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## Value and Safety of High Flow Oxygenation in the Treatment of Inpatient Asthma: A Randomized, Double-blind, Pilot Study

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### ABSTRACT

This study was aimed to compare the value and safety of high-flow nasal cannula (HFNC) and conventional oxygen therapy (COT) in patients with asthma exacerbation.

In this randomized double-blind study, forty patients with moderate-to-severe asthma exacerbations, aged 18 years or older were enrolled. Patients were randomly assigned to receive either HFNC or COT for 24 hours. Dyspnea scale, O<sub>2</sub> saturation, spirometer indexes, respiratory and heart rate, and arterial blood gas (ABG) were compared within 2 and 24 hours of intervention.

Dyspnea scale decreased significantly from  $7.58 \pm 1.04$  to  $6.45 \pm 0.51$  ( $p=0.000$ ), and from  $7.84 \pm 1.7$  to  $6.89 \pm 0.9$  ( $p=0.049$ ) within 2 hours in HFNC and COT groups, respectively. In the HFNC group, forced expiratory volume in one second (FEV<sub>1</sub>) was  $1.48 \pm 0.94$  L at the time of admission and increased to  $1.61 \pm 0.66$  L ( $p=0.19$ ) and  $1.82 \pm 0.92$  L ( $p=0.003$ ) after 2 and 24 hours of experience, respectively. In addition, in the COT group, FEV<sub>1</sub> increased from  $1.43 \pm 0.65$  L to  $1.46 \pm 0.53$  L and  $1.64 \pm 0.6$  L in the respective time-points, ( $p=0.071, 0.079$ ). PaO<sub>2</sub> and O<sub>2</sub> saturation increased significantly in both groups during the first 2 hours. Two patients in the HFNC group had the complaint of nasal irritation and the device-produced heat; while one patient in the COT group needed more respiratory care.

HFNC could be a therapeutic option for asthma exacerbation among adult patients after considering the patient's selection.

**Keywords:** Asthma; Disease exacerbation; High-flow nasal cannula (HFNC); Oxygen inhalation therapy

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### INTRODUCTION

Recently, high flow nasal cannula (HFNC) oxygen delivery has become popular for the treatment of

certain hypoxic situations like bronchiolitis in neonate HFNC acts as a non-invasive ventilator by reducing airway resistance and improving CO<sub>2</sub> clearance by providing positive end-expiratory pressure (PEEP). Therefore, it is feasible to employ NFC in the case of obstructive pulmonary diseases.

Asthma, as a common obstructive airway disorder in children and adults, has a mortality rate of 0.16-0.21 death per 100,000 people according to the data obtained from 46 countries.<sup>3</sup> It should be noted that the intubation rate in asthma attacks is 0.04% of all asthmatic patients.<sup>4</sup> Furthermore, the decreasing trend in asthma mortality has shown that both the management and medication affect the outcomes.<sup>5</sup>

Since HFNC can open the airway by inducing stenting effects,<sup>6</sup> it supplies more effective oxygenation with stable fraction of inspired oxygen (FIO<sub>2</sub>) in the range of 21 to 100% and a flow rate of up to 60 L/min.<sup>7</sup> Likewise, proper warm humidity provided by HFNC, makes it a reasonable alternative for conventional oxygen therapy (COT), preventing tracheal intubation and invasive respiratory support in the management of severe asthma.<sup>8,9</sup>

There is a controversial issue associated with the patient's outcome in the case of HFNC oxygenation. Several studies have indicated the lower intubation rate in patients undergoing HFNC compared to COT. Conversely, some researchers have also shown that the intubation rate in HFNC patients is not significantly different from that of the standard oxygen therapy.<sup>10,11</sup> However, Frat et al observed a higher number of ventilator-free days following two weeks as well as a lower hazard ratio in the high flow oxygen group, revealing the advantages of HFNC.<sup>11</sup> Rea et al showed that in patients with respiratory distress, mucosal cleansing increases with humidification therapy and consequently leads to fewer exacerbations and higher quality of life.<sup>12</sup> This is while HFNC has the ability to provide both moisture and oxygen. Additionally, in patients with severe hypoxia, treatment failure and mortality rates were not significantly different; using continuous positive airway pressure (CPAP) or HFNC,<sup>13</sup> for which the literature lacks supporting evidence. Accordingly, the aim of this study was to compare the impact of HFNC and COT on the management of asthma among hospitalized adult patients.

## MATERIALS AND METHODS

### Study Design

The present pilot study was conducted in a single-center (Masih Daneshvery Hospital) from August 2016 to July 2017. We performed a double-blind randomized clinical trial to compare HFNC with COT in patients with moderate-to-severe asthma exacerbation. The study was registered at the Iranian Registry Clinical Trial (IRCT2016081727929N2).

### Participants and Inclusion/Exclusion Criteria

Patients aged 18-65 years who were referred to the emergency department or admitted to the ward, were eligible for inclusion if clinically diagnosed with moderate to severe asthma; using equipment from TNI medical AG(Würzburg).

Pregnant patients with a history of smoking and occupational asthma, hypercapnic respiratory failure, and infiltration in chest X-ray (CXR) were excluded in order to manage the confounding variables. Additionally, low -flow oxygen is not a proper standard of care for some patients. The number of patients in each group was 20.

### Randomization and Masking

Patients were randomly assigned to groups 1 or 2; using a single computer-generated (nQuery Advisor) random number sequence by a physician. The experimental group received a high flow of oxygen, and the control group received conventional oxygen therapy. The investigators and the patients were blind to the medication. The treating physician was not blind to the study so that he/she could employ special devices and monitor the HFNC group closely.

### Study Intervention and Follow-up

In the HFNC group, high-flow oxygen with a flow rate of 15–35 L/min (37°C) was delivered continuously through a nasal cannula. The initial flow rate was 19.5–30 L/min and FIO<sub>2</sub> was adjusted to maintain a SaO<sub>2</sub> of 94% or more and relative humidity of 30–34%. HFNC was administered under close monitoring to manage any suspected side effects.

In the COT group, nasal oxygen was administered via nasal cannula; using a flow rate of 2-5 L/min to maintain a minimum SaO<sub>2</sub> of 94%.<sup>14</sup>

Borg scale for dyspnea score, vital signs such as respiratory rate, heart rate, blood pressure, body

temperature, arterial blood gas (ABG) values, and lung function test parameters (LFT) were collected at the baseline (prior to any study intervention), after 2 and 24 hours of intervention.

LFT was performed to measure the forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC. Furthermore, ABG was performed to measure Pao<sub>2</sub>, Paco<sub>2</sub>, and PH.

It is to be noted that both groups received other treatments for acute asthma attacks according to GINA2015 regulation.

### Data and Study Outcomes

Demographic data (age, sex, weight, and height), admission duration, and clinical symptoms such as cough, sputum, and chest pain were initially collected from the patients' medical records.

The main outcomes were respiratory rate, dyspnea score, and PaO<sub>2</sub>. Secondary outcomes were peak expiratory flow and FEV1. Furthermore, refractory hypoxemia (arterial oxygen saturation < 88% with FIO<sub>2</sub>=100%), ICU admission, and intubation were compared as secondary outcomes.

### Statistical Analysis

For statistical analysis, SPSS statistics software version 22.0 was used. The Kolmogorov spinoff was performed to evaluate the normal distribution of quantitative data. Pearson's chi-squared test was used for the analysis of the categorical data. Baseline conditions were compared; using Mann Whitney U or independent student t-test. To compare the outcomes in each study group, ANOVA repeated measures were

used prior to and following the intervention. Data were expressed as mean±SD and the statistical significance level was considered by the *p*-value of <0.01, CI: 99% for Borg scale or *p*<0.05, CI: 95% for paraclinical findings.

### Ethical Considerations

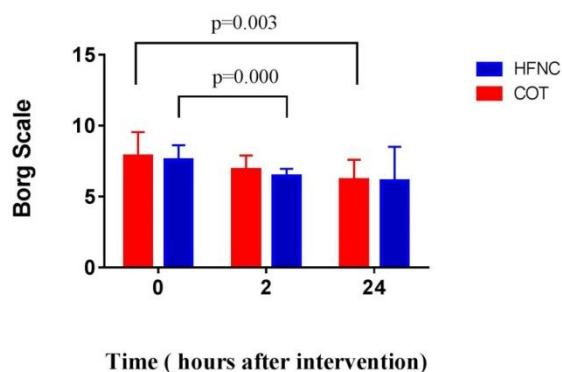
The study was approved in the Ethics committee of Shahid Beheshti University of medical sciences (reference number: IR.SBMU.NRITLD.REC.1395.230). The participation was free of charge and the participants were free to withdraw from the study at any moment. Written informed consent was obtained from the patients before randomization.

## RESULTS

Forty patients were included in the study according to the inclusion criteria. Twenty patients were enrolled in each group. The baseline characteristics are shown in Table 1.

Age, gender, weight, height, Borg scale, spirometry parameters, ABG parameters, ESR, and leukocyte count were similar between the two groups. The only significant difference was the eosinophil count in HFNC and COT groups (8.7±4.4 vs. 5.2±2.5, *p*=0.04, CI: 95%).

During the study, two patients from the HFNC group complained from device-induced heat and nasal irritation; while one patient from the COT group had refractory asthma with an O<sub>2</sub> saturation of 85% despite receiving standard treatment.



**Figure 1.** Borg scale at the beginning of the study and during the intervention. There was a significant decrease after 2 hours of oxygenation via high flow and 24 hours of oxygenation via the conventional method. After 24 hours of treatment, the Borg scale was almost similar in both study groups. HFNC: High-Flow Nasal Cannula; COT: Conventional Oxygen Therapy.

**Table1. Baseline characteristics prior to the intervention**

	Baseline characteristics (Mean±SD)		
	HFNC	COT	
Age (years)	50.75 ±10.7	44.4 ±11.6	NS
Sex % (female)	15 (75%)	13 (65%)	NS
Height (m)	1.63±0.08	1.69±1.08	NS
Weight (Kg)	74.8±9.9	73.7±8.1	NS
Borg scale	7.58 ±1.04	7.84 ± 1.7	NS
FEV1-actual (liter)	1.48 ±0.94	1.43 ±0.15	NS
FVC%	60±23.3	66.5±18.99	NS
FEV1/FVC %	62.18±11.8	65.7±11.5	NS
RR	23.05±4.8	21.6±2.8	NS
HR	93.4±15.90	96.3±7.7	NS
Pao2 mmHg	52.8±14.2	49.6±20.1	NS
Paco2 mmHg	35.08±7.02	37.8±5.1	NS
O2 saturation%	89.7±3.7	89.5±3.8	NS
PH	7.4±0.06	7.4±0.1	NS
ESR (mm)	29.4±17.3	25.5±16.2	NS
Leukocytosis	9429.5±3095	10080.5±2967.9	NS
PMN%	60.34±15	65.3±13.6	NS
EOS%	8.7±4.4	5.2±2.5	0.05
History of Asthma Diagnosis (years)	5.3±2.7	6.4±3.4	NS

HFNC: High-Flow Nasal Cannula; COT: Conventional Oxygen Therapy; FEV1: Forced Expiratory Volume in the first second; FVC: Forced Volume Vital Capacity; RR: Respiratory Rate; HR: Heart Rate; NS: Not Significant; ESR: Erythrocyte Sedimentation Rate; PMN: Polymorphonuclear; EOS: Eosinophils. CI 99% for Borg scale and 95% for Paraclinical data.

As depicted in Figure 1, the Borg Scale decreased significantly after two hours of treatment in the HFNC group compared with the COT group. In HFNC, the scale reached  $6.45 \pm 0.51$  ( $p=0.000$ , CI: 99%) within 2 hours of experience and reached  $6.1 \pm 2.4$  ( $p=0.014$ , CI: 99%) after 24 hours of treatment. However, the Borg Scale decreased by 12% (from  $7.84 \pm 1.7$  to  $6.89 \pm 0.9$ ) ( $p=0.049$ , CI: 0.99%) within 2 hours of treatment with COT and the score dropped significantly and reached to  $6.1 \pm 1.4$  ( $p=0.003$ , CI:99%) within a 24-hour period.

FEV1 was  $1.61 \pm 0.16$  L and  $1.46 \pm 0.53$  L at two hours post-treatment in the HFNC and the control group, respectively. The two groups were not significantly different in this aspect ( $p=0.6$ , CI:95%). Furthermore, FEV1 was  $1.8 \pm 0.92$  L in the HFNC and  $1.64 \pm 0.64$  L in the COT at 24 hours post-treatment ( $p=0.46$ , CI: 65%). The within-group analysis revealed that after 24 hours of treatment, FEV1 improved significantly in both groups. However, the mean change was  $0.44 \pm 0.13$  and  $0.20 \pm 0.07$  ( $p=0.695$ ) and the final FEV1 was not significantly different in none of

the treatment groups. No other significant differences were noted in this regard between the two groups (Figure2A, B).

The within-group analysis indicated that the FVC predicts at two- hour post-treatment were almost similar to the baseline values and no significant difference was found in none of the groups. Accordingly, it changed from  $60 \pm 23.3$  L to  $58.8 \pm 22.7$  L in the HFNC group ( $p=0.858$  CI:95%) and from  $66.5 \pm 18.99$  L to  $69.6 \pm 19.1$  L in the COT group ( $p=0.19$ , CI:95%).

In this regards, the FVC predict was significantly higher in 24 hours post-treatment than that of the 2 hours post-treatment in both HFNC and COT ( $71.1 \pm 5.0$  L  $p=0.000$  vs.  $75.1 \pm 18.4$  L,  $p=0.003$ ).

However, the between-group analysis revealed no considerable difference in the 24 hours post-treatment data. In the HFNC, FVC was improved from 2 to 24 hours of experience ( $25.7 \pm 26.6\%$ ); while in the COT, FVC increased significantly ( $9 \pm 7\%$ ,  $p=0.024$ , CI: 95%) (Figure 3-A).

Moreover, the FEV1/FVC values were not significantly different between the two groups after 2 and 24 hours of treatment; however, after 24 hours, the response to treatment was evaluated in both groups. FEV1/FVC values changed from 67.5±8 at 2 hours post-treatment to 73.5±9 at 24 hours post-treatment in the HFNC group. In the COT group, it changed from 65.9±9 to 71.7±9.4 at these two time-points. The variation coefficient of FEV1/FVC was also higher in the HFNC group in the first 2 hours than the COT group (Figure 3-B).

The within-group analysis proved that respiratory

rate decreased significantly in each time point of treatment in both groups (Figure 4-A). But, the between-group analysis indicated no difference in none of the three time-points. At 2-hour post-treatment, the heart rate was significantly lower in the HFNC group than that of the COT group ( $p=0.004$  CI:95%). Following 24 hours in both groups, the heart rate reached the normal range (Figure 4-B).

The change in ABG parameters is depicted in Figures 4-C, D, E, F. There was a parallel pattern in HFNC and COT groups so that no significant difference was seen in either time points.

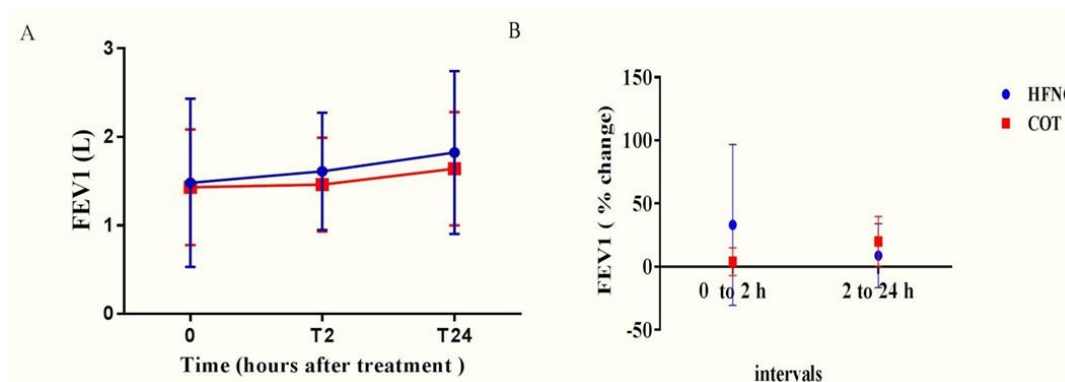


Figure 2. The FEV1 values and its changes among HFNC and COT patients in 3 time-points revealed a considerable change in the first 2 hours in HFNC. At 2 hours post-treatment, the two groups were not significantly different. Also after 24 hours of treatment, the FEV1 was almost similar. HFNC: High-Flow Nasal Cannula; COT: Conventional Oxygen Therapy; FEV1: Forced Expiratory Volume in the first second.

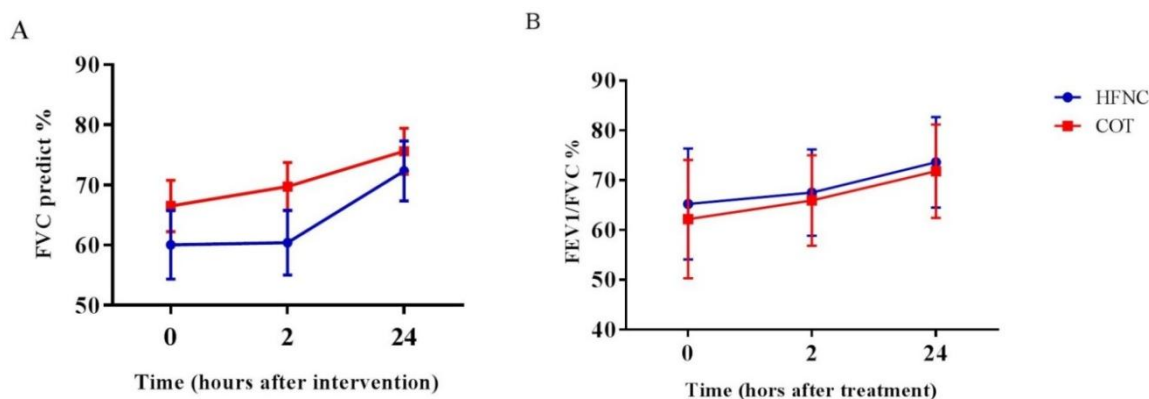
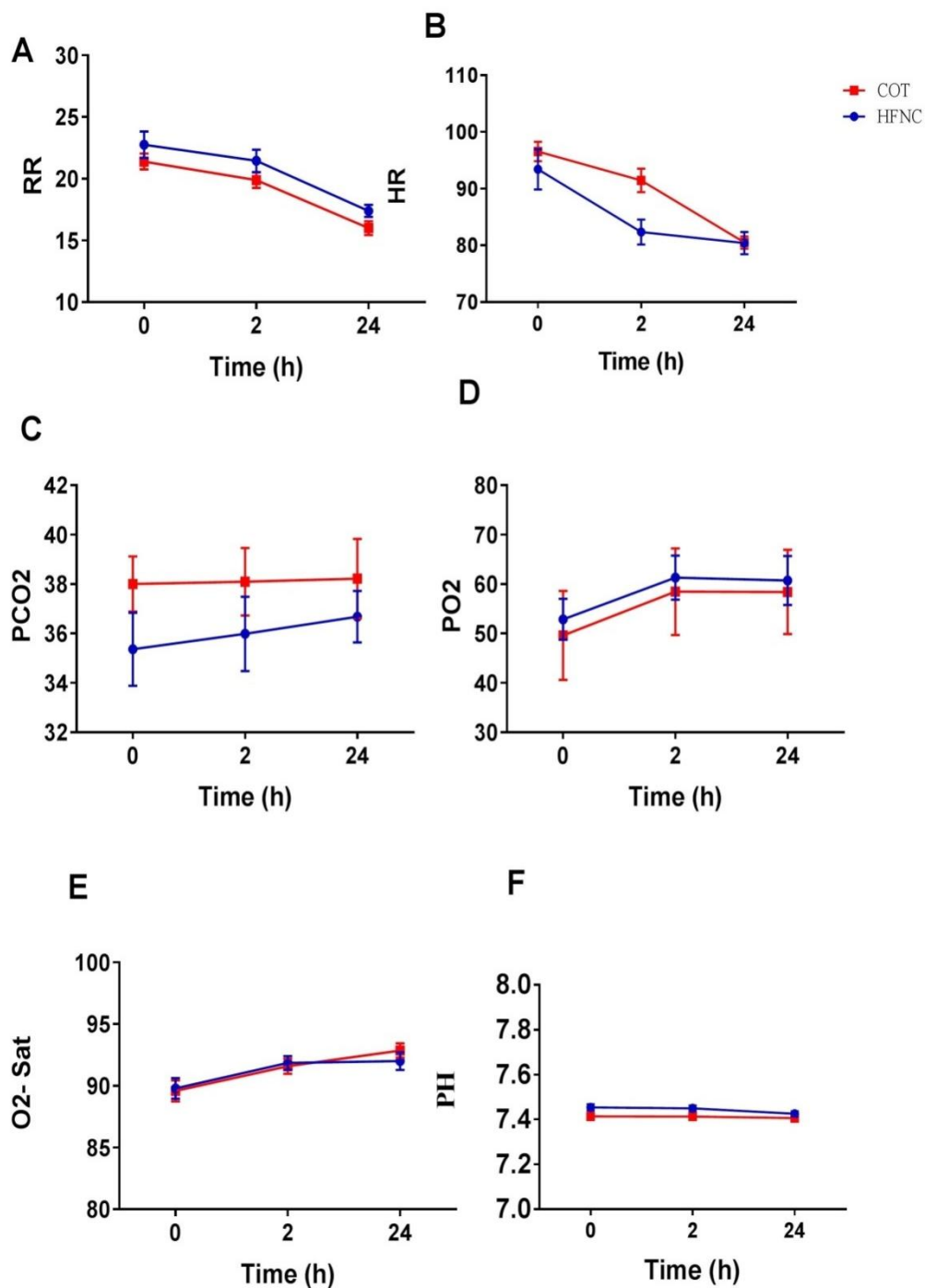


Figure 3. A: The FVC value during the oxygenation. B: FEV1/FVC in both study groups showed parallel changes during oxygenation via HFNC or COT. FVC: Forced Volume Vital Capacity; FEV1/ FVC: Forced Expiratory Volume in the first second to the Forced Volume Vital Capacity; HFNC: High-Flow Nasal Cannula; COT: Conventional Oxygen Therapy.



**Figure 4.** Respiratory rate (RR), Heart rate (HR), and arterial blood gas (ABG) parameters at different time points of the study. The RR decreased significantly in each time point of treatment in both groups (A). The heart rate decreased significantly in the first 2 hours of oxygenation via HFNC (B). In the case of ABG parameters including PO<sub>2</sub>, PCO<sub>2</sub>, and PH, there was a parallel pattern in HFNC and COT groups, so that no significant difference was seen in none of the time points (C,D,F). Also, O<sub>2</sub> saturation improved at the first 2 hours of treatment in both groups and followed a similar pattern in HFNC and COT. HFNC: High-Flow Nasal Cannula; COT: Conventional Oxygen Therapy.

## DISCUSSION

In this study, we described the use of HFNC for the treatment of moderate to severe asthma exacerbation in the adult ward setting. We observed clinical improvements in both dyspnea score and heart rate. Likewise, within the first 2 hours of treatment, the percentage of increase in FEV1 revealed is higher slope in the HFNC group during the first 2 hours compared with the COT group. Though, this change was modified from 2 to 24 hours of experience in both groups. However, ABG indexes and O<sub>2</sub> saturation improvement were similar in both study groups. One patient in the COT group suffered from refractory asthma and needed more respiratory support; while two patients in the HFNC group complained from nasal irritation and warmth.

Appropriate oxygen therapy is crucial for the prevention of respiratory failure in the primary stages of respiratory impairment.<sup>15</sup> HFNC is currently utilized in a variety of respiratory and cardiovascular or post-surgery conditions to reduce the FIO<sub>2</sub>.<sup>16</sup> Unlike high concentration oxygen masks, providing proper humidity via HFNC reduces the respiratory distress and makes it more tolerable. Moreover, air flushing in the respiratory tract would diminish the dead space. Therefore, it seems that the higher dead space in pediatrics (3cc/kg until 6 years of old) makes it a good candidate for such treatments.<sup>6</sup> Nowadays, there is plenty of information regarding the HFNC utilization in pediatric.<sup>17-19</sup> Ballester et al found better oxygenation during the first 2 hours in children with moderate-to-severe asthma. In their study, hospital stay was the same between the HFNC and COT groups, and no complication corresponded to high flow oxygen was reported.<sup>20</sup> We found a significant decrease in the HR of patients in the HFNC group compared to the COT group in the first 2 hours of treatment but contrary to the study of Martines et al the RR in both study groups showed the same pattern of changes.<sup>21</sup> In this regard, Rittayamai et al also showed that the RR was not affected by the HFNC.<sup>22</sup> Target group of the current investigation and the study of Rittayamai et al was adult patients while the median age in the study of Martines et al was 5 years. Given the significant decrease in the RR, the pulmonary score and the HR in the patients, Martines et al concluded that HFNC therapy could be useful in the management of asthma exacerbations in the pediatric ward as well as the

pediatric intensive care units (PICU) or emergency departments.

Indeed, the role of HFNC in mucosal hydration and mucosal clearance is another strong point, rendering it more promising than COT. In this regard, in some PICUs, HFNC is the first-line treatment choice for children with moderate-to-severe asthma who needs closer monitoring in the first hours of admission and early initiation of support.<sup>23</sup> There has been a 17.5% increase in HFNC utilization for chronic obstructive pulmonary disease and pneumonia compared with the 10.2% for Non Invasive Ventilation (NIV) and 1.6% for invasive mechanical ventilation during 7 years of experience in Baystate Medical Center.<sup>8</sup>

There have been certain complications associated with unpredictable fluctuations of pressure induced by high airflow including pneumothorax and pneumomediastinum.<sup>23,24</sup> Higher noise pollution compared to other positive pressure producing devices,<sup>25</sup> is another limitation of HFNC, although there has been no patient complaint about noise pollution in the literature. In our study, no pneumothorax or pneumomediastinum was observed, but an unpleasant nasal burning sensation was reported by a patient. Thus, to detect treatment failure or complications, close monitoring is required in HFNC.

From an economic point of view, the total expenditures per patient in HFNC is higher than the COT. However, given the decrease in treatment failure and the rate of tracheal intubation, cost-benefit is discussed. As reported by pilar et al in 2017, the outcomes of patients with severe asthma in the ICU including hospital stay were similar in HFNC and NIV groups. Accordingly, 60% of the patients in the HFNC group were successfully treated with no NIV. The remaining 40% of the subjects with HFNC failure underwent a longer duration of respiratory support.<sup>26</sup> The authors stated that HFNC could probably postpone the initiation of NIV "in more severe cases that may result in a longer stay in PICU as well as increasing the morbidity and costs".<sup>26</sup> It seems that the estimation of the total cost may indicate the other benefits of HFNC in case of proper case selection and patient monitoring.

There are some limitations to our study, including the small sample size as well as limitation of the cases being referred to a single-center. So, case selection bias may affect the external validity. Also, there was a delay between the admission time and protocol initiation so that the patients may have received standard treatment

and the first spirometry was performed after primary stabilization. Given that both control and HFNC groups were in a similar situation, pre and post-treatment findings were compared. Moreover, the dyspnea score (Borg scale) was a subjective parameter. So, we used a 99% confidence interval for the interpretation of related findings. And finally, the underlying disease, cause of exacerbation and co-treatment may confound the results. So, multicenter trials are needed for better evaluation.

HFNC appears to be more effective than COT in reducing the dyspnea score within the first 2 hours of treatment in asthma exacerbation with an indication of hospitalization. Optimization of the device and developing proper guidelines for case selection and airflow modification will ultimately cover the limitations. For example, recent reports demonstrated no difference in consumption of 2 or 3 L/kg of O<sub>2</sub> in young infants with acute viral bronchitis;<sup>19</sup> while Martínez et al believe in the impact of flow rate on PICU admission.<sup>21</sup> Overall, considering numerous parameters affecting the outcome, patient selection is a major factor in the success of this therapeutic approach.<sup>22,27</sup> The comparison of HFNC and COT or HFNC and NIV has to be carefully interpreted to avoid the misconduct of cost-benefit analysis of the potential risks.

#### ACKNOWLEDGEMENTS

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