

Effect of high-flow nasal cannula oxygen therapy in adults with acute hypoxemic respiratory failure: a meta-analysis of randomized controlled trials

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ABSTRACT

BACKGROUND: Conflicting recommendations exist on whether high-flow nasal cannula (HFNC) oxygen therapy should be administered to adult patients in critical care with acute hypoxemic respiratory failure. We performed a meta-analysis of randomized controlled trials (RCTs) to evaluate its effect on intubation rates.

METHODS: We searched electronic databases from inception to April 2016. We included RCTs that compared HFNC oxygen therapy with usual care (conventional oxygen therapy or noninvasive ventilation) in adults with acute hypoxemic respiratory failure. Because of the different

methodologies and variation in clinical outcomes, we conducted 2 subgroup analyses according to oxygen therapy used and disease severity. We pooled data using random-effects models. The primary outcome was the proportion of patients who required endotracheal intubation.

RESULTS: We included 6 RCTs ($n = 1892$). Compared with conventional oxygen therapy, HFNC oxygen therapy was associated with a lower intubation rate (risk ratio [RR] 0.60, 95% confidence interval [CI] 0.38 to 0.94; $P = 49\%$). We found no significant difference in the rate between HFNC oxygen therapy and noninvasive ventilation (RR

0.86, 95% CI 0.68 to 1.09; $I^2 = 2\%$). In the subgroup analysis by disease severity, no significant differences were found in the intubation rate between HFNC oxygen therapy and either conventional oxygen therapy or noninvasive ventilation (interaction $p = 0.3$ and 0.4 , respectively).

INTERPRETATION: The intubation rate with HFNC oxygen therapy was lower than the rate with conventional oxygen therapy and similar to the rate with noninvasive ventilation among patients with acute hypoxemic respiratory failure. Larger, high-quality RCTs are needed to confirm these findings.

Acute respiratory failure is common in the intensive care unit (ICU), often requiring endotracheal intubation. For patients with acute hypoxemic respiratory failure who require intubation, mechanical ventilation is usually needed, which is associated with high mortality.¹ Preventing acute respiratory failure and endotracheal intubation is therefore important. Oxygen therapy is used to correct hypoxemia and to alleviate breathlessness and removal of the endotracheal tube,² but knowing which form of oxygen therapy to choose is unclear.

Noninvasive ventilation is often used to avoid reintubation and improve outcomes.^{3,4} However, results of studies of its effectiveness in the prevention of intubation and improvement of outcomes of patients with acute respiratory failure have been conflicting.⁵⁻¹² Several observational studies showed that noninvasive ventilation was unsuccessful in as many as half of patients with acute respiratory failure⁸⁻¹⁰ and was often associated with high mortality.^{11,12} In

addition, it is not convenient to implement because it requires substantial resources and may cause patient discomfort.^{3,13,14}

High-flow nasal cannula (HFNC) oxygen therapy is increasingly being used for noninvasive respiratory support in ICUs. It delivers humidified oxygen at a flow rate of up to 60 L/min through a nasal cannula. By delivering oxygen at high flow rates, this form of oxygen therapy not only provides a constant fraction of inspired oxygen (F_{iO_2}), which can be adjusted by changing the fraction of oxygen in the driving gas,¹⁵ it also increases end-expiratory lung volume, decreases physiologic dead space and reduces the patient's breathing effort.^{16,17}

Although some studies have found that HFNC oxygen therapy improves oxygenation,¹⁸ survival,¹⁹ tolerance and comfort,^{20,21} and eases drainage of respiratory secretions,²² its effect on intubation rates remains unclear. A systematic review showed that it may improve oxygenation compared with conventional oxygen therapy.²³

However, its effect on intubation rates was not studied, and some limitations, such as small samples, poor-quality trials and the narrative synthesis of data, were prone to generate bias and heterogeneity.²⁴

We conducted a meta-analysis of randomized controlled trials (RCTs) to evaluate the effect of HFNC oxygen therapy on intubation rates among adults in ICU with acute hypoxemic respiratory failure.

Methods

We conducted this study according to the methods in the *Cochrane Handbook for Systematic Reviews of Interventions*.²⁵ We report the findings according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.²⁶

Literature search

We searched MEDLINE, Embase and the Cochrane Central Register of Controlled Trials from inception to Apr. 18, 2016; the Chinese Biomedical Literature Database from 1978 to April 2016; and the Wanfang Data database from 1990 to 2016. Language was restricted to English and Chinese. We also searched the ClinicalTrials.gov registry in April 2016 to identify additional clinical trials. Details of the search strategy are provided in Appendix 1 (available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.160570/-/DC1).

Study selection

After the screening of titles, we evaluated abstracts for relevance and identified them as included, excluded or requiring further assessment. We considered RCTs eligible if they compared HFNC oxygen therapy with other oxygen therapies and included adults (age > 16 yr) in ICUs with acute hypoxemic respiratory failure (ratio of partial pressure of arterial oxygen to inspired fraction of oxygen [$\text{PaO}_2:\text{FiO}_2$] ≤ 300 mm Hg).

Oxygen therapies included HFNC oxygen therapy, conventional oxygen therapy and noninvasive ventilation. High-flow nasal cannula oxygen therapy was described as the delivery of oxygen through a heated humidifier and nasal cannula at a flow rate greater than 15 L/min. Conventional oxygen therapy involved oxygen delivery by nasal cannula or mask. Noninvasive ventilation involved the use of a face mask connected to an ICU ventilator, with pressure support applied in a noninvasive ventilation mode.

We excluded studies published in narrative reviews, commentaries and editorials. We also excluded trials whose participants were volunteers, immunocompromised patients or patients with advanced cancer or trauma-related hypoxemia.

Data extraction and quality assessment

The primary outcome measure was the proportion of patients who required endotracheal intubation. The secondary outcome measures were physiologic outcomes (oxygenation [as measured by $\text{PaO}_2:\text{FiO}_2$ ratio], partial pressure of carbon dioxide [PaCO_2], arterial pH and respiratory rate), mortality in ICU, length of ICU stay and ventilator-induced lung injury (e.g., pneumothorax).

Two of us (X.O. and Y.H.) used a standardized spreadsheet to independently extract data on study eligibility, methods, methodologic quality and outcomes. Disagreements were resolved by consensus after contact with the trial authors. We assessed the risk of

bias for each trial using the Cochrane risk-of-bias tool.²⁷ We assigned a value of low, unclear or high risk of bias to the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. After extracting data on methods of randomization, allocation concealment²⁸ and blinding of outcome assessors,²⁹ we extracted the following study features: first author, publication year, country, number of participants, protocols of oxygen therapies, and the primary and secondary outcomes.

Data synthesis

We pooled data using random-effects models. For binary outcomes, we calculated risk ratios (RRs) with 95% confidence intervals (CIs). For continuous outcomes, we calculated mean differences (MDs) with 95% CIs. We considered a p value of less than 0.05 to be statistically significant.

We assessed heterogeneity using the Mantel-Haenszel χ^2 test and the I^2 statistic. We considered heterogeneity to be substantial if the I^2 value was 50% or greater or the p value was 0.1 or less.^{30,31} We did not assess publication bias because of the low power associated with the low number of included studies.

We conducted 2 subgroup analyses. First, because of the quite different methodologies and clinical features of each oxygen therapy, we analyzed separately the trials that compared HFNC oxygen therapy with conventional oxygen therapy and those that compared HFNC with noninvasive ventilation. Second, because the

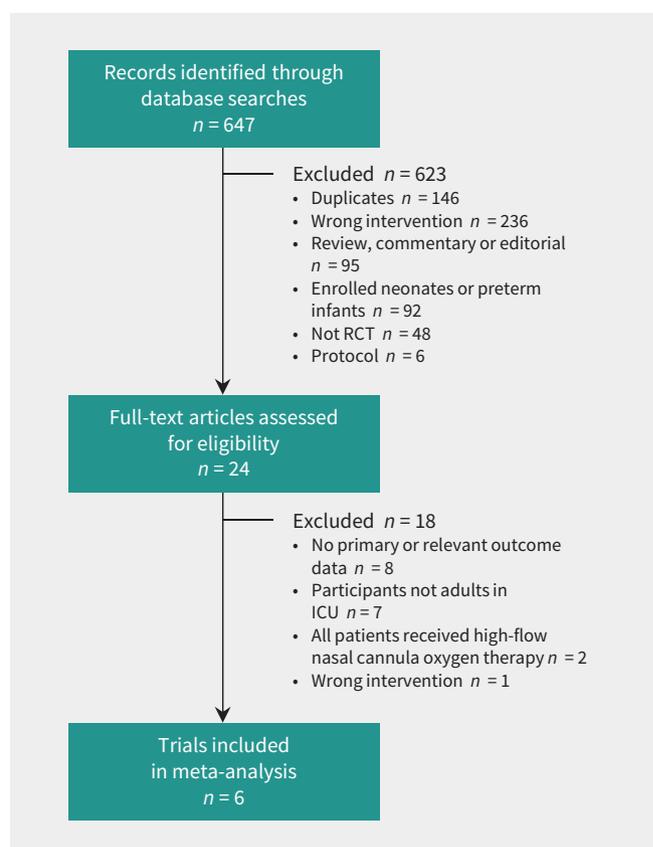


Figure 1: Selection of randomized controlled trials (RCTs) for the meta-analysis.

participants' disease severity may have affected study outcomes, we conducted a subgroup analysis according to disease severity based on patients' Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score (< 15 v. ≥ 15) and Simplified Acute Physiology Score (SAPS II) (< 30 v. ≥ 30). We described patients' disease severity as low risk, unknown risk and high risk.

To assess the robustness of the results of our meta-analysis, we conducted sensitivity analyses using alternative effect measures (odds ratios v. RRs) and statistical models regarding heterogeneity (random v. fixed effects).

We performed all statistical analyses using Review Manager software (RevMan version 5.3; Cochrane Collaboration).

Results

Search results and study characteristics

We identified 647 citations through the literature search. After screening the titles and abstracts, we reviewed 24 records in full; 6 RCTs ($n = 1892$)^{19,21,32-35} met our inclusion criteria and were included in the meta-analysis (Figure 1). (Details of the 18 excluded

trials are shown in Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.160570/-/DC1.)

The characteristics of the 6 included trials are listed in Table 1. One of the trials compared HFNC oxygen therapy with both conventional oxygen therapy and noninvasive ventilation,¹⁹ 3 trials compared it with conventional oxygen therapy only,^{21,33,34} and 2 trials compared it with noninvasive ventilation only.^{32,35} The primary outcome measure of 3 trials^{19,32,33} was the intubation rate, consistent with our study. Two trials considered oxygenation ($\text{PaO}_2\text{:FiO}_2$ ratio) as their primary outcome.^{21,35} One trial was published as an abstract only, and its primary outcome was lung aeration variation.³⁴

Five trials were judged to have high methodologic quality and a low risk of bias,^{19,21,32,33,35} with adequate randomized sequences, concealed allocation and analyzed clinical outcomes for patients by assigned group (Appendix 3, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.160570/-/DC1). The methodologic quality and risk of bias of the trial published as an abstract was assessed to be unclear because insufficient data were available after contacting the study investigators.³⁴ Two trials reported that 2 (4.7%)³⁵ and 3 (1.0%)¹⁹ patients, respectively, were withdrawn because

Table 1: Characteristics of randomized controlled trials included in the meta-analysis

Trial	Setting	No. of patients (% male)	Age, yr, mean	Disease severity scores, mean	Enrolment criteria	Oxygen therapy protocol, mean \pm SD	
						HFNC group	Control group
Frat et al., 2015 ¹⁹	23 ICUs in France and Belgium	310 (68.4)	• HFNC: 61 • Conventional oxygen: 59 • NIV: 61	SAPS II: • HFNC: 25 • Conventional oxygen: 24 • NIV: 27	$\text{PaO}_2\text{:FiO}_2$ ratio ≤ 300 mm Hg; $\text{Paco}_2 \leq 45$ mm Hg; respiratory rate ≥ 25 beats/min; no history of chronic respiratory failure	• Gas flow rate: 48 ± 11 L/min • FiO_2 : 0.82 ± 0.21	Group 1: Non-rebreather mask • Gas flow rate: 13 ± 5 L/min • FiO_2 : 0.82 ± 0.21 Group 2: NIV • PS: 8 ± 3 cm H ₂ O • PEEP: 5 ± 1 cm H ₂ O • FiO_2 : 0.67 ± 0.24 • VT: 9.2 ± 3.0 mL/kg
Hernandez et al., 2016 ³³	7 ICUs in Spain	527 (62.0)	• HFNC: 51 • Conventional oxygen: 52	APACHE II: • HFNC: 14 • Conventional oxygen: 13	$\text{PaO}_2\text{:FiO}_2$ ratio > 150 mm Hg; $\text{Paco}_2 \leq 45$ mm Hg; pH > 7.35	• Gas flow rate: 30.9 ± 7.6 L/min • FiO_2 : 0.32 ± 0.08	Nasal cannula or non-rebreather mask • Gas flow rate adjusted to maintain SpO_2 at ≥ 92 mm Hg • FiO_2 : 0.4 ± 0.09
Maggiore et al., 2014 ²¹	2 ICUs in Italy	105 (64.8)	• HFNC: 65 • Conventional oxygen: 64	SAPS II: • HFNC: 43 • Conventional oxygen: 44	$\text{PaO}_2\text{:FiO}_2$ ratio ≤ 300 mm Hg; $\text{Paco}_2 \geq 45$ mm Hg; respiratory rate ≥ 25 beats/min	• Gas flow rate: 50 L/min • FiO_2 adjusted to maintain SpO_2 at 92–98 mm Hg	Venturi mask • Gas flow rate and FiO_2 adjusted to maintain SpO_2 at 92–98 mm Hg
Perbet et al., 2014 ^{34*}	4 ICUs in France	80	NA	NA	NA	NA	Conventional oxygen therapy
Simon et al., 2014 ³⁵	1 ICU in Germany	40 (60.0)	• HFNC: 64 • NIV: 68	SAPS II: • HFNC: 43 • NIV: 46	$\text{PaO}_2\text{:FiO}_2$ ratio < 300 mm Hg	• Gas flow rate: 50 L/min • FiO_2 adjusted to maintain Sao_2 at > 90 mm Hg	NIV • PEEP: 3–10 cm H ₂ O • Inspiratory pressure: 15–20 cm H ₂ O
Stephan et al., 2015 ³²	6 ICUs in France	830 (66.4)	• HFNC: 64 • NIV: 64	SAPS II: • HFNC: 29 • NIV: 29	$\text{PaO}_2\text{:FiO}_2$ ratio ≤ 300 mm Hg; respiratory rate ≥ 25 beats/min	• Gas flow rate: 50 L/min • FiO_2 adjusted to maintain SpO_2 at 92–98 mm Hg	BiPAP • PEEP: 4 cm H ₂ O • PS: 8 cm H ₂ O (initial) • FiO_2 : 0.5 (initial)

Note: APACHE II = Acute Physiology and Chronic Health Evaluation II score (range 0 to 71 points, with higher scores indicating more severe disease), BiPAP = bilevel positive airway pressure, HFNC = high-flow nasal cannula oxygen therapy, ICU = intensive care unit, NA = not available, NIV = noninvasive ventilation, Paco_2 = partial pressure of arterial carbon dioxide, $\text{PaO}_2\text{:FiO}_2$ = ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, PEEP = positive end-expiratory pressure, PS = pressure support, Sao_2 = arterial oxygen saturation, SAPS = Simplified Acute Physiology Score (range 0 to 163 points, with higher scores indicating more severe disease), SD = standard deviation, SpO_2 = peripheral capillary oxygen saturation, VT = tidal volume.

*Conference abstract; details about the trial and some outcomes were not available after author contact.

consent was declined. None of the trials were double-blinded because it was too difficult to have patients and clinicians unaware of the protocol; however, the primary outcome was not likely to be influenced.

Effect on intubation rate

All 6 RCTs reported data on the proportion of patients requiring endotracheal intubation (Table 2). Overall, 19.1% of patients required intubation. The subgroup analyses by type of oxygen therapy showed no statistically significant difference between subgroups (interaction $p = 0.2$). Within subgroups, the intubation rate was significantly lower with HFNC oxygen therapy than with conventional oxygen therapy (RR 0.60, 95% CI 0.38 to 0.94; $I^2 = 49%$). No significant difference was found between HFNC oxygen therapy and noninvasive ventilation (RR 0.86, 95% CI 0.68 to 1.09; $I^2 = 2%$) (Figure 2).

In the subgroup analyses by disease severity, we described patients' disease severity as low risk in 3 trials,^{19,32,33} unknown risk in 1 trial³⁴ and high risk in 2 trials.^{21,35} We found no significant difference between subgroups (interaction $p = 0.3$ for comparison of HFNC v. conventional oxygen therapy, and 0.4 for comparison of HFNC v. noninvasive ventilation). Within subgroups, we found no significant difference in intubation rates between HFNC and conventional oxygen therapy (low-risk patients: RR 0.59, 95% CI 0.30 to 0.19; high-risk patients: RR 0.37, 95% CI 0.16 to 0.87) or between HFNC and noninvasive ventilation (low-risk patients: RR 0.89, 95% CI 0.66 to 1.20; high-risk patients: RR 0.69, 95% CI 0.39 to 1.24) (Figure 3).

Effect on secondary outcome measures

The effect of HFNC oxygen therapy on physiologic outcomes is summarized in Table 3.

Data on $P_{aO_2}:F_{iO_2}$ ratios and P_{aCO_2} levels were available from 5 trials ($n = 1812$). No significant difference in either measure was found between HFNC oxygen therapy and conventional oxygen therapy ($P_{aO_2}:F_{iO_2}$ ratio: MD 4.72 mm Hg, 95% CI -28.90 to 38.33 mm Hg, $I^2 = 90%$; P_{aCO_2} level: MD -0.40 mm Hg, 95% CI -2.54 to 1.74 mm Hg, $I^2 = 71%$). Subgroup analyses by disease severity showed significant differences in both $P_{aO_2}:F_{iO_2}$ ratio and P_{aCO_2} level (interaction $p < 0.001$ and 0.01, respectively).

When we compared HFNC oxygen therapy and noninvasive ventilation, we found a significantly lower $P_{aO_2}:F_{iO_2}$ ratio in the HFNC group (MD -53.84, 95% CI -71.43 to -36.24 mm Hg; $I^2 = 44%$) but no significant difference in the P_{aCO_2} level (MD -0.53, 95% CI -2.34 to 1.28; $I^2 = 62%$). Subgroup analyses by disease severity showed no significant differences in $P_{aO_2}:F_{iO_2}$ ratio or P_{aCO_2} level (interaction $p = 0.07$ and 0.3, respectively) (Table 3).

When we analyzed data on arterial pH (3 trials; $n = 1667$ low-risk patients), we found no significant difference between patient groups by type of oxygen therapy (Table 3). Respiratory rate (3 trials; $n = 1245$) was significantly lower in the HFNC group than in either the conventional oxygen group (MD -3.68 breaths/min, 95% CI -6.81 to -0.55; $I^2 = 83%$) or the noninvasive ventilation group (MD -1.13 breaths/min, 95% CI -2.01 to -0.25; $I^2 = 8%$) (Table 3).

Table 2: Proportion of participants who required endotracheal intubation

Trial	No. (%) of patients	Intubation required, no. (%) of patients	<i>p</i> value
Frat et al., 2015 ¹⁹			0.2
HFNC	106	40 (37.7)	
Conventional oxygen therapy	94	44 (46.8)	
NIV	110	55 (50.0)	
Hernandez et al., 2016 ³³			0.004
HFNC	264	13 (4.9)	
Conventional oxygen therapy	263	32 (12.2)	
Maggiore et al., 2014 ²¹			0.01
HFNC	53	6 (11.3)	
Conventional oxygen therapy	52	16 (30.8)	
Perbet et al., 2014 ³⁴			0.8
HFNC	40	9 (22.5)	
Conventional oxygen therapy	40	10 (25.0)	
Simon et al., 2014 ³⁵			0.2
HFNC	20	9 (45.0)	
NIV	20	13 (65.0)	
Stephan et al., 2015 ³²			> 0.9
HFNC	414	57 (13.8)	
NIV	416	58 (13.9)	

Note: HFNC = high-flow nasal cannula oxygen therapy, NIV = noninvasive ventilation.

Five trials ($n = 1852$) described data on ICU mortality, and 4 ($n = 1772$) reported information on length of ICU stay. There were 52 (5.9%) deaths in the HFNC group, 30 (6.7%) in the conventional oxygen therapy group and 50 (9.5%) in the noninvasive ventilation group. Pooled analyses of the results showed no difference in these outcome measures by type of oxygen therapy or by disease severity ($p > 0.05$) (Table 3).

Two trials mentioned the incidence of ventilator-induced lung injury.^{19,32} One of them found that noninvasive ventilation was associated with an increased incidence of ventilator-induced lung injury because of increasing tidal volumes.¹⁹ In the other trial,³² pneumothorax developed in 8 (1.9%) patients in the HFNC group and 7 (1.7%) in the noninvasive ventilation group; the difference was not significant (RR 1.15, 95% CI 0.42 to 3.14) (Table 3).

Sensitivity analysis

When we repeated our meta-analyses using alternative effect measures (odds ratios v. risk ratios) and statistical models regarding heterogeneity (random v. fixed effects), the results were statistically similar to those from the primary analyses (Appendices 4–9, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.160570/-/DC1).

Interpretation

Our study showed that the proportion of patients with acute hypoxic respiratory failure who required endotracheal intubation was lower among those who received HFNC oxygen therapy than among those given conventional oxygen therapy. The intubation rate did not differ significantly between HFNC oxygen therapy and

noninvasive ventilation. In the subgroup analyses by disease severity, high-risk patients had a lower intubation rate with HFNC oxygen therapy than with conventional oxygen therapy. However, this result was based on only 1 trial with small samples.²¹ Larger trials are needed to confirm the effects of HFNC in this patient group.

The improvement in the intubation rate with HFNC oxygen therapy was consistent with the results of some observational studies.^{36,37} Our results showed that the intubation rate with noninvasive ventilation was only 23%, which was much lower than the reported range of 46%–54%.^{3,8,9,25} This difference may have been because most (76%) of the participants with low disease severity came from 1 trial, which reported an intubation rate of only 14%.³²

An improvement in the $Pao_2:Fio_2$ ratio was observed among patients receiving noninvasive ventilation compared with HFNC oxygen therapy, as has been reported previously.³⁸ This result may have been due to the higher positive end-expiratory pressure or higher mean airway pressure being applied during noninvasive ventilation.^{39,40} We found no significant differences between HFNC oxygen therapy and the control groups in ICU mortality or length of ICU stay. This is perhaps because the rate of death in the low-risk population in the study by Hernandez and colleagues,³³ the second largest study included in our meta-analysis, was too low to drive these results in the entire group.

These oxygen therapies are not without risks. One trial indicated that noninvasive ventilation was associated with increased risk of ventilator-induced lung injury.¹⁹ Although no significant difference in the incidence of pneumothorax was found between HFNC oxygen therapy and noninvasive ventilation, the available data were limited, and these adverse events may occur more frequently with increasing tidal volumes.

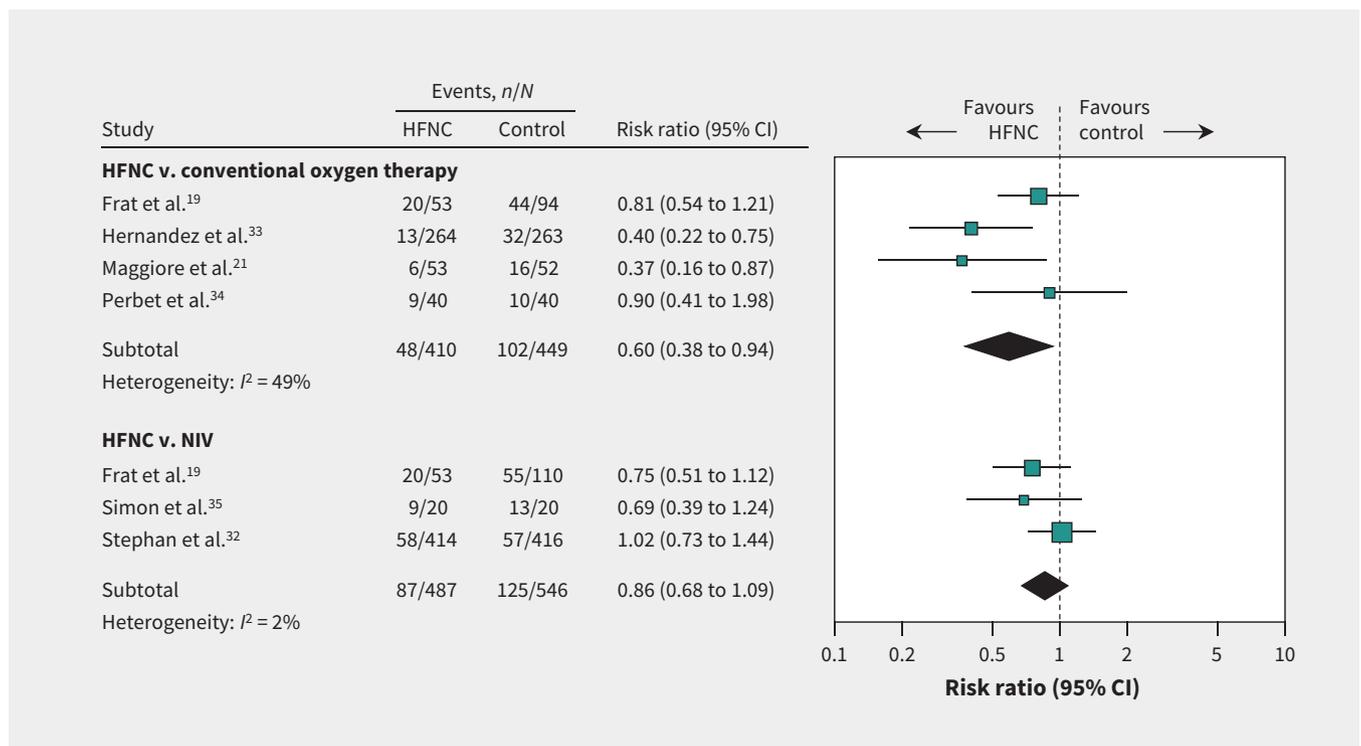


Figure 2: Subgroup analysis of intubation rate by type of oxygen therapy. A risk ratio of less than 1.0 indicates an effect in favour of HFNC oxygen therapy. Error bars represent 95% confidence intervals. CI = confidence interval, HFNC = high-flow nasal cannula oxygen therapy, NIV = noninvasive ventilation.

Limitations

Although we found high-quality evidence and used rigorous methodology, our study has several limitations. First, the included trials were diverse with respect to inclusion criteria, disease severity and use of oxygen therapy protocols. Three trials included 1462 patients (77.3% of total study population) and were conducted in the setting of post-extubation respiratory failure,^{21,32,33} which may generate potential bias. Four trials included 1747 low-risk patients (92.3% of total study population), who tended to have better outcomes and lower intubation rates than high-risk patients.^{19,32-34} However, we strengthened the stability and accuracy of our meta-analysis by using strict trial identification, data extraction and subgroup analysis.

Second, our meta-analysis was based on relatively few trials and 2 of them had small samples (< 100).^{34,35} This may have underestimated heterogeneity and reduced precision. In addition, we restricted our literature search to trials published in English or Chinese. Although a systematic review found that English-language restriction did not introduce a language bias,⁴¹ we conducted a comprehensive literature search including grey literature sources to minimize systematic bias.

Finally, the trials were not double-blinded because of the nature of the intervention and logistical problems. However, in 3 trials the investigators and statisticians were unaware of group allocation,^{19,33,35} and in 2 trials a predefined plan was

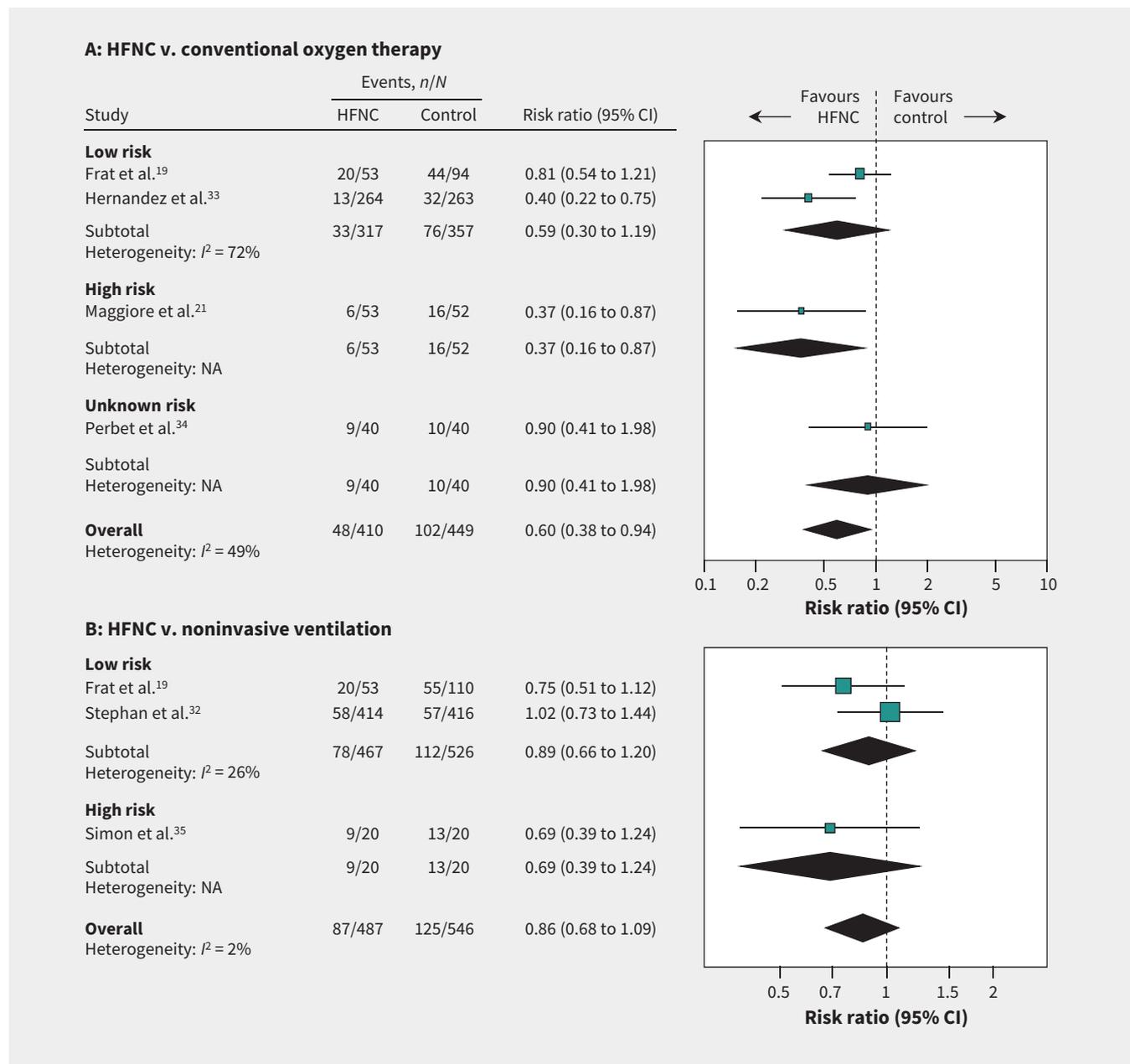


Figure 3: Subgroup analysis of intubation rate by disease severity for comparison of (A) high-flow nasal cannula (HFNC) oxygen therapy versus conventional oxygen therapy and (B) HFNC oxygen therapy versus noninvasive ventilation (NIV). Low risk = Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) II score < 15 or Simplified Acute Physiology Score (SAPS) II score < 30. A risk ratio of less than 1.0 indicates an effect in favour of HFNC oxygen therapy. Error bars represent 95% confidence intervals. CI = confidence interval, NA = not applicable.

implemented to minimize bias.^{21,32} Therefore, the lack of double-blinding may not have influenced the primary outcome.

Conclusion

In patients with acute hypoxemic respiratory failure, HFNC oxygen therapy was associated with a reduction in the proportion requiring endotracheal intubation and a decreased respiratory rate compared with conventional oxygen therapy, but it had no effect

on the Pao₂:Fio₂ ratio, Paco₂ level or arterial pH. In the comparison of HFNC oxygen therapy and noninvasive ventilation, no differences were observed in the intubation rate, Paco₂ level or arterial pH, but the respiratory rate was significantly lower in the HFNC group. In addition, our study showed that oxygenation was significantly better with noninvasive ventilation than with HFNC oxygen therapy; however, ICU mortality did not differ between groups. The correlation between oxygenation and ICU mortality should be re-evaluated.

Table 3: Pooled analysis of secondary outcome measures

Outcome measure	No. of patients	No. of trials	MD or RR (95% CI)	I ² value, %	Interaction p value
Pao₂:Fio₂ ratio, mm Hg					0.002*
HFNC v. conventional oxygen therapy	832	3	4.72 (-28.90 to 38.33)	90	< 0.001†
Low risk		2	-15.41 (-42.68 to 11.85)	87	
High risk		1	63.10 (25.65 to 100.55)		
HFNC v. NIV	1086	3	-53.84 (-71.43 to -36.24)	44	0.07†
Low risk		2	-60.05 (-72.75 to -47.34)	0	
High risk		1	-21 (-61.33 to 19.33)		
Paco₂ level, mm Hg					0.9*
HFNC v. conventional oxygen therapy	832	3	-0.40 (-2.54 to 1.74)	71	0.01†
Low risk		2	0.69 (-0.31 to 1.69)	0	
High risk		1	-4.10 (-2.54 to 1.74)		
HFNC v. NIV	1086	3	-0.53 (-2.34 to 1.28)	62	0.3†
Low risk		2	-0.18 (-2.22 to 1.86)	77	
High risk		1	-3.00 (-7.66 to 1.66)		
Arterial pH					0.8*
HFNC v. conventional oxygen therapy	727	2	0.00 (-0.03 to 0.03)	37	
HFNC v. NIV	1046	2	0.01 (-0.00 to 0.02)	24	
Respiratory rate, breaths/min					0.1*
HFNC v. conventional oxygen therapy	305	2	-3.68 (-6.81 to -0.55)	83	
HFNC v. NIV	1046	2	-1.13 (-2.01 to -0.25)	8	
ICU mortality					0.6*
HFNC v. conventional oxygen therapy	859	4	0.79 (0.44 to 1.40)	0	0.4†
Low risk		3	0.68 (0.35 to 1.33)	0	
High risk		1	1.18 (0.38 to 3.62)		
HFNC v. NIV	993	2	0.79 (0.31 to 2.05)	74	
Length of ICU stay, d					0.9*
HFNC v. conventional oxygen therapy	832	3	0.02 (-0.26 to 0.30)	0	0.5†
Low risk		2	0.01 (-0.27 to 0.29)	0	
High risk		1	1.30 (-2.29 to 4.89)		
HFNC v. NIV	1046	2	0.00 (-0.20 to 0.20)	0	
Pneumothorax rate					
HFNC v. NIV	830	1	1.15 (0.42 to 3.14)		

Note: APACHE = Acute Physiologic Assessment and Chronic Health Evaluation, CI = confidence intervals, HFNC = high-flow nasal cannula oxygen therapy, ICU = intensive care unit, MD = weighted mean difference, NIV = noninvasive ventilation, Paco₂ = partial pressure of arterial carbon dioxide, Pao₂:Fio₂ = ratio of partial pressure of arterial oxygen to fraction of inspired oxygen, RR = risk ratio, SAPS = Simplified Acute Physiology Score.

*Denotes p value of subgroup analyses according to type of oxygen therapy used in control group.

†Denotes p value of subgroup analyses according to disease severity of participants (low risk = APACHE II score < 15 or SAPS II score < 30).

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