Effect of high-flow nasal cannula versus conventional oxygen therapy and non-invasive ventilation for preventing reintubation: a Bayesian network meta-analysis and systematic review

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Background: Adequate respiratory support can improve clinical outcomes in patients who are ready for weaning from a ventilator. We aimed to investigate the efficacy of respiratory methods in adults undergoing planned extubation using a Bayesian network meta-analysis.

Methods: We searched PubMed, Embase, and ClinicalTrials.gov for unpublished and ongoing trials up to November 2019 for randomized controlled trials (RCTs) published in English that compared conventional oxygen therapy (COT), a high-flow nasal cannula (HFNC), and noninvasive ventilation (NIV) for post-extubation respiratory support. Screening of citations, study selection, data extraction, and assessment of risk were performed independently by two authors. The primary outcome was the reintubation rate.

Results: Twenty-two studies (4,218 patients) were included in our meta-analysis. Extubated patients supported with NIV had a significantly lower incidence of reintubation than those supported with COT [odds ratio (OR): 0.63, 95% confidence interval (CI): 0.42, 0.89]. However, there was no significant difference in the reintubation rate between the HFNC and NIV, and HFNC and COT groups (OR: 1.05, 95% CI: 0.60, 1.81; OR: 0.60, 95% CI: 0.33, 1.02, respectively). HFNC and NIV reduced the incidence of hospital-acquired pneumonia (HAP) (OR: 0.50, 95% CI: 0.25, 0.93; OR: 0.55, 95% CI: 0.27, 0.87, respectively) and post-extubation acute respiratory failure (ARF) (OR: 0.35, 95% CI: 0.14, 0.89; OR: 0.31, 95% CI: 0.14, 0.63, respectively) compared with COT. There was no significant difference in a decreased incidence of HAP (OR: 1.1, 95% CI: 0.56, 1.8) or post-extubation ARF (OR: 0.87, 95% CI: 0.33, 2.1) between NIV and HFNC. There were also no significant differences in improvements in other clinical outcomes, including intensive care unit (ICU) and hospital mortality and the length of stay (LOS) between NIV and HFNC.

Conclusions: NIV reduces the reintubation rate in adult patients undergoing planned extubation compared with COT and HFNC.

Keywords: Reintubation; noninvasive ventilation (NIV); high-flow nasal cannula (HFNC); conventional oxygen therapy (COT); meta-analysis

Submitted Feb 26, 2020. Accepted for publication Jun 04, 2020.
doi: 10.21037/jtd-20-1050
View this article at: http://dx.doi.org/10.21037/jtd-20-1050
Introduction

Mechanical ventilation (MV) is a lifesaving treatment for patients with acute respiratory failure (ARF). However, delayed MV weaning in patients who are ready for extubation is associated with complications, such as pneumonia, and thus has a negative effect on patients’ outcomes (1). That said patients who successfully pass a spontaneous breathing trial may develop ARF after extubation and require reintubation, which is associated with higher mortality and a poorer prognosis (2,3).

Guidelines recommend that preventive non-invasive ventilation should be applied in patients who are considered to be at high risk of extubation failure, with moderate-grade evidence (4). However, a recent meta-analysis showed that this strategy failed to decrease ARF after extubation in the general critically ill population compared with conventional oxygen therapy (COT) (5). Notably, intolerance to noninvasive ventilation (NIV) is also common, and can worsen the patient’s outcome (6-9).

A high-flow nasal cannula (HFNC) is a novel device that can provide fully humidified, high-flow oxygen (up to 60 L/min), a constant fraction of inspiratory oxygen, and flow-dependent continuous positive airway pressure (10-12). HFNCs improve patients’ outcomes after extubation compared with COT (13-16). However, only 44% of physicians who completed a recent survey considered HFNC as potentially relevant for improving outcomes in extubated patients (17).

HFNC and NIV can provide adequate respiratory support after extubation. However, only two randomized controlled trials (RCTs) (18,19) and one retrospective study (20) directly compared the effectiveness of these two strategies. Both of these trials showed that HFNC was not inferior to NIV in the selected populations. Therefore, the optimal respiratory support strategy after extubation remains controversial.

We performed a network meta-analysis that involved a combination of direct and indirect estimates of effects to evaluate the roles of HFNC, NIV, and COT in the post-extubation period.

Methods

This study adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension statement for reporting network meta-analyses (PRISMA-NMA) (21).
for dichotomous outcomes. Medians and interquartile ranges were converted to means and standard deviations using a previously published method (23).

The network meta-analysis was performed using the package “gemtc” (version 0.8-2) in R (version 3.4.4, The R Foundation for Statistical Computing). This package is based on an approach that follows the graph-theoretical methodology. We ranked the treatments using the P-score to represent the degree of certainty that a specific treatment was better than the other treatments. A P-score close to 1 indicated that the treatment was certain to be the best and a score close to 0 indicated that the treatment was certain to be the worst. The value of $I^2 \geq 50\%$ would be considered substantial heterogeneity. Trial sequential analysis (TSA) was conducted with TSA version 0.9.5.10 to limit the possibility of type I error.

Results

Literature search

We identified 2,344 citations, of which 47 were considered potentially eligible after reviewing the full-text articles. We finally included 22 studies with 4,218 patients (Figure 1).

Of the 22 eligible trials, four compared HFNC with COT, 15 compared NIV with COT, and three compared NIV with HFNC (Table 1). The trial sample sizes ranged from 38 to 830 patients. The RoB was high in 10 trials and low in 12 trials (Figures 2,3).

Clinical outcomes

Reintubation rate

Twenty-two eligible articles (4,218 patients)
Table 1 Characteristics of individual studies included in the network meta-analysis

| Study and published year | Settings | Participants | Interventions | Reintubation rate | Other key outcomes |
|-------------------------|----------|--------------|---------------|-------------------|--------------------|
| Jiang et al. (24), 1999 | Single-center ICU | N=93 | COT: N=46; NIV: N=47 | COT: 7 (15.20%); NIV: 13 (27.66%) | NA |
| Keenan et al. (25), 2002 | Single-center ICU | N=81 | COT: N=42; NIV: N=39 | COT: 29 (69%); NIV: 28 (72%) | HAP, ICU-stay, hospital-stay, ICU-mortality, hospital-mortality |
| Esteban et al. (26), 2004 | 37 ICU centers | N=221 | COT: N=107; NIV: N=114 | COT: 51 (48%); NIV: 55 (48%) | ARF, ICU-stay, ICU-mortality |
| Kindgen-Milles et al. (27), 2005 | Single-center ICU in Germany | N=50 | COT: N=25; NIV: N=25 | COT: 4 (16%); NIV: 1 (4%) | ARF, HAP, ICU-stay, hospital-stay, ICU-mortality, hospital-mortality |
| Nava et al. (28), 2005 | 3 ICU centers in Italy | N=97 | COT: N=49; NIV: N=48 | COT: 12 (24%); NIV: 4 (8%) | ICU-stay, hospital-stay, ICU-mortality |
| Ferrer et al. (29), 2009 | 3 ICU centers in Spain | N=106 | COT: N=52; NIV: N=54 | COT: 10 (19.2%); NIV: 6 (11.1%) | ARF, HAP, ICU-stay, hospital-stay, ICU-mortality, hospital-mortality |
| Girault et al. (30), 2011 | 13 ICU centers in France, Tunisian | N=139 | COT: N=70; NIV: N=69 | COT: 26 (37%); NIV: 22 (32%) | ARF, HAP, ICU-stay, ICU-mortality, hospital-mortality |
| Khilnani et al. (31), 2011 | Single-center ICU in India | N=40 | COT: N=20; NIV: N=20 | COT: 5 (25%); NIV: 3 (15%) | ICU-stay, hospital-stay |
| Cekmen et al. (32), Single-center ICU in Turkey 2011 | N=40 | COT: N=20; NIV: N=20 | COT: 5 (25%); NIV: 3 (15%) | NA |
| Su et al. (33), 2012 | 3 ICU centers in Taiwan, China | N=406 | COT: N=204; NIV: N=202 | COT: 16 (7.7%); NIV: 21 (10.4%) | ARF, ICU-mortality |
| Al Jaaly et al. (34), 2013 | Single-center ICU in England | N=126 | COT: N=63; NIV: N=63 | COT: 2 (3.2%); NIV: 1 (1.6%) | ARF, HAP, ICU-stay, hospital-stay, ICU-mortality, hospital-mortality |
| Mohamed et al. (35), 2013 | Single-center ICU in Saudi Arabia | N=120 | COT: N=60; NIV: N=60 | COT: 15 (25%); NIV: 9 (15%) | ICU-stay, ICU-mortality |
| Ormico et al. (36), 2013 | Single-center ICU in Brazil | N=38 | COT: N=18; NIV: N=20 | COT: 7 (39%); NIV: 1 (5%) | ICU-stay, hospital-mortality |
| Maggiore et al. (15), 2014 | 2 ICU centers in Italy | N=105 | COT: N=52; HFNC: N=53 | COT: 16 (30.8%); HFNC: 6 (11.3%) | ARF, ICU-stay, hospital-mortality |
| Stéphan et al. (18), 2015 | 6 ICU centers in France | N=830 | HFNC: N=414; NIV: N=416 | HFNC: 87 (21%); NIV: 91 (21.8%) | ARF, HAP, ICU-stay, hospital-stay, ICU-mortality |
| Hernández et al. (19), 2016 | 3 ICU centers in Spain | N=604 | HFNC: N=290; NIV: N=314 | HFNC: 66 (22.8%); NIV: 60 (19.1%) | ARF, HAP, ICU-stay, hospital-stay, ICU-mortality, hospital-mortality |
| Futier et al. (37), 2016 | 3 ICU centers in France | N=220 | COT: N=112; HFNC: N=108 | COT: 7 (6.3%); HFNC: 4 (3.7%) | ARF, HAP, ICU-stay, hospital-stay, hospital-mortality |
| Hernández et al. (16), 2016 | 7 ICU centers in Spain | N=527 | COT: N=263; HFNC: N=264 | COT: 32 (12.2%); HFNC: 13 (4.9%) | ARF, HAP, ICU-stay, hospital-stay, ICU-mortality, hospital-mortality |
| Song et al. (38), 2017 | Single-center ICU in China | N=60 | COT: N=30; HFNC: N=30 | COT: 3 (10%); HFNC: 1 (3.3%) | NA |
| Vargas et al. (39), 2017 | 6 ICU centers in France | N=144 | COT: N=72; NIV: N=71 | COT: 13 (18.1%); NIV: 6 (8.5%) | ARF, ICU-stay, ICU-mortality |
| Vaschetto et al. (40), 2019 | 9 ICU centers in China, Italy | N=130 | COT: N=65; NIV: N=65 | COT: 7 (10.7%); NIV: 3 (4.6%) | ARF, HAP, ICU-stay, hospital-stay, ICU-mortality, hospital-mortality |
| Jing et al. (41), 2019 | Single-center ICU in China | N=42 | HFNC: N=22; NIV: N=20 | HFNC: 2 (9.0%); NIV: 1 (5.0%) | ARF, ICU-stay, hospital-mortality |

HAP, hospital-acquired pneumonia; ARF, acute respiratory failure; ICU, intensive care unit; NIV, noninvasive ventilation; COT, conventional oxygen therapy; HFNC, high-flow nasal cannula.
(15,16,18,24-41) reported the reintubation rate. The network geometry is shown in Figure 4. Extubated patients who were supported with NIV had a significantly lower incidence of reintubation than patients who were supported with COT [OR: 0.63, 95% confidence interval (CI): 0.42, 0.89] (Figure 5). However, there was no significant difference in the reintubation rate between HFNC and NIV (OR: 1.05, 95% CI: 0.60, 1.81) (Figure 5). Bayesian analysis identified COT as the worst respiratory support method for potentially increasing the incidence of reintubation, while NIV was ranked second and HFNC as third worst among these three strategies. There was no significant difference in reintubation between NIV and HFNC, and between HFNC and COT in pooled estimates in the network meta-analysis (Table 2, Figure 6). Among the 22 included articles, four (983 patients) (19,28,30,39) focused on patients at high risk for reintubation. The network meta-analysis in this subpopulation showed no significant difference in the risk for reintubation among the three strategies (HFNC vs. COT: OR: 0.63, 95% CI: 0.11, 3.1; NIV vs. COT: OR: 0.49, 95% CI: 0.18, 1.2; NIV vs. HFNC: OR: 0.80, 95% CI: 0.19, 3.2) (Figure 5).

Secondary outcomes

We divided the included trials into low- and high-bias studies. Analysis of 12 low-bias trials (3,043 patients) (15,16,18,19,25,26,29,30,36,37,40,41) showed that patients who were supported with NIV had a significantly lower...
incidence of reintubation than patients who were supported with COT. However, there was no significant difference in the reintubation rate between NIV and HFNC, and between HFNC and COT. However, 10 trials with high bias (24,27,28,31-35,38,39) showed no benefit of HFNC or NIV for reducing the reintubation rate compared with COT, and there was no significant difference in the reintubation rate between HFNC and NIV (Figure 7).

We also carried out subgroup analysis according to receiving surgery. Of the 22 included trials, four (1,226 patients) (18,27,34,37) focused on surgery patients and the other 18 (2,992 patients) (15,16,19,24-26,28-33,35,36,38-41) focused on non-surgery patients. There was no significant difference in the reintubation rate in the surgery subgroup among the three strategies. However, HFNC or NIV reduced the reintubation rate compared with COT among the non-surgery subgroup, and there was no significant difference between NIV and HFNC (Figure 8). Of the 22 eligible trials, 10 (2,813 patients) (16,18,19,25,27,29,30,34,37,41) reported the incidence of post-extubation HAP. HFNC and NIV reduced the incidence of HAP compared with COT, with no significant difference between

Figure 5 Forest plot of included trials and trials focusing on high-risk patients. High-risk patients for reintubation were defined as patients who fulfilled at least one of the following criteria: (I) age >65 years; (II) APACHE II score >12 on the extubation day; (III) inability to cope with respiratory secretions; (IV) patients with difficult weaning or prolonged MV made the first attempt to disconnect the ventilator; (V) two or more comorbidities; (VI) heart failure as the main indication for MV; (VII) moderate to severe chronic obstructive pulmonary disease; (VIII) airway patency problems, including a high risk of developing throat edema; and (IX) MV for >7 days. MV, mechanical ventilation; NIV, noninvasive ventilation; COT, conventional oxygen therapy; HFNC, high-flow nasal cannula.

Table 2 Pooled estimates of the network meta-analysis

| Relative effects | COT          | HFNC | NIV          |
|------------------|--------------|------|--------------|
| COT              | –            | 0.60 (0.33, 1.02) | 0.63 (0.42, 0.89) |
| HFNC             | 1.66 (0.98, 3.02) | –    | 1.05 (0.60, 1.81) |
| NIV              | 0.95 (0.55, 1.67) | 1.58 (1.13, 2.40) | –    |

Results are ORs in the column-defining treatment compared with ORs in the row-defining treatment. For efficacy, ORs >1 favored the column-defining treatment. OR, odds ratio; NIV, noninvasive ventilation; COT, conventional oxygen therapy; HFNC, high-flow nasal cannula.

Figure 6 Ranking of treatments in terms of reintubation. NIV, noninvasive ventilation; COT, conventional oxygen therapy; HFNC, high-flow nasal cannula.
NIV and HFNC (Figure 9). Fourteen trials (3,649 patients) (15,16,18,19,26,27,29,30,33,34,37,39-41) reported the incidence of post-extubation ARF, and we found that HFNC or NIV reduced the incidence of ARF compared with COT, with no significant difference between NIV and HFNC (Figure 9). A total of 14 trials (3,580 patients) (16,18,19,25-30,33-35,39,41) reported ICU mortality and 12 (2,168 patients) (15,16,19,25,27,29,30,34,36,37,40,41) reported hospital mortality. There was no significant difference in either form of mortality among the three strategies (Figure 9). Eighteen trials (3,619 patients) (15,16,18,19,25-31,34-37,39-41) reported ICU LOS and 11 (2,811 patients) (16,18,19,25,27-29,31,34,37,41) reported hospital LOS. Similarly, there was no significant difference in these LOSs among the three strategies (Figure 10).

**Discussion**

This network meta-analysis compared three post-extubation respiratory support methods (HFNC, NIV, and COT) in 22 RCTs (4,218 patients). NIV reduced the reintubation rate compared with COT overall and in low bias trials. However, neither HFNC nor NIV showed any benefit in terms of preventing reintubation in high-risk patients and surgery patients. Additionally, HFNC and NIV had similar effects on reducing the incidence of post-extubation ARF and HAP compared with COT. None of the strategies decreased ICU or hospital mortality or shortened the ICU or hospital LOS. However, our research was unable to draw a conclusion regarding the superiority of HFNC or NIV in terms of all of the clinical outcomes.
ICU clinicians must wean and extubate patients as expeditiously as possible. Failure to wean patients from MV is often characterized by an imbalance between respiratory muscle capacity and the respiratory load confronted by those muscles. This imbalance might be caused by factors, such as increased breathing work, the effects of intrinsic positive end-expiratory pressure, and abnormal gas exchange. NIV reduces the work of breathing, provides respiratory muscle unloading, improves alveolar ventilation, and increases oxygenation. Therefore, preventive NIV can theoretically benefit extubated patients (42). However, interestingly, a recent international survey showed significant variation in the use of NIV for weaning and peri-extubation across regions (43). This finding suggests that only some physicians consider NIV to be effective during the post-extubation period. However, HFNC, which has been proposed for adult ARF (44), is widely used for post-extubation respiratory support. However, the results of a recent survey showed that less than half of all physicians, both senior and junior, considered that HFNC would benefit extubated patients (17). The current analysis showed that NIV and HFNC should be used for post-extubation respiratory support, and that HFNC was significantly better tolerated than NIV (45). However, in our study, only NIV benefited extubated patients and there was insufficient evidence to prove that HFNC is good
Figure 11 Plot of TSA for the effect of HFNC, COT, and NIV for preventing reintubation. (A) TSA for HFNC vs. COT; (B) TSA for NIV vs. COT; and (C) TSA for NIV vs. HFNC. TSA, trial sequential analysis; NIV, noninvasive ventilation; COT, conventional oxygen therapy; HFNC, high-flow nasal cannula.

for patients. Therefore, HFNC requires further study. Furthermore, HFNC was not mentioned in the ATS/ACCP clinical practice guidelines for weaning (4). We consider that HFNC is probably more useful for acute hypoxemic respiratory failure than hypercapnic respiratory failure and the reverse is probably true for NIV. However, our study did not have sufficient data to prove this possibility.

Surprisingly, we found that HFNC and NIV failed to reduce the reintubation rate compared with COT in high-risk patients. This finding is in contrast to two previous meta-analyses, including general and high-risk patients, which concluded that early use of NIV decreased the reintubation rate. However, patients at high-risk of reintubation only accounted for 35% of the total weight in the meta-analyses in these studies, and the ORs and 95% CIs in both meta-analyses were not significant (5,46). The current study evaluated the efficacies of HFNC and NIV in reducing the reintubation rate compared with COT in high-risk patients using data from four articles (983 patients) (19,28,32,41). Only one study with a relatively
small sample size showed that NIV was more effective than COT (28). Two studies could not preclude the possibility that such patients could benefit from NIV compared with COT (30,39), and a large study showed that HFNC was not inferior to NIV for preventing reintubation (19). However, these studies showed that NIV may improve weaning results in these patients by reducing the risk of post-extubation ARF. From this point of view, HFNC could also be used in such a population.

Our study showed that the efficacy of HFNC and NIV in reducing the reintubation rate was most obvious in non-surgery patients. Although Nava et al. provided a moderate level of evidence (grade 2) to support the use of NIV for postoperative ARF (47), other studies showed that it failed in approximately 20% of patients after cardiothoracic surgery (48,49). This could be explained by the fact that two eligible trials (27,34) in patients who had surgery compared NIV with COT and one compared HFNC with NIV (18), but no trial directly compared HFNC with COT.

Finally, we found that NIV decreased the reintubation rate in the general ICU population, but they both (NIV and HFNC) decrease HAP and post-extubation ARF. However, our study failed to show that HFNC and NIV could improve other clinical outcomes, such as ICU and hospital mortality, and ICU and hospital LOS. Furthermore, because both HFNC and NIV had similar effects in this study, the effect of combining these two methods may be of interest. A recent multicenter RCT addressed this issue (50). This trial showed that HFNC plus NIV applied immediately after extubation significantly decreased the risks of reintubation and post-extubation ARF in patients with MV at high risk of extubation failure compared with HFNC alone. This result might provide further insight into selection of post-extubation respiratory support methods.

Although this is the first network meta-analysis on this issue and the first to study heterogeneous populations of critically ill patients, there are several limitations of this study. First, we limited the included studies to full-text English publications because we assumed that non-English reports would not provide sufficient methodological or outcome data. Second, among 22 eligible trials, only four compared HFNC with COT and three compared HFNC with NIV. There were relatively few studies on HFNC compared with NIV, which may have caused overestimation of the intervention effect, and the quality of evidence should possibly be rated down. Third, we did not include the duration of NIV, HFNC, conventional oxygen, and this would have caused bias. Finally, limited statistical power was present in evaluation of the outcome, and this was confirmed through TSA. This limited statistical power needs to be taken into account in the overall scientific interpretation.

**Conclusions**

NIV reduces the reintubation rate in adult patients undergoing planned extubation compared with COT and HFNC. Further research is required to evaluate the benefits of the combination of NIV plus HFNC.

**Acknowledgments**

*Funding:* The study was funded by the National Science and Technology Major Project (No. 2017ZX10204401), National Natural Science Foundation of China (81970071 and 81870069) and the Natural Science Foundation of Guangdong Province, China (No. 2020A1515011459).

**Footnote**

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at [http://dx.doi.org/10.21037/jtd-20-1050](http://dx.doi.org/10.21037/jtd-20-1050)). The authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Sang L, Nong L, Zheng Y, Xu Y, Chen S, Zhang Y, Huang Y, Liu X, Li Y. Effect of high-flow nasal cannula versus conventional oxygen therapy and non-invasive ventilation for preventing reintubation: a Bayesian network meta-analysis and systematic review. J Thorac Dis 2020;12(7):3725-3736. doi: 10.21037/jtd-20-1050