High-flow nasal cannula versus noninvasive ventilation in the prevention of escalation to invasive mechanical ventilation in patients with acute hypoxemic respiratory failure

Gamal Agmy, Mohamed Adam, Entsar H.M. Hsanen, Manal A. Mahmoud

Department of Chest Diseases and Tuberculosis, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Manal A. Mahmoud, MD of Chest Diseases, Department of Chest Diseases and Tuberculosis, Faculty of Medicine, Assiut University, 71515, Egypt. Tel: 088 2413717; Fax: 088 2332278; e-mail: mw@aun.edu.eg

Received: 23 November 2020
Revised: 22 March 2021
Accepted: 15 May 2021
Published: xx xx 2022

The Egyptian Journal of Chest Diseases and Tuberculosis 2022, 71:81–87

Background
High-flow nasal cannula (HFNC) is a device for conveying oxygen therapy. Emerging clinical evidence supports that it may be a compatible alternative for noninvasive ventilation (NIV) in patients with acute hypoxemic respiratory failure (ARF).
Objective
To compare the outcome of NIV versus HFNC oxygen therapy in preventing escalation to invasive mechanical ventilation in patients with ARF.
Patients and methods
A randomized controlled trial was conducted. One hundred consecutive patients who had ARF were allocated randomly to HFNC and NIV groups. The patients' need for endotracheal intubation, dyspnea score, comfort scores, gasometric, in-hospital mortality, and vital sign parameters were the outcome measures. Patients' baseline characteristics and the serial changes after HFNC or NIV therapy were measured.
Results
The HFNC group had 18% endotracheal intubation rate and 18% in-hospital mortality versus 50% and 48% for the NIV group (P=0.001). The median values of visual analog scale at 24, 48, 72, and 96 h were lower in the NIV group (P=0.000 for all). The median modified Borg scale at 24, 48, 72, and 96 h was lower in the HFNC group (P=0.00, 0.024, 0.040, and 0.001, respectively). The HFNC group had a significantly lower respiratory rate. Significant differences in baseline vital sign parameters between the NIV and HFNC groups were noticed after 1, 6, 24, and 48 h follow-up.
Conclusion
Delivering oxygen by HFNC is a new and efficient option for treating adults with ARF. HFNC showed a reduced rate of escalation to invasive mechanical ventilation and in-hospital mortality in comparison to NIV.

Keywords:
high-flow nasal cannula, intubation, noninvasive ventilation, respiratory failure

Egypt J Chest Dis Tuberc 71:81–87

2090-9950

Introduction

Oxygen therapy is considered the primary treatment option for managing acute hypoxemic respiratory failure (ARF). Several devices for delivering oxygen are available, including low-flow systems (simple face mask, nonrebreathing reservoir mask, nasal cannula) and high-flow systems (e.g. venturi mask) [1]. In the past two decades, strong evidence supported using noninvasive ventilation (NIV) for cardiogenic pulmonary edema and acute exacerbation of chronic obstructive pulmonary disease. The positive pressure in NIV augments better gas exchange and decreases the inspiratory effort [2]. However, good tolerance to NIV is not easily achieved due to frequent mask leaks, possibly causing patient–ventilator dyssynchrony and even intubation [3]. High-flow nasal cannula (HFNC) oxygen therapy is a new modality that can deliver up to 60 l/min of fully humidified and heated oxygen. The fraction of inspired oxygen (FiO_2) ranges from 21% to 100% [4]. NIV has been addressed to prevent invasive mechanical ventilation and its complications in a wide range of hypoxemic ARF patients; however, it is postulated that HFNC has the same effect as NIV with added advantages like easier tolerability, being more physiological [5–9], and patients can eat, drink, and talk while connected to HFNC [1].

Patients and methods

Prospective, parallel-group randomized clinical trial was conducted between March 2019 and May 2020.

One hundred consecutive patients were admitted to the Respiratory Intensive Care Unit (RICU) with an episode of ARF. All patients gave a written consent and the research ethics committee approved the study.

Inclusion criteria

Admitted patients to the RICU having ARF defined by PaO2/FiO2 less than or equal to 300 mmHg despite supplying oxygen at a flow rate more than or equal to 10 l/min for more than or equal to 15 min or requiring ventilatory support due to increased respiratory rate more than 25 breaths/min, using accessory muscles of respiration with a negative clinical history for an underlying chronic respiratory failure.

Exclusion criteria

Patients were excluded if they had any of the following:

(1) Absolute indication for intubation like coma, hemodynamic instability, or life-threatening arrhythmia.
(2) Contraindication to NIV like untreated pneumothorax, pneumothorax with air leak, widespread facial burn or trauma, tracheotomy, or active upper gastrointestinal bleeding.
(3) $PaCO_2$ of more than 45 mmHg.
(4) Chronic respiratory failure.
(5) Refusal to participate.

Intervention

Patients were randomized to HFNC or NIV groups.

Group I (the noninvasive ventilation group)

Patients were connected to a Puritan Bennett™ 840 (Galway, Ireland) ventilator for conventional NIV with a full-face mask. Positive end-expiratory pressure (PEEP) was initially adjusted between 2– and 10 cmH_2O. The PEEP level or FiO2 (or both) was later on set to keep the SaO2 more than or equal to 92%. The pressure-support level was set to achieve 7–10 ml/kg expired tidal volume.

Group II (high-flow nasal cannula group)

Heated humidified oxygen (31–37°C) (MR850, Fisher and Paykel Healthcare, Auckland, New Zealand) was continuously supplied through binasal large-bore prongs. The initially adjusted oxygen flow rate was 50 l/min at an FiO2 of 1.0 (Optiflow, Fisher and Paykel Healthcare). The FiO2 was then adjusted to attain a SaO2 more than or equal to 92%.

Data collection

The Acute Physiology and Chronic Health Evaluation II was calculated during the first 24 h of admission to the RICU. The Sequential Organ Failure Assessment (SOFA) score, modified Borg scale, the visual analog scale, and patients' vital signs were recorded at inclusion and at 24, 48, 72, and 96 h. Arterial blood gas samples were withdrawn and recorded at randomization and 1, 6, 24, and 48 h of study treatment.

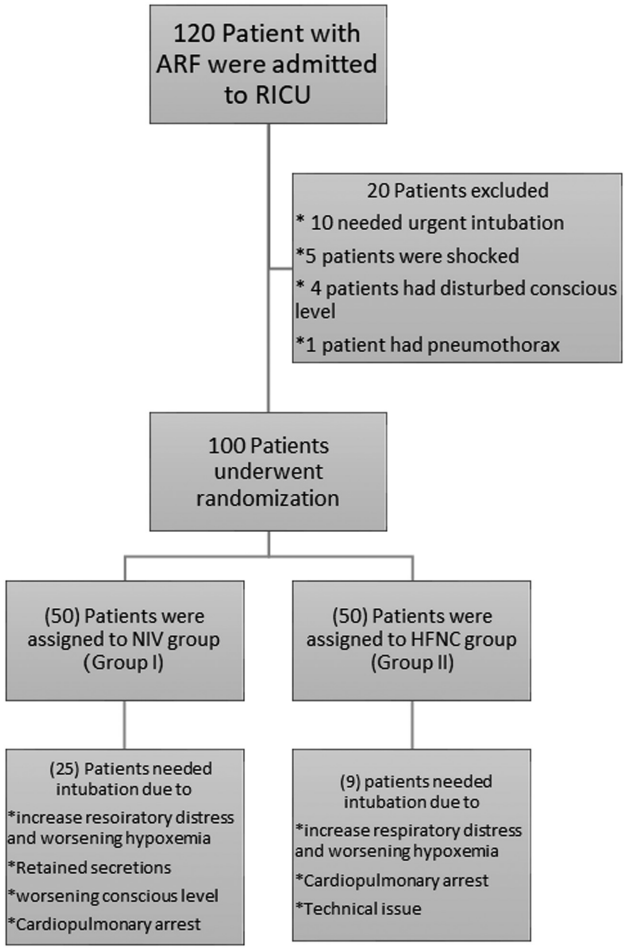
Outcomes

The necessity for endotracheal intubation during the ICU stay was the primary outcome. Secondary outcomes were the visual analog scale, SOFA score, modified Borg scale, respiratory rate, and heart rate, and arterial blood gas parameters and occurrence of complications.

Statistical analysis

SPSS (version 18.0; SPSS Inc., Chicago, Illinois, USA) was used for analyzing the results of this study. Mean±SD or median (range) were used to express continuous data. Categorical data were expressed as counts (%). Differences between groups were evaluated by independent samples *t* test,

Figure 1



Study participants enrollment, randomization, and follow-up. HFNC, high-flow nasal cannula; NIV, noninvasive ventilation.

Table 1 Baseline patient characteristics

Personal data	NIV (*N*=50)	HFNC (*N*=50)	*P* value
Age: (years), (mean±SD)	49.50±18.21	44.58±15.59	0.150
Male [*n* (%)]	22 (44.0)	24 (48.0)	
Female [*n* (%)]	28 (56.0)	26 (52.0)	
Current or past smoking [*n* (%)]	20 (40)	25 (50)	0.077
APACHE II score (mean±SD)	11.76±4.51	11.50±5.65	0.800
SOFA score (mean±SD)	4.84±1.18	4.68±1.20	0.504
Systolic BP (mmHg)	122.80±17.73	118.20±12.24	0.134
Diastolic BP (mmHg)	77.00±10.35	74.60±7.06	0.179
Heart rate (beats/min)	112.98±20.77	112.94±13.81	0.991
Respiratory rate (breaths/min)	38.50±7.20	40.08±5.77	0.229
Arterial blood gas			
pH	7.48±0.06	7.49±0.05	0.428
$PaCO_2$	29.32±6.91	27.38±4.52	0.100
PaO_2	48.30±14.06	51.28±12.94	0.273
SaO_2	82.50±9.69	83.36±10.08	0.665
PaO2\FiO2 (mean±SD)	228.76±67.56	240.52±66.70	0.383
Previous hospital admission [*n* (%)]	19 (38)	17 (34)	0.677
Previous ICU admission [*n* (%)]	7 (14)	13 (26)	0.134
Cause of acute respiratory failure [*n* (%)]			
Exacerbation of ILD	22 (44)	18 (36)	0.542
Pneumonia/bronchopneumonia	16 (32)	25 (50)	0.073
Pulmonary embolism	6 (12)	2 (4)	0.269
Exacerbation of bronchial asthma	2 (4)	1 (2)	1.000
Lung secondaries	0	1 (2)	1.000
Acute exacerbation of COPD	2 (4)	2 (4)	1.000
Massive malignant pleural effusion	1 (2)	0	1.000

APACHE II, Acute Physiology and Chronic Health Evaluation II; COPD, chronic obstructive pulmonary disease; FiO_2, fraction of inspired oxygen; HFNC, high-flow nasal cannula; ILD, interstitial lung disease; NIV, noninvasive ventilation; PaO_2, partial pressure of carbon dioxide in the blood; PaO_2, partial pressure of oxygen in the blood; SaO_2, arterial blood oxygen saturation measured by blood analysis; SOFA, Sequential Organ Failure Assessment score. Significant *P* value less than 0.05.

Table 2 Primary and secondary outcomes in the study groups

End points	NIV (*N*=50)	HFNC (*N*=50)	*P* value
ICU stay duration (days, mean±SD)	7.42±4.24	5.06±2.80	0.001*
Hospital stay duration (days, mean±SD)	10.84±5.96	7.46±3.36	0.002*
Days from admission to MV(median, range)	3.0 (1.0–8.0)	6.0 (3.0–11.0)	0.002*
Frequency of ventilation interruption			0.000*
On first day (median, range)	6.0 (1.0–23.0)	1.5 (0.0–7.0)	
On second day (median, range)	8.0 (2.0–15.0)	1.0 (0.0–4.0)	0.000*
Fate [*n* (%)]			0.001*
Survival	26 (52.0)	41 (82.0)	
Death	24 (48.0)	9 (18.0)	
Complications [*n* (%)]			
Nasal bridge ulceration	24 (48.0)	0	0.000*
Leak	42 (84.0)	0	0.000*
Asynchrony	37 (74.0)	0	0.000*
Claustrophobia	20 (40.0)	0	0.000*
Nasal dryness and ulceration	24 (48.0)	0	0.000*
Retained secretion	16 (32.0)	0	0.000*
Facial laceration	16 (32.0)	0	0.000*
Escalation to mechanical ventilation [*n* (%)]	25 (50.0)	8 (18.0)	0.001*
Cause of mechanical ventilation [*n* (%)]			
Increased respiratory distress	18 (72.0)	7 (77.8)	1.000
Worsening hypoxemia	18 (72.0)	7 (77.8)	1.000
Worsening conscious level	3 (12.0)	0	0.042*
Retained secretion	12 (48.0)	0	0.010*
Cardiopulmonary arrest	5 (10.0)	1 (11.1)	1.000

HFNC, high-flow nasal cannula; NIV, noninvasive ventilation. *Significant *P* value less than 0.05.

Mann–Whitney test, χ^2 test, and Fisher's exact test as appropriate. *P* value of 0.05 or less was considered statistically significant.

Results

Figure 1 illustrates the patients' flowchart. One hundred patients met the inclusion criteria. Each intervention group included 50 patients.

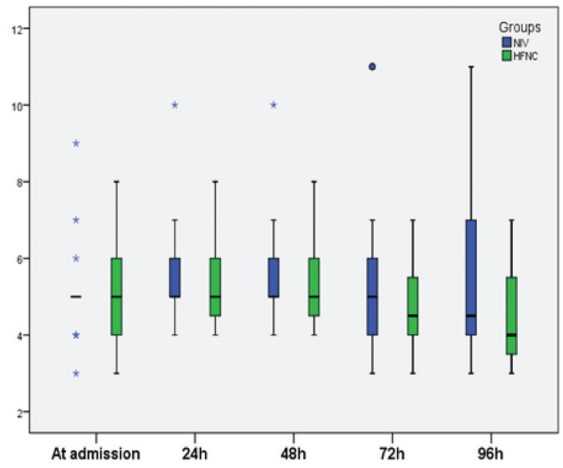
The differences between the NIV and HFNC groups (Table 1) regarding age, previous hospital stay, previous ICU admission, and cause of ICU admission were nonsignificant.

The length of ICU stay and hospital stay were significantly lower in the HFNC group (Table 2) in comparison to the NIV group (*P*=0.001, 0.002, respectively). The NIV group showed significantly higher in-hospital mortality (*P*=0.001).

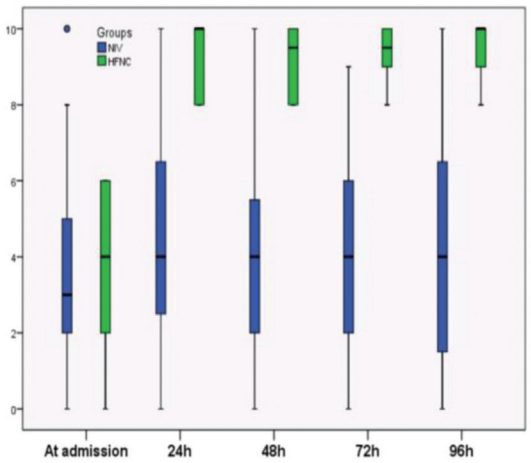
Moreover, the complications were significantly higher in the NIV group (*P*=0.000). Escalation to mechanical ventilation was predominantly in the NIV group (*P*=0.001). Worsening hypoxemia and increased respiratory distress were the most common causes for escalation to mechanical ventilation in both study groups. At admission the difference between NIV and HFNC groups in median SOFA score (Fig. 2a) was nonsignificant (*P*=0.404), meanwhile this difference became statistically significant after 24, 48, and 72 h (*P*=0.004, 0.007, 0.002, respectively). The median values of visual analog scale (Fig. 2b) in the HFNC group was 10 indicating maximum patient's comfort (*P*=0.000 for all). The median modified Borg scale (Fig. 2c) at 24, 48, 72, and 96 h was significantly lower in the HFNC group (*P*=0.00, 0.024, 0.040, and 0.001, respectively)

As regards vital signs (Table 3), the differences in baseline vital sign parameters between both groups

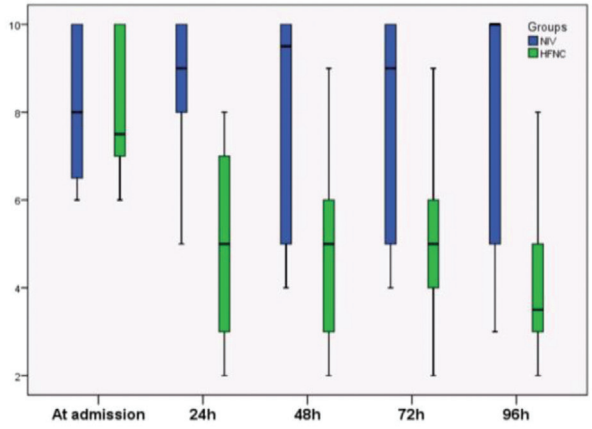
Figure 2



(a) Sofa Score



(b) Visual Analogue Scale



(c) Modified Borg Score

Changes in SOFA score (panel A), visual analog scale (panel B) and modified Borg score (panel C) during the 96 h study period: (a) SOFA score, (b) visual analog scale, and (c) modified Borg score. SOFA, Sequential Organ Failure Assessment.

Table 3 Baseline and follow-up vital sign parameters of the study population

	NIV (*N*=50) (mean±SD)	HFNC (*N*=50) (mean±SD)	*P* value
Baseline			
Systolic BP (mm/Hg)	122.80±17.73	118.20±12.24	0.134
Diastolic BP (mm/Hg)	77.00±10.35	74.60±7.06	0.179
HR (beat/min)	112.98±20.77	112.94±13.81	0.991
RR (cycle/min)	38.50±7.20	40.08±5.77	0.229
After 1 h			
Systolic BP (mm/Hg)	121.00±14.18	114.20±8.35	0.004*
Diastolic BP (mm/Hg)	76.80±7.68	73.60±5.98	0.022*
HR (beat/min)	111.10±20.38	109.66±14.10	0.682
RR (cycle/min)	35.78±6.78	29.70±5.63	0.027*
After 6 h			
Systolic BP (mm/Hg)	118.40±11.84	115.63±8.73	0.191
Diastolic BP (mm/Hg)	74.60±5.79	74.58±6.17	0.989
HR (beat/min)	110.30±19.22	104.33±12.67	0.074
RR (cycle/min)	34.14±7.58	27.73±4.02	0.040*
After 24 h			
Systolic BP (mm/Hg)	117.73±7.11	115.11±5.85	0.057
Diastolic BP (mm/Hg)	75.91±5.83	75.11±6.55	0.540
HR (beat/min)	101.59±13.64	99.94±11.78	0.536
RR (cycle/min)	31.25±5.09	26.13±4.54	0.029*
After 48 h			
Systolic BP (mm/Hg)	117.91±10.36	113.78±6.14	0.025*
Diastolic BP (mm/Hg)	74.42±6.29	65.01±5.29	0.047*
HR (beat/min)	98.91±14.42	87.00±10.35	0.015*
RR (cycle/min)	30.67±4.61	24.11±4.35	0.018*

BP, blood pressure; HFNC, high-flow nasal cannula; HR, heart rate; NIV, noninvasive ventilation; RR, respiratory rate. *Significant *P* value less than 0.05.

were nonsignificant. Meanwhile, after 48 h of intervention all parameters showed significant differences between both groups.

Baseline arterial blood gas parameters (Table 4) did not differ significantly between the two study groups at admission. One hour later, the PaCO2 was significantly lower in the HFNC (*P*=0.020). Follow-up parameters after 6 h showed significantly higher values for PaO2 and SaO2 and lower values for PaCO2 in the HFNC group.

Discussion

Invasive mechanical ventilation carries many complications [10]; therefore, safety considerations encouraged delivering respiratory support through noninvasive methods without the need for endotracheal intubation [11].

The application of NIV in hypoxemic ARF is still doubtful [12]. HFNC has been introduced as a possible alternative to NIV or standard oxygen therapy [13]. This new modality provides a high flow rate of heated humidified oxygen, which is expected to set up low levels of PEEP. This new technique of delivering oxygen is expected to minimize the work of breathing and to be more tolerable by patients [13,14].

The current study aimed to compare the outcomes of HFNC versus NIV for patients having ARF.

The predominant cause of ARF in our study was pneumonia (41%), followed by acute exacerbation of interstitial lung disease (40%). Comparable results were obtained by Güngör *et al.* [15], Aliberti *et al.* [16], Frat *et al.* [18], and Rangappa and Moran [17].

The current results showed that HFNC was associated with lower rates of in-hospital mortality, which agreed with the results of Frat *et al.* [18]. The HFNC group showed significantly lower rate of endotracheal intubation (*P*=0.001). This was concordant with Frat *et al.* [18] who did a post-hoc adjusted analysis, which involved only severe hypoxemic patients (PaO_2 : FiO_2 ≤200 mmHg) and found a significantly lower intubation rate in the group of patients who received oxygen at high flow than NIV and standard oxygen therapy groups.

Shen and Zhang [19] conducted a subgroup meta-analysis based on the PaO2/FiO2 levels, and found

Table 4 Baseline and follow-up arterial blood gas parameters of the study population

ABG	NIV (*N*=50) (mean±SD)	HFNC (*N*=50) (mean±SD)	*P* value
Room air			
pH	7.48±0.06	7.49±0.05	0.428
$PaCO_2$	29.32±6.91	27.38±4.52	0.100
PaO_2	48.30±14.06	51.28±12.94	0.273
HCO_3	19.56±4.89	18.58±3.23	0.240
SaO_2	82.50±9.69	83.36±10.08	0.665
After 1 h			
pH	7.47±0.06	7.49±0.04	0.119
$PaCO_2$	32.12±8.67	28.94±3.92	0.020*
PaO_2	73.98±14.05	78.62±12.35	0.083
HCO_3	21.10±5.98	20.16±3.06	0.325
SaO_2	94.58±2.91	95.04±4.49	0.544
After 6 h			
pH	7.46±0.05	7.48±0.04	0.235
PCO_2	32.98±7.66	30.21±4.37	0.031*
PO_2	76.76±17.36	83.29±14.23	0.045*
HCO_3	21.78±6.01	20.92±3.03	0.374
SaO_2	94.98±3.56	96.19±2.10	0.045*
After 24 h			
pH	7.46±0.05	7.46±0.03	0.785
$PaCO_2$	33.16±6.18	31.28±3.88	0.083
PaO_2	77.20±14.60	83.26±10.61	0.025*
HCO_3	22.33±5.40	21.32±2.65	0.252
SaO_2	95.16±2.62	97.45±2.08	0.010*
After 48 h			
pH	7.46±0.05	7.46±0.06	0.846
$PaCO_2$	34.21±6.06	33.40±4.08	0.462
PaO_2	73.38±16.80	85.80±11.44	0.000*
HCO_3	22.90±4.65	21.51±2.29	0.077
SaO_2	92.45±9.37	98.89±1.58	0.002*

ABG, arterial blood gas; HFNC, high-flow nasal cannula; NIV, noninvasive ventilation; PaO_2, partial pressure of oxygen in the blood; $PaCO_2$, partial pressure of carbon dioxide in the blood; SaO_2, arterial blood oxygen saturation measured by blood analysis. *Significant *P* value less than 0.05.

lower intubation rates in HFNC when compared with NIV in patients having low baseline PaO2/FiO2, while in patients having high baseline PaO2/FiO2, the comparison was insignificant.

To the contrary, Koga *et al.* [20] showed that the HFNC group had a higher rate of treatment failure in comparison to the NIV group (*P*=0.001), but the subgroup analyses revealed that failure of treatment in the HFNC group was noticed predominantly in cases with cardiogenic pulmonary edema due to lack of significant PEEP effect. They also reported that in pneumonia patients, the HFNC group had a reduced 30-day mortality rate in comparison to the NIV group (28% vs. 56%, *P*=0.001).

Considering patients' satisfaction and comfort, this study found that HFNC achieved the best subjective scores for dyspnea, discomfort, and patient preferences. These results agreed with the findings of Schwabbauer *et al.* [21].

Stéphan *et al.* [22] studied HFNC versus NIV in patients who developed hypoxemia postcardiothoracic surgery and found that the differences in comfort and dyspnea scores were insignificant between the NIV and HFNC groups.

In this study, the most common cause for escalation to mechanical ventilation was increased respiratory distress in both groups, followed by worsening hypoxemia; this was in line with Koga *et al.* [20].

Airway clearance is crucial especially in pneumonia patients. Excessive secretions pose a major risk factor for treatment failure in NIV as NIV interfaces interfere with sputum clearance. To the contrary, HFNC was declared to enhance airway clearance due to the presence of simple nasal prongs and humidified air [23]. In this study, 48.0% of patients were mechanically ventilated due to secretion retention. Therefore, in patients suffering from excessive secretion, HFNC is expected to be more favorable. NIV may create higher tidal volumes leading to ventilator-associated lung injury. HFNC oxygen therapy was declared to reduce the minute ventilation and work of breathing without a subsequent increase in the tidal volume,

possibly because a washout effect is exhibited on the upper airways. For these reasons, HFNC may be accompanied with decreased potential of aggravating lung injury caused by excessive expansion of the lungs in comparison to NIV, which may be the cause of lower mortality in the HFNC group [3].In the current study, HFNC has significantly lower ICU mortality agreeing with the results of The FLORALI study [18], Koga *et al.* [20], Coudroy *et al.* [24], and Shebl and Embarak [25].

The present study had several limitations. First, the sample size was relatively small. Second, we did not do a subanalysis at various stages of hypoxemia to address patient benefit from each of the two studied interventions.

Conclusion

Delivering oxygen by HFNC is a new and efficient option for early treatment of adults with ARF. The use of HFNC was accompanied with reduced rate of escalation to endotracheal intubation and decreased in-hospital mortality in comparison to NIV.

Acknowledgements

Criteria for inclusion in the authors'/contributors' list: Dr Gamal M.R. Agmy: conceptualization, study design, and revision of the manuscript. Dr Mohamed F. Adam: study design, and writing the initial manuscript. Dr Manal A. Mahmoud: conceptualization, study design, writing the initial and final manuscript, and data analysis. Dr Entsar H.M. Hsanen: data collection and data analysis.

The manuscript has been read and approved by all the authors; the requirements for authorship have been met; and each author believes that the manuscript represents honest work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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