Tocilizumab Therapy in Critically Ill Patients with Coronavirus Disease-2019 Pneumonia. A Propensity Score-adjusted Analysis

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Abstract

BACKGROUND: Extubation failure of patients on mechanical ventilation is relatively a frequent finding in the intensive care unit (ICU) and associated with poor prognosis.

AIM: We conducted this study in Critical Care Department, Cairo University hospitals in which we aimed to assess if there is advantage to use high flow nasal cannula (HFNC) or non-invasive ventilation (NIV) over conventional oxygen therapy (COT) in success of extubation of patients.

METHODS: The study included 60 patients and was randomized into three equal groups. The first group used HFNC, the second group used COT, while the third group used NIV. The reintubation rate, ICU stay, ICU mortality, and 28-day mortality were followed in all groups.

RESULTS: The all study population had a mean age of 62 ± 21, 31 patients were male, and 21 patients were smokers. SOFA score on admission, APACHE II, and SOFA pre-extubation was not significantly different in the three groups. Reintubation rate was higher in COT group compared to HFNC or NIV groups (p < 0.05). ICU stay was longer in COT compared to the other two groups, while ICU and 28-day mortality showed no significant difference among the all groups.

CONCLUSION: Use of HFNC and NIV was associated with lower reintubation rate, improved oxygenation and shorter ICU stay but no significant effect on mortality in comparison with COT.

Introduction

Prolonged intubation and mechanical ventilation were associated with a higher complications rate, such as ventilator-associated pneumonia (VAP) and higher fatality [1].

Extrusion lowers the risk for VAP, removes the work of breathing caused by intubation, and increases patient satisfaction [2]. However, after this procedure, functional residual capacity which was kept by positive end-expiratory pressure (PEEP) might decrease rapidly, leading to hypoxemia and failure of extrusion, defined as the need for re-intubation within 24–72h after a planned extubation, with rates of 10–20% [3], [4], [5]. It is associated with an increase in the duration of artificial ventilation, an increased demand for tracheostomy, more economic costs, and a higher fatality [5], [6], [7].

Conventional oxygen therapy (COT) is the main oxygenation modality given to patients after extubation. The maximal oxygen flow rate delivered by COT is only 15 L/min, which is far lower than the needs of post-extubation patients with acute respiratory failure [8]. Therefore, the fraction of inspired oxygen (FiO2) is significantly reduced in the alveoli and it is hard to meet the requirements of heating and humidification [9].

Non-invasive positive-pressure ventilation provides many techniques for increasing alveolar ventilation without an endotracheal tube which could be used post-extubation [10].

High-flow nasal cannula (HFNC) can give a mixture of air and oxygen through a heated and humidified circuit at a very high flow. It can provide almost pure oxygen with a FiO2 of approximately 100% and a maximal flow rate up to 60 L/min [8]. The use of a HFNC may generate a positive airway pressure, improve oxygenation and dyspnea, reduce the
respiratory rate and work of breathing, and increase comfort [8], [11], [12], [13], [14], [15], [16], [17].

However, the benefit of HFNC therapy after planned extubation still inconclusive. Some studies demonstrate that HFNC after extubation may decrease the need for escalation of the respiratory support, result in better oxygenation [18], [19], and be associated with increase patient comfort and a lower re-intubation rate [13].

**Aim of work**

The aim of the study was to assess the benefits of HFNC for patients after planned extubation by observing post-extubation respiratory failure and short term hospital outcomes compared to COT and non-invasive ventilation (NIV).

**Patients and Methods**

This is a single-center, interventional, randomized, and controlled trial that was conducted on 60 patients admitted to the Critical Care Department, Cairo University hospitals, who were intubated and mechanically ventilated (Figure 1).

The study took place from November 2020 to June 2021. Informed written consents were taken from all patients first degree relatives. Approval from the Local Ethics Committee was obtained [MS-313-2019] and registered on Clinicaltrials.gov (NCT04441736).

**Inclusion criteria**

The following criteria were included in the study:
1. Intubated and mechanically ventilated patients due to Type I or Type II respiratory failure and planned for extubation
2. Age between 18 and 80 years.

**Exclusion criteria**

The following criteria were excluded from the study:
1. Patients who are not fit for extubation
2. Patients with tracheostomy
3. Reintubation due to causes other than respiratory deterioration.

Include patients were evaluated for the following:
1. Full medical history and clinical examination
2. Routine Laboratory investigations and chest X-ray
3. Arterial Blood gases
4. APACHE II score on admission

**Weaning protocol**

The weaning protocol included daily screening for weaning according to the following criteria:

- Recovery from the precipitating illness for MV
- Respiratory criteria (PaO$_2$/FiO$_2$ ratio >150 mm Hg with FiO$_2$ ≤0.4, PEEP <8 cm H$_2$O, and arterial pH >7.35)
- Clinical criteria (no vasoactive drugs or only low doses of vasopressors, heart rate <100/min, hemoglobin >8 g/dL, temperature <38°C, no need for sedatives, and ability to protect air way).

Patients fulfilling these criteria received a spontaneous breathing trial with either T-tube or 8 cm H$_2$O of pressure support for 30–120 min [20].

The patients were randomized into three groups where the first 20 patients have received oxygen therapy through HFNC, the second 20 patients have received oxygen therapy through conventional methods (COT) like oxygen mask or nasal prongs, and the third group of 20 patients have received oxygen therapy through NIV.

**Interventions**

HFNC (Airvo 2, Fisher and Paykel Co., New Zealand) was applied immediately after extubation through nasal cannula. Flow will be initially set at 60 L/min and will be titrated downward in 5 L/min steps until patients experience discomfort. Temperature was initially set to 37°C, and FiO$_2$ was regularly adjusted to target peripheral capillary oxygen saturation (SpO$_2$) >92%. After 24 h, high-flow therapy was gradually weaned and, if necessary, patients received COT.

COT was applied continuously through nasal cannula or oxygen facemask or non-rebreather facemask, and oxygen flow was adjusted to maintain SpO$_2$ >92%.
NIV was applied directly after extubation through a CPAP mask, pressure support was adjusted initially at 8 cmH\textsubscript{2}O, PEEP 5 cmH\textsubscript{2}O, and FiO\textsubscript{2} 100\% that was decreased gradually to achieve SO\textsubscript{2} more than 92\%.

**Primary outcomes**

Exhustion failure defined as the need for reinitiation of ventilatory support within 24–72 h of planned endotracheal tube removal [21].

**Secondary outcomes**

1. ICU stay
2. ICU mortality
3. 28-day mortality.

**Indications of reintubation included in this study [22]**

1. Hypoxemia despite oxygen supply modality in the form of PO\textsubscript{2}<200 on FiO\textsubscript{2} 100\%
2. Respiratory rate >40 or <6.

**Statistical analysis**

Data were coded and entered using the Statistical Package for the Social Sciences version 26 (IBM Corp., Armonk, NY, USA). Data were summarized using mean, standard deviation in quantitative data, and using frequency and percentage for categorical data. Comparisons between quantitative variables were done using the non-parametric Mann–Whitney test. For comparing categorical data, Chi-square test was performed. Correlations between quantitative variables were done using Spearman correlation coefficient. p < 0.05 was considered as statistically significant.

**Results**

This study included 60 patients divided as 20 patients in each group (HFNC, COT, and NIV groups).

**Demographic data**

The three groups had no statistically significant differences regarding demographic and clinical data (p > 0.05), which means that the three groups were matched, as shown in Table 1.

### Table 1: General characteristics, assessment scores, and comorbidities of the study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>HFNC (n = 20)</th>
<th>COT (n = 20)</th>
<th>NIV (n = 20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>General characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>61 ± 17</td>
<td>65 ± 21</td>
<td>60 ± 20</td>
<td>0.654</td>
</tr>
<tr>
<td>Male Freq. (%)</td>
<td>13 (85)</td>
<td>9 (45)</td>
<td>10 (50)</td>
<td>0.519</td>
</tr>
<tr>
<td>BMI (kg/m\textsuperscript{2})</td>
<td>28.5 ± 6</td>
<td>29.8 ± 6</td>
<td>28.7 ± 4</td>
<td>0.769</td>
</tr>
<tr>
<td>Smokers</td>
<td>6 (30)</td>
<td>5 (25)</td>
<td>10 (50)</td>
<td>0.318</td>
</tr>
<tr>
<td>Assessment scores</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOFA on admission</td>
<td>4.9 ± 2</td>
<td>4 ± 2</td>
<td>4.2 ± 1</td>
<td>0.59</td>
</tr>
<tr>
<td>SOFA pre-extubation</td>
<td>3.6 ± 2</td>
<td>3.3 ± 2</td>
<td>3.1 ± 0.9</td>
<td>0.742</td>
</tr>
<tr>
<td>APACHE</td>
<td>17.3 ± 5</td>
<td>16 ± 5</td>
<td>18.2 ± 6</td>
<td>0.357</td>
</tr>
<tr>
<td>Comorbidities Freq. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>8 (40)</td>
<td>6 (30)</td>
<td>9 (45)</td>
<td>0.713</td>
</tr>
<tr>
<td>HTN</td>
<td>10 (50)</td>
<td>13 (65)</td>
<td>13 (65)</td>
<td>0.672</td>
</tr>
<tr>
<td>HF</td>
<td>1 (5)</td>
<td>1 (5)</td>
<td>3 (15)</td>
<td>0.603</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>9 (45)</td>
<td>3 (15)</td>
<td>6 (30)</td>
<td>0.135</td>
</tr>
<tr>
<td>COPD</td>
<td>4 (20)</td>
<td>5 (25)</td>
<td>1 (5)</td>
<td>0.305</td>
</tr>
<tr>
<td>Intubation data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>16 (80)</td>
<td>15 (75)</td>
<td>18 (90)</td>
<td>0.729</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>2 (10)</td>
<td>3 (15)</td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>ARDS</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>COPD exacerbation</td>
<td>1 (5)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Duration of intubation (days)</td>
<td>4.7 ± 3</td>
<td>6.9 ± 3.1</td>
<td>5 ± 3</td>
<td>0.068</td>
</tr>
<tr>
<td>Laboratory investigations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L\textsubscript{O}2 (ml/min/m\textsuperscript{2})</td>
<td>13.3 ± 7</td>
<td>12.8 ± 6</td>
<td>14.2 ± 6</td>
<td>0.833</td>
</tr>
<tr>
<td>Creat. (mg/dl)</td>
<td>2.7 ± 2</td>
<td>1.9 ± 2</td>
<td>2.3 ± 1</td>
<td>0.342</td>
</tr>
<tr>
<td>Urea (mg/dl)</td>
<td>51 ± 12</td>
<td>58 ± 52</td>
<td>50.8 ± 46</td>
<td>0.152</td>
</tr>
</tbody>
</table>


### Lung mechanics before extubation (Table 2 and Figure 2).

<table>
<thead>
<tr>
<th>Lung mechanics</th>
<th>HFNC (n = 20)</th>
<th>COT (n = 20)</th>
<th>NIV (n = 20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak pressure (cmH\textsubscript{2}O)</td>
<td>24.1 ± 3</td>
<td>23.5 ± 5</td>
<td>24.5 ± 3</td>
<td>0.321</td>
</tr>
<tr>
<td>Plateau pressure (cmH\textsubscript{2}O)</td>
<td>16.8 ± 2</td>
<td>16.9 ± 3</td>
<td>17.5 ± 3</td>
<td>0.77</td>
</tr>
<tr>
<td>Compliance (ml/cmH\textsubscript{2}O)</td>
<td>72 ± 6</td>
<td>73 ± 11</td>
<td>72.6 ± 13</td>
<td>0.668</td>
</tr>
</tbody>
</table>


**Respiratory rate (RR)**

RR was compared among the three groups on four occasions as shown in Table 3 and Figure 3.

1. On admission: RR was significantly higher in HFNC and NIV (p = 0.001)
2. 1-h post-extubation: RR was of no statistically significant difference. (p = 0.176)
3. 24-h post-extubation: RR was of no statistically significant difference. (p = 0.166)
4. 72-h post-extubation: RR was significantly higher in COT group in comparison with other two groups (p = 0.002).

### Table 3: Respiratory rate in the studied population

<table>
<thead>
<tr>
<th>Respiratory rate</th>
<th>HFNC Mean ± SD</th>
<th>COT Mean ± SD</th>
<th>NIV Mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>On admission</td>
<td>33.5 ± 4</td>
<td>27.9 ± 6.6</td>
<td>35.8 ± 4</td>
<td>0.001</td>
</tr>
<tr>
<td>1-h after extubation</td>
<td>21.4 ± 3.4</td>
<td>22.8 ± 3.9</td>
<td>20.5 ± 4</td>
<td>0.176</td>
</tr>
<tr>
<td>24-h after extubation</td>
<td>20.5 ± 4</td>
<td>23.6 ± 6</td>
<td>20.23 ± 5</td>
<td>0.169</td>
</tr>
<tr>
<td>72-h after extubation</td>
<td>23.1 ± 4</td>
<td>26.4 ± 5.6</td>
<td>20.25 ± 5</td>
<td>0.002</td>
</tr>
</tbody>
</table>

HFNC: High flow nasal canula, COT: Conventional oxygen therapy, NIV: Non-invasive ventilation, p1 HFNC to COT, p2 NIV to COT, p3 HFNC to NIV.
**PO\_FiO\_2 ratio**

P/F ratio was higher significantly in HFNC all the time post-extubation up to 72 h and in NIV 1-h and 27-h post-extubation when compared to COT after extubation and of p < 0.05 (Table 4 and Figure 4).

### Table 4: P/F ratio of the studied patients (n = 60)

<table>
<thead>
<tr>
<th>P/F ratio</th>
<th>HFNC (n = 20) Mean ± SD</th>
<th>COT (n = 20) Mean ± SD</th>
<th>NIV (n = 20) Mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>On admission</td>
<td>158 ± 35</td>
<td>147 ± 63</td>
<td>175 ± 18</td>
<td>0.007</td>
</tr>
<tr>
<td>Pre-extubation</td>
<td>285 ± 55</td>
<td>233 ± 52</td>
<td>264 ± 71</td>
<td>0.008</td>
</tr>
<tr>
<td>1-h Post-extubation</td>
<td>260 ± 64</td>
<td>197 ± 62</td>
<td>251 ± 84</td>
<td>0.054</td>
</tr>
<tr>
<td>24-h post-extubation</td>
<td>268 ± 56</td>
<td>204 ± 77</td>
<td>241 ± 67</td>
<td>0.006</td>
</tr>
<tr>
<td>72-h post-extubation</td>
<td>279 ± 52</td>
<td>226 ± 41</td>
<td>298 ± 21</td>
<td>0.001</td>
</tr>
</tbody>
</table>

HFNC: High flow nasal canula, COT: Conventional oxygen therapy, NIV: Non-invasive ventilation. p1 HFNC to COT, p2 NIV to COT, p3 HFNC to NIV.

**Arterial blood gases (ABG)**

The three groups had no statistically significant differences ABG parameters (p > 0.05), except for

1. Pre-extubation: SaO\_2 was higher in COT group (p = 0.028)
2. 72-h post-extubation: PaO\_2 and PCO\_2 were lower in COT group (p = 0.04 and 0.046), respectively (Table 5 and Figure 5).

### Table 5: ABGs of the studied patients (n = 60)

<table>
<thead>
<tr>
<th>ABGs</th>
<th>HFNC (n = 20) Mean ± SD</th>
<th>COT (n = 20) Mean ± SD</th>
<th>NIV (n = 20) Mean ± SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-extubation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCO_2 (mmHg)</td>
<td>34.8 ± 5</td>
<td>37.2 ± 8</td>
<td>36.6 ± 2</td>
<td>0.688</td>
</tr>
<tr>
<td>PO_2 (mmHg)</td>
<td>94.8 ± 18</td>
<td>92.6 ± 24</td>
<td>83.3 ± 9</td>
<td>0.125</td>
</tr>
<tr>
<td>SaO_2</td>
<td>94.6 ± 18</td>
<td>97.7 ± 2.4</td>
<td>96.9 ± 2</td>
<td>0.028*</td>
</tr>
<tr>
<td>1-h Post-extubation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.42 ± 0</td>
<td>7.44 ± 0.1</td>
<td>7.38 ± 0.1</td>
<td>0.02*</td>
</tr>
<tr>
<td>PCO_2 (mmHg)</td>
<td>35.7 ± 4</td>
<td>37.8 ± 11</td>
<td>36.9 ± 5</td>
<td>0.916</td>
</tr>
<tr>
<td>PO_2 (mmHg)</td>
<td>78.9 ± 7</td>
<td>90 ± 50</td>
<td>77 ± 8</td>
<td>0.134</td>
</tr>
<tr>
<td>SaO_2</td>
<td>95.1 ± 2</td>
<td>95.2 ± 3</td>
<td>94.2 ± 2</td>
<td>0.213</td>
</tr>
<tr>
<td>24-h post-extubation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.4 ± 0.1</td>
<td>7.4 ± 0.1</td>
<td>7.4 ± 0</td>
<td>0.073</td>
</tr>
<tr>
<td>PCO_2 (mmHg)</td>
<td>36.7 ± 3</td>
<td>39 ± 11</td>
<td>35.8 ± 3</td>
<td>0.52</td>
</tr>
<tr>
<td>PO_2 (mmHg)</td>
<td>80.9 ± 16</td>
<td>78 ± 24</td>
<td>77 ± 7</td>
<td>0.4</td>
</tr>
<tr>
<td>SaO_2</td>
<td>95.9 ± 2</td>
<td>94.9 ± 4</td>
<td>96 ± 3</td>
<td>0.546</td>
</tr>
<tr>
<td>72 h post-extubation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.42 ± 0.1</td>
<td>7.46 ± 0.1</td>
<td>7.37 ± 0.2</td>
<td>0.266</td>
</tr>
<tr>
<td>PCO_2 (mmHg)</td>
<td>36.7 ± 3</td>
<td>30.8 ± 11</td>
<td>37.8 ± 3</td>
<td>0.04*</td>
</tr>
<tr>
<td>PO_2 (mmHg)</td>
<td>82.3 ± 16</td>
<td>72 ± 24</td>
<td>85 ± 6</td>
<td></td>
</tr>
<tr>
<td>SaO_2</td>
<td>96</td>
<td>93.9 ± 5</td>
<td>95 ± 3</td>
<td>0.152</td>
</tr>
</tbody>
</table>

HFNC: High flow nasal canula, COT: Conventional oxygen therapy, NIV: Non-invasive ventilation. p1 HFNC to COT, p2 NIV to COT, p3 HFNC to NIV.

**Extubation failure (reintubation)**

The reintubation rate was significantly higher in the COT group (50%) in comparison with HFNC (20%) and NIV (20%) groups (p = 0.046 for both).

**ICU stay and outcome**

COT group demonstrated significant longer ICU stay when compared to HFNC group and NIV group (p = 0.075 and 0.01, respectively) as shown in Table 6.

### Table 6: ICU stay and mortality data of the studied patients (n = 60)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HFNC (n = 20)</th>
<th>COT (n = 20)</th>
<th>NIV (n = 20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reintubation rate (%)</td>
<td>4 (20%)</td>
<td>10 (50%)</td>
<td>4 (20%)</td>
<td>0.046</td>
</tr>
<tr>
<td>ICU stay in days (Mean ± SD)</td>
<td>8.7 ± 4</td>
<td>12 ± 7</td>
<td>7.4 ± 3</td>
<td>0.004</td>
</tr>
<tr>
<td>ICU mortality (Freq%)</td>
<td>5 (25)</td>
<td>5 (25)</td>
<td>4 (20)</td>
<td>0.919</td>
</tr>
<tr>
<td>28-day mortality (Freq%)</td>
<td>4 (20)</td>
<td>9 (45)</td>
<td>4 (20)</td>
<td>0.164</td>
</tr>
</tbody>
</table>

HFNC: High flow nasal canula, COT: Conventional oxygen therapy, NIV: Non-invasive ventilation. p1 HFNC to COT, p2 NIV to COT, p3 HFNC to NIV.

ICU mortality and 28-days mortality data showed no significant difference among the three groups (p = 0.91 and 0.16, respectively).

**Figure 2: Pre-extubation lung mechanics comparison in the three groups**

**Discussion**

Extubation failure, which is often defined as the need for reintubation within 24–72h after extubation, is frequent, with rates of 10–20% [3], [4], [5] associated with an increase in the duration of artificial ventilation, a higher trend for tracheostomy, more economic costs, and an increased fatality [5], [6], [7].
Figure 3: Respiratory rate trend in study population

This study was conducted on 60 patients divided into three sequential groups. The first group received oxygen therapy through HFNC, the second group received COT, and the third group received oxygen therapy through non-invasive ventilation (NIV).

Figure 4: P/F ratio trend in study population

Respiratory rate

Our study showed that RR was significantly lower in the HFNC and NIV compared to COT 72 h after extubation with p = 0.002, while there was no statistically significant difference between the three groups in RR 1 h and 24 h after extubation.

This might be explained by the high flow which can reach up to 60 L/min in HFNC and NIV compared to maximum of 15 L in COT. The high flow can correct hypoxemia, hence decreasing respiratory rate [23].

Figure 5: PCO₂ trend in study population

In agreement with our study, Nassar et al. [24] in 2017 found that there was significantly lower RR (18.03 ± 2.11 vs. 22.65 ± 3.52, p = 0.001) in NIV versus COT, respectively, 12 h and (17.65 ± 2.33 vs. 20.65 ± 2.22, p = 0.001) in NIV versus COT, respectively, 24 h after extubation.

Furthermore, Rittayamai et al. [14] found a significant improvement in RR in HFNC group compared to COT with (p = 0.009).

On the other hand, Tiruvoipati et al. [25] demonstrated no difference in RR in the group receiving HFNC than the group receiving COT with mean RR of (18.7 vs. 19.6). However, Tiruvoipati et al. [25] had a different methodology as he compared the groups after only 30 min of treatment. Furthermore, many other studies failed to get significant difference in RR between NIV and COT groups [26], [27], [28].

Post extubation gas exchange

We demonstrated that the P/F ratio was significantly higher in HFNC group and NIV group when compared with COT 1-h, 24-h, and 72-h (p = 0.008, 0.004, and 0.006) respectively, after extubation which is most probably due to the PEEP effect generated by the high flow from HFNC and the PEEP effect in the NIV.

Furthermore, Groves and Tobin [29] in 2007 found that the high flow generated by HFNC creates positive pressure that helps in alveolar recruitment.

We also demonstrated that PaCO₂ was significantly lower in COT group when compared to HFNC and NIV group 72-h after extubation (p = 0.046). This might be explained by the increased RR in COT as mentioned above.

In agreement to our study, Nassar et al. [24] in 2017 showed a significant advantage for the use of NIV over COT in improving oxygenation in which PO₂ was higher after 2 h (80.3 ± 9.6 vs. 71.3 ± 11.6, p = 0.041), after 6 h (79.6 ± 9.7 vs. 71.9 ± 11.6, p = 0.011) and after 24 h (77.8 ± 15.5 vs. 70.1 ± 12.9, p = 0.012) in NIV group versus COT, respectively.

On the other hand, Hernández et al. [30] showed no significant differences in P/F ratio and PaCO₂ between HFNC and COT which can be explained by that in Hernández et al. study only one reading of ABG was taken 12 h after extubation which did not give treatment enough time to make a significant difference.

Hernández et al. [31] showed no significant difference between NIV and HFNC in gas exchange in which the P/F ratio and PaCO₂ were almost the same.

Reintubation rate

Reintubation rate was higher in COT group (50%) compared with HFNC (20%) and NIV group (20%) (p < 0.05).

Hernández et al. [30] in 2016 demonstrated that there was significant advantage for HFNC over...
COT where 13 patients (4.9%) received HFNC versus 32 patients (12.2%) received COT group needed reintubation.

Hernández et al. in 2016 [31] showed that HFNC was not inferior to NIV in extubation failure where 50 patients (15.9%) and 49 patients (16.9%) in NIV and HFNC groups, respectively, needed reintubation.

Ornico et al. [27] compared in 2013 NIV and COT after planned extubation and found that NIV had positive impact on decreasing rate of reintubation where only one patient (5%) in NIV group needed reintubation compared to 7 patients (39%) in the COT group.

Mohamed et al. [26] in 2013 compared COT to NIV post-extubation and found significant advantage for NIV over COT where 9 patients (15%) receiving NIV needed reintubation compared to 15 patients (25%) receiving COT (p = 0.049).

On the other hand, Corley et al. in 2015 [28] found no advantage for HFNC over COT post-extubation, this difference is most likely because Corley et al. study was done on patients with BMI >30 kg/m² post-cardiac surgery while our study was conducted on patients with mean BMI 28.9 kg/m² who were originally intubated due to acute respiratory failure caused by different medical causes.

In 2017 Nassar et al. [24] compared NIV to HFNC in medical and cardiac surgery patients and found a non-significant trend toward decreased reintubation rate in NIV group, 8 patients (20%) versus 12 patients (30%) in HFNC and COT, respectively (p > 0.05).

ICU stay

Our study showed that the use of HFNC or NIV post-extubation decreased ICU stay as the mean ICU stay for the COT was 12 ± 7 days compared to mean ICU stay in NIV of 7.4 ± 3 days and 8.7 ± 4 days in HFNC group (p < 0.05).

In agreement with our study, Hernández et al. [31] in 2016 showed that there was no significant difference in the length of ICU stay between HFNC and NIV 3 days versus 4 days, respectively (p > 0.05).

Mohamed et al. [26] in 2013 found a significant advantage for NIV over COT where the ICU length of stay was 8.3 ± 3.1 days in NIV group and 11.6 ± 2.6 days in COT groups (p < 0.035).

On the other hand, Hernández et al. [30] in 2016 showed no significant advantage for the use of HFNC over COT regarding the ICU length of stay. The mean ICU stay was 6 days in both HFNC and COT group (p > 0.05), this difference is most likely because Hernández et al. conducted his study in low-risk patients with APACHE II score not exceeding 12 while our study was conducted on a study population with mean APACHE II 17.6.

Corley et al. in 2015 [28] showed that there was no advantage for use of HFNC over COT regarding ICU length of stay with mean stay (38.65 h vs. 38.63 h) (p > 0.05). This discrepancy in results may be due to different study population as mentioned above.

Ornico et al. [27] in 2013 showed that the length of stay was not different between the groups, with a mean of 16.8 ± 11.6 days in the NIV group and 18.4 ± 12.2 days in the COT group (p > 0.05).

Nassar et al. [24] in 2017 found no significant differences in ICU length of stay but found a trend toward shorter ICU stay in NIV group.

Mortality

Our study demonstrated a non-significant trend toward decreased 28-day mortality in HFNC group and NIV group when compared to use of COT, four patients in each one of HFNC and NIV groups and nine patients in COT group died within 28 days (p > 0.05).

In agreement with our study, Nassar et al. [24] showed a trend toward decreasing mortality rate in NIV group, 8 (20%) versus 9 (22.5%) patients, but without statistical significance.

In 2016, Hernández et al. [31] showed no difference in mortality between HFNC group and NIV group with 19 versus 18 ICU mortality in HFNC and NIV groups, respectively (p > 0.05).

Hernández et al. [31] found no difference in mortality between the HFNC group and COT group which as mentioned above possibly because it was conducted on very low-risk patients.

On the other hand, Esteban et al. [32] in 2004 reported higher mortality in patients receiving NIV 28 patients (25%) compared to 15 patients (14%) receiving COT (p < 0.05), this difference is most likely due to different methodology. In our study, the patients received NIV directly after extubation while Esteban et al. waited for the patients to develop respiratory failure first to have NIV applied. This discrepancy in results could be because the loss of PEEP effect generated by mechanical ventilation, hence increasing risk of atelectasis and increasing the incidence of extubation failure.

Mohamed et al. [26] showed a significant decrease in mortality in patients receiving NIV post-extubation compared to COT with 4 (6.6%) deaths in NIV group and 10 (16.6%) deaths (p = 0.047).

Ornico’s study [27] in (2013) showed a significantly lower mortality rate in NIV group (no deaths) versus 4 (22.2%) in OM group with p = 0.04, apparently in a relatively small sample size (38 patients).
Conclusion

Use of HFNC and NIV was associated with lower reintubation rate, improved oxygenation, and shorter ICU stay but no significant effect on mortality in comparison with COT.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Farouk Mohamed, Yasser Nassar, Farouk Mostafa, and Walid Omar. The first draft of the manuscript was written by Walid Omar and Farouk Mostafa and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of college of medicine, Cairo university (MS-313-2019) and registered on Clinicaltrials.gov (NCT04441736).

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