Original Article

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TANAFFOS

The Effect of Intermittent Use of Oxygen Therapy via High-Flow Nasal Cannula Alternating with Noninvasive Ventilation on Critically Ill Patients

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Background: Despite limited research on high-flow nasal cannula (HFNC) alternating with noninvasive ventilation (NIV), this study investigates its effect on intensive care unit (ICU) patients.

Materials and Methods: This clinical trial study at Masih Deneshvari Hospital (Tehran) compared NIV vs. alternating NIV with HFNC for ICU patients. It assessed intubation, mortality, and vitals. Patients were informed, and nurses were trained for optimal care. Daily follow-up ensured data collection.

Results: The mean age of the patients was 66.3±19.7 years, which was 67.1±14.8 years in the NIV group and 65.5±14.9 years in the HFNC+NIV group, respectively. The distribution of patients in terms of APACHE and symptoms showed no significant difference (P=0.453). The mean HR in the two groups, NIV and HFNC+NIV, before the study was 113.30±5.25 and 112.43±5.80, respectively. At the end of the study, it was 94.78±17.53 and 94.48±17.47, respectively, with no significant difference found between the two groups. The mean RR before the beginning of this study was not significantly different between the two groups, while it was 16.61±4.23 and 17.91±1.78 in the NIV and HFNC+NIV groups, respectively, at the end of the study (P=0.043). PO_2 created a greater distinction between the two groups based on the decision tree analysis, where the NIV group was more likely to have values of PO_2<70.

Conclusion: Based on the findings presented in our study, no difference was found between the use of NIV and NIV + HFNC, but HFNC + NIV was a more tolerable technique for patients.

Keywords: High-flow nasal cannula; Noninvasive mechanical ventilation; Intensive Care Units

INTRODUCTION

The use of noninvasive mechanical ventilation (NIV) is the first line of ventilatory support in many lung diseases, such as chronic obstructive pulmonary disease (COPD) and cardiogenic pulmonary edema (1-3). On the other hand, there are contradictory results regarding the improvement of the oxygenation status of patients with hypoxemic respiratory failure (AHRF), and the probability of their intubation can increase by up to 60% (4, 5). Despite these concerns, studies showed that NIV can be the first

choice for ventilation of these patients, even in situations that exist in patients with acute respiratory distress syndrome (6-8).

The results of other research demonstrated that the use of NIV alone, patients' poor tolerance to this supportive ventilation, and the increase of patients' hypoxemia caused by the accumulation of CO_2 have led to their intubation in 5-25% of cases (9-11). It will also lead to oxygenation disorder and, finally, intubation in case of not tolerating NIV and replacing this method with standard oxygen therapy. For this reason, a suitable method of improving oxygenation and reducing CO_2 can produce positive results in the clinical process of patients. The use of moist oxygen with high flow through high-flow nasal cannulae (HFNC) can transfer heated humidified oxygen at the highest level via the nasal cannulae (6, 12). One of the most important benefits of this method is to create adequate humidity, mucociliary clearance of the airways, favorable release of FiO_2, and low positive pressure in the airways (13). Compared to conventional oxygen therapy methods, HFNC has been associated with greater patient comfort and has also been linked to improving oxygenation and reducing the need for intubation.

In addition to better oxygenation, a combination of the above two methods may improve the CO_2 level, leading to increased patient comfort and tolerance. Although there are few studies in this regard, HFNC did not lead to improved oxygenation in some cases as well (14). Therefore, the exact efficiency of this oxygen support method is still questionable.

The primary objective of this study is to assess the combined effect of intermittent HFNC and NIV on oxygenation and CO_2 clearance in critically ill patients. We hypothesize that the alternating use of these two modalities will result in improved oxygenation and CO_2 elimination compared to either method used alone. Additionally, we aim to investigate whether this combination can reduce the need for invasive intubation and enhance patient comfort and tolerance to ventilatory support. On the other hand, no comprehensive study has been conducted on the efficiency of this oxygenation method in patients with bronchiectasis. Therefore, we aimed to investigate the combined effect of these two methods on all types of patients who need ventilatory support.

MATERIALS AND METHODS

This clinical trial was conducted on patients admitted to the special care units of Masih Deneshvari Hospital in Tehran, Iran. Patients who met the inclusion and exclusion criteria were randomly included in the study. The inclusion criteria were as follows: all adult patients (aged 18 years and older) admitted to the ICU who required noninvasive ventilatory support for acute respiratory failure and who provided informed consent were considered eligible. Patients with COPD, ARDS, or hypoxemic respiratory failure were also eligible.

The exclusion criteria were: patients with known underlying malignancy, patients with end-stage renal disease (ESRD) requiring dialysis, those with significant pericardial effusion, previously diagnosed nasopharyngeal or airway obstructions, or patients who had undergone recent major upper airway surgery or had a contraindication to noninvasive ventilation.

The data, to estimate the sample size, was obtained from the study conducted by Yoo et al. (15). Based on the following formula, the required sample size in each study group was calculated to be 20 people, assuming a confidence factor of 0.05 and a study power of 90%.

$$n_1 = n_2 = \frac{(S_1^2 + S_2^2)(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2}{(\bar{X}_1 - \bar{X}_2)^2}$$

Procedure

First, patient information including demographic characteristics, etiology of admission to ICU, medical history of patients, hemodynamic indicators, were registered.

The outcomes considered for evaluation included the rate of intubation, mortality, SOFA score, APACHE score, length of stay (the number of hospital days) in the intensive care unit, blood hemoglobin, and vital signs. To avoid a loss of follow-up, an attempt was made to explain to the patient the full knowledge about this treatment method, the limitations, and the way the patient breathes using HFNO before starting the treatment. So, the nurses were also trained about the settings of the device and the humidity and temperature levels of this oxygen therapy

method, to provide more comfortable conditions. Also, follow-up was done only during the patient's hospitalization; patients were visited daily, and vital signs and tests were recorded.

Data analysis

The information of all quantitative variables was presented as mean and standard deviation, and qualitative variables were expressed as numbers (percentages). The normality of quantitative variables was investigated by the Kolmogorov-Smirnov test and box plots. To compare the parametric variables in the two groups, the t-test and, if necessary, the non-parametric Mann-Whitney U test were employed. To compare non-parametric variables in two groups, the Pearson chi-square test and Fisher's exact test were used if necessary. The data obtained from this study were analyzed using SPSS software version 21. A significant level of 5% was considered.

Ethical declarations

No additional costs were imposed on patients in conducting this study. Also, the questionnaires were anonymous, the information was considered confidential, and the results were published only in groups. The Helsinki ethical principles for medical research were observed. The study was approved by the Ethics Committee of Iran University of Medical Sciences (IR.SBMU.NRITLD.REC.1397.044). It was also approved in the registry of the clinical trial center (code: IRCT20150107020592N20).

RESULTS

A total of 46 patients were included in one of the two groups of NIV and NIV +HFN. The distribution of patients according to age, gender, and some other background variables was the same between groups. The mortality of the NIV and NIV+HFN groups was reported as 21.7% and 13%, respectively. Although this difference was not found to be statistically significant, it could indicate a better and relative performance of the NIV+HFN group compared to NIV. Furthermore, the results show that 14 and 12 patients in the NIV+HFN and NIV groups have EF above 45%, where no statistically significant difference was found between the two groups. Moreover, 2 patients of the NIV+HFN group were reported with symptoms of epistaxis, and 5 cases with complaints of heat (Table 1).

Table 1. Demographic variables analysis of the study groups

Variables	Group		Total	P-value
	NIV	NIV+HFN		
Gender (Male)	12(52.2)	15(65.2)	27(58.7)	0.369
Age(year)	67.1±14.8	65.5±14.9	66.3±19.7	0.708
APACHE (<15)	10(52.6)	14(66.7)	24(52.2)	0.453
BMI(kg/m^2)	17.9±7.7	20.3±2.6	19.1±5.8	0.170
<18.5	12(52.2)	8(34.8)	20(43.5)	-
18.5-24.9	9(39.1)	14(60.9)	23(50.0)	
25-28.9	1(4.3)	1(4.3)	2(4.3)	
>29	1(4.3)	0(0.0)	1(2.2)	
Hb	10.2±2.5	10.1±2.2	10.2±2.3	0.886
Plt	222.3±57.3	233.4±57.9	227.8±57.2	0.517
LEVF	41.6±6.2	43.3±4.6	42.5±5.4	0.299
SPAP	33.1±8.5	34.6±4.9	33.8±6.9	0.463
Symptom				
Fever(yes)	21(91.3)	21(91.3)	42(91.3)	1.000
DOE(yes)	0(0.0)	0(0.0)	0(0.0)	-
Cough(yes)	23(100.0)	23(100.0)	46(100.0)	-
Sputum(yes)	22(95.7)	21(91.3)	43(93.5)	1.000
IOC(yes)	2(8.7)	1(4.3)	3(6.5)	1.000
Hemoptysis(yes)	4(17.4)	6(26.1)	10(21.7)	0.722
Outcome				
Intubation(yes)	6(26.1)	5(21.7)	11(23.9)	0.729
Reintubation(yes)	4(17.4)	2(8.7)	6(13.0)	0.875
IOS(yes)	1(4.3)	0(0.0)	1(2.2)	1.000
Mortality(yes)	5(21.7)	3(13.0)	8(17.4)	0.699
Sputum(+)	4(17.4)	2(8.7)	6(13.0)	0.621
Smear(+)	7(30.4)	9(39.1)	16(34.8)	0.757
SPAP(<25mmHg)	1(4.3)	0(0.0)	1(2.2)	0.235
CXR(Non-Normal)	21(91.5)	22(95.7)	43(93.5)	0.550

Table 2 shows the comparison results of the two groups in terms of HR and RR indicators before and after the study. The mean HR and RR in both groups have changed significantly over time, and this change has decreased in both groups. There was no statistically significant difference between the two groups regarding mean HR. We found that the mean RR over time was higher in the NIV+HFN group than in the NIV group. Figure 1 shows the changes in HR and RR in two groups over time.

Figure 2 compares the confidence intervals of FIO2, temperature, and flow variables in two groups. The mean difference of these variables was not found to be statistically significant (P>0.05).

Figure 3 shows the distribution of patients according to chest results, showing the same distribution pattern in the two groups.

Table 3 shows the comparison results of the two groups regarding the IVC index before and after the study. No statistically significant difference was found between the two groups in terms of IVC changes. The mean in the NIV+HFN group remained stable over time, while it increased in the NIV group.

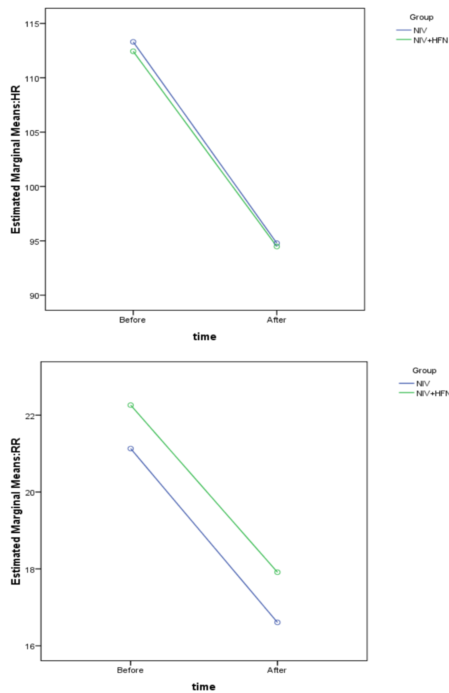
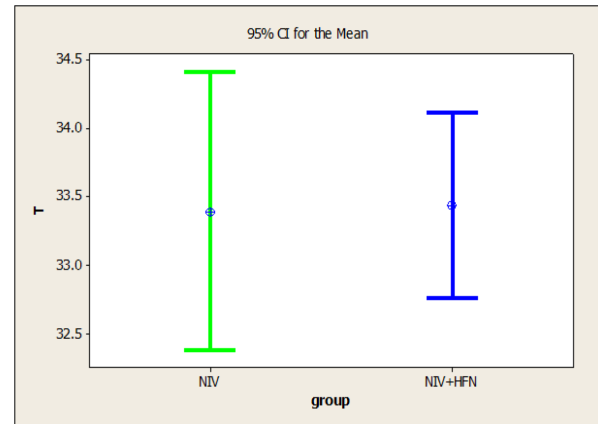
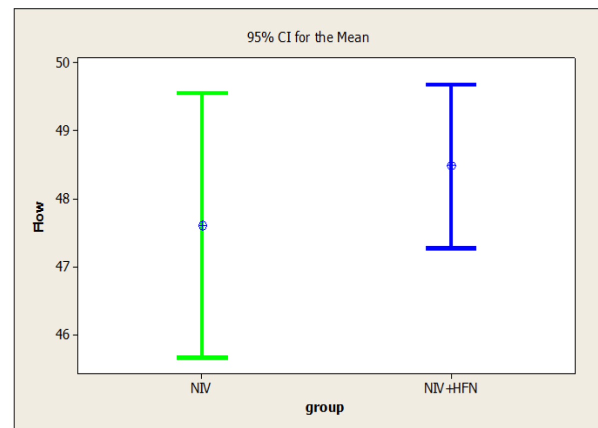


Figure 1. Changes in mean HR and RR before and after the study in two groups





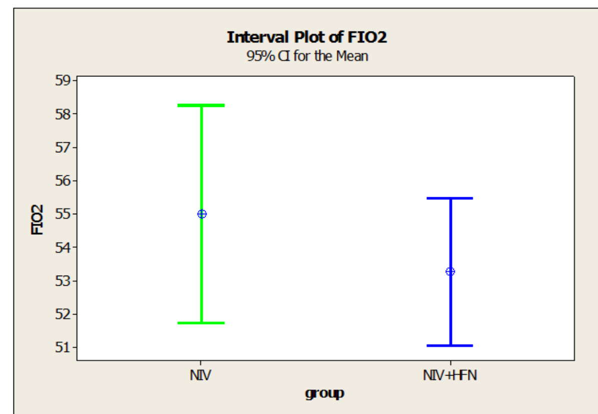


Figure 2. Flow confidence interval, temperature (T), and FIO_2 in two groups

Repeated measures analysis was performed to examine changes and compare clinical indicators between the two groups over time, as shown in Table 4. Although the means of PH, PO_2, PCO_2, HCO_3, and PF variables have changed significantly in general, the change of means

between the two groups was not found to be statistically significant.

Figure 4 shows the changes of PH, PO_2, PCO_2, HCO_3, and PF over time in the two groups, where the pattern of changes in these variables was almost the same in the two groups.

Decision tree analysis was performed to categorize patients based on the most important and effective variable among the variables of PH, PO_2, PCO_2, HCO_3, and PF. It was found that PO_2 creates a greater distinction between the two groups, where the NIV group was more likely to have values of PO_2<70 (Figure 5).

Table 2. Comparison of average RR and HR over time between the two groups

Item	Group	Before	After	Mauchly's Test of Sphericity	P-value Time	P-value Group
HR	NIV	113.30±5.25	94.78±17.53	1.00	0.001*	0.835
	NIV+HFN	112.43±5.80	94.48±17.47			
	Total	112.87±5.49	94.63±17.30			
RR	NIV	21.13±3.36	16.61±4.23	0.07	<0.001*	0.043*
	NIV+HFN	22.26±1.71	17.91±1.78			
	Total	21.70±2.69	17.26±3.3			

*: Significant at the 0.05 level.

Table 3. Comparison of the average IVC over time between the two groups

Item	Group	Before	After	Mauchly's Test of Sphericity	P-value Time	P-value Group
	NIV	12.09±0.90	12.48±1.23			
IVC	NIV+HFN	12.43±0.84	12.43±1.27	0.109	0.396	0.498
	Total	12.26±0.88	12.46±1.24			

Table 4. Repeated measures analysis to investigate the effect of treatment time and method on the investigated indicators

Item	Group	Before	12 Hr	24 Hr	48 Hr	72 Hr	Mauchly's Test of Sphericity	P-value (Time)	P-value (Group)
	NIV	7.35±0.04	7.36±0.05	7.37±0.05	7.37±0.05	7.38±0.05			
PH	NIV+HFN	7.34±0.04	7.36±0.04	7.38±0.04	7.38±0.05	7.39±0.05	0.059	<0.001*	0.584
	Total	7.34±0.04	7.36±0.05	7.37±0.05	7.38±0.05	7.38±0.04			
	NIV	60.41±11.7	55.1±11.6	50.66±9.6	48.97±8.3	47.42±8.1			
PCO_2	NIV+HFN	63.40±12.8	54.25±8.8	50.26±8.8	47.63±6.2	46.8±6.7	0.147	<0.001*	0.989
	Total	62.20±12.2	54.64±10.2	50.45±9.1	48.29±7.2	47.1±7.4			
	NIV	70.22±5.9	68.91±5.2	71.44±6.7	76.22±5.9	72.88±8.0			
PO_2	NIV+HFN	70.45±7.2	75.88±5.3	73.36±7.8	75.63±5.6	72.90±7.4	0.691	0.019*	0.249
	Total	70.35±6.5	72.70±6.2	72.5±7.23	75.90±5.6	72.90±7.9			
	NIV	29.38±4.4	29.08+4.0	27.76+3.9	26.76+3.6	26.05+1.5			
HCO_3	NIV+HFN	30.17+4.2	29.46+4.3	27.76+3.6	26.84+2.9	26.28+1.8	0.090	<0.001*	0.756
	Total	29.78+4.1	29.27+4.1	27.76+3.7	26.80+2.9	26.16+1.4			
	NIV	2.45+1.89	2.42+1.48	2.51+1.97	2.46+0.91	2.50+2.06			
PF	NIV+HFN	2.40+2.27	2.49+1.67	2.54+1.54	2.47+1.17	2.57+2.15	0.114	0.018*	0.239
	Total	2.43+2.08	2.45+1.60	2.52+1.75	2.47+1.04	2.59+2.12			

*: Significant at the 0.05 level.

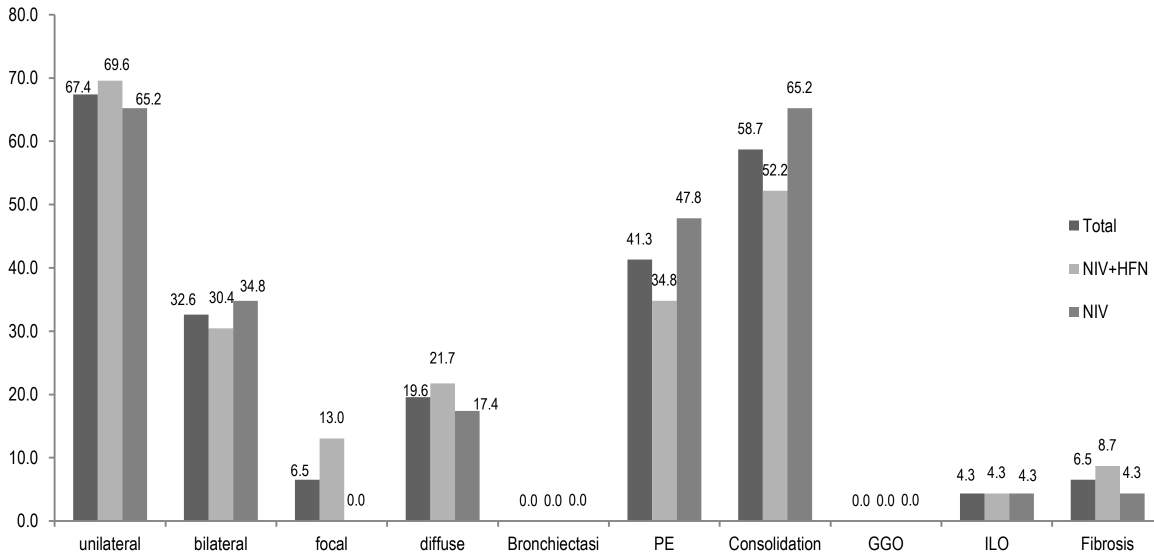


Figure 3. Distribution of patients according to chest results in two groups

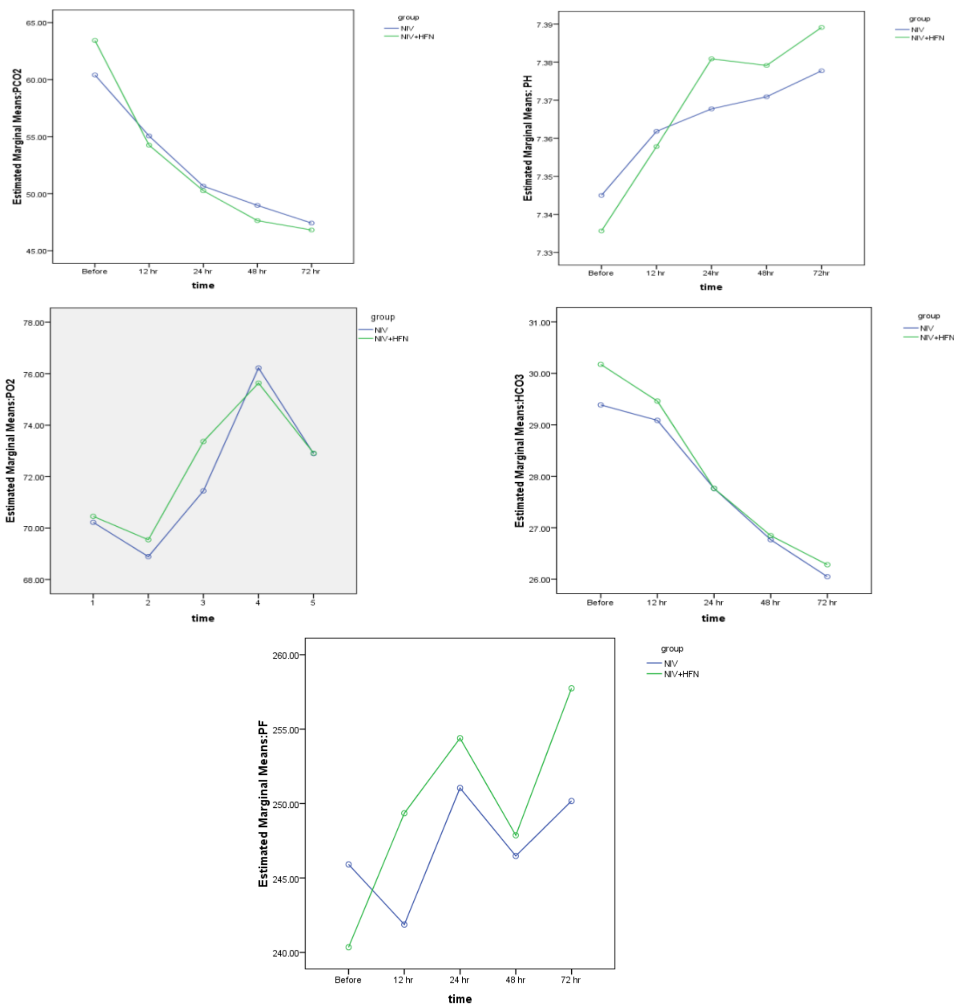


Figure 4. Changes in PH, PO_2, PCO_2, HCO_3, and PF over time in two groups

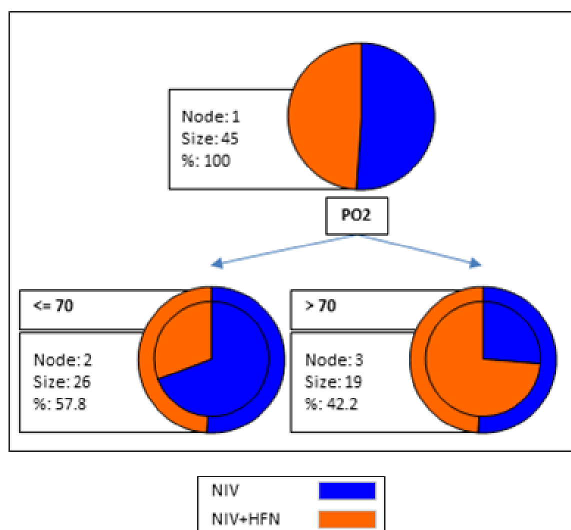


Figure 5. Decision tree of differentiation between two groups based on PO_2

DISCUSSION

Managing patients admitted to the ICU is crucial, especially regarding ensuring adequate oxygenation (16) and reducing the need for invasive procedures like intubation (17,18). The appropriate treatment protocol significantly impacts the treatment process in patients admitted to the intensive care unit. Proper ventilatory support can also be related to better oxygenation, reducing intubation needs, and reducing stay in the ICU (19). This study aimed to evaluate the efficacy of HFNC alternating with NIV in ICU patients to determine whether this combined approach could lead to better outcomes compared to using NIV alone.

In this study, 58.7% of patients were male. The mean age of the patients was 66.3±19.7 years, which was 67.1±14.8 and 65.5±14.9 years in both NIV and HFNC+NIV groups, respectively. The distribution of patients in terms of APACHE and symptoms was found to be the same, so 52.6% and 66.7% of patients in both groups had APACHE < 15 (P=0.453). Additionally, the incidence of Fever, DOE, Cough, Sputum, IOC, and Hemoptysis was the same in both groups, where no statistically significant difference was found.

The mortality rate in the NIV group was 21.7%, while in the NIV+HFNC group, it was 13%. Although this difference was not statistically significant (P=0.699), it suggests a possible clinical benefit for the NIV+HFNC group. Additionally, the rate of intubation and reintubation in both groups was similar, with 26.1% and 17.4% in the NIV group, and 21.7% and 8.7% in the NIV+HFNC group, respectively. Moreover, both groups' mean heart rate (HR) significantly improved. In the NIV group, HR decreased from 113.30±5.25 to 94.78±17.53, and in the NIV+HFNC group, from 112.43±5.80 to 94.48±17.47. There was no statistically significant difference between the two groups regarding HR (P=0.835). The respiratory rate (RR) also decreased significantly in both groups. Still, the NIV+HFNC group showed a higher RR than the NIV group at the end of the study (P=0.043), indicating that HFNC might offer better control of respiratory function. Decision tree analysis showed that PO_2 was the most significant variable distinguishing between the two groups, with the NIV group more likely to have PO_2 levels <70, indicating worse oxygenation status than the NIV+HFNC group.

Regarding other clinical indicators, such as ejection fraction (EF) and inferior vena cava (IVC) index, no statistically significant differences were found between the two groups. However, the IVC index remained stable over time in the NIV+HFNC group and increased in the NIV group. There were also no significant differences in the mean FIO_2, temperature, or flow between the two groups, although these variables tended to be slightly higher in the NIV group. Notably, 2 patients in the NIV+HFNC group experienced epistaxis, and 5 reported feeling hot, which were minor side effects associated with HFNC use.

The results of our study align with previous research by Liesching and Lei, which found no significant difference in oxygenation, intubation rates, or mortality between patients treated with HFNC and those treated with NIV. However, our findings suggest that alternating HFNC with NIV may offer some clinical benefits, as seen in the trend toward lower mortality in the NIV+HFNC group (20). Similarly, Yoo et al. conducted a study on 73 patients with post-extubation respiratory failure (PERF). Of these, 34 underwent HFNC, and 39 underwent NIV (66.7% vs. 79.4%). There was no significant difference in reintubation rates between HFNC and NIV. However, the shorter ICU stay in the HFNC group suggests its potential as a more effective treatment for improving patient outcomes (15).

Our heart and respiratory rate findings are also consistent with those of Simon et al. (21). Their study compared the clinical results of two non-invasive ventilation techniques, NIV and HFNC, in 40 patients with acute hypoxaemic respiratory failure undergoing flexible bronchoscopy. The results showed that oxygen levels were significantly higher in the group receiving HFNC than in NIV. In contrast, the patients who received NIV had a significantly lower PCO_2 level. The results showed no significant difference in patients' heart rate, mean arterial pressure, and respiratory rate in the two groups. Based on their results, they found that HFNC was associated with better oxygenation, while NIV was more effective in reducing CO_2 retention. Another study assessed the efficacy of sequential oxygen therapy through HFNC alternating with noninvasive (NIV in AHRF). A total of 28 patients with AHRF and 23 patients with ARDS were evaluated. The results showed that PaO_2 increased from 83 mm Hg to 108 mm Hg using HFNC and to 125 mm Hg using NIV compared with standard oxygen, while breathing frequency was found to decrease significantly. Moreover, HFNC was significantly better tolerated by patients than NIV. From the study's results, it can be concluded that non-invasive ventilation has significantly improved the patient's clinical conditions. Among the two mentioned methods, HFNC was a more tolerable technique for patients, allowing for remarkable improvement in oxygenation and tachypnea (22).

This study offers valuable insights into the efficacy of alternating HFNC with NIV compared to using NIV alone in ICU patients. One of its key strengths is its comparative design, which directly evaluates the combined approach versus NIV alone, addressing critical aspects of ventilatory support in a high-risk population. The study's detailed analysis of various clinical parameters, including mortality rates, intubation rates, heart rate, respiratory rate, and oxygenation levels, enhances the comprehensiveness of the findings. Moreover, aligning the study's results with previous research strengthened its validity and contributed to the choice of appropriate treatment strategies. However, there are notable limitations. Despite observing trends, the differences in key outcomes, such as mortality rates between the groups, were not statistically significant, indicating that the study may need more power to detect smaller, clinically relevant differences. The study focuses on short-term outcomes and does not address long-term effects, leaving a gap in understanding the overall impact of the treatment strategies beyond the ICU stay. Lastly, although the study controlled for several variables, potential unmeasured confounding factors could influence the outcomes. Future research should address these limitations to provide a more comprehensive evaluation of HFNC and NIV strategies.

CONCLUSION

This study suggests that alternating HFNC with NIV may offer some clinical benefits compared to using NIV alone, including improved oxygenation and potentially reduced mortality. However, the differences observed were not statistically significant. The decrease in mortality and improvement in vital signs in the NIV+HFNC group, along with results from similar previous studies, highlight the potential of this approach to enhance patient outcomes in the ICU. While these findings are promising, further research with larger populations is needed to confirm these results. Combining HFNC with NIV is a viable option for improving clinical outcomes in ICU patients.

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