Pilot Clinical Trial of High-Flow Oxygen Therapy in Children with Asthma in the Emergency Service

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Objectives To assess the efficacy of high-flow nasal cannula (HFNC) oxygen therapy and safety in children with asthma and moderate respiratory failure in the emergency department (ED).

Study design This was a prospective randomized pilot trial of children (aged 1-14 years) presenting to a tertiary academic pediatric ED with moderate-to-severe asthma exacerbations between September 2012 and December 2015. Patients with a pulmonary score (PS) ≥6 or oxygen saturation <94% with a face mask despite initial treatment (salbutamol/ipratropium bromide and corticosteroids) were randomized to HFNC or to conventional oxygen therapy. Pharmacologic treatment was at the discretion of attending physicians. The primary outcome was a decrease in PS ≥2 in the first 2 hours. Secondary outcomes included disposition, length of stay, and need for additional therapies.

Results We randomly allocated 62 children to receive either HFNC (n = 30) or standard oxygen therapy (n = 32). Baseline patient characteristics were similar in the 2 groups. At 2 hours after the start of therapy, PS had decreased by ≥2 points in 16 patients in the HFNC group (53%) compared with 9 controls (28%) ($P = .01$). Between-group differences in disposition, length of stay, and need for additional therapies were not significant. No side effects were reported.

Conclusion HFNC appears to be superior to conventional oxygen therapy for reducing respiratory distress within the first 2 hours of treatment in children with moderate-to-severe asthma exacerbation refractory to first-line treatment. Further studies are needed to demonstrate its overall efficacy in the management of asthma and respiratory failure in the ED. *(J Pediatr 2018;194:204-10).*

Trial registration EudraCT: 2012-001771-36.

Asthma is the most common chronic childhood disease, with a prevalence of 5%-20%.[1-4] Acute asthma exacerbation episodes account for nearly 5% of pediatric emergency department (ED) visits, peaking to up to 10%-15% during certain times of the year,[5,6] and approximately 15% of children require admission.[6-8] High-flow nasal cannula (HFNC) is a new, noninvasive oxygen delivery method that shows potential to reduce the need for intubation[9-11] and to be better tolerated by children compared with other noninvasive forms of support.[9,11] Its main advantages are that it enables administration of high concentrations of oxygen with adequate relative humidity and temperature,[12] improves airway conductance and pulmonary compliance, and achieves a certain level of continuous positive airway pressure,[13-18] decreasing respiratory work. In addition, it could reduce dead space[19-23] and inspiratory resistance by providing sufficient flow to match or exceed inspiratory flow.[21,23,24]

Despite a lack of randomized controlled trial evidence for the effectiveness of HFNC therapy in infants and older children,[9,10,16,25] the increasing availability of HFNC devices, first in pediatric intensive care units (PICUs)[9,11,25-27] and more recently in pediatric wards,[15,28-32] as well as their ease of use and children's tolerance of them, has led to the incorporation of this therapy into management protocols for children with respiratory diseases, especially bronchiolitis. Various observational studies in infants with bronchiolitis have found HFNC therapy to be feasible, safe, and effective, but further studies are needed to ensure that guidelines for its use are evidence-based.[23] Recent publications suggest that it also may be effective and safe applied to a broader spectrum of ages and diagnoses.[10,25,33]

ED	Emergency department
FiO_2	Fraction of inspired oxygen
HFNC	High-flow nasal cannula
HR	Heart rate
n.s	Not significant
PICU	Pediatric intensive care unit
PS	Pulmonary score
RR	Respiratory rate
SpO_2	Oxygen saturation

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From a physiological perspective, HFNC therapy appears attractive for patients with asthma. As in bronchiolitis, the continuous positive airway pressure generated may reduce the burden on the inspiratory muscles related to auto-positive end-expiratory pressure; however, there is limited evidence supporting this indication.[23] In addition, there are few data concerning the use of HFNC therapy in the ED, and a complete lack of clinical trials assessing its utility in terms of such clinical parameters as morbidity, mortality, and hospital or PICU stay, rather than just intermediate variables, such as respiratory rate (RR), oxygen saturation (SpO_2), and respiratory work.

The aim of this study was to assess the efficacy and safety of HFNC therapy given to children with asthma and moderate respiratory failure in a pediatric ED in improving patient clinical condition, in terms of asthma severity, and reducing admissions to the ward or PICU.

Methods

The study was designed as a pilot study to derive preliminary effect sizes that could be used to justify the design of a subsequent, more definitive study. Therefore, we conducted a single-center, nonblinded, randomized controlled trial to compare HFNC with conventional oxygen therapy in children presenting for moderate-to-severe asthma exacerbation who were refractory to first-line treatments. This study was conducted in a tertiary teaching hospital near Bilbao, in the Basque country of Spain. The pediatric ED provides care to children aged ≤14 years and has an average of 60 000 annual visits, of which approximately 5% are due to acute asthma attacks. The study was registered at the European Union Clinical Trials Register (EudraCT: 2012-001771-36) before enrollment of the first participant.

In this pilot study, we enrolled patients aged 1-14 years with asthma exacerbation who met at least 1 of the following criteria: moderate to severe respiratory failure, defined as a pulmonary score (PS) ≥6 (**Table I**; available at www.jpeds.com),[34] or the need for a high level of oxygen support (SpO_2 <94% with a face mask) despite initial treatment with nebulized salbutamol (<20 kg, 2.5 mg/dose; ≥20 kg, 5 mg/dose) and ipratropium (<20 kg, 250 μg/dose; ≥20 kg, 500 μg/dose) every 20 minutes during the first hour (at least 3 doses) and systemic corticosteroids (prednisone or methylprednisolone 2 mg/kg).

Asthma was defined as either a previous medical diagnosis of asthma or at least 2 previous episodes of β_2-agonist–responsive wheeze or a first episode of wheezing in children aged >2 years and a history of atopy. An exacerbation of asthma was defined as acute asthma prompting ED assessment, with any or all of the following clinical features: dyspnea, wheeze, acute cough, increased work of breathing, and increased requirement for bronchodilators from baseline use.[35,36] Patients who required advanced airway management and those in whom informed consent was not obtained were excluded.

Parents or legal guardians of eligible participants received oral and written information about the study before informed consent was requested. When applicable, informed assent was obtained from the patient.

Randomization

Once written informed consent was obtained, enrolled patients were randomized to 1 of 2 treatment groups using nQuery Advisor 7.0 (Statistical Solutions, Boston, Massachusetts). Allocation concealment was maintained using sequentially numbered opaque envelopes containing group allocation, which were opened by the treating physician in the ED after enrollment. The experimental group received HFNC oxygen therapy, and the control group received conventional oxygen therapy.

Experimental Group

In the HFNC group, oxygen therapy was delivered by an MR850 humidifier and an RT330 junior breathing circuit kit (flow range, 2-25 L/min) for infants and young children, with OPT316 and OPT318 nasal cannulas, respectively, or an RT202 adult breathing circuit kit (flow range, 5-60 L/min) with an OPT842 nasal cannula for older children and adolescents (all from Fisher & Paykel Healthcare, Auckland, New Zealand).

Before the trial, nursing and medical staff of the ED received training on appropriate indications for use and the proper setup and maintenance of these systems. Moreover, formal guidelines on the use of HFNC therapy in pediatric patients were introduced in our ED (**Figure 1**; available at www.jpeds.com). The initial flow rate depends on patient weight and clinical status. Depending on the degree of respiratory distress, PS, SpO_2, and RR, clinicians are allowed to increase the flow rate if necessary up to the maximum that the patient can tolerate, without exceeding a flow of 2 L/kg/min for the first 10 ± 0.5 L/kg/min per kg above 10 kg. Once the PS reaches 3-4, oxygenation improves, and distress and the need for bronchodilators decrease, the oxygen support can be withdrawn progressively.

Control Group

Conventional oxygen delivery systems were used, ranging from nasal prongs to a Venturi mask or non-rebreather mask, depending on the patient's level of distress and oxygen requirement. In both groups, along with oxygen therapy, the pharmacologic treatment of asthma exacerbation (nebulized salbutamol together with systemic corticosteroids and magnesium sulfate) was at the discretion of the attending physician. In addition, following our hospital's asthma care guidelines, children were monitored with SpO_2, RR, and heart rate (HR) measurements, and PS was assessed every 30 minutes during the first 2 hours and then every 2 hours until the decision for disposition, which was based on the patient's clinical condition, workload, and management pressure in the ED and on guidelines for the management of asthma (**Figure 2**; available at www.jpeds.com). Children also were monitored until hospital discharge for possible side effects of HFNC therapy, including nasal or facial trauma, abdominal distention, air leak, and infection.

Outcome Measures

The primary outcome was a change in asthma severity, with improvement defined as a decrease in PS by ≥2 points in the first 2 hours of treatment. Secondary outcomes were admission rate to the PICU or ward; length of stay; the need for additional therapies as determined by the treating physician, specifically inhaled salbutamol, corticosteroids, or intravenous magnesium sulfate; and additional respiratory support. Each participant received a follow-up telephone call at 72 hours after the study visit to determine whether he or she required an unscheduled return healthcare visit to an ED or primary care physician for asthma symptoms related to the initial ED visit.

Statistical Analyses

To estimate the sample size, we used as the primary outcome a decrease in PS by ≥2 points at 2 hours after starting therapy, assuming a proportion in the control group of 25%, based on previous studies,[34,37] and an expected proportion in the experimental group of 40%. With a power of 80% and a level of significance of 5%, taking into account that the expected percentage of dropouts could be 10%, it would be necessary to recruit 338 patients. This pilot trial aimed to recruit patients in a single center for approximately 2 years. Recruitment was anticipated to range between 50 and 100 patients in this period.

Continuous variables are expressed as median and interquartile range, and categorical variables are expressed as frequency and percentage. The overall comparisons of repeated measures over time were made using the Friedman test (2-way ANOVA by rank). Comparisons between each measure at baseline and each time point after starting HFNC therapy were then performed with the Wilcoxon test for paired samples.

To assess the independent association of clinical variables with improvement and PICU admission, we first performed univariate logistic regression analysis. We then included all the variables with $P < .20$ in a multivariable logistic regression analysis (using a manual stepwise procedure). In the final multivariable model, only variables with a P value <.05 were included. We report the results as OR and 95% CI. The significance level was set at $P < .05$ for all analyses. Data were analyzed on an intention-to-treat basis, using IBM SPSS for Windows, version 22.0 (IBM, Armonk, New York).

This trial was approved by the Human Research Ethics Committee of the hospital and authorized by the Spanish Agency of Medicines and Medical Devices.

Results

Of a total of 162 802 children treated in the pediatric ED during the study period (September 20, 2012, to December 2, 2015), 8116 (5%) were diagnosed with asthma. Seventy-five patients who met the inclusion criteria were invited to participate in the study. Finally, 62 children aged 1-14 years were enrolled, including 30 in the HFNC group and 32 in the control group (13 with nasal prongs, 5 with a Venturi mask, and 14 with a non-rebreather mask), and these children constituted the study population (**Figure 3**; available at www.jpeds.com). The 2 groups were similar in baseline demographic characteristics, asthma severity, and treatment received before the study (**Table II**).

Almost twice as many patients in the HFNC group as in control group met the improvement criteria (16 [53%] vs 9 [28%]; $P = .01$). Furthermore, during the first 2 hours after starting treatment, there was an increase in SpO_2/fraction of inspired oxygen (FiO_2), with significant decreases in RR, HR, and PS in both groups. Notably, only the decrease in the PS was significantly larger in the intervention group ($P = .01$) (**Figure 4**). In multivariable analysis, 2 variables were strongly associated with improvement in the first 2 hours: treatment with HFNC therapy (OR, 4.70; 95% CI, 1.23-17.89; $P = .02$)

Table II. Baseline characteristics of the HFNC oxygen therapy and control groups

Variables	HFNC group (n = 30)	Control group (n = 32)	*P* value
Male sex, n (%)	16 (53)	18 (56)	n.s.
Age y, median (range)*	3.0 (1.7-6.0)	3.0 (2.0-6.0)	n.s.
Medical history of asthma, n (%)	25 (83%)	26 (81)	n.s.
Maintenance treatment, n (%)	9 (30%)	8 (25)	n.s.
Characteristics of exacerbation before trial, median (range)			
PS	6.0 (6.0-7.0)	6.0 (6.0-6.75)	n.s.
End-tidal CO_2	30.0 (14.7-48.2)	31.5 (16.2-49.2)	n.s.
RR	48.0 (40.7-52.5)	48.0 (40.0-60.0)	n.s.
HR	162.0 (144.7-175.2)	152.5 (139.2-173.0)	n.s.
SpO_2 (with oxygen therapy)	98.0 (95.7-99.0)	97.5 (95.0-100.0)	n.s.
Venous blood gas values before trial	n = 26 (86)	n = 26 (81)	n.s.
pH, median (range)	7.3 (7.2-7.4)	7.3 (7.2-7.4)	n.s.
pCO_2, median (range)	44.0 (38.7-53.2)	44.0 (39.7-49.5)	n.s.
pO_2, median (range)	44.0 (36.5-92.5)	43.0 (34.0-48.5)	n.s.
Treatment before trial, n (%)			
Oxygen therapy at ED	30 (100)	32 (100)	n.s.
Salbutamol at ED	30 (100)	32 (100)	n.s.
Ipratropium bromide at ED	28 (93)	31 (96)	n.s.
Corticosteroids at ED	19 (63)	21 (66)	n.s.
Corticosteroids before arrival to ED	11 (37)	11 (34)	n.s.

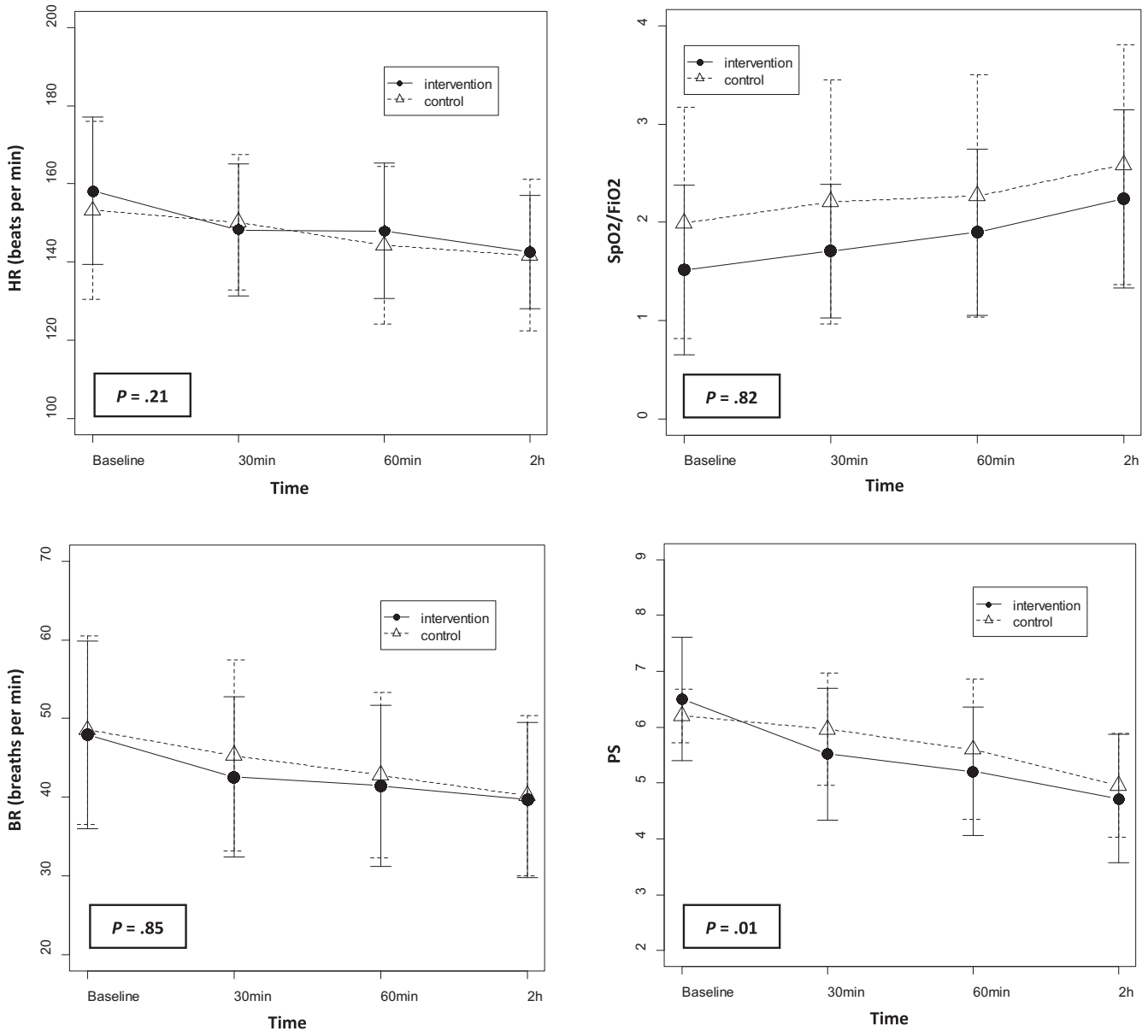

Figure 4. Changes in HR, RR, SpO_2/FiO_2, and PS during the first 2 hours of therapy in the 2 treatment groups.

and baseline pCO_2 (OR, 0.91; 95% CI, 0.83-0.99; $P = .04$) (**Table III**).

Final destination did not differ significantly between the 2 groups, with 13 patients in the experimental group (43%) discharged from the ED, compared with 14 controls (43%) (*P* not significant [n.s.]). Slightly more than one-quarter of the patients in each group were admitted to the PICU, including 8 (26%) in the HFNC group and 9 (28%) controls (*P*, n.s.). Among the patients admitted to the PICU, the admission occurred within the first 2 hours of treatment in only 1 patient (12%) in the HFNC group compared with 6 controls (66%; $P = .03$). The other 7 patients (88%) in the HFNC group admitted to the PICU were transferred between 2 and 36 hours after starting therapy, 4 patients (57%) due to failed attempts to wean off HFNC therapy and 3 (43%) due to a lack of response to increased respiratory support after clinical worsening. In multivariable analysis, no variables were related to the risk of PICU admission. Regarding ward admission, the same number of patients in each group were transferred to the pediatric ward: 9 (30%) in the HFNC group and 9 (28%) controls (*P*, n.s.).

There were no significant between-group differences in length of stay in either the PICU or ward, the need for respiratory support or its duration, or the need for additional therapies in the ED. Follow-up phone calls were completed for 60 of 62 patients (97%); complete 72-hour return data were available for 29 patients in the HFNC group and for 31 patients in the control group. Three patients in each group returned to the

Table III. Multivariable analysis associated with improvement in the first 2 hours

	Multivariable		Multivariate	
Variables	***P* value**	**OR (95% CI)**	***P* value**	**OR (95% CI)**
Sex	.71	0.82 (0.29-2.28)		
Age	.25	1.09 (0.93-1.29)		
Medical history of asthma	.70	1.29 (0.34-4.80)		
Triage				
Level I	.80	1.43 (0.08-24.7)		
Level II	.82	0.88 (0.29-2.65)		
Corticosteroids in previous 24 h	.49	1.44 (0.01-4.20)		
Exacerbation characteristics before trial				
PS	.54	1.20 (0.65-2.23)		
RR	.74	0.99 (0.94-1.04)		
HR	.40	1.01 (0.98-1.03)		
SpO_2	.78	0.96 (0.81-1.16)		
pH before study	.53	19.63 (0.01-2398.94)		
pCO_2 before study	.06	0.93 (0.86-1.01)	.04	0.91 (0.83-0.99)
Experimental group	.01	3.92 (1.33-11.57)	.02	4.70 (1.23-17.89)

ED within 72 hours, none of whom was admitted. No side effects attributable to HFNC therapy were recorded (Table IV).

Discussion

The present study demonstrates that HFNC oxygen therapy is effective and safe for the treatment of children who experience episodes of severe asthma while in the ED. Although HFNC therapy has not been found to be more effective in terms of reducing hospitalization, its beneficial effects during the first hours of treatment make it an option to consider in the early treatment of severe asthma attacks.

As mentioned above, the rapid decrease in respiratory work observed after starting HFNC therapy[16,29,30] and the increasing availability of HFNC devices have led to the inclusion of this therapy in protocols for patients with respiratory diseases. Nevertheless, the literature on HFNC use during asthmatic exacerbations is scant.[23] A Cochrane review on the role of HFNC therapy in children (excluding those with bronchiolitis) found that no study has been able to provide indications and guidelines for its use in pediatric patients with a high level of evidence.[38] This limited evidence and the lack of studies in patients with asthma were the main motivations for the present study.

In our study, as in previous observational studies,[9,29,30] we observed improvements in both PS and respiratory variables (HR, RR, and SpO_2/FiO_2) within the first 2 hours. The level of improvement was similar in both groups, except for the decrease in PS, which was larger and earlier in the HFNC group. An early reduction in respiratory work and subsequent improvement in patient comfort are vital to avoid complications such as atelectasis and progressive respiratory exhaustion. These complications can lead to respiratory failure and the need to escalate to other forms of respiratory support. Likewise, Bressan et al[29] and González et al[30] have reported similar improvements in respiratory parameters within the first 2-3 hours after changing from standard to HFNC therapy in infants with bronchiolitis.

In the present study, we found no between-group differences in patients' final destination. Previous observational studies with infants with bronchiolitis found a decrease in PICU admission after the introduction of HFNC therapy for treating patients admitted to a pediatric ward; González et al[30] observed a 62% relative risk reduction, and Mayfield et al[32] reported a 4-fold lower risk (OR, 4.086; 95% CI, 1.0-8.2;

Table IV. Secondary outcomes in the HFNC and control groups

Variables	**HFNC group (n = 30)**	**Control group (n = 32)**	***P* value**
In the ED: additional therapies			
Doses per h of salbutamol, median (range)	1.60 (0.89-2.48)	1.47 (0.52-2.13)	n.s.
Corticosteroids, n (%)	24 (80)	23 (72)	n.s.
Intravenous magnesium, n (%)	30 (100)	31 (97)	n.s.
In the PICU:			
Length of stay, min, median (range)	48.0 (24.0-48.0)	48.0 (24.0-64.8)	n.s.
HFNC, n (%)	1/8 (12)	0/9 (0	n.s.
Noninvasive ventilation, n (%)	7/8 (87)	9/9 (100)	n.s.
Length of respiratory support, min, median (range)	24.0 (12.0-48.0)	27.0 (15.7-63.0)	n.s.
In the ward: length of stay, min, median (range)	48.0 (36.0-72.0)	48.0 (24.0-84.0)	n.s.
ED return within 72 h, n (%)	3 (10)	3 (9)	n.s.
Admission within 72 h, n (%)	0 (0)	0 (0)	n.s.
Side effects, n (%)	0 (0)	0 (0)	n.s.

$P = .043$). These differences could be due to the small sample sizes and/or differences in patient characteristics. We believe that the main reason was that those studies included infants admitted to wards with no limitation on the duration of HFNC therapy. In our study, most children in the experimental group were admitted to the PICU to continue HFNC therapy beyond 36 hours, because this treatment is not currently offered in our pediatric ward. Thus, had this type of therapy been available in the pediatric ward, the PICU admission rate could have been 50% lower. The benefits for patients and their families and potential cost savings highlight the possible advantages of using this therapy in the initial treatment of severe asthma exacerbation in the ED.

In the present study, no variables were found to independently predict the need to escalate respiratory support. Such predictors would help identify patients at greater risk of therapeutic failure or even those who should not be started on HFNC therapy but instead transferred to the PICU to receive more aggressive respiratory support. In the literature, various studies have identified factors related to HFNC failure in patients with bronchiolitis. Specifically, a high RR for age[25] and high pCO_2[25,26] before starting therapy, as well as a lack of decrease in RR[9,11,26,32] or HR[9,32] within the first few hours of treatment, were found to predict the need for intubation. In our study, none of the patients in either group required intubation. In addition, the duration of respiratory support and lengths of stay in the PICU and ward were similar in the 2 groups, in accordance with findings reported by Wing et al.[10]

No side effects or infections associated with HFNC use were reported during the study period. Several previous studies[9,11,39,40] have also found that HFNC therapy is a well-tolerated method for delivering respiratory support, with very few adverse effects.

Our study has several limitations. It was conducted in a single tertiary-care hospital, and thus our findings might not be generalizable to other settings. Furthermore, in this open-label study, both doctors and nurses knew the intervention, which might have limited the trial's internal validity. Data managers and statistical team were blinded, however.

Finally, given that the present trial was designed as a pilot study, our sample size is not sufficient to render a conclusion as to the effect of the experimental treatment. A large multicenter randomized controlled trial is needed to confirm the efficacy of HFNC oxygen therapy in children experiencing a severe asthma attack in the ED.

HFNC appears to be superior to conventional oxygen therapy for reducing respiratory distress within the first 2 hours of treatment in children with severe asthma attacks refractory to first-line pharmacologic treatment. We were not able to demonstrate that HFNC is superior to conventional oxygen therapy in reducing the overall rates of PICU or ward admission in these patients. Further studies are needed to demonstrate its overall efficacy in the management of pediatric patients with asthma and respiratory failure in the ED. ■

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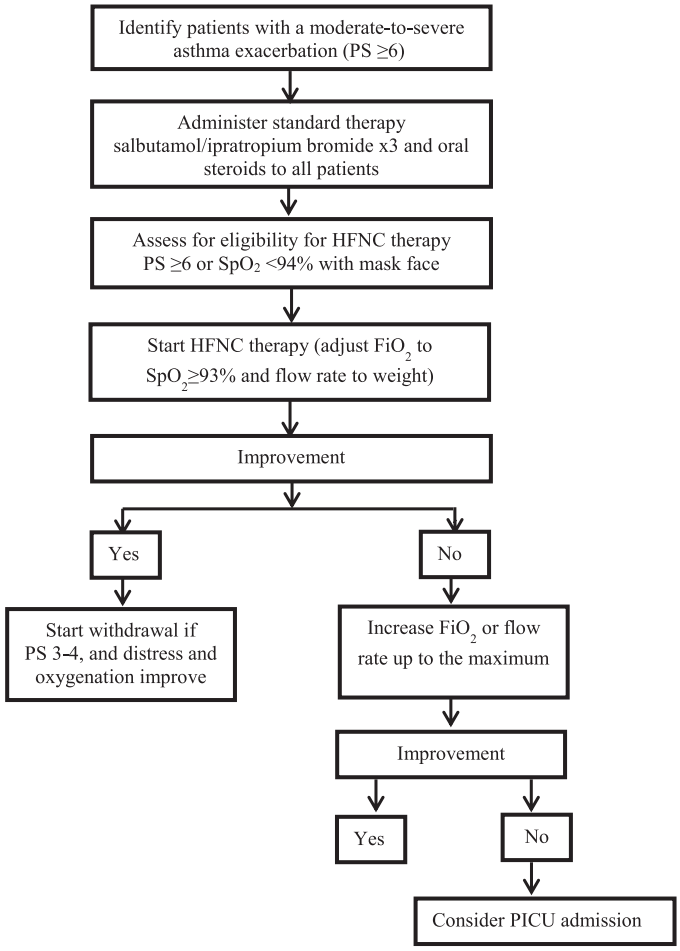

Figure 1. HFNC guideline.

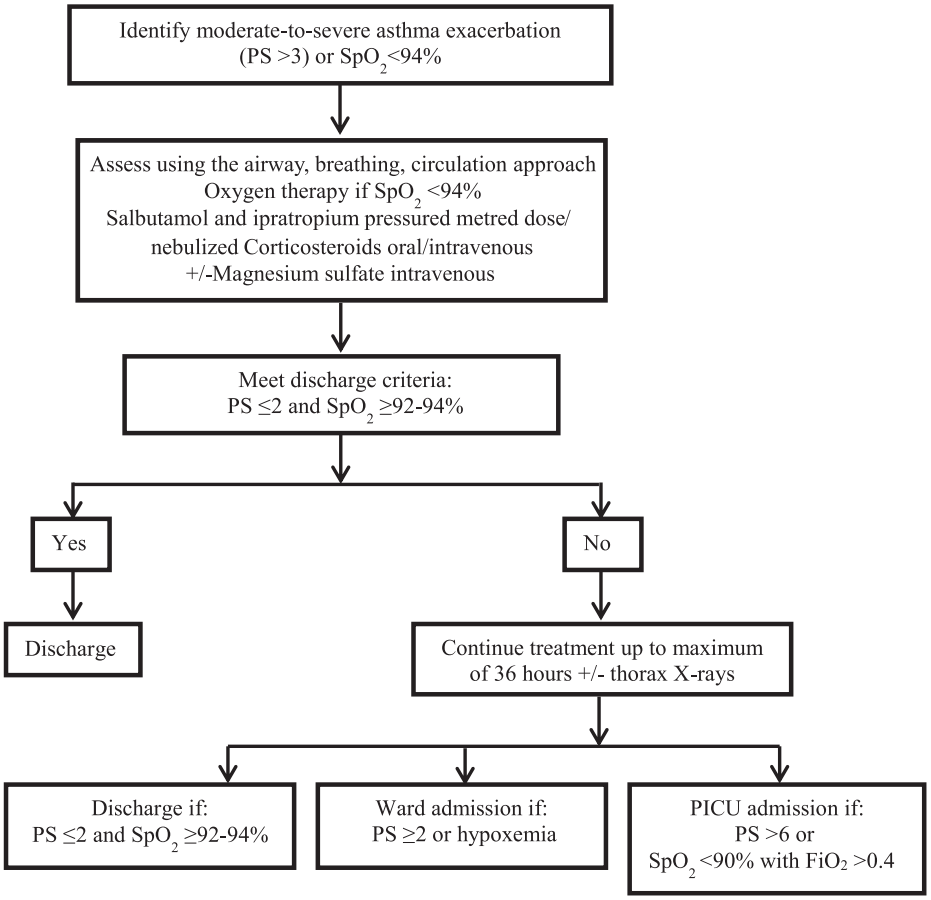

Figure 2. Pharmacologic treatment for asthma exacerbation.

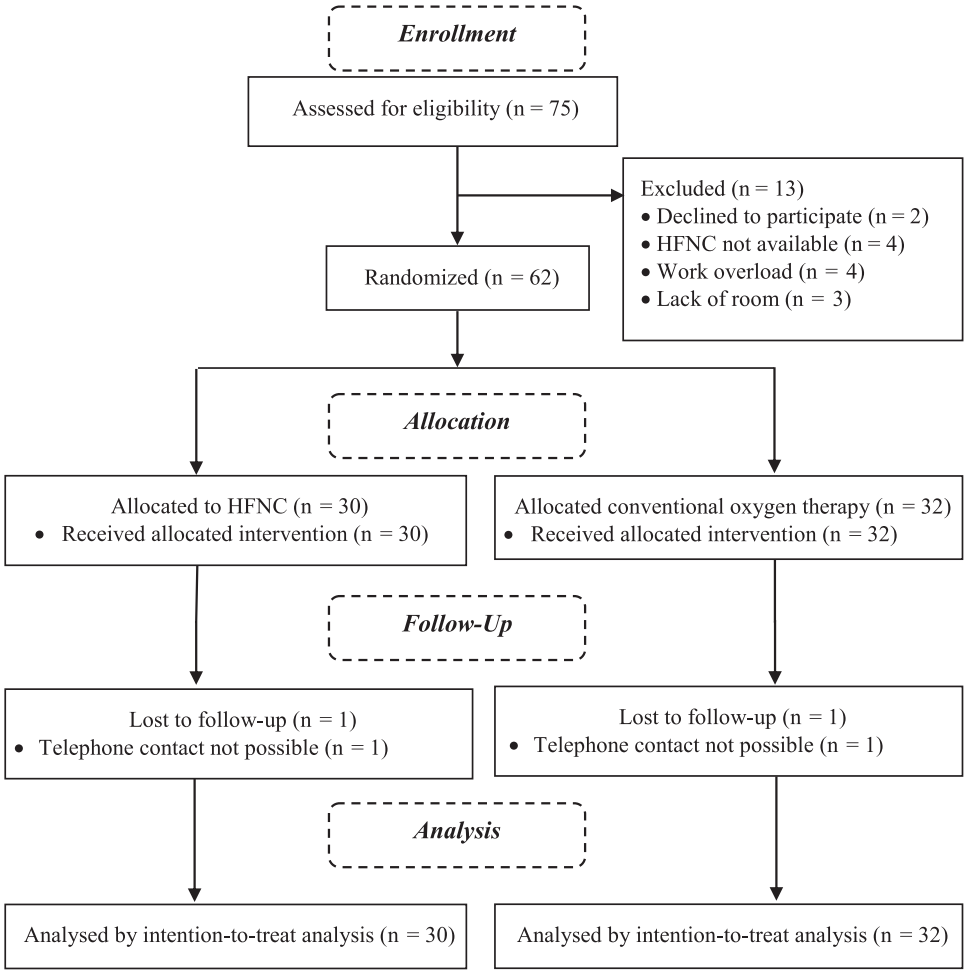

Figure 3. Flow chart of study participants.

Table I. Pulmonary score

Score*	RR <6 y	RR >6 y	Wheezing	Accessory muscle use
0	≤ 30	≤20	No	No
1	31-45	21-35	Terminal expiration with stethoscope	Mild increase
2	46-60	36-50	Entire expiration with stethoscope	Increased
3	>60	>50	Inspiration and expiration without stethoscope†	Maximal activity

*Scored from 0 to 3 in each of the sections (minimum, 0; maximum, 9). Mild asthma exacerbation, PS ≤3; moderate. PS 4-6; severe, PS >6.
†If wheezing is absent but sternocleidomastoid activity is increased, a score of 3 is assigned.