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Comparison of heated humidified high-flow nasal cannula flow rates (1-L·kg·min^{-1} vs 2-L·kg·min^{-1}) in the management of acute bronchiolitis

Ali Yurtseven MD | Caner Turan MD | Eren Erseven MD | Eylem Ulas Saz MD

Department of Pediatrics, Division of Emergency Medicine, School of Medicine, Ege University, Izmir, Turkey

Correspondence
Caner Turan, Department of Pediatrics, Division of Emergency Medicine, School of Medicine, Ege University, Bornova, 35100 Izmir, Turkey.
Email: canertrn@yahoo.com

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Abstract

Objective: We aimed to compare the heated humidified high-flow nasal cannula (HHHFNC) flow rate of 1-L·kg·min^{-1} (1 L) with 2-L·kg·min^{-1} (2 L) in patients with severe bronchiolitis presenting to the pediatric emergency department.

Study design: We performed a study in which all patients were allocated to receive these two flow rates. The primary outcome was admitted as treatment failure, which was defined as a clinical escalation in respiratory status. Secondary outcomes covered a decrease of respiratory rate (RR), heart rate (HR), the clinical respiratory score (CRS), rise of peripheral capillary oxygen saturation (SpO_2), and rates of weaning, intubation, and intensive care unit (ICU) admission.

Results: One hundred and sixty-eight cases (88 received the 1-L flow rate and 80, the 2-L flow rate) were included in the analyses. Treatment failure was 11.4% (10 of 88) in the 1-L group, and 10% (8 of 80) in the 2-L group ($P = .775$). Significant variation in the intubation rate or the ICU admission rate was not determined. At the 2nd hour, the rate of weaning (53.4% vs 35%; $P = .017$), the falling down of the CRS (−2.1 vs −1.5; $P < .001$), RR (−15.2 vs −11.8; $P < .001$), and HR (− 24.8 vs − 21.2; $P < .001$), and the increase of SpO_2 (4.8 vs 3.6; $P < .001$) were significantly more evident in the 1-L group.

Conclusion: HHHFNC with the 1-L·kg·min^{-1} flow rate, which provides a more frequent earlier effect, reached therapy success as high as the 2-L·kg·min^{-1} flow rate in patients with severe acute bronchiolitis.

KEYWORDS
bronchiolitis, emergency deparment, flow rate, high-flow nasal cannula

1 | INTRODUCTION

Bronchiolitis is an acute lower tract respiratory disease that is usually caused by viral infections (most commonly respiratory syncytial virus). This disease mostly affects young children less than 2 and is one of the most common reasons for presentation to the emergency departments (EDs) in infants.[1] Every year, it causes over 300 000 ED visits in the USA and over 3.4 million hospitalizations worldwide.[2,3] Although the majority of children with bronchiolitis have a self-limited mild or moderate illness, some of them may present with severe respiratory distress and require respiratory support.[4] Numerous medications have been frequently used to manage acute bronchiolitis (eg, oxygen, hydration, bronchodilators, corticosteroids, antibiotics, antivirals, nasal decongestants, immunoglobulins), but only oxygen and hydration have been shown to demonstrably improve the condition of infants with bronchiolitis.[5–7] Therefore, the optimal treatment regimen for the management of moderate and severe bronchiolitis (SB) remains unclear. In recent years, heated humidified high-flow nasal cannula

(HHHFNC) therapy has been introduced as a novel alternative method for the management of acute respiratory distress due to bronchiolitis.[8]

HHHFNC can be set up easily, is safe, and well-known as a noninvasive respiratory support therapy method used in the case of respiratory distress.[9] It delivers heated and humidified high flow oxygen and does not irritate the respiratory mucosa.[10] HHHFNC is also able to generate a positive-end expiratory pressure without valve system (fraction of inspired oxygen (FiO_2) can be varied between 21% and 100%).[11] Evidence also indicates that HHHFNC exerts beneficial effects by reducing inspiratory resistance, washing out of the nasopharyngeal anatomical dead space, reducing metabolic work related to gas conditioning, and finally improving the airway conductance and mucociliary clearance.[10] Thus, carbon dioxide (CO_2) is excreted and ventilation–perfusion balance is supported.[12,13]

HHHFNC therapy has been shown to be more efficient than standard care and to reduce the rate of intubation/invasive ventilation in the management of acute SB.[14–16] Despite these beneficial effects of HHHFNC, it has not been recommended by international guidelines. Nevertheless, the data are still limited on using this modality in ED setting.[17]

In young children, few clinical studies compare the effects of various HHHFNC flow rates, and almost all of them were conducted in the intensive care unit (ICU).[18,19] The optimal flow rate is still unknown. Physicians mostly select HHHFNC flow rates empirically without consideration of a patient's weight and age. There is no study comparing flow rates on bronchiolitis 2 L·kg·min^{-1} with 1 L·kg·min^{-1} in the ED setting. Therefore, we performed a prospective clinical study to compare the HHHFNC flow rate of 1-L·kg·min^{-1} with 2-L·kg·min^{-1} in patients with SB admitted to our ED.

2 | MATERIALS AND METHODS

This prospective study was conducted in a pediatric ED between May 2017 and October 2018. The ED is a tertiary-care teaching center and has approximately 80 000 visits annually. The study was approved by the local Institutional Review Boards, and the written informed consent was obtained. To maintain patient confidentiality, the forms did not include any data that would have enabled identification of any patients. The procedures performed in this study followed the ethical standards in the Helsinki Declaration of 1964, as revised in 2008, as well as the national law. The study was supported by the Scientific Research Projects of our university. This trial was registered with Clinicaltrials.gov (number NCT03342781).

All patients who were diagnosed with acute bronchiolitis with any finding of severe respiratory distress (respiratory rate [RR] for ≤2 months ≥70 breaths per minute [bpm], 2-12 months ≥60 bpm and for 12-24 months ≥45 bpm; presence of intercostal, substernal, and supraclavicular retractions; poor feding, no vocalizations, and altered mental status with respiratory distress; inspiratory and expiratory wheeze or diminished breath sounds or both), aged less than 24 months and presenting to the ED were included. The clinical diagnosis of bronchiolitis made was based on the American Academy of Pediatrics clinical practice guideline.[6] The severity of bronchiolitis was also assessed according to the clinical respiratory score (CRS) of Liu et al[20] This clinical score includes RR, retractions, dyspnea/consciousness status, and wheezing. They are scored 0 to 3, based on the severity of the parameter. The patients with CRS >8 were defined SB. Patients who required immediate invasive ventilation and/or ICU admission on ED presentation; patients with venous PCO_2 greater than 55 before HFNC initiation; patients with a known comorbid disease, such as congenital heart disease, chronic lung disease, neuromuscular disease, metabolic disease, craniofacial anomalies, and immunocompromised; patients who received HHHFNC therapy at some other facility before arrival; patients who have coexisting bacterial pneumonia; and patients who have pneumothorax or nasal trauma were excluded.

After the triage assessment, patients were examined by pediatric emergency medicine specialists for acute life-threatening respiratory distress due to bronchiolitis. At the same time, the nurse started cardiorespiratory monitoring (peripheral capillary oxygen saturation [SpO_2], blood pressure, RR, heart rate [HR]). Then, the physician scored the patient's clinical severity based on CRS and also observed the baseline values (RR, HR, and SpO_2) at bedside. The nurse provided vascular access, obtained venous blood gas, and performed nasopharyngeal suction. Patients were re-evaluated after the nasopharyngeal suction. After confirmation of eligibility and parental consent for study inclusion, the patients were started on HHHFNC therapy. A blend of air/oxygen was delivered via nasal cannula with a flow rate of 1-L·kg·min^{-1} or 2-L·kg·min^{-1}. The total flow range was 6 to 25 L/min. FiO_2 was arranged with minimum value to provide SpO_2 with a range of 94% to 99% and the humidifier was autoadjusted at 37°C. Heated and humidified HHHFNC delivery system was Optiflow of Fisher & Paykel Healthcare (Auckland, New Zealand). The optiflow junior nasal cannula (neonatal and infant size), allowed up to 25 L/min flow rate, was also used for all participants. The cannula size was selected as not to be wider than half the diameter of the patient's nares. Sedation was achieved by oral feeding for the majority of patients (breastfeeding was preferred if possible), but if necessary, sedative drugs such as dexmedetomidine or midazolam were administered.

Multiplex real-time polymerase chain reaction was performed on nasopharyngeal swab specimens to identify the viral pathogens (respiratory syncytial virus [A & B], human rhinovirus, parainfluenza virus [type 1-4], influenza virus [A & B], human metapneumovirus, adenovirus, human coronavirus [229E, NL63, OC43], human bocavirus, and enteroviruses) for all enrolled patients.

After HHHFNC initiation, the clinical parameters (CRS, RR, HR, and SpO_2) were recorded hourly by the nurse and ED physician. At the end of the 2nd hour and during the next follow-up period, providing all of the following criteria was defined as weaning criteria. The following were the criteria: decreased the CRS ≤8; decreased RR (for infants ≤2 months <70 bpm, 2-12 months <60 bpm, and 12-24 months <45 bpm); absence of supraclavicular retractions; SpO_2 reached ≥90% with FiO_2 <30%; no confusion. The ICU admission was considered if the CRS >8 and/or SpO_2 <90% with FiO_2 >50% remained. The patients with failed or insufficient response continued

to receive HHHFNC therapy in the ED critical care room until their transfer to the ICU. If the invasive ventilation modality was required at any stage of observation, it was also provided. The protocol lasted a minimum of 24 hours; all study patients were followed-up clinically by recording all their management steps (weaning, restart of HHHFNC therapy, requirement of another modality of noninvasive ventilation [NIV], intubation).

After obtaining consent, the patients were allocated as receiving the flow rate of 1-L·kg·min^{-1} or 2-L·kg·min^{-1} according to simple randomization. While on the odd number days, the flow rate was adjusted as 1-L·kg·min^{-1}, on the even number days, the flow rate was set as 2-L·kg·min^{-1}. Blinded was not possible because of the visual difference between the two interventions.

Treatment failure was described as one or more of the following criteria, if observed within 24 hours of initiation of the HHHFNC therapy. These were the criteria: persistent tachypnea (patients aged 0-2 months with RR ≥70 bpm, 2-12 months ≥60 bpm, and for 12-24 months ≥45 bpm), or increased any amount according to admission; the CRS remained above 9; SpO_2 <90% sustained even if FiO_2 >50%; PCO_2 remained over 50 mm Hg; hypoventilation developed. In these cases, patients received another form of NIV (bilevel positive airway pressure [BiPAP]) or invasive ventilation. The primary outcome was accepted as treatment failure within 24 hours after HHHFNC initiation. It was indicated that the highest risk of failure is within the first 24 hours of the therapy.[13,18–20] The expected potential benefits of HHHFNC therapy are improvement about RR, HR, the CRS, and SpO_2, achieving of the weaning, preventing the intubation, and ICU admission. Therefore, secondary outcomes were declined of RR, HR, the CRS, increase of SpO_2, and the rate of weaning, at the end of 2 hours of treatment; rates of intubation and ICU admission within the first 24 hours.

Before starting the study, the ED nurses and physicians were all trained about the HHHFNC therapy process by the investigators.

2.1 | Statistical analysis

The failure rates of HHHFNC therapy with a flow rate of 1-L·kg·min^{-1} and 2-L·kg·min^{-1} have been shown to be 13% and 25%, respectively. These rates were estimated from principal studies utilizing two various flow rates.[15,16,21–24] According to the power calculation, 168 patients would be required to ensure the power of 80% and $P < .05$.

All analyses that included all children were performed with SPSS for Windows (version 22.0; SPSS Inc, IL). The failure rates were compared with a χ^2 test. Comparison of the changes in RR, HR, the CRS, and SpO_2 after 2 hours of the therapy were performed using linear mixed models with random intercepts for clusters. Differences of the baseline characteristics of two groups (sex, age, comorbidity, prematurity, admitted season, the results of nasopharyngeal aspirate samples, the beginning values of RR, HR, the CRS, SpO_2, pH, PO_2, and PCO_2) were analyzed with χ^2 test, Student's t test, and Mann–Whitney U test, as appropriate and were presented as mean differences with 95% confidence intervals (CIs) and P-values. Therapy effects were reported as hazard ratios with 95% CIs evaluated from the Cox-proportional hazard model. A two-tailed probability value (P) of less than .05 was considered significant.

3 | RESULTS

During the study period, 2665 patients presented to the ED with a diagnosis of acute bronchiolitis and 274 (10%) had SB. Final analysis was performed for 168 (6.3%) patients. After allocation, 88 patients were assigned to receive HHHFNC with a flow rate of 1-L·kg·min^{-1} and 80 patients were assigned to receive 2-L·kg·min^{-1} (Figure 1). The mean age was 10,1 ± 6.7 months, and 73% (n = 123) were male. A single viral pathogen was detected in 97 (58%) cases and multiple viral agents in 47 (28%). Multiple viral agents were more likely determined in a group of HHHFNC 1-L·kg·min^{-1} ($P = .022$). Another baseline demographic and physiological characteristics of the patients were comparable in the two groups (Table 1).

Treatment failure did not differ significantly between the 1-L·kg·min^{-1} group (10 of 88, 11.4%) and the 2-L·kg·min^{-1} group (8 of 80, 10%; HR 1.01 [95% CI, 0.74-1.39]; $P = .775$; Figure 1, Table 2)

Among 18 patients (n = 10 in 1-L·kg·min^{-1} group, n = 8 in 2-L·kg·min^{-1} group) who had treatment failure, 13 (7.7%) underwent orotracheal intubation. The remaining five patients were successfully treated with BiPAP. A total of 28 (16.7%) patients were transferred to the ICU. The intubation rate and the ICU admission rate were not statistically different between the two various flow rate HHHFNC groups (Figure 1, Table 2).

At the 2nd hour of the therapy, the weaning rate was higher in the 1-L·kg·min^{-1} group than the 2-L·kg·min^{-1} group (53.4% vs 35%; HR 1.39 [95% CI, 0.92-2.10]; $P = .017$; Table 2).

The reductions in the CRS ($P < .001$), in RR ($P < .001$), and in HR ($P < .001$), and the increase in SpO_2 ($P < .001$) were significantly higher in the 1-L·kg·min^{-1} group than the 2-L·kg·min^{-1} group at the 2nd hour of evaluation when compared with the baseline (Table 2).

No child died and therapy-related side effects were not developed (such as pneumothorax or pressure injuries).

4 | DISCUSSION

In this single-centre, prospective study, we compared the effectiveness of two HHHFNC flow rates to support young children' respiratory distress due to SB. The use of the 2-L·kg·min^{-1} flow rate did not reduce the risk of treatment failure compared with the flow rate of 1 L·kg·min^{-1}. No marked difference was found in the rate of intubation and ICU admission between the two groups. At the 2nd hour of the therapy, the 1-L·kg·min^{-1} flow rate was significantly more efficient in the rate of weaning, the CRS, RR, HR, and SpO_2 than in the 2-L·kg·min^{-1} flow rate.

HHHFNC has been used widely for patients with respiratory distress in all pediatric units of hospitals in many places across the world. However, some questions such as "which dose should be preferred for infants with bronchiolitis?" about this respiratory support

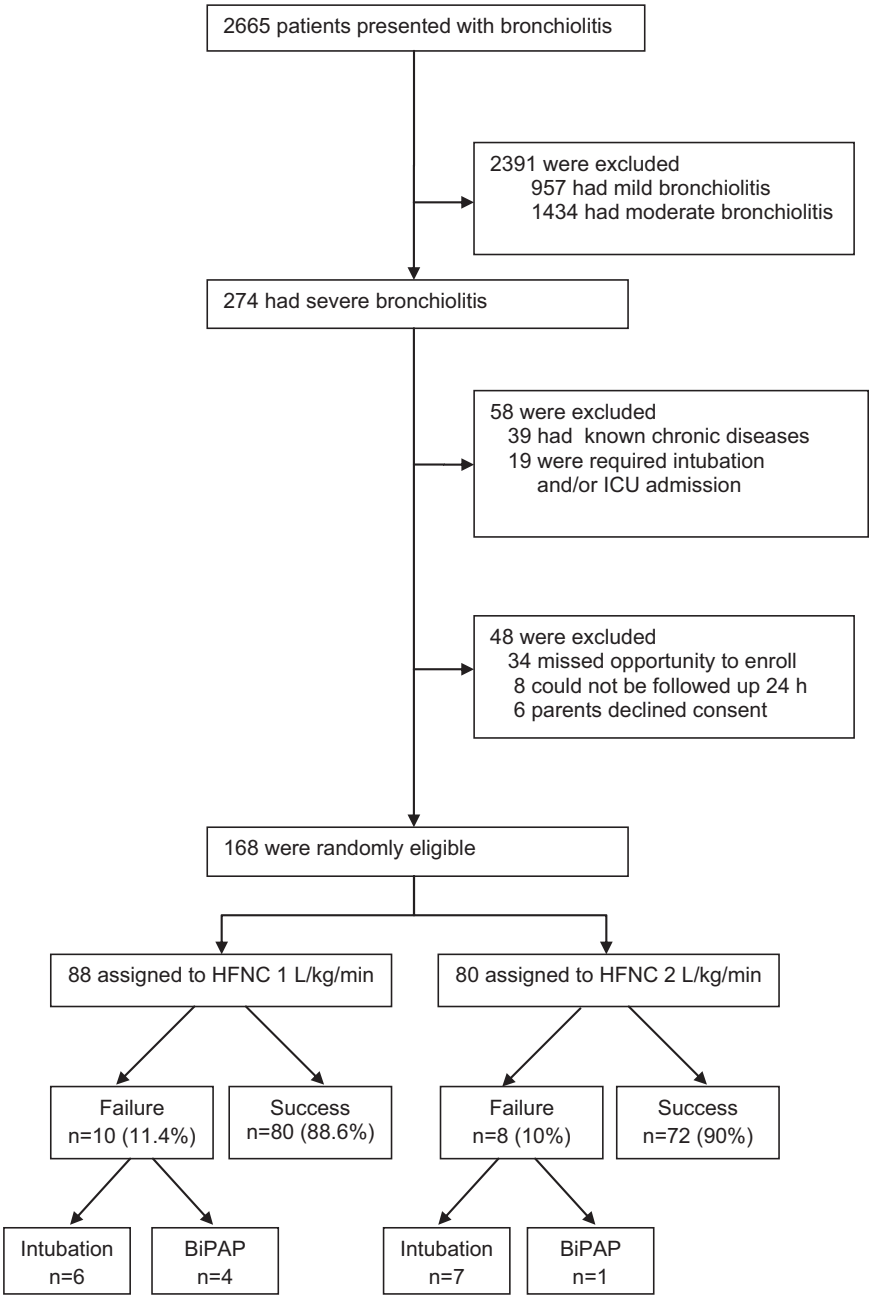

FIGURE 1 Flowchart of the study population and the primary outcomes

modality still have not found an answer.[18] Although previously the 1-L·kg·min^{-1} flow rate or 4 to 8 L/min flow rate was frequently used in patients with bronchiolitis, currently most centers choose the 2-L·kg·min^{-1} flow rate.[14,16,21–27] But this modification is based on only a few physiological studies, and there still has been no satisfactory clinical data to determine the optimal flow rate required for clinical benefit.[28–30]

According to the physiological studies, a flow rate ≥2-L·kg·min^{-1} is required to achieve a clinically adequate pharyngeal pressure, with improved breathing pattern and reduced respiratory muscles workload, in patients with bronchiolitis.[29,30] Contrary to these studies, Milesi et al[19] published a randomized, prospective, and multicenter comparison study of two HHHFNC flow rates, and they indicate that 3 L·kg·min^{-1} was not superior to 2 L·kg·min^{-1} when used for the primary management of moderate or SB. Moreover, the 3 L·kg·min^{-1} flow rate was associated with a higher rate of discomfort and with a longer stay in the ICU. Similarly, our findings also supported these results and showed that using the increased flow rate in children with SB was not associated with treatment success. Although increasing the flow rate might generate more effective positive airway pressure, this hypothesis seemed realistic physiologically but not clinically. Also, it may be that the higher expiratory resistance imposed by a higher flow-rate offsets any benefit of improving mean airway pressure.

One of the most important goals of using HHHFNC in patients with respiratory distress in the ED is an early response. A decrease in RR, in HR, in CRS and an increase in SpO_2 were frequently chosen as early predictors of a good response to HHHFNC.[21,23,24] In our study,

TABLE 1 Baseline characteristics of the patients

	HFNC 1 L·kg·min^{-1} (n = 88)	HFNC 2 L·kg·min^{-1} (n = 80)	Total (n = 168)	*P*-value
Sex				
Male	63 (71.6)	60 (75)	123 (73.2)	0.728
Mean age, mo (±SD)	10.9 (6.5)	9.2 (6.7)	10.1 (6.7)	0.072
Prematurity (<37 wk)	19 (21.6)	14 (17.5)	33 (19.6)	0.505
Detected viruses				
Single virus	51 (58)	46 (57.5)	97 (57.7)	**.022**
Multiple viruses	30 (34)	17 (21.3)	47 (28)	
No viruses	7 (8)	17 (21.3)	24 (14.3)	
Admited season				
Spring	31 (35.2)	35 (43.8)	66 (39.3)	0.161
Winter	39 (44.3)	23 (28.7)	62 (36.9)	
Autumn	13 (14.8)	13 (16.2)	26 (15.5)	
Summer	5 (5.7)	9 (11.3)	14 (8.3)	
Initial RCS[a]	9.09 (0.8)	8.94 (0.9)	9.02 (0.8)	0.161
Initial respiratory rate, breath/min	65.2 (9.1)	64.1 (8.6)	64.7 (8.9)	0.542
Initial heart rate, beat/min	170.8 (16.5)	171.8 (16.6)	171.3 (16.5)	0.680
Initial SpO_2,[b] %	94.2 (5.6)	95.3 (5.9)	94.7 (5.8)	0.050
Initial venous PCO_2,[c] mm Hg	37 (7.5)	37.9 (8.3)	37.4 (7.9)	0.427
Initial venous PO_2,[d] mm Hg	56.7 (18.5)	54.5 (18.7)	55.7 (18.6)	0.394
Initial venous pH	7.35 (0.1)	7.36 (0.1)	7.35 (0.1)	0.525

Abbreviation: HFNC, high-flow nasal cannula
Note. Values are mean (SD) or n (%)
[a]Respiratory clinical score
[b]Peripheral capillary oxygen saturation
[c]Partial carbon dioxide
[d]Partial oxygen

TABLE 2 Primary and secondary outcomes in the study cohort

	HFNC 1 L·kg·min^{-1} (n = 88)	HFNC 2 L·kg·min^{-1} (n = 80)	*P*-value	Hazard ratio or mean difference
Therapy failure	10 (11.4)	8 (10)	0.775	1.01 (0.74–1.39)
ICU[a] transfer	14 (15.9)	14 (17.5)	0.782	0.98 (0.70-1.36)
Intubation	6 (6.8)	7 (8.8)	0.640	0.97 (0.71-1.34)
At the 2nd hour of HFNC therapy				
Weaning[b]	47 (53.4)	28 (35)	**0.017**	1.39 (0.92-2.10)
Reduction in RCS[c]	−2.1 (−2.3 to −1.8)	−1.5 (−1.7 to −1.2)	**<0.001**	−0.6 (−0.2 to −0.9)
Reduction in RR[d]	−15.2 (−17.4 to −13)	−11.8 (−13.9 to −9.7)	**<0.001**	−3.4 (−6.4 to −0.4)
Reduction in HR[e]	−24.8 (−28.1 to −21.4)	−21.2 (−25 to −17.3)	**<0.001**	−3.6 (−1.5 to 8.7)
Rise in SpO_2	4.8 (3.9-5.7)	3.6 (2.4-4.8)	**<0.001**	1.2 (−0.2 to 2.6)

Abbreviation: HFNC, high-flow nasal cannula
Ranges in parentheses are 95% CIs. Values are mean or n (%)
[a]Intensive care unit
[b]At the 2nd hour of HFNC therapy, the patients were weaned and admited to the pediatric ward without requiring respiratory support within 24 h followed-up
[c]Respiratory clinical score
[d]Respiratory rate (breath/min)
[e]Heart rate (beat/min)

there were manifest differences in these early predictors between the two groups at the 2nd-hour evaluation. Improvement in the early predictors was much better (17%-40%) in the 1-L·kg·min^{-1} group than the 2-L·kg·min^{-1} group. As the second outcome, the early weaning rate was also higher (nearly 50%) in the 1-L·kg·min^{-1} group, and it probably depends on the improvement of the early predictors. The differences may be explained by more frequent discomfort, which occurs at a higher flow rate.

HHHFNC treatment achieved a wide popularity to reduce the rate of intubation and ICU admission. Previous studies reported that the overall rate of intubation and ICU admission declined 50%-70% in patients with bronchiolitis by HHHFNC therapy.[14,15,31,32] However, the optimal flow rate to provide the lowest intubation rate and ICU admission in the ED setting is still unknown. In Milesi et al's study, the intubation rate was shown to be higher in the 3-L·kg·min^{-1} group than the 2-L·kg·min^{-1} group (6.9% vs 2.8%), but this difference was not statistically significant.[16] The present study also found that increasing the flow rate did not reduce the rate of intubation and ICU admission in the management of SB in young children.

This study had some limitations. First, since it was a single center, its findings might not be generalizable to other settings. Second, for certain visual reasons, the physicians were not blinded to the regulated flow rate. Therefore, their assessments may have been influenced. Third, we considered that the study was conducted in the ED; that is why following up the patients 24 hours is enough. However, this decision may have caused us to lose some data. The last one, the patients were not allocated to receive either therapy (1:1) using stratified randomization. Hence, a numerical difference occurred between the two groups. The results may have been affected by this diversity.

In conclusion, this study showed that HHHFNC therapy with the 2-L·kg·min^{-1} flow rate was not clinically more effective than 1-L·kg·min^{-1} in patients with SB in the ED. The 1-L·kg·min^{-1} flow-rate ensured earlier impact and was well tolerated. It should be chosen for patients with SB in the EDs.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests

ORCID

Caner Turan http://orcid.org/0000-0001-9469-5162

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