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To cite this version:

Dipayan Chaudhuri, David Granton, Dominic Xiang Wang, Sharon Einav, Yigal Helviz, et al.. Moderate Certainty Evidence Suggests the Use of High-Flow Nasal Cannula Does Not Decrease Hypoxia When Compared With Conventional Oxygen Therapy in the Peri-Intubation Period. Critical Care Medicine, 2020, 48 (4), pp.571-578. 10.1097/CCM.0000000000004217 . hal-02436055

HAL Id: hal-02436055

https://hal.science/hal-02436055v1

Submitted on 1 Jul 2020

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Moderate Certainty Evidence Suggests the Use of High-Flow Nasal Cannula Does Not Decrease Hypoxia When Compared With Conventional Oxygen Therapy in the Peri-Intubation Period: Results of a Systematic Review and Meta-Analysis

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Objective: The role of high-flow nasal cannula during and before intubation is unclear despite a number of randomized clinical trials. Our objective was to conduct a systematic review and meta-analysis examining the benefits of high-flow nasal cannula in the peri-intubation period.

Data Sources: We performed a comprehensive search of relevant databases (MEDLINE, EMBASE, and Web of Science).

Study Selection: We included randomized clinical trials that compared high-flow nasal cannula to other noninvasive oxygen delivery systems in the peri-intubation period.

Data Extraction: Our primary outcome was severe desaturation (defined as peripheral oxygen saturation reading < 80% during intubation). Secondary outcomes included peri-intubation complications, apneic time, Pa_{O_2} before and after intubation, Pa_{CO_2} after intubation, ICU length of stay, and short-term mortality.

Data Synthesis: We included 10 randomized clinical trials (n = 1,017 patients). High-flow nasal cannula had no effect on the occurrence rate of peri-intubation hypoxemia (relative risk, 0.98; 95% CI, 0.68–1.42; 0.3% absolute risk reduction, moderate certainty), serious complications (relative risk, 0.87; 95% CI, 0.71–1.06), apneic time (mean difference, 10.3 s higher with high-flow nasal cannula; 95% CI, 11.0 s lower to 31.7 s higher), Pa_{O_2} measured after preoxygenation (mean difference, 3.6 mm Hg higher; 95% CI, 3.5 mm Hg lower to 10.7 mm Hg higher), or Pa_{O_2} measured after intubation (mean difference, 27.0 mm Hg higher; 95% CI, 13.2 mm Hg lower to 67.2 mm Hg higher), when compared with conventional oxygen therapy. There was also no effect on postintubation Pa_{CO_2}, ICU length of stay, or 28-day mortality.

Conclusions: We found moderate-to-low certainty evidence that the use of high-flow nasal cannula likely has no effect on severe desaturation, serious complications, apneic time, oxygenation, ICU length of stay, or overall survival when used in the peri-intu-

bation period when compared with conventional oxygen therapy.

Key Words: artificial respiration; hypoxia; intubation; noninvasive ventilation; oxygen inhalation therapy; systematic review

Oxygen delivery via a high-flow nasal cannula (HFNC) is increasingly being used as an alternative to standard oxygen therapy or noninvasive ventilation (NIV) for patients with hypoxemic respiratory failure (1, 2). HFNC allows for delivery of high rates of humidified and heated oxygen (up to 70 L/min) (1). This method of oxygen delivery also creates a modest amount of positive end-expiratory pressure, enables carbon dioxide (CO_2) washout, and decreases nasopharyngeal resistance (3, 4). Furthermore, it is hypothesized that high-flow therapy results in washout of the upper airways because of the increased airway pressures it generates. As a result, the patient rebreathes less expired air from the upper airways and more fresh air is delivered by the nasal high flow (5, 6). When compared with other oxygen delivery devices, HFNC may be more comfortable and less obtrusive (4). Consequently, HFNC may confer benefit by preventing hypoxemia and increasing apnea time prior to intubation (4). In fact, a recent narrative review on HFNC use presents it as a reasonable option for preoxygenation in the peri-intubation period (7).

The largest randomized clinical trial comparing HFNC to other modes of NIV in the peri-intubation period was published in March 2019 and showed no difference in clinical outcomes related to the use of alternative oxygen delivery devices (8). We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) examining the effects of HFNC compared with bag mask or NIV in the peri-intubation period.

MATERIALS AND METHODS

We registered the protocol for this systematic review and meta-analysis on International prospective register of systematic reviews (# 42019120959) and used the Preferred Reporting Items for Systematic Reviews and Meta-Analysis checklist to report our findings (**Supplementary Table 4**, Supplemental Digital Content 1, http://links.lww.com/CCM/F294).

Data Sources and Searches

We performed a comprehensive search of all relevant databases from January 1, 2007, to October 25, 2018, recognizing that HFNC was not widely used before 2007. Our search strategy used key words including "human" OR "adult" OR "mature" or "grown" AND "high flow nasal cannula" OR "high flow nasal therapy" OR "high flow nasal oxygen" OR "high flow oxygen therapy" OR "high flow therapy" OR "optiflow (respiration)" OR "nasal highflow." We did not restrict studies to language or quality. An updated search was conducted on April 15, 2019, and on November 6, 2019.

Study Selection

Two reviewers screened citations independently and in duplicate (D.G., D.W.) from our initial search in two stages; first we screened the title and abstract and then, we screened the full text of potentially relevant abstracts. We captured reasons for study exclusion at the full-text review stage. A third author (B.R.) adjudicated disagreements.

We included RCTs that compared HFNC to other noninvasive oxygen delivery modalities in the peri-intubation period. We defined peri-intubation period as the time between induction of anesthesia or administration of sedative agents and until connection of the patient to the mechanical ventilator. We included trials with nonhypoxemic patients (e.g., perioperative) and those with hypoxemic patients (e.g., critically ill patients). We excluded case reports, case series, and observational studies. Our primary outcome was severe desaturation (uniformly defined as peripheral capillary oxygen saturation [Sp_{O_2}] < 80%). Secondary outcomes included peri-intubation complications, apneic time, Pa_{O_2} (post preoxygenation, postintubation), post intubation Pa_{CO_2}, ICU length of stay (LOS), and short-term mortality. We defined post preoxygenation Pa_{O_2} as the first Pa_{O_2} from the first arterial blood gas (ABG) taken after the defined period of preoxygenation was completed and we defined postintubation Pa_{O_2} as the first Pa_{O_2} from the first ABG after intubation. The above definitions held for postintubation Pa_{CO_2} as well.

Data Extraction and Quality Assessment

Two reviewers (D.C., D.G.) abstracted data independently and in duplicate using a structured data abstraction form. A third reviewer resolved any disagreements. We collected study characteristics, demographic data, details and definitions of the intervention and control, and details and definitions of the predefined study outcomes. If only Sp_{O_2} was reported and not Pa_{O_2}, we converted to Pa_{O_2} using the equations derived by Severinghaus (9).

We assessed risk of bias (ROB) using a modified Cochrane ROB tool for RCTs (10) and assessed for randomization sequence generation, allocation concealment, blinding, incomplete data, selective reporting, and other bias. ROB was assessed independently and in duplicate. We rated the ROB for each domain as "low," "probably low," "high," or "probably high." We rated the overall ROB as the highest risk attributed to any criterion, except for blinding. Because the nature of the intervention in these trials made blinding virtually impossible, we rated the overall ROB to be low for trials that had only had issues with blinding of the intervention. We assessed the overall certainty of evidence regarding each outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework (11).

Data Analysis

We used the DerSimonian-Laird random-effects model with inverse-variance weighting to generate pooled treatment effect across trials. We measured heterogeneity between trials using the Chi-square test (with a p value < 0.10 denoting significant heterogeneity), the I^2 statistic (with a value > 50% denoting substantial heterogeneity), and visual inspection of the forest plots (12). We present results as relative risk (RR) for dichotomous outcomes and mean difference (MD) for continuous outcomes with 95% continuous intervals. We performed all

statistical analyses using RevMan 5.3 (Cochrane Collaboration, Oxford, United Kingdom) software.

We planned three a priori subgroup analyses comparing trials evaluating: 1) operative patients versus critically ill patients with hypoxemic respiratory failure (hypothesizing that patients with hypoxemic respiratory failure would benefit more with HFNC); 2) any form of NIV as a comparator versus facemask and bag mask as comparator (hypothesizing that patients undergoing ventilation with facemask/bag mask would benefit more from HFNC); and 3) high ROB trials versus low ROB trials (hypothesizing that trials with a high ROB would show a greater effect of HFNC compared with trials with low ROB). We also performed sensitivity analyses for the outcomes of post preoxygenation Pa_{O_2} and postintubation Pa_{O_2} excluding trials that reported only Sp_{O_2} (8, 13–15).

We conducted trial sequential analysis (16) using random-effect model for the peri-intubation hypoxemia outcome. We used a statistical significance level of 5%, a power of 80%, and a RR reduction of 15%. We used a model variance-based heterogeneity correction. Trial sequential analysis was performed using Trial Sequential Analysis version 0.9.5.10 beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark, www.ctu.dk/tsa).

RESULTS

Search Strategy and Study Characteristics

We reviewed 649 citations and ultimately included 10 RCTs with a total of 1,017 patients (4, 8, 13–15, 17–21) (**Fig. 1**). We considered, but ultimately excluded, an 11th trial that examined the use of standard nasal cannula for peri-intubation oxygenation (22). Although this trial labeled the intervention "high flow," standard soft plastic nasal cannula were used with flows of 15 L/min of oxygen rather than specialized nasal cannula (e.g., Optiflow system) and average flows employed were significantly less than those of other included trials (15 L/min here as compared with 50–70 L/min in the other high-flow trials) (23).

The characteristics of included trials are shown in **Supplementary Table 3** (Supplemental Digital Content 1, http://links.lww.com/CCM/F294). The trials included had randomized between 33 and 333 patients. Five of the 10 trials examined nonhypoxemic patients undergoing intubation during induction of general anesthesia before surgery (14, 17, 19–21), whereas the other five trials examined critically ill hypoxemic patients (4, 8, 13, 15, 18). Of the preoperative trials, two examined patients undergoing emergency surgery (14, 20), one trial evaluated patients undergoing bariatric surgery (17), one evaluated obese patients undergoing any type of surgery (21), and one examined patients undergoing neurosurgery (19). All the perioperative trials excluded patients with underlying respiratory conditions. All included trials followed a standardized approach during intubation. Once patients were randomized, they were preoxygenated using either the intervention or control device for a set period of time, ranging between 3 and 7 minutes. Once this was completed, patients were sedated, paralyzed, and then intubated. In the intervention arm of all trials, the HFNC was left in place while intubating patients. Successful intubation was confirmed by end tidal CO_2 and was followed by connection to the mechanical ventilator.

Of the trials examining critically ill patients, all except one (15) included patients with hypoxemic respiratory failure. Definitions for hypoxemic respiratory failure varied but all required that patients have a Pa_{O_2}/Fi_{O_2} ratio below 300, along with some combination of an elevated respiratory rate and decreased Sp_{O_2}. One trial (15) examined only patients with mild or moderate hypoxemia and excluded patients with Pa_{O_2}/Fi_{O_2} less than 200. Sensitivity analysis performed excluding this trial showed no difference of significance in any of the outcomes.

Two of the 10 trials compared HFNC to NIV (8, 21), whereas six compared HFNC to facemask or bag mask (4, 13–15, 19, 20). One three-armed trial compared HFNC to NIV and to facemask with bag mask (17). Finally, one

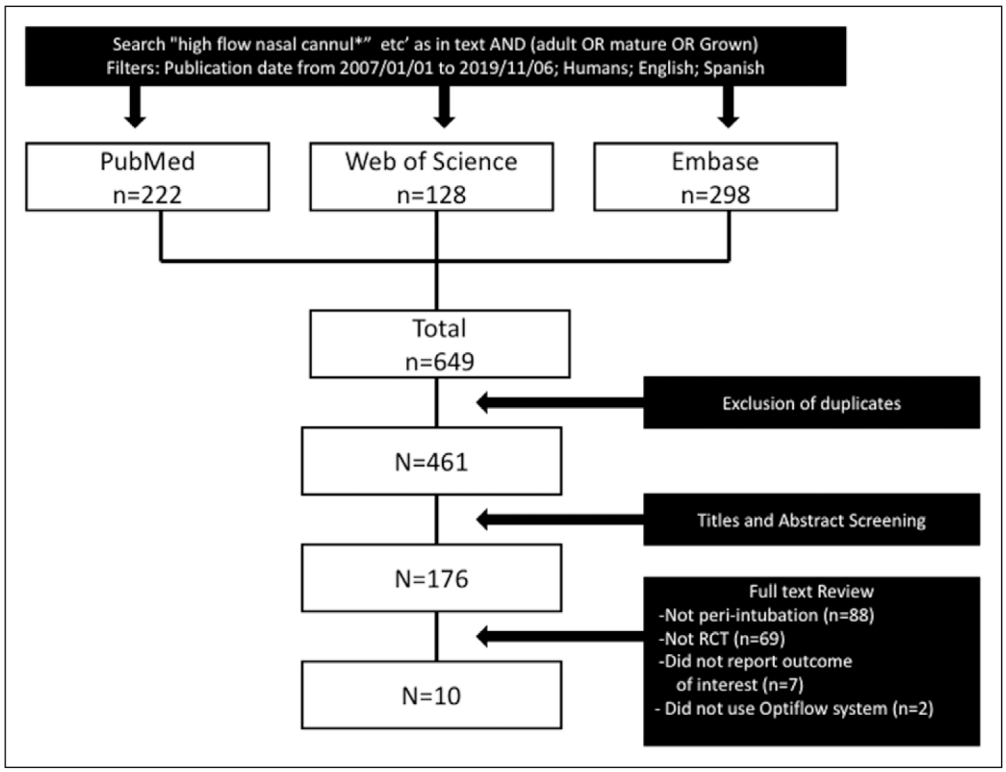

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram—study selection. RCT = randomized clinical trial.

trial compared HFNC with NIV to NIV alone (18). The intervention of choice in all the trials were the high-flow heated and humidified nasal oxygen (Optiflow; Fisher and Paykel Healthcare, Auckland, New Zealand) device set to a FIO_2 of 1.0 and gas flow rates ranging between 50 and 70 L/min.

Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/CCM/F294) summarizes the individual trial ROB. None of the trials blinded patients or clinicians. All trials except one (20) were judged to be at low or probably low risk of other forms of bias.

Outcomes

Supplementary Table 2 (Supplemental Digital Content 1, http://links.lww.com/CCM/F294) shows pooled estimates and GRADE certainties.

Primary Outcome

Compared with conventional oxygen therapy (i.e., face mask and/or bag mask), HFNC demonstrated no effect on peri-intubation hypoxemia (RR, 0.98; 95% CI, 0.68–1.42; 0.3% absolute risk reduction; 95% CI, 4.9% reduction to 6.5% increase, moderate certainty, **Fig. 2**). All trials defined peri-intubation hypoxia as SpO_2 less than 80% in the period between induction of anesthetic medication and/or commencement of laryngoscopy to connection to the mechanical ventilator. No credible subgroup effects were found on peri-intubation hypoxemia based on patient type (ICU vs preoperative patients, Fig. 2), the comparator used (NIV vs face mask/bag mask [**Supplementary Fig. 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/F295; **legend**, Supplemental Digital Content 1, http://links.lww.com/CCM/F294]), or individual study ROB (high risk vs low risk [**Supplementary Fig. 2**, Supplemental Digital Content 3, http://links.lww.com/CCM/F296; legend, Supplemental Digital Content 1, http://links.lww.com/CCM/F294]). The trial sequential analysis for this outcome showed that the required information size for this outcome was not met (**Supplementary Fig. 3**, Supplemental Digital Content 4, http://links.lww.com/CCM/F297; legend, Supplemental Digital Content 1, http://links.lww.com/CCM/F294).

Secondary Outcomes

Similarly, no difference was found in the composite outcome of serious peri-intubation complications with HFNC compared with conventional oxygen therapy (RR, 0.87; 95% CI, 0.71–1.06; 6.2% absolute risk reduction; 95% CI, 13.9% reduction to 2.9% increase, low certainty, **Fig. 3**). Of note, peri-intubation complications were defined differently across studies (Supplementary Table 3, Supplemental Digital Content 1, http://links.lww.com/CCM/F294). All studies reported severe hypoxemia (SpO_2 below 80%) and severe hypotension. However, hypotension was defined differently across studies with some studies defining it as SBP less than 80 mm Hg, and some defining it as systolic blood pressure (SBP) less than 90 mm Hg.

When comparing HFNC to conventional oxygen therapy, no effect was found on total apneic time (MD, 10.3 s longer; 95% CI, 11.0 s shorter to 31.7 s longer, low certainty; **Fig. 4**). There was also no effect on PaO_2 after preoxygenation (MD, 3.6 mm Hg higher; 95% CI, 3.5 mm Hg lower to 10.7 mm Hg higher, moderate certainty; **Fig. 5**) or PaO_2 after intubation (MD, 27.0 mm Hg higher; 95% CI, 13.2 mm Hg lower to 67.2 mm Hg higher, moderate certainty; **Supplementary Fig. 4**, Supplemental Digital Content 5, http://links.lww.com/CCM/F298; legend, Supplemental Digital Content 1, http://links.lww.com/CCM/F294) with HFNC. Furthermore, there was no effect of HFNC when compared with conventional oxygen therapy in any of the other secondary outcomes including postintubation

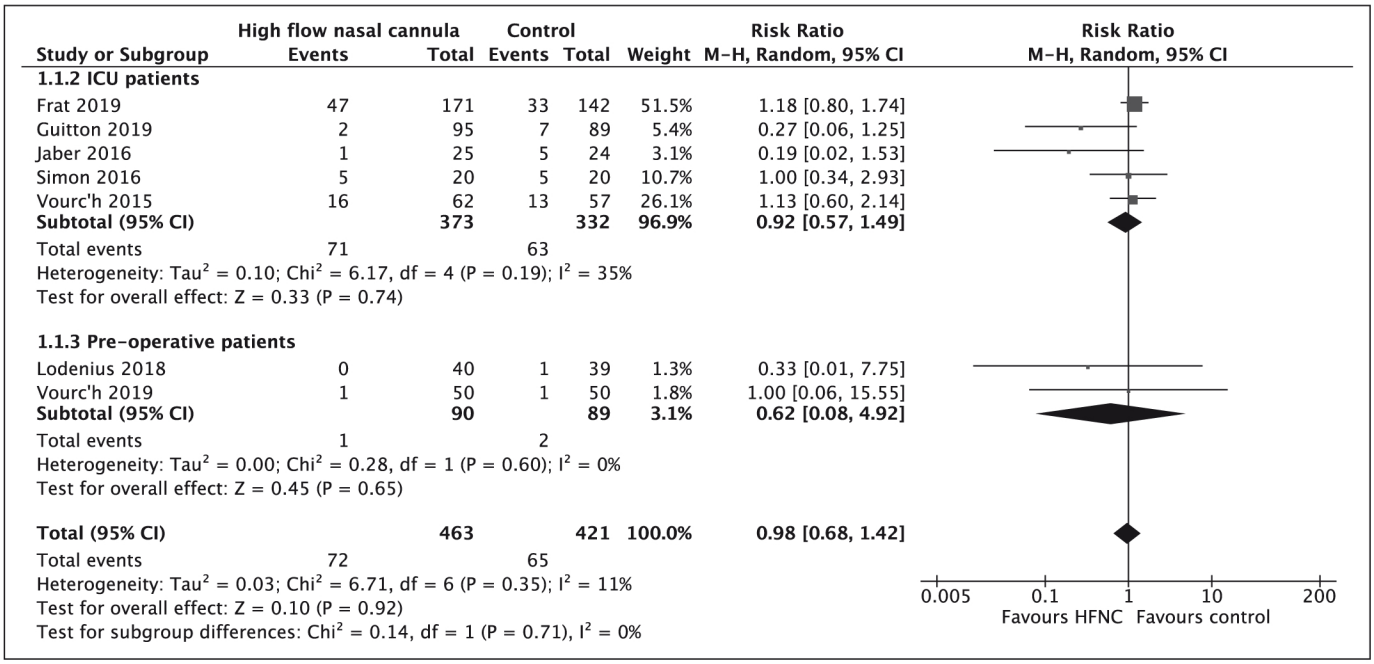

Figure 2. Peri-intubation hypoxemia forest plot. *df* = degrees of freedom, M-H = Mantel-Haenszel.

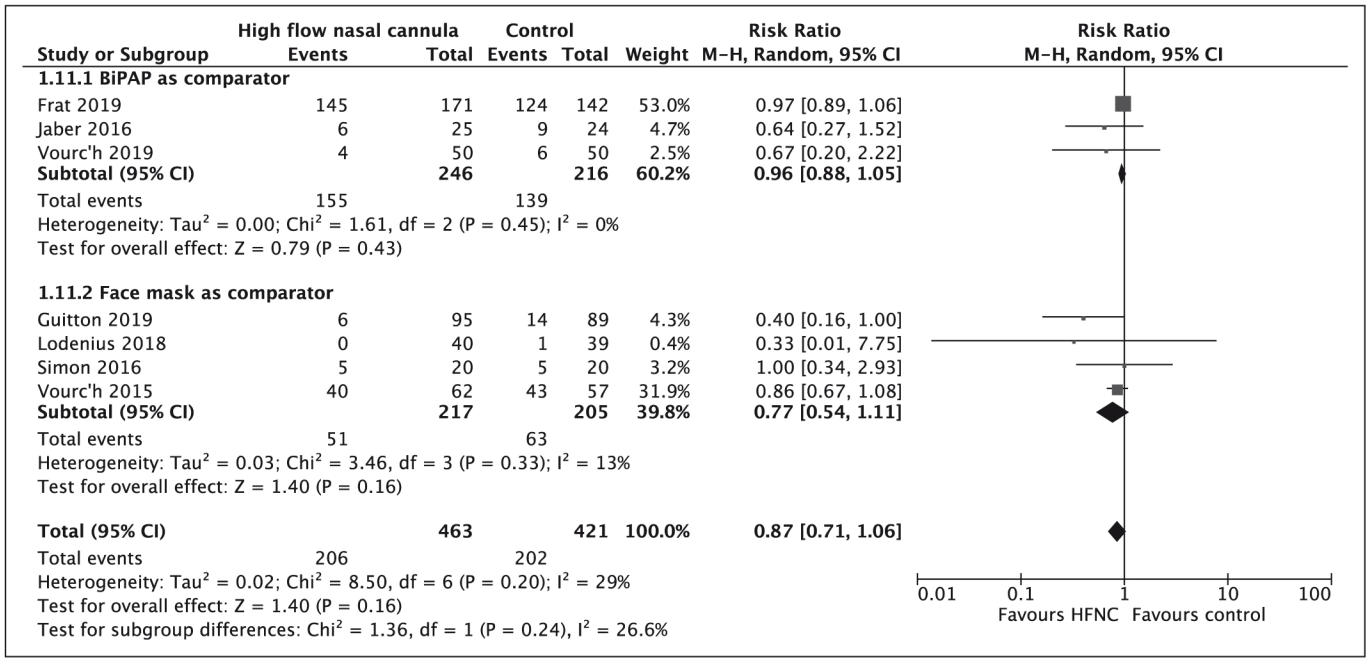

Figure 3. Serious peri-intubation complications forest plot. BiPAP = bilevel positive airway pressure, *df* = degrees of freedom, HFNC = high-flow nasal cannula.

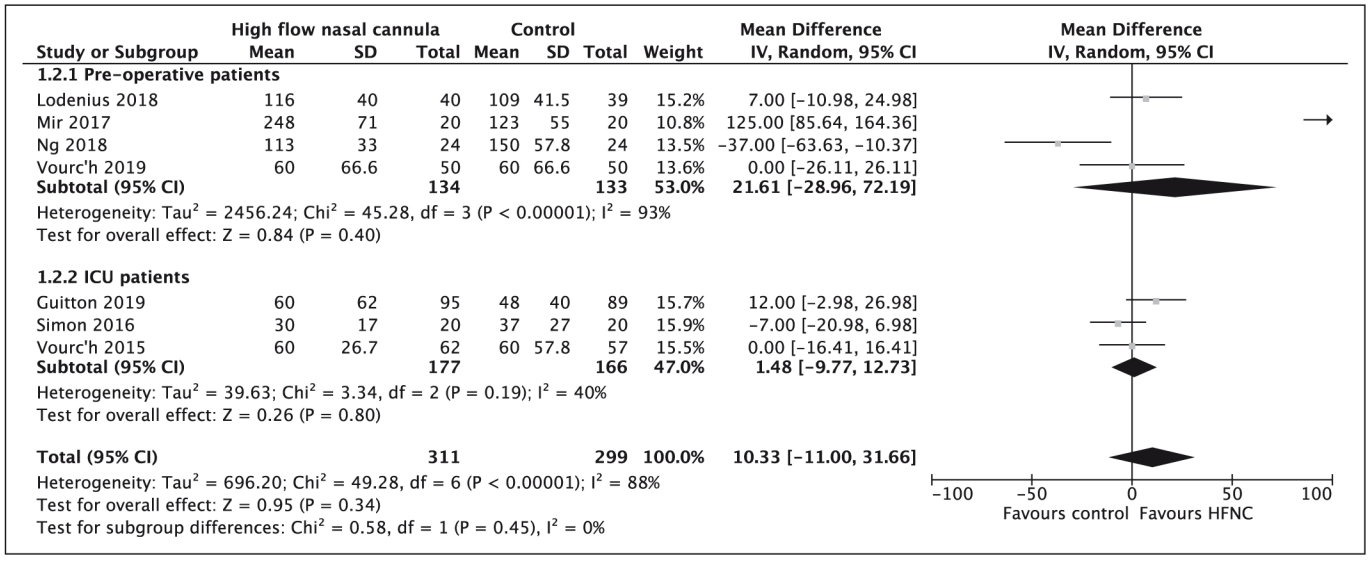

Figure 4. Total apneic time in seconds forest plot subdivided by patient subtype. *df* = degrees of freedom, HFNC = high-flow nasal cannula.

Pa_{CO_2}, ICU LOS, and 28-day mortality (**Supplementary Fig. 5**, Supplemental Digital Content 6, http://links.lww.com/CCM/F299; **Supplementary Fig. 6**, Supplemental Digital Content 7, http://links.lww.com/CCM/F300; and **Supplementary Fig. 7**, Supplemental Digital Content 8, http://links.lww.com/CCM/F301; legend, Supplemental Digital Content 1, http://links.lww.com/CCM/F294).

Subgroup and Sensitivity Analyses

Further subgroup analyses based on patient or comparator subtype showed that there was a significant increase in Pa_{O_2} levels after preoxygenation in the operative subgroup of patients who received HFNC (Fig. 4). There was no credible effect on any of the other outcomes of interest (Supplementary Fig. 4, Supplemental Digital Content 5, http://links.lww.com/CCM/F298; Supplementary Fig. 5, Supplemental Digital Content 6, http://links.lww.com/CCM/F299; Supplementary Fig. 6, Supplemental Digital Content 7, http://links.lww.com/CCM/F300; Supplementary Fig. 7, Supplemental Digital Content 8, http://links.lww.com/CCM/F301; **Supplementary Fig. 8**, Supplemental Digital Content 9, http://links.lww.com/CCM/F302; and **Supplementary Fig. 9**, Supplemental Digital Content 10, http://links.lww.com/CCM/F303; legend, Supplemental Digital Content 1, http://links.lww.com/CCM/F294).

Sensitivity analysis excluding trials that reported only Sp_{O_2} did not alter the conclusions (**Supplementary Fig. 10**, Supplemental Digital Content 11, http://links.lww.com/CCM/F304; and **Supplementary Fig. 11**, Supplemental

Study or Subgroup	High flow nasal cannula Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.5.1 Pre-operative patients								
Heinrich BiPAP 2014	405	99	6	373	88	11	0.5%	32.00 [-62.76, 126.76]
Heinrich Facemask 2014	405	99	5	315	62	11	0.6%	90.00 [-4.19, 184.19]
Ng 2018	471	64	24	357	93	24	2.3%	114.00 [68.83, 159.17]
Subtotal (95% CI)			**35**			**46**	**3.4%**	**93.68 [49.81, 137.55]**
Heterogeneity: $Tau^2 = 282.88$; $Chi^2 = 2.37$, df = 2 (P = 0.31); $I^2 = 16\%$								
Test for overall effect: Z = 4.19 (P < 0.0001)								
1.5.2 ICU patients								
Frat 2019	82	6	171	91	5	142	31.5%	-9.00 [-10.22, -7.78]
Guitton 2019	167	0.001	95	167	0.001	89	31.8%	0.00 [-0.00, 0.00]
Jaber 2016	171	181	25	100	104	24	0.7%	71.00 [-11.25, 153.25]
Simon 2016	184	107	20	173	86	20	1.3%	11.00 [-49.16, 71.16]
Vourc'h 2015	92	5	62	84	5	57	31.2%	8.00 [6.20, 9.80]
Subtotal (95% CI)			**373**			**332**	**96.6%**	**0.27 [-6.64, 7.19]**
Heterogeneity: $Tau^2 = 37.68$; $Chi^2 = 288.54$, df = 4 (P < 0.00001); $I^2 = 99\%$								
Test for overall effect: Z = 0.08 (P = 0.94)								
Total (95% CI)			**408**			**378**	**100.0%**	**3.59 [-3.49, 10.68]**
Heterogeneity: $Tau^2 = 41.01$; $Chi^2 = 316.96$, df = 7 (P < 0.00001); $I^2 = 98\%$								
Test for overall effect: Z = 0.99 (P = 0.32)								
Test for subgroup differences: $Chi^2 = 16.99$, df = 1 (P < 0.0001), $I^2 = 94.1\%$								

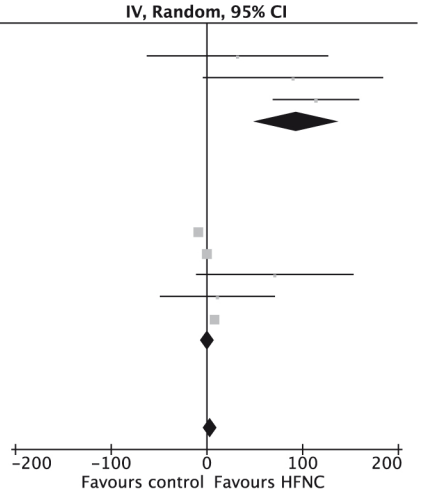

Figure 5. Pa_{O_2} after preoxygenation forest plot subdivided by patient subtype. *df* = degrees of freedom, HFNC = high-flow nasal cannula.

Digital Content 12, http://links.lww.com/CCM/F305; legend, Supplemental Digital Content 1, http://links.lww.com/CCM/F294).

DISCUSSION

This systematic review and meta-analysis demonstrate that the use of HFNC in the peri-intubation period likely provides no benefit compared with alternative oxygen delivery devices with regard to physiologically and clinically important outcomes. Further, subgroup analysis based on patient subtype, comparator, and individual study ROB did not identify any specific populations or groups that would require alternative consideration. Of note, most events, specifically for the outcomes of serious complications, hypoxemic events, and deaths, were reported in trials that evaluated critically ill patients. The overall certainty of evidence was moderate to low and was limited primarily by imprecision.

Although other reviews have examined the role HFNC (2, 22, 24–26) in various clinical scenarios, only one other review has looked at HFNC use in the peri-intubation period (27). However, although Cabrini et al (27) looked at all RCTs that examined any drug, technique or device that could improve tracheal intubation, this review was the first one to focus specifically on HFNC. Furthermore, our review includes data from three very recently published RCTs, one of which is the largest trial included in this systematic review (8, 15), making this also the most up-to-date review on the topic. Our comprehensive search strategy, preregistered methodology, and assessment of certainty using the GRADE approach are also strengths of this study.

Our review also has limitations. First, the trials included varied in the patients enrolled and the comparators used. However, this clinical heterogeneity did not also manifest as a high degree of statistical heterogeneity. Furthermore, we found no evidence to support credible subgroup differences when we examined these variables. Second, one secondary outcome (peri-intubation complications) was comprised of several components with variable clinical importance. In addition, trials did not consistently report Sp_{O_2} or Pa_{O_2} levels when measuring hypoxia. As a result, for trials that reported only Sp_{O_2} levels, we had to use a conversion equation to convert those levels to Pa_{O_2}. Because this equation is not always reliable and varies based on pH, this may have introduced a degree of error in our Pa_{O_2}-dependent outcomes. However, when we performed a sensitivity analysis excluding these studies, our results did not change. Finally, all trials included in this review were unblinded.

Given that no demonstrable benefit was found in the outcomes measured with the use of HFNC peri-intubation, it may be claimed that it confers no advantage in this clinical situation. Our primary hypothesis for lack of HFNC superiority was that most patients, even in the critically ill subgroup, likely had enough functional residual capacity even with conventional oxygen preoxygenation to prevent severe desaturation and related complications during the intubation period. Mean apnea times were less than 2 minutes for all studies included except for one study in the preoperative group that had a mean apnea time of 4 minutes in the HFNC arm (14). In the critically ill patient population, who are at much higher risk of hypoxia, the mean apnea times were on average less than a minute. Because HFNC (delivered through the nostrils) allows for apneic oxygenation in contrast to face mask therapy, it likely has a beneficial effect during prolonged apneic periods or very severe hypoxia. As a result, we hypothesize that the benefits of HFNC may only be seen during prolonged intubations or patients with very severe hypoxia (partial pressure of arterial oxygen/fraction of inhaled oxygen ratio < 100), subgroups that we were unable to isolate in our included studies.

However, our study is only as good as the data reported. The HFNC may be better tolerated by selected patients, especially those more awake or claustrophobic. These benefits could contribute to patient comfort and or facilitate intubation for clinicians when used during intubation. Only one of the included

trials, reported on the number of intubation attempts, type of device used for intubation, overall hypoxemic time, or the quality of airway visualization (21). Studies have also shown that such emergency airway situations are accompanied by considerable physician stress. This too was not measured. Some authors have suggested that apneic time may be a surrogate for operator difficulty during intubation (28). Although this review did not demonstrate a difference in apneic time, only seven of the 10 trials reported this outcome. Notwithstanding, variance in apneic time has also been reported in patients who are considered to be easy or moderately difficult intubations (28). These findings may be influenced by other factors. For example, operators may take their time with patients who are easier to intubate or allow less-experienced operators attempt intubation first recognizing that selected patients may have greater reserve. Further research on many of these aspects is still required.

CONCLUSIONS

The studies published to date suggest with low-to-moderate certainty evidence that the use of HFNC has no measurable effect on hypoxemia, serious complications, oxygenation, ICU LOS, or overall survival when used in the peri-intubation period. These findings do not support routine use of HFNC during endotracheal intubation of critically ill adults. However, further studies on this topic will be needed to answer this question with higher certainty. Furthermore, questions regarding performance of HFNC for ease of intubation procedure, operator stress level, difficult intubations, and severe hypoxia remain to be addressed.

Dr. Mauri received speaking fees from Fisher and Paykel unrelated to the present work. Dr. Mancebo received funding from Faron, Medtronic, and IMT medical (travel support); personal fees from Faron and Medtronic; and he disclosed that Fisher Paykel and A-Lung provided medical equipment to participate in multicenter clinical trials (high-flow nasal oxygen therapy and extracorporeal carbon dioxide removal, respectively), and Covidien (Medtronic) and Canadian Institutes of Health Research sponsored a multicenter randomized clinical trial. IMT Medical provided travel and hotel expenses to attend a meeting. Dr. Maggiore disclosed that he is the principal investigator of the Impact of Nasal High-flow vs Venturi Mask Oxygen Therapy on Weaning Outcome: A Multicenter, Randomized, Controlled Trial (RINO trial) (Clinicaltrials.gov, NCT02107183), which was supported by Fisher and Paykel Healthcare, and he received funding from lecturing for General Electric Healthcare and Draeger Medical. Dr. Brochard's institution received funding from Medtronic Covidien and Fisher and Paykel. Dr. Rochwerg is supported by a Hamilton Health Sciences Early Career Research Award. The remaining authors have disclosed that they do not have any potential conflicts of interest.

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