High-Flow Nasal Cannula in Critically Ill Subjects With or at Risk for Respiratory Failure: A Systematic Review and Meta-Analysis

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High-flow nasal cannula (HFNC) oxygen delivery has been gaining attention as an alternative means of respiratory support for critically ill patients, with recent studies suggesting equivalent outcomes when compared with other forms of oxygen therapy delivery. The main objective of this review was to extract current data about the efficacy of HFNC in critically ill subjects with or at risk for respiratory failure. We performed a systematic review of publications (from database inception to October 2015) that evaluated HFNC in critically ill subjects with or at risk for acute respiratory failure and performed a meta-analysis comparing HFNC with noninvasive ventilation (NIV) and with standard oxygen therapy regarding major outcomes: incidence of invasive mechanical ventilation and ICU mortality. A total of 9 studies were included. HFNC was not associated with a reduction in the incidence of invasive mechanical ventilation compared with NIV (odds ratio [OR] 0.83, 95% CI 0.57–1.20, $P = .31$) or standard oxygen therapy (OR 0.49, 95% CI 0.22–1.08, $P = .17$). Additionally, HFNC use did not reduce ICU mortality compared with NIV (OR 0.72, 95% CI 0.23–2.21, $P = .56$) or with standard oxygen therapy (OR 0.69, 95% CI 0.33–1.42, $P = .29$). There was a trend toward better oxygenation compared with conventional oxygen therapy but a worse gas exchange compared with NIV. At this moment, HFNC therapy seems not to be superior to conventional oxygen therapy or NIV in terms of invasive mechanical ventilation rate or ICU mortality in critical illness, but new studies are needed to determine whether HFNC is associated with any difference in major outcomes when compared with other techniques. *Key words: high-flow nasal cannula; noninvasive ventilation; oxygen therapy.* [Respir Care 2017;62(1):123–132.

Introduction

Oxygen therapy is one of the most prescribed treatments in medicine, especially in critical care patients. It is an adjunctive therapy in respiratory support, the purpose of which is to maintain adequate ventilation and oxygenation, thereby providing adequate alveolar gas exchange. High-flow nasal cannula (HFNC) oxygen delivery has been gaining attention as an alternative means of oxygen therapy for

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critically ill patients. The apparatus comprises an air-oxygen blender, an active heated humidifier, a single heated circuit, and a nasal cannula. At the air-oxygen blender, F_{IO_2} is set up to 1.0 at a maximum flow of 60 L/min via a nasal cannula. The gas is heated and humidified with the active humidifier and delivered through the heated circuit, which increases patient tolerance[1] without the potential side effects of an increased dead space provided by noninvasive ventilation (NIV). HFNC offers several physiological advantages that might encourage its use, including, but not limited to, improvements in oxygenation, the generation of a flow-dependent PEEP, reduction of nasopharyngeal resistance and pharyngeal dead space washout, and an increase in end-expiratory lung volume.[2,3]

Most of the available data regarding this technique have been published in the neonatal field.[4,5] Currently, HFNC use is increasing in a variety of critically ill adult patients with diverse underlying conditions, including acute respiratory failure,[6-8] during bronchoscopy,[9] or to prevent severe desaturation during intubation of patients with mild-to-moderate hypoxemia, despite the lack of reliable, large, controlled clinical trials published.[10-12] Some authors even define the postextubation scenario as "at risk for respiratory failure," despite the same clinical management as compared with true "respiratory failure."[11]

The objective of this study was to extract current data about the actual efficacy of HFNC in critically ill subjects with or at risk for respiratory failure, and, through a meta-analysis, specify the effects of this support in terms of relevant outcomes (mortality, need for invasive mechanical ventilation, improvement in gas exchange).

Methods

Our study was performed according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[13] The study protocol was published in the PROSPERO database (www.crd.york.ac.uk/PROSPERO) with number CRD42015025912. We performed a systematic search of MEDLINE, the Cochrane Database, and EMBASE (from the inception of each database to June 2015) to identify full-text publications in English, Spanish, French, and Portuguese that evaluated the use of HFNC treatment in clinical-surgical critically ill subjects with acute hypoxemic respiratory failure or at risk for this complication, compared with standard oxygen therapy or NIV. The primary outcome was the intubation rate in different groups, whereas the secondary outcomes were oxygenation improvement (defined as P_{aO_2}/F_{IO_2}), mechanical ventilation time, and ICU mortality. The following major medical subject headings terms were included: ("respiratory insufficiency" OR "respiratory distress syndrome, adult" OR "shock lung" OR "acute lung injury" OR "lung diseases, obstructive" OR "pneumonia") AND (high-flow AND ("nose" OR "nasal") AND ("catheters" OR "cannula")) OR (high-flow AND "oxygen") OR optiflow OR "oxygen inhalation therapy." The references of review articles were also reviewed to identify any other potentially eligible articles.

The review was limited to adult subjects, and only original peer-reviewed randomized controlled trials were selected. Exclusion criteria were observational studies and quasi-experimental trials and patients with a do-not-intubate order in the emergency room or in the general ward. Two authors (WLN and EMRF) independently reviewed the abstracts of all citations from the search and the full articles for inclusion. Then selected articles were compared by a third author (CD) who resolved any disagreements. The following data were extracted: study location, enrollment period, sample size, inclusion and exclusion criteria, baseline characteristics, details of intervention and comparator groups, and clinical outcomes. To ascertain the validity and the risk of bias of the eligible randomized studies, 2 reviewers working independently used the Cochrane Collaboration's tool for assessing the risk of bias (version 5.1.0; http://handbook.cochrane.org).

The statistical analysis was performed using the MetaView statistical program within Review Manager software (RevMan 5.3.4, the Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark) using the Mantel-Haenszel random effects model. Statistical heterogeneity across trials was assessed using the Cochrane chi-square test and the Higgins inconsistency test. We analyzed the probability of publication bias using funnel plots and considered plot asymmetry to be suggestive of reporting bias.

Results

The initial search identified 5,560 studies in PubMed, 5,610 in EMBASE, and 1,223 in Cochrane; after the removal of duplicates, 6,806 articles were reviewed. After review of the abstracts, 49 studies were retrieved and reviewed in detail. Finally, after full-text review, we excluded 42 records, and 9 articles met the inclusion criteria and were selected by both reviewers (Fig. 1). The main characteristics of the included studies are summarized in Table 1.

Three studies evaluated postextubation subjects[14,17]: one in obese post-cardiac surgery subjects,[18] one in sub-

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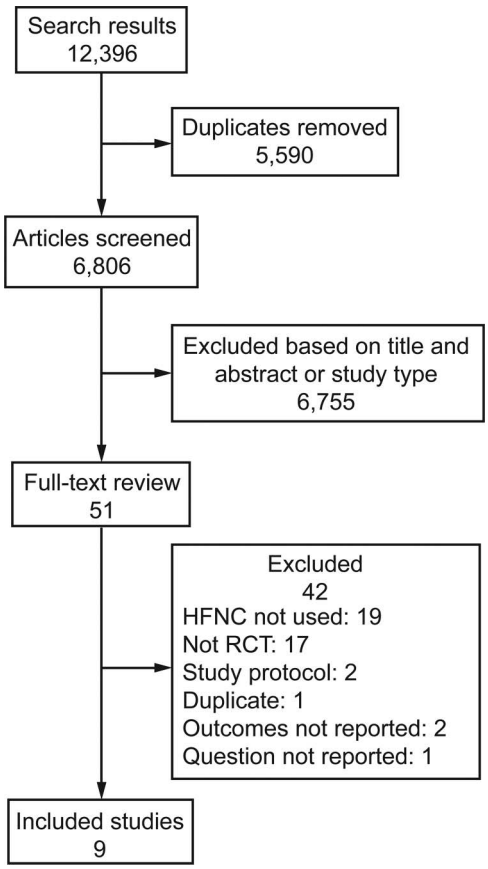

Fig. 1. Flow chart. HFNC = high-flow nasal cannula, RCT = randomized controlled trial.

jects with hypoxemic respiratory failure undergoing diagnostic fibrobronchoscopy,[9] and 3 in medical subjects with acute respiratory failure,[12,15,16] including one in immunosuppressed subjects.[19] One randomized controlled trial was performed in a crossover fashion,[14] 5 were single-center,[14,15,16,18] and 4 were multi-center.[11,12,17,19] The main comparator was conventional oxygen therapy; 3 studies compared with air-entrainment mask,[16,17,19] 2 studies compared with standard oxygen therapy,[12,18] and 2 studies compared with high-flow face mask.[14,15] Two studies compared with NIV,[9,16] whereas one compared with NIV and conventional oxygen therapy.[12]

Overall, subjects had well-balanced baseline characteristics in each group (with the exception of the study by Simon et al,[9] in which more subjects with hematological disorders and more subjects with hospital-acquired pneumonia were allocated in the HFNC group). The Simplified Acute Physiology Score II was the main disease severity score employed by the studies,[9,11,12,16,17,19] with scores varying between 25[12] and 46.[9] The breathing frequency was also variable in a range between 18[15] and 33 breaths/min[12]; similarly, there was heterogeneity in the reported P_{aO_2}/F_{IO_2} (from 128 in Lemiale et al[19] to 241 in Maggiore et al[17]). There were no significant differences between studies about baseline arterial pH (from 7.37 to 7.46) or in baseline P_{CO_2} (from 35 to 42). The length of ICU stay varied from 1.5 d in Corley et al[18] to 11 d in Maggiore et al[17] Results of the Cochrane Risk of Bias Tool of the included studies are presented in Table 2. Overall, there was a preponderance of good methodological randomized controlled trials, with the great majority of trials reporting sequence generation, allocation concealment, and intention-to-treat analysis. None of the studies, however, presented blinding of outcome assessment and, due to the nature of the intervention, none of them performed blinding of participants and personnel.

HFNC and Invasive Mechanical Ventilation

HFNC demonstrated outcomes similar to NIV with respect to the need for invasive mechanical ventilation in a meta-analysis of 3 trials (OR 0.83, 95% CI 0.57–1.20, $P = .31$, $I^2 = 22\%$) with a low heterogeneity among studies (Fig. 2). Similar outcomes to conventional oxygen therapy were also observed (OR 0.49, 95% CI 0.22–1.08, $P = .17$, $I^2 = 37\%$) in a moderate heterogeneity meta-analysis of 5 trials (Fig. 3) of hypoxemic respiratory failure in medical (3 trials, one in immunosuppressed subjects), surgical (one study), and post-procedure (one study) subjects.

HFNC and Mortality

Two studies compared HFNC and NIV mortality in hypoxemic respiratory failure, and there was no difference between groups in their meta-analysis (OR 0.72, 95% CI 0.23–2.21, $P = .56$, $I^2 = 83\%$) (Fig. 4); that meta-analysis also showed no difference between groups in the comparison of HFNC and standard oxygen therapy (OR 0.69, 95% CI 0.33–1.42, $P = .29$, $I^2 = 11\%$) (Fig. 5).

HFNC and Oxygenation Improvement

Overall, we identified 6 studies comparing oxygenation pre- and post-HFNC therapy, 4 with conventional oxygen therapy and 2 with NIV. We opted not to subject these data to meta-analysis because of the substantial heterogeneity among the studies in terms of interventions, measured outcomes, and different time intervals. Compared with high-flow face mask, there was no difference in post-intervention P_{aO_2} between groups[14]; however, better P_{aO_2}/F_{IO_2} ratios were observed at 4 h post-intervention. In another study, the regression analysis found that HFNC was also associated with fewer desaturation episodes.[20] In 2 studies, HFNC was inferior to NIV with regard to P_{aO_2} 30 min post-intervention

Table 1. Characteristics of Included Studies

Study	Year	Study Type	*N**	Age†	Sex, % male‡	Study Population	Main Intervention	Control	Inclusion Criteria	Exclusion Criteria	Main Outcome	Secondary Outcome(s)	Main Results
Tiruvoipati et al[14]	2010	Randomized crossover trial	42	65 ± 17.5	47	Subjects following endotracheal tube extubation	HFNP	HFFM	Patients >18 y and the following criteria before extubation: pH 7.35–7.45, S_{pO_2} >90%, F_{IO_2} <40%, PEEP ≤5 cm H_2O	Previous diagnosis of COPD, previous CO_2 retainers	Efficacy of HFNP with HFFM in maintaining gas exchange (P_{aO_2}, P_{CO_2}, S_{pO_2}, HCO_3, pH)	Comparison of relative effects on heart rate, BP, breathing frequency, patient comfort and tolerance	There was no difference in oxygenation between groups (P_{aO_2}, S_{pO_2}, P_{CO_2}, and pH). HFNP associated with better tolerance than standard therapy
Parke et al[15]	2011	RCT	60	64	78	Subjects with mild to moderate hypoxemic respiratory failure	HFNC	HFFM	Patients with mild to moderate hypoxemic respiratory failure	Patients requiring imminent mechanical ventilation or patients under orders not to receive mechanical ventilation	Failure of therapy, defined as worsening respiratory failure that required a change in the respiratory support device within 24 h of study enrollment	Number of patients with oxygen desaturations, time to ICU and hospital discharge	HFNC were associated with fewer desaturations than HFFM (42% vs 71%, $P = .009$). P_{aO_2}/F_{IO_2} did not significantly differ between groups ($P = .08$).
Simon et al[9]	2014	Prospective randomized trial	40	66 ± 11.5	60	Subjects with hypoxemic respiratory failure undergoing FBC	HFNC	NIV	Patients with respiratory failure with hypoxemia (P_{aO_2}/F_{IO_2} <300) with indication for diagnostic or therapeutic FBC, age > 18 y	Contraindications to NIV or HFNC, nasopharyngeal obstruction, indication for intubation, pre-existing invasive ventilation	Lowest oxygen saturation recorded by pulse oximetry during FBC	Changes in blood gases for up to 50 min after the procedure, requirement for intubation within 8 h after completion of FBC and at any other point of ICU stay	The lowest S_{pO_2} during FBC was 95 ± 5% in the NIV group and 92 ± 7% in the HFNC group ($P = .07$). P_{aO_2}/F_{IO_2} significantly better in the NIV group after 15 min post-intervention ($P = .002$). There was no difference in intubation rate in 24-h after FBC ($P = .29$)
Schwabbauer et al[16]	2014	RCT	14	55 ± 21.1	Not reported	Subjects with acute hypoxemic respiratory failure (P_{aO_2} <55 mm Hg in breathing air)	HFNC	NIV and Venturi mask	Patients with ARF (P_{aO_2} <55 mm Hg)	Clinical evidence for cardiac pulmonary edema, COPD or ventilatory failure, hemodynamic instability, contraindications to NIV, impaired consciousness or disorientation, inability to give informed consent	P_{aO_2} post-intervention	Breathing frequency, dyspnea (Borg scale), discomfort (10-point NRS), P_{aCO_2}, heart rate, blood pressure, S_{pO_2}, global rating, patient preference	P_{aO_2} highest under NIV (129 ± 38 mm Hg) compared with HFNC (101 ± 34 mm Hg, $P < .01$) and Venturi mask (85 ± 21 mm Hg, $P < .01$ vs NIV, $P < .01$ vs HFNC). Dyspnea score significantly better using HFNC (2.9 ± 2.1) compared with NIV (5.0 ± 3.3, $P < .05$) but not when compared with HFNC and Venturi mask (3.3 ± 2.3, $P > .05$).

(*continued*)

Table 1. Continued

Study	Year	Study Type	N*	Age†	Sex, % male‡	Study Population	Main Intervention	Control	Inclusion Criteria	Exclusion Criteria	Main Outcome	Secondary Outcome(s)	Main Results
Maggiore et al[17]	2014	Randomized, multi-center, controlled, open-label trial	105	64 ± 17.5	65	Subjects who successfully passed a spontaneous breathing trial and had a P_{aO_2}/F_{IO_2} ≤300 at the end of SBT	HFNC	Venturi mask	Patients who successfully passed an SBT and had a P_{aO_2}/F_{IO_2} ≤300 at the end of SBT	age <18 y, pregnancy, tracheostomy, do-not-intubate status, and planned use of NIV after extubation	P_{aO_2}/F_{IO_2} ratio at 24 h post-intervention	Patient's discomfort, episodes of device displacement, episodes of oxygen desaturation, occurrence of post-extubation ARF requiring any form of ventilatory support and re-intubation	P_{aO_2}/F_{IO_2} higher with HFNC at 24 h ($P = .03$), at 36 h ($P = .0003$), and at 48 h ($P = .01$). S_{aO_2} was significantly greater with HFNC than with Venturi mask at all time steps, P_{aCO_2} and was lower with the HFNC and breathing frequency significantly lower in HFNC. Heart rate and mean arterial pressure were always similar between groups. Discomfort related to the interface was significantly lower with HFNC at 12th h. Fewer patients in the HFNC group had episodes of oxygen desaturation, detected electronically ($P < .001$). During study period, 7.5% in the HFNC group and 34.6% in the Venturi group requiring any form of ventilatory support, fewer required NIV ($P = .04$) and required endotracheal intubation ($P < .01$) in the HFNC group.
Stéphan et al[11]	2015	RCT	830	64 ± 1.9	66	Subjects who had undergone cardiothoracic surgery who developed ARF or were deemed at risk for respiratory failure after extubation	HFNC (optiflow): flow 50 L/min and F_{IO_2} = 50%	NIV delivered by full face mask for ≥4 h/d	Patients who had undergone cardiothoracic surgery and met any of the following criteria: failure of SBT, successful SBT in patients with risk factors for postextubation ARF, successful SBT followed by failed extubation	Obstructive sleep apnea, tracheostomy, do-not-intubate status, delirium, nausea and vomiting, bradypnea, impaired consciousness, hemodynamic instability	Treatment failure, defined as re-intubation for mechanical ventilation, switch to the another study treatment, or premature study treatment discontinuation	Changes in respiratory variables after 1 h and between 6 and 12 h, worst daily values of respiratory variables under treatment, dyspnea score, comfort score, skin breakdown score, respiratory and extrapulmonary complications, number of bronchoscopies, ICU mortality	Treatment failure in 21% in HFNC group and 21.9% in BPAP group (absolute difference 0.9%, 95% CI −4.9 to 6.6%, $P = .003$). No significant differences between groups in ICU mortality: BPAP 5.5% and HFNC 6.8% ($P = .66$). P_{aO_2}/F_{IO_2} increasing from day 1 to day 3 in both groups but significantly higher with BPAP ($P < .001$).
Frat et al[12]	2015	RCT	310	60 ± 16.6	68	Subjects with acute hypoxemic respiratory failure in ICU	HFNC (48 ± 11 L/min)	Standard oxygen group (13 ± 5 L/min) and NIV	Patients >18 y and the following criteria: P_{aO_2}/F_{IO_2} ≤300 mm Hg (with oxygen at flow of 10 L/min), P_{aCO_2} ≤45 mm Hg, and an absence of clinical history of underlying chronic respiratory failure	P_{aCO_2} >45 mm Hg, exacerbation of asthma or COPD, cardiogenic pulmonary edema, severe neutropenia, hemodynamic instability, use of vasopressors, GCS ≤12 points, contraindications to NIV, urgent need of endotracheal intubation, a do-not-intubate order, and a decision to not participate	Proportion of patients who required endotracheal intubation within 28 d after randomization	Mortality in ICU, mortality at 90 d, number of ventilator-free days between day 1 and day 28, duration of ICU stay	Intubation rate at day 28 was 38% in HFNC, 47% in standard oxygen group, and 50% in NIV group ($P = .18$; $P = .17$). Heart rate for death at 90 d was 2.01 (95% CI 1.01–3.99) in standard oxygen group compared with HFNC group ($P = .0046$) and 2.5 (95% CI 1.31–4.78) in the NIV compared with HFNC group ($P = .006$). In the subgroup of patients with $P_{aO_2}:F_{IO_2}$ < 200 mm Hg, the intubation rate was significantly lower in the HFNC group than the 2 other groups, heart rate 2.07 (95% CI 1.09–3.94) vs standard oxygen and heart rate 2.57 (95% CI 1.37–4.84).

(*continued*)

Table 1. Continued

Study	Year	Study Type	*N**	Age†	Sex, % male‡	Study Population	Main Intervention	Control	Inclusion Criteria	Exclusion Criteria	Main Outcome	Secondary Outcome(s)	Main Results
Corley et al[18]	2015	RCT	155	64 ± 11.3	74	Post-cardiac surgery subjects with BMI ≥30 kg/m^2 following extubation	HFNC to a maximum of 50 L/min	Standard oxygen group 2–4 L/min via nasal cannula or 6 L/min via simple face mask	Patients >18 y with a BMI >30 kg/m^2 and scheduled to undergo cardiac surgery on cardiopulmonary bypass	Ventilation time >36 h, ventilation onto NIV, requirement for tracheostomy, and extubation as part of end-of-life treatment	Degree of atelectasis on chest radiograph by radiological atelectasis score, day 1 and day 5 postoperatively	Oxygenation, dyspnea, breathing frequency, failure of allocated treatment, and ICU length of stay	No difference in atelectasis score in day 1 and in day 5 between groups, no significant difference between groups in P_{aO_2}/F_{IO_2} between groups in the first 24 h post-extubation (HFNC 227 and standard oxygen 253, mean difference 25.4 (95% CI −2.5 to 52); $P = .08$). No difference between groups in dyspnea scores. No difference between groups for failure of allocated therapy (OR 0.53, 95% CI 0.11–2.24, $P = .40$), by logistic regression model.
Lemiale et al[19]	2015	RCT	100	61 ± 23	70	Immunocompromised subjects admitted to ICU for ARF	HFNC at initial flow in 40–50 L/min with an F_{IO_2} of 100%, adjusted as needed to maintain S_{pO_2} of ≥95%	Venturi mask at 15 L/min (F_{IO_2} 60%)	Patients >18 y with immunosuppression (solid or hematological malignancy, solid organ transplant, steroid therapy, other immunosuppressive therapy, HIV infection	Hypercapnia (>45 mm Hg), mechanical ventilation before ICU admission, need for immediate NIV or mechanical ventilation, patient refusal to participate in the study	Need for mechanical ventilation or NIV during or at the end of the 2-h study period	Visual analogue scale scores for comfort, thirst, and dyspnea; breathing frequency, heart rate	No significant difference between groups in need for mechanical ventilation or NIV (15% with HFNC and 8% with Venturi mask, $P = .36$) at 120 min. There was also no difference between groups in visual analogue scale score for discomfort ($P = .88$), dyspnea ($P = .87$), or thirst ($P = .40$).

* Number of patients.
† Mean ± SD.
HFNP = high-flow nasal prong
HFFM = high-flow face mask
BP = blood pressure
HFNC = high-flow nasal cannula
NIV = noninvasive mechanical ventilation
RCT = randomized controlled trial
FBC = fibrobronchoscopy
ARF = acute respiratory failure
NRS = numerical rating scale
SBT = spontaneous breathing trial
BPAP = bi-level positive airway pressure
GCS = Glasgow coma scale
BMI = body mass index
OR = odds ratio

Table 2. Cochrane Risk of Bias Tool

Study	Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Intention-to-Treat Analysis
Tiruvoipati et al (2010)[14]	Uncertain	Yes	No	No	Uncertain	Yes	No
Parke et al (2011)[15]	Yes	Yes	Uncertain	Uncertain	Uncertan	Yes	Yes
Simon et al (2014)[9]	Yes	Yes	No	No	Uncertain	Yes	No
Schwabbauer et al (2014)[16]	No	No	No	No	Uncertain	No	Uncertain
Maggiore et al (2014)[17]	Yes	Yes	No	No	Yes	Yes	Yes
Stéphan et al (2015)[11]	Yes	Yes	No	No	Uncertain	Yes	Yes
Frat et al (2015)[12]	Yes	Yes	No	No	Yes	Yes	Yes
Corley et al (2015)[18]	Yes	Yes	No	No	No	Yes	Yes
Lemiale et al (2015)[19]	Yes	Yes	No	No	No	Yes	Yes

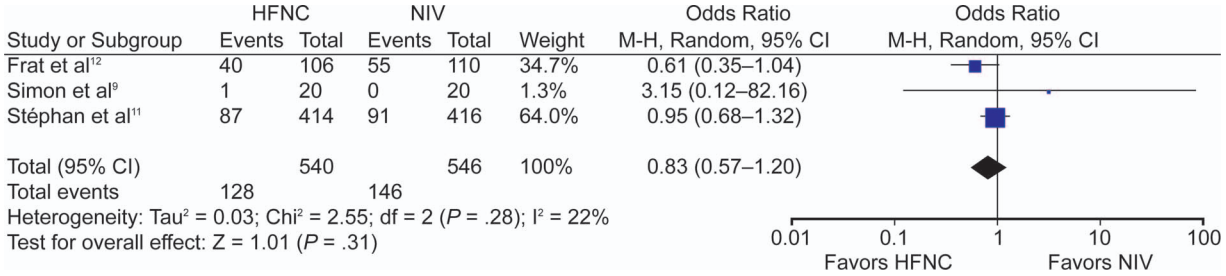

Fig. 2. Invasive mechanical ventilation: high-flow nasal cannula (HFNC) versus noninvasive ventilation (NIV).

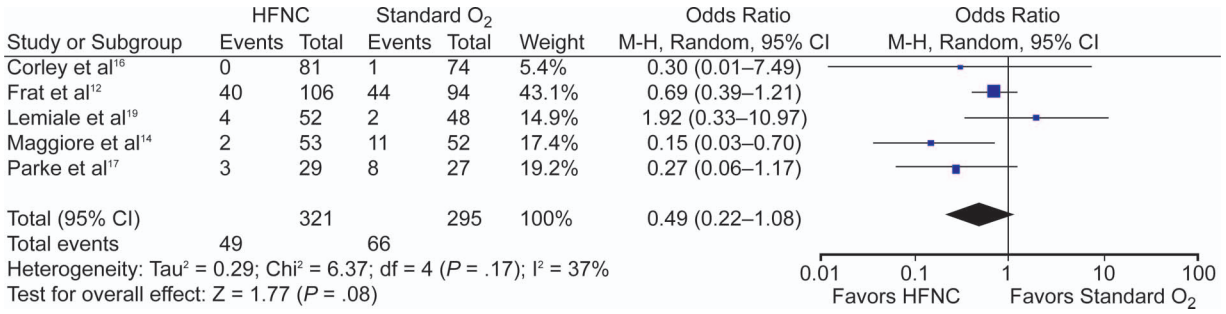

Fig. 3. Invasive mechanical ventilation: high-flow nasal cannula (HFNC) versus standard O_2 therapy.

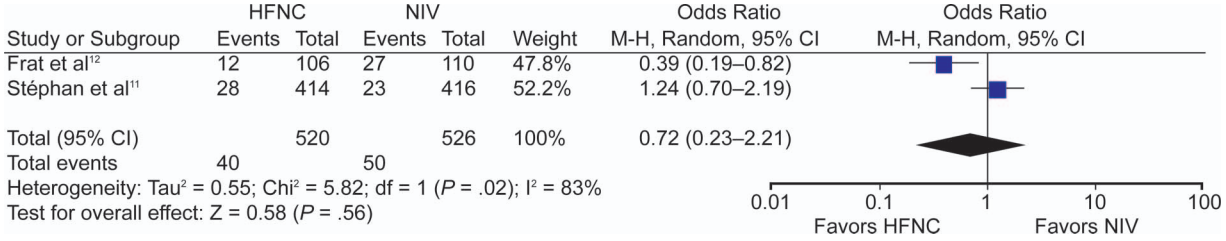

Fig. 4. ICU mortality: high-flow nasal cannula (HFNC) versus noninvasive ventilation (NIV).

(101 ± 34 mm Hg vs 129 ± 38 mm Hg, $P < .01$)[16] and in terms of P_{aO_2}/F_{IO_2} 1 h and 6–12 h post-intervention in surgical subjects.[11] HFNC was associated with an increased P_{aO_2}/F_{IO_2} ratio compared with an air-entrainment mask in 2 studies: 101 ± 34 mm Hg versus 85 ± 21 mm Hg ($P < .001$)[16] (30 min post-intervention) and at 24–48 h post-intervention but not in the first 24-h period in another study.[17] In obese post-cardiac surgery subjects following extubation, there was no difference between HFNC and standard oxygen therapy in

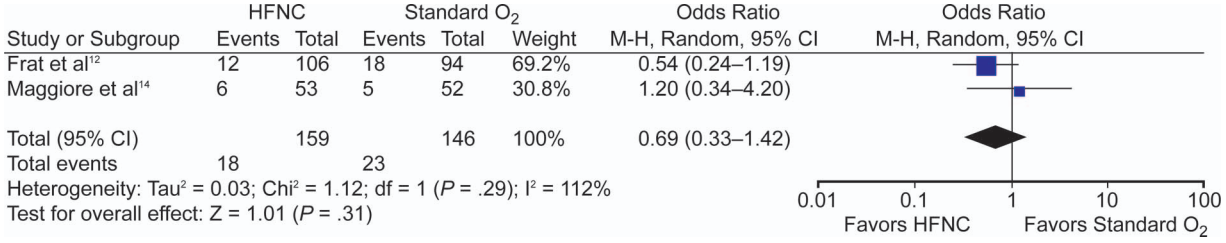

Fig. 5. ICU mortality: high-flow nasal cannula (HFNC) versus standard O_2 therapy.

P_{aO_2}/F_{IO_2} in the first 24 h.[18] There was no evidence of publication bias in the 4 meta-analyses performed, without asymmetry in the top or in the bottom of the funnel plot, based on visual inspection.

Discussion

This systematic review and meta-analysis suggested that there was no difference in mortality or the need for invasive mechanical ventilation when HFNC is compared with NIV; the same conclusions can be reached when compared with standard oxygen therapy. These outcomes were compared in a highly heterogeneous population, in clinical,[12,15,19] surgical,[11,17,18] and periprocedure subjects,[9] in acute respiratory failure or in a postextubation context.[17,18] It is important to highlight that the main exclusion criteria in most studies were COPD and hypercapnia, conditions in which NIV is a well-established indication that has an impact on mortality rate.[21] In other settings, when NIV use is open to debate, as in postextubation patients,[21] HFNC should be a useful alternative that has been associated in many studies with increased patient comfort and reductions in dyspnea scores.[14,16,17] This outcome, however, due to heterogeneous measurement between studies and different forms of "patient comfort" characterization, an issue with several assessment tools without a validated approach in critically ill patients,[22] limits our ability to reach a definitive conclusion about this point. Assessing dyspnea by a patient report instrument, such as the modified Borg scale, can be an important proposal for future studies to evaluate this outcome, and new studies will be necessary to determine whether this outcome will be an important factor in choosing an oxygen therapy interface, because mask intolerance and discomfort still represent a major cause of NIV failure.[23]

Another important study limitation is that different measurements were used for oxygenation improvement in the studies, which prohibits a definitive measurement of the magnitude of the intervention. This remains an open debate, despite apparent superior results associated with HFNC use when compared with standard oxygen therapy and inferior results when compared with NIV as presented in this paper. These results should be interpreted with great caution because quite different clinical scenarios existed when HFNC was tested; different times of administration of therapy and, consequently, different times for outcome evaluation were used. The analyzed studies included outcome measurements as early as 2 h and as late as 2 calendar days.[12]

Inspired gases in HFNC are warmed and humidified, improving comfort and possibly reducing airway inflammation,[24] leading to improved drainage of respiratory secretions.[17] Additionally, the high flows match the high spontaneous inspiratory flows generated by patients with dyspnea, reducing entrainment of room air and permitting delivery of more reliable F_{IO_2}.[25] A reduction in tachypnea also should occur by flushing out anatomical dead space in the upper airway by high oxygen flux.[26]

Despite several physiological advantages of HFNC, such as constant F_{IO_2} during peak inspiratory flow, improvements in oxygenation, washout of the nasopharyngeal dead space, reducing the work of breathing,[19] generation of flow-dependent PEEP, and an increase in end-expiratory lung volume,[27] its use is not free of limitations, such as those that have been established in postextubation postoperative cardiac surgery patients with body mass index $\geq$30 kg/m^2, in whom HFNC did not improve atelectasis, when a low level of PEEP (no more than 3–4 cm H_2O) provided by HFNC should not be sufficient.[2,18] It should be noted that prolonged HFNC use ($\geq$48 h) is associated with sequential failure and delayed intubation and may increase ICU mortality.[28]

Acute respiratory failure is not a unique physiopathologic model, and HFNC is not appropriate in all cases. In a patient with hypoxemia alone, oxygen therapy is often sufficient to correct the condition. In contrast, although HFNC may normalize oxygen saturation, it may not be sufficient to correct the underlying disturbance when there is a ventilation-to-perfusion ratio mismatch or in the context of alveolar hypoventilation, when a reduction in the work of breathing is necessary with PEEP and inspiratory pressure support.

New perspectives for HFNC trials are open, and more studies will be needed to determine whether the early ap-

plication of HFNC avoids ICU admission in patients presenting to the emergency department with acute respiratory failure[3] and in severe acute respiratory infection, situations in which HFNC therapy appears to be an effective modality for early treatment in patients who were unable to maintain adequate pulse oximetry with conventional oxygen therapy.[29] In acute heart failure, important results in a pilot study[30] identified a promising research agenda, especially concerning the degree of discomfort and intolerance associated with NIV that could be related to treatment failure.

Conclusions

In critical illness acute respiratory failure or in subjects at risk for it, HFNC did not demonstrate inferior results compared with conventional oxygen therapy or NIV in terms of ICU mortality and invasive mechanical ventilation rate. The data on oxygenation improvement suggest that HFNC could be superior to standard oxygen therapy but inferior to NIV, but with current knowledge, this is still an open question. Patient comfort and reduction in dyspnea scores will require further investigation because these are concerns in the consideration of HFNC as a promising therapy.

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