)	
1	81 (69.8)	35 (63.6)	
≥2	36 (29.3)	20 (36.4)	

Note: Data are expressed as mean (±SD), median (IQR) or number (%) as appropriate.

Abbreviations: HFNC, High-flow nasal cannulas; SOT, standard oxygen therapy.

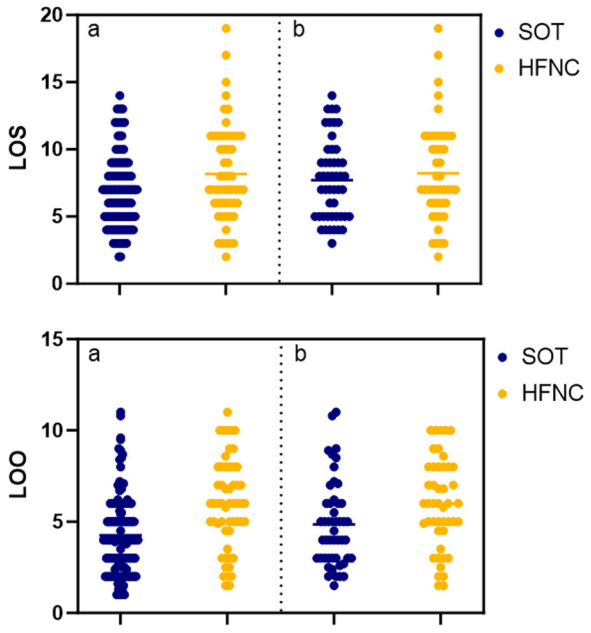

FIGURE 2 LOO and LOS distribution in patients according to initial oxygen therapy. (a) total population (b) population around RDD's set threshold. HFNC, High-flow nasal cannulas; LOO, length of oxygen therapy; LOS, length of hospitalization; RDD, regression discontinuity design; SOT, standard oxygen therapy. [Color figure can be viewed at wileyonlinelibrary.com]

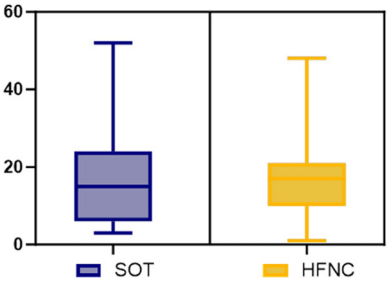

FIGURE 3 Time to treatment failure in patients according to initial oxygen therapy. HFNC, High-flow nasal cannulas; SOT, standard oxygen therapy. [Color figure can be viewed at wileyonlinelibrary.com]

Figures 2 and 3). This result is confirmed by the quasi-experimental analysis (RDD *p*: 0.522, coeff. 14.201).

All patients had a nasopharyngeal swab collected at admission, in one case no virus was isolated, while in the rest of patients from 1 to 4 different viruses were detected. There was no statistically significant difference in coinfection rates between the SOT and the HFNC group (29.3% and 36.4%, respectively, *p*: 0.668). Also, no difference in the distribution of viral isolates was detected between the two groups (Table 1).

Thirty-six patients who were started on SOT experienced treatment failure, among them one patient required immediate transition to HCPAP and 35 were started on HFNC as a rescue therapy. Twelve of these patients required HCPAP after further deterioration, whereas HFNC reversed the clinical worsening of the other 23 patients who remained in the ward.

The 21 patients who had treatment failure on HFNC required transition to HCPAP; only one required further escalation of care and received IMV (Figure 4).

Treatment failure did not show significantly different rates of incidence in the two treatment groups (*p*: 0.354) and the Kaplan-Meier analysis confirmed this finding (*p*: 0.296). In addition, the quasi-experimental analysis proved that HFNC did not reduce HCPAP treatment rates (*p*: 0.935).

No major oxygen-related adverse effects occurred in both SOT and HFNC group.

Only one patient did not tolerate HFNC and was switched to SOT, with good compliance and therapeutic success.

No significant differences emerged in the demographic characteristics between responders and non-responders to oxygen therapy in SOT and in HFNC groups (Table 2). Within the responder group, those who were started on HFNC had a significantly longer LOO, compared to those that were started on SOT (5.24 vs 3.37 days, respectively).

4 | DISCUSSION

The use of HFNC is one of the most recent non-invasive ventilation support modalities, and it has been advocated as a promising approach for bronchiolitis management in the last

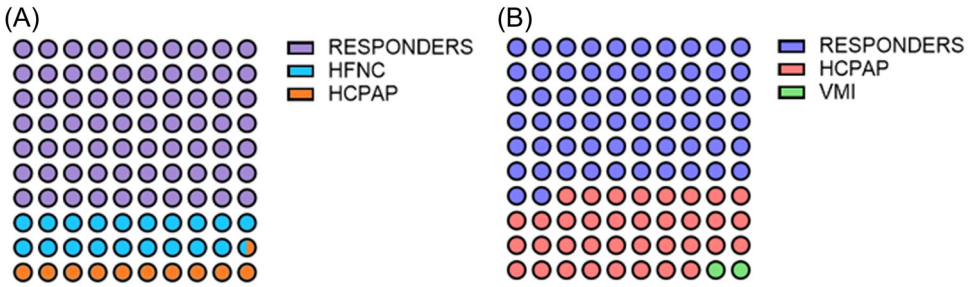

FIGURE 4 Treatment failure in patients according to initial oxygen therapy (A: SOT; B: HFNC). HFNC, High-flow nasal cannulas; SOT, standard oxygen therapy. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Demographic characteristics between responders (R) and non-responders (NR) to oxygen therapy in SOT and in HFNC groups.

	SOT NR *n* = 36	HFNC NR *n* = 21	*P*-value	SOT R *n* = 80	HFNC R *n* = 34	*P*-value
Age (days)	53.5 (42.5–75)	51 (29–72)	0.661	63 (41–94)	50 (32–96)	0.229
Weight at admission (g)	4850 (4425–5650)	4915 (4295–6000)	0.979	5110 (4275–5850)	4820 (4150– 6100)	0.839
RSV	34 (94.4)	20 (95.2)	0.897	68 (85.0)	28 (82.3)	0.723
Breastfeeding	27 (75.0)	16 (76.2)	0.671	63 (84.0)	28 (82.3)	0.830
Siblings	25 (75.7)	16 (88.9)	0.259	55 (76.4)	25 (78.1)	0.846
LOO	6.28 (±2.14)	7.10 (±1.97)	0.156	3.37 (±1.56)	5.24 (±2.50)	<0.001
LOS	9.00 (±2.69)	10.71 (±3.65)	0.047	5.94 (±2.23)	6.62 (±2.62)	0.161
Time to treatment failure (hours)	15 (6.5–24)	17 (10–19)	0.696	N.A.	N.A.	

Note: Data are expressed as mean (±SD), median (IQR) or number (%) as appropriate.

Abbreviations: HFNC, High-flow nasal cannulas; LOO, length of oxygen therapy; LOS, length of hospitalization; N.A., not applicable; SOT, standard oxygen therapy.

decades.[12–14] Initial studies suggested that HFNC use reduces work of breathing and prevents complications such as atelectasis, as well as progressive respiratory exhaustion which may lead to respiratory failure.[19] In addition, it was suggested that HFNC therapy could reduce the need for IVM of infants with bronchiolitis.[13]

Recently, however, several authors have questioned its efficacy and its cost-effectiveness ratio. The first RCT, published in 2017 by Kepreotes et al.,[10] was a single-center study designed to demonstrate a reduction of oxygen therapy duration in the HFNC group compared to the SOT group; the authors found no difference for the primary outcome. These findings were confirmed by those from Franklin et al.,[9] who performed a multicenter RCT on 1472 patients and found neither reduction in the duration of oxygen therapy nor in the hospital stay in patients who were started on HFNC compared to those who were started on SOT.

The quasi-experimental analysis of the data in the present study suggests that early use of HFNC does not reduce the duration of oxygen therapy compared to SOT in patients with moderate bronchiolitis younger than 12 months. Not surprisingly, our data also do not show any role of HFNC in reducing LOS. Our findings confirm the results of the latest studies[8–10] that compared the efficacy of SOT and HFNC in children with moderate bronchiolitis.

HFNC demonstrates excellent levels of safety and tolerability. Recently there is increasingly agreement in literature on its use as a rescue therapy when SOT is not effective in reducing work of breathing. In agreement with literature,[9,10] 64.7% of the children who experienced treatment failure on SOT were adequately supported by HFNC and did not require further escalation of care. Treatment failure rates were not significantly different in the HFNC group compared to the SOT group, but the quasi-experimental analysis suggests that HFNC might reduce the likelihood of treatment escalation, although the small size of our cohort and the high degree of variability likely hampered the achievement of any statistical significance (coeff. −0.190, *p*: 0.814, standard error 0.810).

Kepreotes et al.[10] report lower treatment failure rates in the HFNC group than in the SOT group (14% and 33%, respectively), while as Franklin et al.[9] found similar results (12% and 23%, respectively). In the latter RCT, and in the present study, the time between initiation of oxygen therapy and escalation of care was not significantly different between the two groups of non-responders.

Franklin et al. and Kepreotes et al. do not describe significant reduction in ICU transfer rates in the HFNC group compared to the SOT group. Durand et al.[16] and Kooiman et al.[8] recently published two RCTs, with a substantial difference with previous studies: they both did not allow crossover between treatment groups. Indeed, they

questioned that in previous trials, as well as in our study, crossover between groups was permitted, thus indicating that the real comparison occurred between early and late HFNC use. However, their conclusions were similar to the previous RCTs: ICU transfer rates did not differ between HFNC and SOT groups.

It is not possible to compare our data with the ones from literature, as there is high variability in experience and treatment settings between hospital centers. Specifically, in our center, ventilation with HFNC is performed in specific wards with specifically trained staff, and HCPAP is used in specific wards with adequate training, setting and staff-to-patient ratio. However, in other centers the use of HCPAP, if not both HCPAP and HFNC, is relegated to ICUs. Papers based on multicenter protocols show an important variability in the clinical approach across various hospital centers, and consequently an important variability in the decision to escalate oxygen therapy, depending on the presence or absence of ICUs in situ.[9,10] Therefore, we believe it would be more useful in the future to compare more reliable indexes of severity such as HCPAP and VMI rates, data that cannot always be extrapolated from studies. Among the RCTs that used an HFNC protocol similar to ours, i.e., 2 L/kg/min with maximum FiO2 0.40, unfortunately, CPAP utilization data are not available, while VMI rates are essentially overlapping (0.6% vs 0%–0.8%).[9,16]

In fact, the lack of standardization of HFNC therapy raises concerns about its protocol of use, which is extremely heterogeneous among centers: maximum oxygen flow varies from 1 to 3 L/kg/min, while FiO2 varies from 40% to 60%.[8,9,16,20]

Although secondary goals should be interpreted with caution, the potential of HFNC to reduce the likelihood of treatment escalation and their role as rescue therapy may have important implications in clinical practice. Thus, data from our study suggest that, when used as rescue therapy in children who are not adequately supported by SOT, HFNC may reduce the number of patients requiring escalation of care.

HFNC therapy has an estimated cost 16 times higher than SOT[10] and its use requires specifically trained staff and congruent nurse-to-patient ratios. While, therefore, HFNC has potential utility in preventing costs associated with ICU stay, their use needs to be appropriately rated only in patients who do not respond to SOT, to contain costs associated with the method itself and reduce patient discomfort, which is a side-effect.

The evidence from our study and existing literature suggest the need to perform additional RCTs with strictly uniformed protocols to more accurately determine the efficacy of HFNC in the treatment of bronchiolitis.

This study has limitations. Our study design (fuzzy RDD) helps simulate a quasi-experimental setting, making the study more robust compared to a retrospective study, but still not as robust as a true randomized controlled trial. Secondarily, the small sample size may have reduced statistical power.

In conclusion, HFNC does not reduce the duration of oxygen therapy compared to SOT, suggesting that early use of HFNC does not change the course of disease in patients with moderate bronchiolitis. In view of the greater complexity of therapy and higher cost, HFNC should not be routinely used as first-line treatment in children with moderate respiratory distress and mild hypoxemia.

HFNC have been shown to be safe at 2 L/min/kg and maximum FiO2 of 40%, and their use has prevented escalation of care in a conspicuous proportion of patients who were not adequately supported by SOT.

Further prospective studies with standardized patient selection and homogeneous protocols for the use of HFNC are needed to more accurately evaluate the effectiveness of this ventilation in the treatment of bronchiolitis.

AUTHOR CONTRIBUTIONS

Livia Antilici: Writing—original draft; conceptualization; formal analysis; data curation; investigation; methodology. **Anna C. Vittucci**: Conceptualization; writing—review and editing; supervision; investigation. **Sebastian Cristaldi**: Writing—review and editing; supervision. **Anna M. C. Musolino**: Supervision; writing—review and editing. **Mara Pisani**: Writing—review and editing; supervision. **Lelia R. Aufiero**: Writing—review and editing; supervision. **Chiara V. Di Maio**: Writing—review and editing; supervision. **Rossana Scutari**: Writing—review and editing; supervision. **Renato Cutrera**: Writing—review and editing; supervision. **Andrea Dotta**: Writing—review and editing; supervision. **Carlo F. Perno**: Writing—review and editing; supervision. **Alberto Villani**: Writing—review and editing; supervision; conceptualization.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The study was approved by the Ethics Comittee of the Bambino Gesù Children's Hospital.

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REFERENCES

1. Florin TA, Plint AC, Zorc JJ. Viral bronchiolitis. *The Lancet*. 2017;389:211-224.
2. Snow KD, Mansbach JM, Gao J, Shanahan KH, Hasegawa K, Camargo CA. Trends in emergency department visits for bronchiolitis, 1993–2019. *Pediatr Pulmonol*. 2024;59:930-937.
3. Meissner HC. Viral bronchiolitis in children. *N Engl J Med*. 2016;374:62-72.

4. Manti S, Staiano A, Orfeo L, et al. UPDATE—2022 Italian guidelines on the management of bronchiolitis in infants. *Ital J Pediatr*. 2023;49:19.
5. National Collaborating Centre for Women's and Children's Health (UK). Bronchiolitis: diagnosis and Management of Bronchiolitis in Children. National Institute for Health and Care Excellence (NICE); 2015.
6. Friedman JN, Rieder MJ, Walton JM. Bronchiolitis: recommendations for diagnosis, monitoring and management of children one to 24 months of age. *Paediatr Child Health*. 2014;19:485-491.
7. Dalziel SR, Haskell L, O'Brien S, et al. Bronchiolitis. *The Lancet*. 2022;400:392-406.
8. Kooiman L, Blankespoor F, Hofman R, et al. High-flow oxygen therapy in moderate to severe bronchiolitis: a randomised controlled trial. *Arch Dis Child*. 2023;108:455-460.
9. Franklin D, Babl FE, Schlapbach LJ, et al. A randomized trial of high-flow oxygen therapy in infants with bronchiolitis. *N Engl J Med*. 2018;378:1121-1131.
10. Kepreotes E, Whitehead B, Attia J, et al. High-flow warm humidified oxygen versus standard low-flow nasal cannula oxygen for moderate bronchiolitis (HFWHO RCT): an open, phase 4, randomised controlled trial. *The Lancet*. 2017;389:930-939.
11. Beggs S, Wong ZH, Kaul S, Ogden KJ, Walters JA. High-flow nasal cannula therapy for infants with bronchiolitis. *Cochrane Database Syst Rev*. 2014;2014(1):CD009609. doi:10.1002/14651858.CD009609.pub2
12. Hough JL, Pham TMT, Schibler A. Physiologic effect of high-flow nasal cannula in infants with bronchiolitis. *Pediatr Crit Care Med*. 2014;15:e214-e219.
13. Schibler A, Pham TMT, Dunster KR, et al. Reduced intubation rates for infants after introduction of high-flow nasal prong oxygen delivery. *Intensive Care Med*. 2011;37:847-852.
14. Milani GP, Plebani AM, Arturi E, et al. Using a high-flow nasal cannula provided superior results to low-flow oxygen delivery in moderate to severe bronchiolitis. *Acta Paediatr (Stockholm)*. 2016;105:8e368-e372.
15. Franklin D, Fraser JF, Schibler A. Respiratory support for infants with bronchiolitis, a narrative review of the literature. *Paediatr Respir Rev*. 2019;30:16-24.
16. Durand P, Guiddir T, Kyheng C, et al. A randomised trial of high-flow nasal cannula in infants with moderate bronchiolitis. *Eur Respir J*. 2020;56:1901926.
17. Hagemeier A, Samel C, Hellmich M. The regression discontinuity design: methods and implementation with a worked example in health services research. *Z Evid Fortbild Qual Gesundhwes*. 2022;172:71-77.
18. O'Keeffe AG, Geneletti S, Baio G, Sharples LD, Nazareth I, Petersen I. Regression discontinuity designs: an approach to the evaluation of treatment efficacy in primary care using observational data. *BMJ*. 2014;349:g5293.
19. Bressan S, Balzani M, Krauss B, Pettenazzo A, Zanconato S, Baraldi E. High-flow nasal cannula oxygen for bronchiolitis in a pediatric ward: a pilot study. *Eur J Pediatr*. 2013;172:1649-1656.
20. Kannikeswaran N, Ehrman RR, Spencer P, et al. Impact of initial high flow nasal cannula flow rates on clinical outcomes in children with bronchiolitis. *Pediatr Pulmonol*. 2024;59:1281-1287.

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