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Original Article

High-flow nasal cannula and in-line aerosolised bronchodilator delivery during severe exacerbation of asthma in adults: a feasibility observational study

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ABSTRACT

Background: Asthma is a common chronic respiratory disease affecting 1–29% of the population in different countries. Exacerbations represent a change in symptoms and lung function from the patient's usual condition that requires emergency department (ED) admission. Recently, the use of a High-Flow Nasal Cannula (HFNC) plus an in-line vibrating mesh nebulizer (VMN) for aerosol drug delivery has been advocated in clinical practice. Thus, this pilot observational study aims to investigate the feasibility of HFNC treatment with VMN for in-line bronchodilator delivery in patients with severe asthma.

Methods: This study was conducted from May 2022 to May 2023. Subjects ≥18 years old with a previous diagnosis of asthma who were admitted to the ED during severe exacerbation were included. The primary endpoint was the change in peak expiratory flow ratio (PEFR) after 2-h of treatment with bronchodilator delivered by HFNC with in-line VMN. Additional outcomes were changes in forced expiratory volume in 1 s (FEV_1) and clinical variables before treatment.

Results: 30 patients, mean age of 43 (SD$\chi\pm$ 16) years, mostly female (67%) were studied. A significant change in PEFR (147 ± 31 L/m *vs.* 220 ± 38 L/m; $p < 0.001$) was observed after treatment with HFNC and in-line VMN with significant improvement in clinical variables. And no subjects required invasive mechanical ventilation (IMV) during the study.

Conclusions: HFNC treatment with in-line VMN for bronchodilator delivery appears feasible and safe for patients with severe asthma exacerbation. These preliminary promising results should be confirmed with appropriately large-designed studies.

Introduction

Asthma is a common chronic respiratory disease that affects 1–29% of the population in different countries [1,2]. Asthma prevalence in Argentina is 6.4%, leading to an annual mortality rate of 5.8% [3]. Asthma exacerbations are characterized by a change in symptoms and lung function compared to the patient's usual condition which often needs urgent care in the emergency department (ED) [4,5]. According to the Global Initiative for Asthma (GINA) recommendations, the management of acute asthma exacerbation includes the administration of conventional oxygen therapy (COT) to maintain adequate oxygen saturation levels, as well as repeated doses of nebulised bronchodilator and systemic corticosteroids to relieve airflow obstruction and alleviate airway symptoms [6]. Additionally, frequent assessment of the patient's clinical progress and improvement in lung function is essential to timely detect clinical severity markers of the acute episode [7]. Measurements of pulmonary function tests (PFT) such as Peak Expiratory Flow Rate (PEFR) or Forced Expiratory Volume in 1 s (FEV_1) should be performed to quantify

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the decrease in expiratory airflow compared to the patient's previous PFT or predicted values [4] and assess the response to treatment [6].

Nonetheless, some patients may continue to experience respiratory distress and hypoxemia and occasionally develop hypercapnia and in the most severe form of life-threatening or near-fatal asthma, non-invasive ventilation (NIV) can be applied [8,9]. However, the clinical efficacy of NIV in acute asthma exacerbation for avoiding invasive mechanical ventilation (IMV) is debated, with limited and conflicting evidence supporting its use [10–12]. High-Flow Nasal Cannula (HFNC) is an attractive alternative given that it increases oropharyngeal pressures during its use and increases lung volumes while reducing work of breathing (WOB) [13,14]. A low level of positive airway pressure is also generated through nasal prongs designed specifically to supply 30−80 L/min of a heated and humidified mixture of air and oxygen [15] that can protect the lung from dry and cold inspired air, which can further induce bronchoconstriction [16]. Recently, several small studies evaluated the effectiveness of HFNC in the treatment of asthma exacerbation [17–20]. Interestingly, during HFNC therapy, patients may simultaneously receive repeated doses of inhaled bronchodilator using a vibrating mesh nebuliser (VMN) placed at the inlet of the humidifier without discontinuing HFNC treatment [21,22]. Notably, this integrated system achieves a greater lung aerosol deposition (17%) than conventional jet nebulisers (JNs) using a mouthpiece or face mask (8–12%) [23]. The combination of aerosolised medication delivery with HFNC therapy through an in-line VMN has been described in the literature, although there is limited evidence available [24]. We aim to evaluate the feasibility and effectiveness of aerosol delivery with HFNC therapy through an in-line VMN in patients admitted to the ED with an acute asthma exacerbation.

Methods

Study design

This was a single-center prospective observational study conducted from May 2022 to May 2023 in patients admitted to the Hospital de Agudos Juan A. Fernández, Buenos Aires, Argentina. The institutional review board reviewed the protocol and authorised prospective data collection (code register 2263). Informed written consent was obtained from all the subjects before inclusion in the study.

Subjects

Adult subjects ≥18 years with a previous diagnosis of asthma who were admitted to the ED for an acute asthma exacerbation were included. Inclusion criteria were as follows: (1) confirmed severe asthma exacerbation according to GINA diagnostic criteria [6] (2) P_aO_2/F_iO_2 (P/F) ≤300 (3) COT requirement for $SpO_2 > 90\%$ (4) Respiratory Rate (RR) ≥25 breaths/min. Exclusion criteria were: (1) Requirement for immediate endotracheal intubation and IMV, (2) alteration of consciousness, (3) myocardial injury (electrocardiogram changes or increased levels of myocardial enzymes), (4) hemodynamic instability (blood pressure < 90/60 mmHg), (5) pregnancy, (6) pH < 7.30 (7) untreated pneumothorax, (8) History of chronic obstructive pulmonary disease (COPD).

Interventions

Immediately upon admission, the subjects were evaluated by the treating physicians and respiratory therapists.

HFNC

HFNC therapy was administered using a dedicated high-flow system (Airvo 2, Fisher & Paykel, Auckland, New Zealand) through nasal prongs using a medium-sized cannula. We used a gas flow between 40 and 60 L/min, a temperature between 34−37 °C titrated according to the patient's comfort, and F_iO_2 adjusted to maintain SpO_2 at 92–96 %.

Nebulisation

A VMN (Aerogen Solo nebuliser and Aerogen Pro-X controller, Aerogen, Galway, Ireland) was placed at the outlet of the Airvo 2 humidification chamber in accordance with the manufacturer's recommendations. Salbutamol (2.5 mg) and ipratropium bromide (0.5 mg) were nebulised using the VMN. During in-line bronchodilator administration, the HFNC gas flow rate was set to 30 L/min. The complete delivery of the bronchodilator was confirmed at the end of each dose, and notes were taken of any equipment alarms. At the end of bronchodilator administration, the HFNC gas flow rate was restored to the initial settings.

Concomitant treatment

All the patients received systemic corticosteroids within 1 -h of ED presentation.

Data collection

Demographic data, clinical parameters and laboratory blood test results were collected on admission to the ED. Clinical parameters were measured before performing pulmonary function tests (PFTs); dyspnea was assessed by using the Borg scale, which ranges from 0 to 10 points, with a higher score indicating maximum dyspnea. All PFTs were performed using a spirometer (Smart One, MIR, Rome, Italy) before the administration of bronchodilator therapy and 2 h after bronchodilator therapy through HFNC in-line bronchodilator. For the performance of the PEFR, HFNC was removed; for each test, three measurements of PEFR and FEV_1 were performed, and the best of them was recorded. The peak flow meter procedure was performed following GINA for standardization of the PEFR technique [6].

Endpoints

The primary endpoint was the change in PEFR after bronchodilator treatment delivered by HFNC and in-line VMN at 2 h. Secondary endpoints included changes in FEV_1 at 2 h and clinical variables (RR, Heart Rate [HR], Dyspnea [Borg scale] and SpO_2) at baseline, 2, 6 and 12 h post-intervention. Additionally, we recorded the need for escalation NIV or ETI, days on HFNC and the length of hospital stay (LoHS).

Statistical analysis

Continuous variables are presented as mean and SD (if data were normally distributed) and median and interquartile range (IQR) values (if data were not normally distributed). Categorical variables were described as frequency rates and percentages. Means for continuous variables were compared by paired T-tests or analysis of variance test. Proportions of categorical variables were compared by using the chi-square test or Fisher exact test. A p-value < .05 was considered statistically significant. The statistical analysis was performed using R Studio (Version 1.3.1093, R Foundation for Statistical Computing, Vienna, Austria) and Graphpad Prism version 8.0 (Graphpad Software, Inc. La Jolla, Ca, USA).

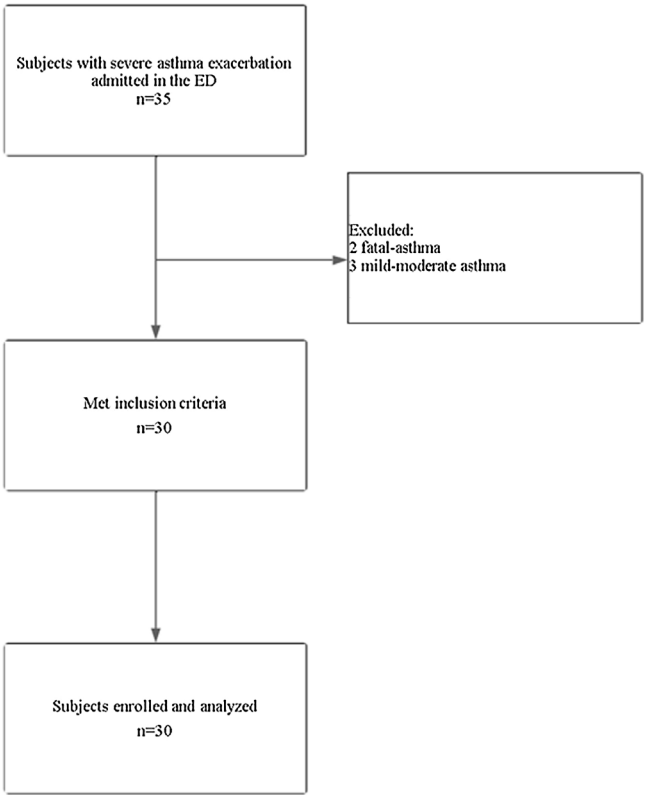

Fig. 1. Flow chart. ED emergency department.

Results

Thirty-five patients with asthma exacerbation were consecutively evaluated for eligibility. Five patients were excluded (three had a diagnosis of mild-moderate asthma and two were admitted for an episode of near-fatal asthma). Thirty patients were included in the final analysis (Fig. 1). The overall mean (± SD) age was 43χ± 16 years. Most included subjects were female (20/30, 67%) with a mean BMI (Body Mass Index) of 32.9 ± 8 kg/m^2. The baseline characteristics of the subjects are shown in Table. 1. Regarding clinical variables, from baseline and up to 12 h post-intervention we observed a significant decrease in RR (30 ± 5 *vs.* 19 ± 5 breaths/min; $p < 0.001$). We also recorded that HR decreased significantly (104 ± *vs.* 98 ± 11 beats/min; $p = 0.017$) and SpO_2 improved significantly (91 ± 4% *vs.* 95 ± 1%; $p < 0.001$) as shown in Fig. 2.

Assessing the primary endpoint, subjects were measured at admission (baseline) and 2 h post-HFNC and in-line bronchodilator by VMN. PEFR showed significant changes (147 ± 31 vs. 220 ± 38 L/m; $p < 0.001$) after bronchodilator treatment. Similarly, FEV_1 underwent changes before and 2 h post-intervention (0.61 ± 0.22 L/s *vs.* 1.15 ± 0.31 L/s; $p < 0.001$). Fig. 3 illustrates the individual responses of each subject. Changes in Pulmonary Function Tests and dyspnea before and after HFNC in-line bronchodilator by VMN are shown in Table 2.

HFNC was used for a mean of 3 ± 1 days and LoHS was 5 ± 1 days. No interruptions to nebulisation or alarms on the HFNC device were detected throughout the study. None of the patients required escalation of treatment with NIV or IMV, no adverse effects were recorded, and no data were lost to follow-up.

Discussion

The main finding of our study was that HFNC and in-line VMN to deliver bronchodilator might be feasible and effective methods for improving lung function in patients with acute respiratory failure due to severe asthma attacks, with no safety concerns. We observed a statistically significant change in PEFR after treatment with HFNC and in-line VMN measured at 2-h. Moreover, all the additional secondary outcome measures showed a statistically significant difference at all the explored time points.

Asthma-related airway obstruction leads to reduced and variable PEFR, which is typically reduced in asthma. Recent asthma guidelines recommend assessing the severity of exacerbations based on the evaluation of the most severe symptoms and PEFR [6]. However, the impact of airflow improvement after bronchodilator therapy in patients with severe asthma exacerbation in the ED is well documented in multiple studies and has been associated with favourable clinical outcomes, such as a reduced need for respiratory support and lower admission rates [25]. While no standard criteria for response to bronchodilation are defined by the ATS/ERS (American Thoracic Society/European Respiratory Society) for the asthmatic population, these criteria are validated in subjects with COPD [26]. Piovesan *et al.*, in a prospective cohort study involving patients with acute asthma aged 12–55 years with PEFR ≤ 50% of predicted, reported that a PEFR ≥ 40% after 15 min of bronchodilator therapy showed a significant ability to predict favourable outcomes [27]. Another study by Santanello and coworkers reported that in adults with stable asthma increases from baseline in absolute PEFR of 18.8 L/min or 5.4% and in absolute FEV_1 of 230 ml or 10.4% were considered clinically meaningful responses to bronchodilation [28]. It is important to note that these studies did not use bronchodilators in line with HFNC. In our study, subjects presented a baseline PEFR ≤ 50% and

Table 1
Baseline characteristics of patients with severe asthma exacerbation.

Characteristics	Results
Age, mean, years (SD)	43 (16)
Sex: Men/Women, n	10/20
BMI, kg/m^2 (SD)	32.9 (9)
APACHE II, score (SD)	7 (5)
History of previous exacerbation, n (%)	8 (27)
History of asthma medication (ICS/LABA or ICS), n (%)	7 (23)
Comorbidities	
Diabetes, n (%)	4 (13)
Hypertension, n (%)	6 (20)
Bronchiectasis, n (%)	1 (3)
Anxiety, n (%)	5 (16)
Pulmonary function estimated	
PEFR estimated, mean (SD), L/m	453 (79)
FEV_1 estimated, mean (SD), L/m	3.2 (0.6)
Clinical parameters at admission	
RR, breaths/min (SD)	30 (5)
HR, beats/min (SD)	104 (15)
S_pO_2, % (SD)	90 (4)
Laboratory blood test	
pH, value (SD)	7.38 (0.1)
P_aO_2, mmHg (SD)	57 (11)
P_aCO_2, mmHg (SD)	40 (7)
HCO_3-, mEq/L (SD)	22.2 (2.8)
P_aO_2/F_iO_2, mean (SD), ratio	242 (50)
HFNC settings at admission	
Flow, L/m (SD)	50 (10)
F_iO_2, % (SD)	0.3 (1)
Site of transfer	
Home, n (%)	4 (13)
RICU, n (%)	26 (87)

Data are presented as number (n) and percentage (%) for dichotomous values or median and interquartile range (IQR) for continuous values.
BMI: body mass index, APACHE II: acute physiology and chronic health evaluation, ICS: inhaled corticosteroids, LABA: long-acting β-adrenoceptor agonist, PEFR: peak expiratory flow rate; FEV_1: forced expiratory flow 1 s, RR: respiratory rate, HR: heart rate, S_pO_2: peripheral arterial oxygenation, $PaCO_2$: partial pressure of carbon dioxide; P_aO_2: partial pressure of arterial oxygen, HFNC: high-flow nasal cannula, F_iO_2: fraction of inspired oxygen, RICU: respiratory intermediate care unit.

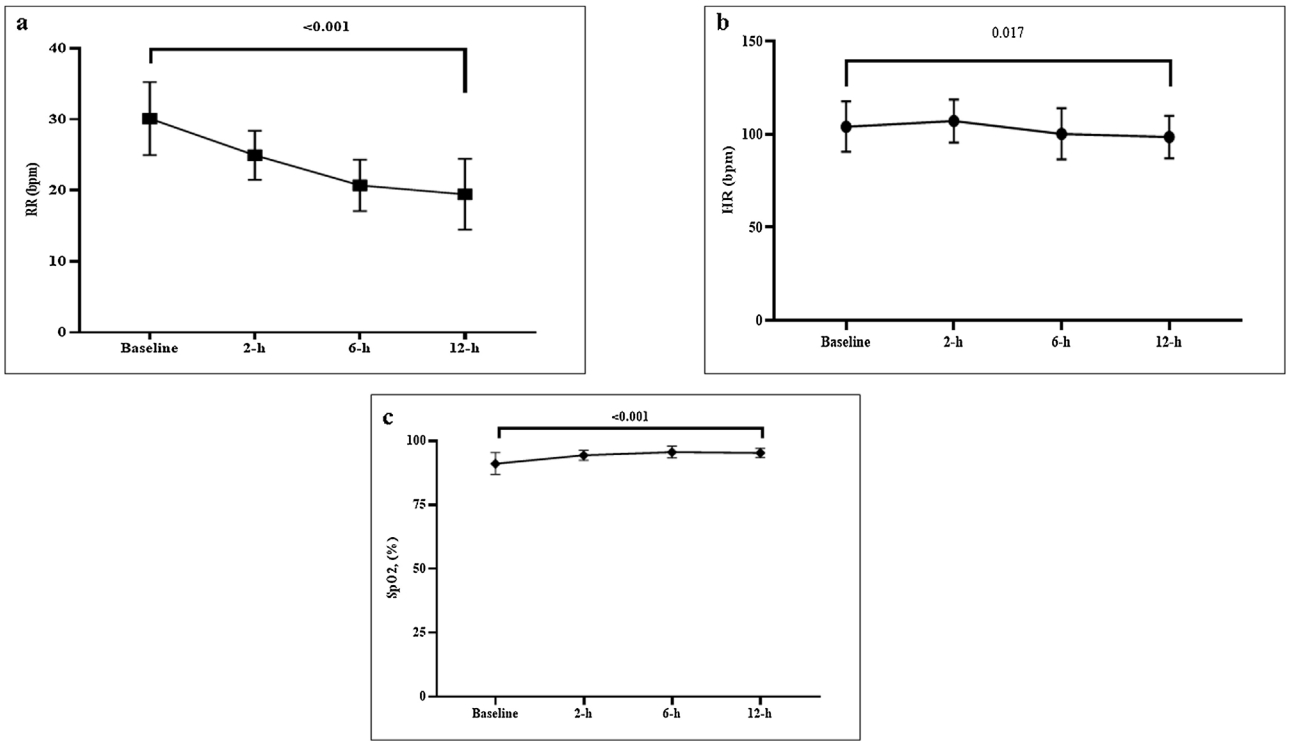

Fig. 2. (a) Respiratory Rate at different times. (b) Heart Rate at different times. (c) SpO2 at different time points.
RR, respiratory rate; HR, heart rate; SpO_2, peripheral arterial oxygenation.

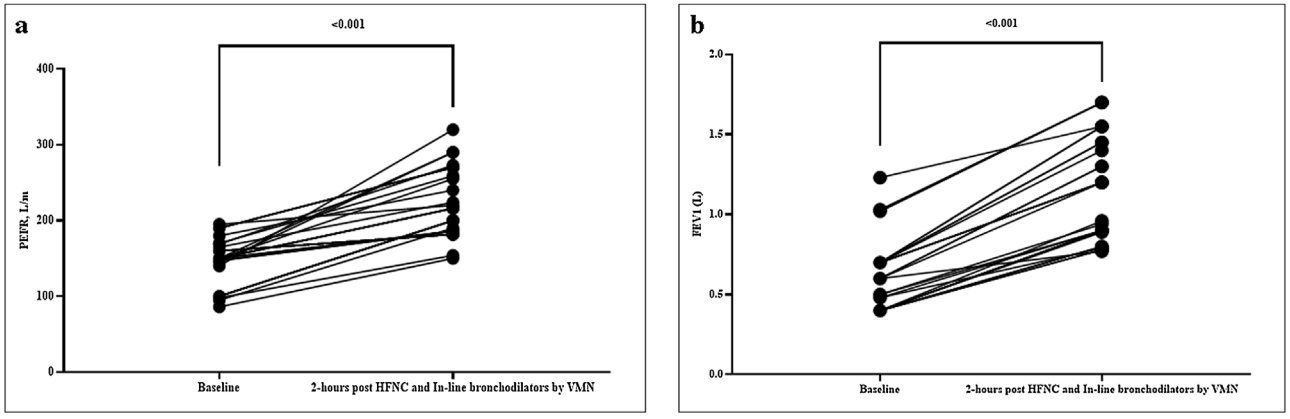

Fig. 3. (a) Baseline values and individual PEFR (L/m) response at 2-hs post HFNC and 4bronchodilator in-line by VMN. (b) Baseline values and individual FEV_1 (L/m) response at 2-h post-HFNC and bronchodilator in line by VMN. PEFR, peak expiratory flow rate; HFNC, high-flow nasal cannula; VMN, vibrating mesh nebulizer.

showed a 49% improvement in PEFR with respect to the predicted percentage at 2 h post-HFNC in-line aerosolised bronchodilator delivery and an improvement in FEV_1 (530 mL or 17% over baseline). In this clinical setting, the efficacy of aerosol delivery systems depends on the ability to generate droplets within the respirable range of 1–5 microns that reach the small airways. JNs deliver aerosols with variable particle sizes, they might influence the delivered F_iO_2 and gas flow rates and can lead to a reduction in that low-level CPAP when the jet nebuliser is opened for drug refill [29,30]. Some HFNC systems, such as the Airvo2 (Fisher & Paykel Healthcare), specifically advise against the use of JN [31]. On the contrary, VMNs have been shown to be more efficient in *in-vivo* and scintigraphy studies in delivering higher concentrations of medication during HFNC compared to JNs [32,33]. Moreover, several equipment considerations such as the starting droplet size, nasal cannula size, gas flow rate, and position of the nebuliser in the circuit [24,34] as well as patient breath pattern (distressed, obstructive, restrictive) can influence the aerosol dose delivered [35–37].

However, to our knowledge, the efficacy of HFNC with concurrent in-line bronchodilators for treating severe asthma exacerbation in adult patients has not been reported. This approach has the potential to prevent the risks associated with uncontrolled oxygen administration, which may adversely influence gas exchange in acutely ill asthmatic subjects [38–40]. Concurrently, it can alleviate the typical clinical signs of respiratory distress observed in patients with a severe asthma attack such as tachypnea, tachycardia, wheezing, hyperinflation, use of accessory muscles, paradoxical pulse, diaphoresis, cyanosis and obnubilation [41] to achieve a rapid clinical improvement with minimal burden on patient's comfort [42]. Furthermore, the delivery of warmed humidified gas by HFNC protects the lung from dry and cold

Table 2
Changes in pulmonary function tests and dyspnea before and after bronchodilator delivery via HFNC with in-line VMN.

Variables	Baseline	2-hs post bronchodilator via HFNC with in-line VMN
PEFR of predicted, % (SD)	32 (9)	49 (14)*
PEFR, L/m (SD)	147 (31)	220 (38)*
FEV_1 of predicted, % (SD)	20 (10)	37 (15)*
FEV_1, L/s (SD)	0.61 (0.22)	1.15 (0.31)*
Borg scale, mean (SD), points	6 (2)	2 (1)*

PEFR: peak expiratory flow rate, FEV_1: forced expiratory flow 1 s, HFNC: high-flow nasal cannula, VMN: vibrating mesh nebulizer.
* $p < 0.05$.

inspired air, which can further induce bronchoconstriction, preserve mucociliary transport and promote mobilisation of secretions, thereby preventing mucus plugging, which have a documented central role in deaths for fatal asthma [43].

The role of HFNC as respiratory support during acute respiratory failure (ARF) is well established in different underlying clinical contexts [44–46]. A few studies have shown that HFNC improved oxygenation compared to COT [17] and decreased dyspnea, HR and RR in acute severe asthma [20,47] without the need for ETI. Similar results were reported in a randomised control study by Magdy *et al.*, who compared the effectiveness of HFNC *vs.* NIV in adult subjects with ARF secondary to severe asthma. The authors observed better P_aO_2 and P/F ratio, lower RR and greater comfort in the HFNC group compared to the NIV group, with no need for escalation to IMV [19]. Based on these findings, we believe that HFNC would be a preferred option to treat adult patients with acute severe asthma exacerbation with the advantage of maintaining adequate oxygenation while concurrently delivering aerosolised bronchodilator treatment.

The delivery of bronchodilators via HFNC is becoming a common practice, with favourable clinical outcomes noted [21,22,48]. A recent randomized cross-over found that delivering nebulised albuterol via HFNC with concurrent in-line VMN induces similar bronchodilation to standard facial mask JN and that HFNC itself alone can induce a small but significant bronchodilatation [49]. It is important to emphasise that VMN do not add additional flow or pressure to the circuit; this allows for synergy of treatments without affecting the performance of the different respiratory supports (NIV or HFNC) [24,50].

To our knowledge, this is the first study to report the effectiveness of combined HFNC treatment and in-line VMN to deliver bronchodilators during an episode of acute respiratory failure due to a severe asthma exacerbation in adults. None of the patients required an escalation of treatment with NIV or IMV, highlighting the feasibility of using HFNC in these circumstances. Similar reasoning may be applied to other drug inhalations, such as tobramycin's efficacy in eradicating gram-negative pneumonia or salbutamol inhalation before general anaesthesia in paediatric patients through HFNC [51,52].

Our study has some limitations. First, the single-center design and the small sample size do not allow for generalizability in the studied populations. Second, the lack of a comparative group makes it difficult to assess the impact of the interventions separately. Third, concomitant medications were not systematically recorded, preventing to isolation of the effects of the intervention.

The study also has strengths, such as the prospective design that allows us to perform a clinical evaluation of feasibility and efficacy in a specific population, such as subjects with acute severe exacerbation of asthma. First, prospective assessment of lung function, including PEFR, allowed for accurate diagnosis of asthma severity and evaluation of treatment response. Second, applying HFNC with concurrent in-line VMN for bronchodilator delivery made it possible to avoid unnecessary disconnections to apply JN or other types of techniques that require suspension of HFNC or coordination with the patient's inspiratory effort ensuring uninterrupted combined respiratory support and bronchodilator treatment. Third, staying in a closed area facilitated continuous clinical assessment of the subjects in the ED without loss of follow-up data. Finally, by using one combined system for delivering HFNC therapy and aerosolized bronchodilator, the same circuit was used for delivering HFNC therapy without the need for an extra mouthpiece or face mask, minimizing plastic waste and potentially improving the environmental sustainability of the ED.

Conclusions

HFNC treatment with in-line VMN for aerosolised bronchodilator delivery during an acute asthma exacerbation in adult subjects admitted to ED appears to be safe and effective in improving PEFR, FEV_1, rapidly, alleviating dyspnea, decreasing RR and HR and allowing for adequate S_pO_2. There were no ETI events and no adverse events during therapies. These preliminary results should be confirmed in appropriately designed research with an adequate sample size and should be considered hypothesis-generating for the design of further randomized controlled trials.

Author contributions

NMCA and LV designed the study, enrolled the patients, analyzed the data, and wrote the paper and should be considered as first authors. AT, GM, MCA, NCA, CC and LV made substantial contributions to the literature review, data collection, and paper writing. NCA, CC and LV reviewed the literature, wrote the manuscript, and produced the figures. CC analyzed data and critically reviewed the manuscript. NCA and GM designed the study, wrote, reviewed, and edited the manuscript. All authors have read and approved the final version of the manuscript. NCA and LV share first authorship. CC and GM share senior authorship.

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Ethics approval and consent to participate

The study was approved by the ethical committee (code register 2663) and informed consent was obtained from participants.

Conflict of interest

Authors have no competing interests with any organization or entity with a financial interest in competition with the subject, matter or materials discussed in the manuscript.

Data availability

Data available upon request.

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