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Keywords:	high flow nasal cannula, surgical patients, reintubation, escalation of respiratory support, pulmonary complications

The effect of high-flow nasal cannula oxygen therapy compared with conventional oxygen therapy in postoperative patient: a systematic review and meta-analysis

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Objective: Postoperative respiratory failure is common in postoperative patient after extubation, with increased reintubation rate and mortality. We aim to evaluate the effect of high flow nasal cannula oxygen therapy (HFNC) on reintubation rate compared with conventional oxygen therapy (COT) in post-operative patients in this meta-analysis.

Design: Systematic review and meta-analysis of published literature.

Data sources: PubMed, Embase, the Cochrane Library, web of science of studies, China National Knowledge Index (CNKI) and Wan fang databases were searched up to August 2018.

Eligibility criteria: Eligible articles comparing HFNC with COT in adult post-extubated surgical patients were included. The primary outcome was the intubation rate and escalation rate of respiratory support; the secondary outcome was incidence of postoperative pulmonary complications (PPCs) and mortality.

Data extraction and synthesis: two investigators extracted the data independently. We assessed internal validity using the risk of bias tool for RCTs according to the Cochrane Collaboration methodology and Newcastle-Ottawa scale to assess case-control or cohort study.

Results: Ten studies (1327 patients) were included. The pooled effect showed that HFNC significantly reduced the reintubation rate (risk ratio (RR) 0.31, 95% CI 0.18-0.52, P <0.0001) and escalation rate of respiratory support (RR 0.43, 95% CI 0.26-0.73, P =0.002), compared with COT. In addition, Weak evidence of a reduction of PPCs (RR 0.85, 95% CI 0.68-1.07, P =0.17) and mortality (RR 0.42, 95% CI 0.15-1.17, P =0.10) with HFNC versus COT were revealed.

Conclusions: The results of current meta-analysis suggest that application of HFNC significantly reduce the reintubation rate and escalation rate of respiratory support, and have tendencies to reduce PPCs rate and mortality in postoperative post-extubated patients.

Key Words: high flow nasal cannula; surgical patients; reintubation; escalation of respiratory support; mortality

Strengths and limitations of this study

- This is a meta-analysis comparing the effects of high flow nasal cannula oxygen therapy and conventional oxygen therapy on initial treatment failure, reintubation rate, PPC incidence, and mortality in postoperative patients.
- The possible risk of bias for RCTs, case-control and cohort study were assessed according to the Cochrane Collaboration methodology or Newcastle-Ottawa scale.
- Patients undergoing combined surgery (e.g., thoracoabdominal surgery) probably are a source of heterogeneity.
- Inclusion of non-randomized studies may be an important limitation of this paper; selection bias may confuse observations, so this meta-analysis uses RCT and non-RCT subgroup analysis to solve the problem.

INTRODUCTION

Respiratory failure is the major complication in postoperative patient, which increases perioperative mortality, length of ICU and hospital stay, and also health care expenses [1 2].The etiologies of early postoperative respiratory failure include hypoxemia, diaphragmatic dysfunction, atelectasis due to postoperative alveolar collapse or secretions accumulation etc. [3 4] . Several prophylactic managements have been proposed to reduce the incidence of postoperative pulmonary complications (PPCs) which could possibly reduce the necessity of reintubation and improve the prognosis of surgical patients, including protective intraoperative mechanical ventilation, postoperative physiotherapy and noninvasive mechanical ventilation (NIV) [5]. Although there is more evidence to support non-invasive ventilation for the treatment of postoperative respiratory failure [6], this technique requires substantial resources and higher difficulty techniques to implement, and may cause discomfort to the patients [7].

High flow nasal cannula oxygen therapy (HFNC) is increasingly used in the prevention and treatment of respiratory failure in post-extubated non-surgical patients and surgical patients [6 8-10]. Several mechanisms of HFNC have been proposed and investigated compared with conventional oxygen therapy (COT), such as positive effects on comfort and tolerance, stable fraction of inspired oxygen delivery due to a reduction of room air entrainment, sufficient humidification, dead space wash-out and positive end expiratory pressure (PEEP) effect[3 4 11 12] [13 14] All of these aspects may be valuable for postoperative patients. However, failure of HFNC may cause delayed intubation and worse clinical outcomes leading to higher mortality in patients with respiratory failure [15]. Therefore, whether HFNC can bring benefits in postoperative patients that has been attracting more and more attentions. Recently, several studies on this topic have been published, while the conclusions are inconsistent [16-18].

These considerations led us to conduct a meta-analysis comparing the effect of HFNC with conventional oxygen therapy on the escalation rate of respiratory support and intubation rate, and also the clinical outcomes in postoperative patients after extubation.

METHODS

Study selection

Two authors (Z-H.L., S-S.M.) assessed titles and abstracts independently to determine whether a study met the inclusion criteria. All trials were independently reviewed according to the inclusion and exclusion criteria. Any differences on the inclusion or exclusion of a particular study were resolved by consensus after a discussion with the third reviewer (W.C.).

Data Sources and Searches

We searched PubMed, Embase, the Cochrane Library, web of science of studies, China National Knowledge Index (CNKI) and Wan fang databases from inception to August 31, 2018. We also searched the references from relevant articles in avoiding loss of studies. We used the following keywords for the searches: ("high flow" or "high-flow") and ("operation" or "operative" or "surgery" or "Surgical"). No limits for the location of the original study, study design, conference abstract, gender, sample size, or language were entered for the search.

Inclusion Criteria

To determine which publications were suitable for the meta-analysis, we used the following selection criteria: 1) study population was adult post-extubated surgical patients (≥ 18 years); 2) compared HFNC with COT; 4) the data of respiratory support escalation or reintubation is required, or mortality was available; and 5) number of patients was provided in HFNC and COT groups.

Exclusion Criteria

Exclusion criteria were as follows: 1) Patients who did not use HFNC after post-operative extubation; 2) the trial did not use conventional oxygen therapy as a control; 3) the study was a review, letter, case report, or other type of publication not based on original research; 4) in vitro study or animal experiments.

Data extraction

Two investigators (X-W.Z., Z-H.L.) extracted the data independently. The primary outcome was the reintubation rate and the rate of respiratory support escalation (altered to HFNC, NIV or invasive mechanical ventilation in COT group; and NIV or invasive mechanical ventilation in HFNC group). The secondary outcomes were the incidence of PPCs （which included: PPC diagnosed by original article, new postoperative pneumonia or atelectasis）and mortality. Any disagreements between the two investigators were resolved by discussion and consensus with the third one (W.C.).

Subgroup Analysis

For the primary and secondary outcomes, we performed the following a priori subgroup analyses: patients with different type of surgery (cardiac, thoracic and abdominal surgery); different risks of reintubation (high risk or low risk: the average values of risk-related parameters for reintubation were assessed according to Hernandez G's trials),[9 10] maintaining the different target percutaneous arterial oxygen saturation (SPO2:90%-93% and 95%) ,study design (Non-RCT or RCT) and strategy (prophylactic or therapy).

Assessment of Risk of Bias

The possible risk of bias for RCTs was assessed according to the Cochrane Collaboration methodology[19], which consists of the following domains: adequacy of sequence generation; allocation sequence concealment; blinding of participants and caregivers; blinding for outcome assessment; incomplete outcome data; selective outcome reporting; and the other sources of bias. To assess the possible risk of bias for case-control or cohort study, we adopted the Newcastle-Ottawa scale, which focused on three categories: selection, comparability, and exposure or outcome with each being awarded a maximum of nine stars on items [20].

Data Synthesis and Analysis

We used Review Manager Software (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen Denmark) for the analysis. Categorical variables were presented as proportions or ratios, and compared by risk ratio (RR) with 95% confidence intervals (CIs). The statistical heterogeneity was measured and quantified by chi-square test and the I^2 test. In addition, I^2 index was used to assess heterogeneity in the meta-analysis with 25%, 50% and 75% of I^2 values meaning low, medium and high heterogeneity, respectively proposed by Higgins and colleagues [21]. If the data heterogeneity is obvious ($I^2 > 50\%$), we used the random effects model; otherwise, a fixed effects model was applied. Publication bias was evaluated by visual inspection of funnel plots. We considered a 2-tailed *P* value less than 0.05 as statistically significant.

RESULTS

Search Results, Trial Characteristics and quality

The selection process for the eligible studies is shown in Figure1. Firstly, 4572 potentially relevant records were identified and 624 duplicates were excluded. Secondly, the titles and abstracts were screened for the terms “high flow nasal cannula”, “surgery” or the other operation”, 30 studies were remained for assessment. Finally， after searching and reading all full-text articles or conference abstracts, a total of 1327 patients in 10 trials were included, of which 615 patients were assigned to the HFNC group, and 712 to the COT group. The patients were followed-up until ICU or hospital discharge. The main characteristics of the included studies are shown in **Table 1**. The studies were published from 2013 to 2018 and conducted in Oceania, Europe, Asia and American with 3 cardiac surgery[17 22 23], 5 thoracic surgery [24-28], 1 abdominal surgery[29], and1 mixed patients[16] from different types of surgeries. Seven studies were RCTs, two were retrospective studies, and one was case-control study. The results of quality assessment were shown in **Table 2**.

Table1: Populations and interventions in studies of oxygen therapy in postoperative adults

Study	Study design	Type of surgery	Patient characteristics (HFNC/COT)			Min target SPO2 (%)	Risk of reintubation	Flow rate(L/min)
			Patient number	BMI	Age			
Chen, 2018	Case-control study	Thoracic	44/45	NA	66/64	90	High	35-60
Xu, 2018	Retrospective	Cardiovascular	45/45	26/27	57/54	95	High	35-60
Brainard, 2017	RCT	Thoracic	18/26	26/25	57/59	95	NA	40
Dhillon, 2017	Retrospective	Mixed	46/138	NA	63/58	NA	NA	NA
Geng, 2017	RCT	Thoracic	25/23	NA	63/63	90	High	35-60
Sun, 2017	RCT	Thoracic	24/24	NA	67/65	100	High	40-60
Yu, 2017	RCT	Thoracic	56/54	26/25	56/56	95	High	35-60
Futier, 2016	RCT	Abdominal or combine thoracic	108/112	25/25	62/661	95	NA	50-60
Corley, 2015	RCT	Cardiovascular	81/74	36/35	63/65	95	High	35-50
Parke, 2013	RCT	Cardiovascular	169/171	28/29	65/66	93	High	45

Data are expressed as median (interquartile range), or mean (standard deviation); NA, Not available or not reported

Table 2

Table 2a Quality assessment of RCTs included by the Cochrane collaboration tool

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data assessments	Selective reporting.
Brainard, 2017	Unclear	Low	High	Unclear	Low	Low
Geng, 2017	Low	Unclear	High	Unclear	Low	Low
Sun, 2017	Low	Low	High	Low	Low	Unclear
Yu, 2017	Unclear	Low	High	Low	Unclear	Low
Futier, 2016	Low	Low	High	Unclear	Low	Low
Corley, 2015	Low	Low	High	Low	Low	Low
Parke, 2013	Low	Low	High	Low	Low	Low

Low; low risk of bias, High; high risk of bias, Unclear; unclear risk of bias according to the relative information

Table 2b Quality assessment of studies included by Newcastle-Ottawa scale

Study	Selection				Comparability	Outcome			Overall stars
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Xu, 2018	★	★	★	★	★	-	★	★	7
Dhillon, 2017	★	★	★	★	★	-	★	★	7

★ the quality met the criterion of this specific item; - Self-reported or unstated

Table 2c Quality assessment of studies included by Newcastle-Ottawa scale

Study	Selection				Comparability	Exposure			Overall stars
	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Chen, 2018	★	★	-	★	★	★	★	★	7

★ the quality met the criterion of this specific item; - Self-Hospital population control study or unstated

Outcomes analyses

Nine studies reported the data of reintubation rate. 507 patients treated with HFNC and 600 patients received COT. The reintubation rate in the HFNC group was significantly lower compared with COT group (RR 0.31, 95% CI 0.18 to 0.52, *P* <0.0001, I^2 = 0%) (Figure2, Table 3).

Escalation rate of respiratory support was reported in ten trials included 615 patients treated with HFNC and 712 patients received COT. The pooled results suggested that use of HFNC was associated with a significant reduction in escalation rate of respiratory support (RR 0.43, 95% CI 0.26 to 0.73, *P* =0.002, I^2 = 54%) with publication bias (Figure3, Figure4). There was significant heterogeneity among the pooled studies. Exclusion of study by Futier and colleagues[18] resolved the heterogeneity and the result was consistent (nine trials; RR 0.35, 95% CI 0.24 to 0.50, *P* <0.00001, I^2 = 0%).

Five studies reported the data of the incidence of PPCs. 252 patients treated with HFNC and 354 patients received COT. The incidence of PPC in the HFNC group has a downward trend than the COT group (RR 0.85, 95% CI 0.68 to1.07, *P* =0.1, I^2 = 0%) (Figure 5a, Table 3).

Investigators reported the hospital mortality in 5 trails. Of the 422 patients treated with HFNC, 5 (1.18%) died in the hospital, compared with 19 of the 520 (3.65%) receiving COT. Evidently, Weak evidence of a reduction of mortality with HFNC versus COT was recorded (RR 0.42, 95% CI 0.15-1.17, *P* =0.10) (Figure 5b, Table 3).

The findings of the subgroup analyses for the primary and secondary outcomes of reintubation rate, escalation rate of respiratory support and mortality according to type of surgery, study design, min-target SPO2, risk of reintubation and therapy strategy are summarized in Table 3. For these outcomes, the analyses of intubation rate in thoracic surgery, RCT, Non-RCT, min target SPO2 of 95%, high risk of reintubation, prophylactic and therapy subgroups, and also escalation rate of respiratory support in all subgroups except min target SPO2 of 93% subgroup did not change significantly.

Table3: Summary estimates of effect of high flow oxygen therapy in postoperative adults

Outcome	No studies (No of patients)	Summary estimate (95% CI)	P value (summary estimate)	P value (heterogeneity)	I^2 (%)
Reintubation	9 (1107)	0.31* (0.18 to 0.52)	0.0001	0.53	0
Cardiac surgery	3 (585)	0.41* (0.04 to 3.93)	0.44	0.13	51
Thoracic surgery	5 (338)	0.25* (0.12 to 0.50)	0.0001	0.65	0
RCT	6 (745)	0.34* (0.15 to 0.74)	0.007	0.31	16
Non-RCT	3 (362)	0.28* (0.14 to 0.59)	0.0009	0.59	0
Min target SPO2 (90%-93%)	3 (476)	0.33* (0.05 to 2.09)	0.24	0.07	62
Min target SPO2 (95%)	4 (399)	0.26* (0.08 to 0.84)	0.03	0.71	0
High risk of reintubation	7 (879)	0.26* (0.14 to 0.49)	0.0001	0.42	1
Escalation rate of respiratory support	10 (1327)	0.43* (0.26 to 0.73)	0.002	0.02	54

Cardiac surgery	3 (585)	0.43* (0.24 to 0.76)	0.004	0.51	0
Thoracic surgery	5 (404)	0.24* (0.14 to 0.39)	0.00001	0.4	2
RCT	7 (965)	0.46* (0.22 to 0.93)	0.03	0.01	64
Non-RCT	3 (362)	0.36* (0.20 to 0.66)	0.001	0.60	0
Min target SPO2 (90%-93%)	3 (476)	0.38* (0.23 to 0.61)	0.0001	0.34	8
Min target SPO2 (95%)	5 (619)	0.46* (0.15 to 1.44)	0.18	0.01	70
prophylactic	7 (1143)	0.50* (0.25 to 1.00)	0.05	0.02	59
Therapy	3 (184)	0.31* (0.18 to 0.55)	0.0001	0.45	0
High risk of reintubation	7 (879)	0.33* (0.22 to 0.49)	0.00001	0.5	0
PPCs	5 (606)	0.85* (0.68 to 1.07)	0.17	0.92	0
RCT	4 (422)	0.84* (0.67 to 1.06)	0.14	0.83	0
prophylactic	4 (558)	0.86* (0.68 to 1.08)	0.20	0.87	0

Mortality	5 (942)	0.42* (0.15 to 1.17)	0.10	0.79	0
Cardiac surgery	1 (340)	1.01* (0.06 to 16.05)	0.99	-	-
Thoracic surgery	2 (198)	0.26* (0.03 to 2.25)	0.22	-	-
RCT	3 (670)	0.77* (0.17 to 3.41)	0.73	0.82	0
Non-RCT	2 (272)	0.27* (0.06 to 1.18)	0.08	0.98	0
Min target SPO2 (90%-93%)	2 (428)	0.41* (0.08 to 2.09)	0.29	0.45	0
Min target SPO2 (95%)	2 (330)	0.69* (0.12 to 4.06)	0.68	-	-
High risk of reintubation	3 (538)	0.41* (0.08 to 2.09)	0.29	0.45	0

RCT, randomized controlled trial; PPCs, postoperative pulmonary complications *Relative risk

DISCUSSION

The rationale for using HFNC in the postoperative patients depends mainly on whether HFNC can be an effective tool for treating or preventing PPCs and respiratory failure compared to conventional oxygen therapy. The results of the current systematic review and meta-analysis included 10 studies suggest that: 1) application of HFNC was associated with significant lower rate of respiratory support escalation and reintubation rate compared with COT in postoperative patients after extubation. 2) The trends of reduced PPCs and mortality were found in postoperative patients treated with HFNC. 3) HFNC did significantly reduce reintubation rate and initial treatment failure rate of patients after thoracic surgery or with high risk of reintubation. 4) HFNC may delay intubation in patients after cardiac surgery.

Although the results from this meta-analysis are encouraging, several important issues deserve a detailed discussion. First, there are important differences between previous research and this meta-analysis. Two systematic reviews used traditional pairwise comparisons to evaluate noninvasive respiratory support strategies in postoperative patients [30 31]. However, due to the small sample size of the two reviews (2 studies included 495 patients in Zhu's study, 3 studies included 715 postoperative patients in Huang's study,) the primary results included rate of respiratory support escalation and reintubation rate are inconsistent between them. This current meta-analysis included 10 studies (1327 patients), and the reintubation rate in our meta-analysis was consistent with that of postoperative subgroup patients in the Huang's study[30], the result of respiratory support escalation rate was consistent with Zhu's study [31]. In addition, only cardiac surgery patients was enrolled in Huang's study, and their primary outcomes are similar to our subgroup analysis results, that is that HFNC can reduce the initial treatment failure rate without reducing the rate of reintubation, which indicates that HFNC may delay the intubation time without reducing the reintubation rate in cardiac surgery group. Kang's study found that failure to treat HFNC leads to intubation delay which may be associated with increased mortality [15]. Due to the small number of subgroup studies included in this meta-analysis,

statistically significant results were not available in the analysis of mortality after cardiac surgery, which required more extensive studies to confirm.

Second, heterogeneity was observed among pooled studies in the primary outcome of respiratory support escalation rate. This is not surprising, given the differences in type of surgery, risks of reintubation, target SPO2, study design and therapeutic strategy. Our sensitivity analyses and publication bias based on funnel plot showed that the trial by Futier and colleagues [18] probably contributed to the observed heterogeneity. Unlike other included trials, Futier and colleagues enrolled postoperative patients included patients undergoing combined thoracoabdominal surgery, longer follow-up time infection (7 days), and excluded surgical duration <2 hours and BMI ≥25 kg/m^2; while duration of anesthesia and abdominal surgery are significant risk factors for postoperative pulmonary complications, which was associated with worse prognosis in patients[32] . After excluding this trial, the pooled result of the remaining studies still showed a reduction in initial treatment failure rate, which added robustness to our primary outcome.

Third, the subgroup analysis of RCT suggested that HFNC could reduce intubation rate and respiratory support escalation rate, but not mortality, which is consistent with the overall analysis results. This effect might be attributed to better amenity, tolerance and more stable oxygen concentration of HFNC[33]. Subgroup analysis also showed that HFNC had a better effect on patients after thoracic surgery, which might be because HFNC increase the end-expiratory lung volume due to the provision of end-expiratory pressure (PEEP) effect, decrease airway resistance and reduce breathing work[34 35] ; these effects can minimize partial lung retraction after extubation. Both RCT and non-RCT subgroups showed that HFNC has a positive effect on patients after postoperative extubation, whether it is prevention or treatment of respiratory failure.

Fourth, HFNC can reduce reintubation rate compared with COT in patients with low risk of reintubation [10], and is not inferior to NIV for preventing reintubation and post-extubated respiratory failure in patients at high risk of intubation [9]. We performed a subgroup analysis of high intubation risk and identified 7 studies as high

intubation risk based on the low/high risk criteria for reintubation [9 10] , The results suggest that HFNC is also associated with lower rate of respiratory support escalation and reintubation rate in postoperative patients with high risk of reintubation.

Recent studies reported that among critically ill patients, conservative oxygen therapy (with a slightly lower SPO2 target) vs conventional therapy resulted in lower mechanical ventilation time, hospital or ICU mortality [36 37]. This meta-analysis showed that when SPO2 was maintained above 90%-93%, HFNC may reduce the rate of respiratory support without reducing the intubation rate; however, when maintaining SPO2 above 95%, the result is opposite to the former. Those indicate that although the rate of increase in respiratory support can be reduced at lower SPO2 threshold vs the higher target SPO2, the time to reintubation is delayed, but we did not get the results of delaying intubation leading to poor prognosis like Kang's study[15] . This may be attributed to the inclusion of less research on mortality; more studies are needed to answer this question definitively.

Postoperative low PPC incidence is associated with reduction of postoperative patient mortality [38]. Weak evidence suggests that HFNC can reduce incidence rate of PPCs and improve outcome in postoperative patients compared with COT, and mortality in HFNC group (1.18%) has a lower trend than COT (3.65%), and that may require a larger RCT study to confirm.

Finally, to the best of our knowledge, this is the largest sample size meta-analysis to assess the efficacy of HFNC as a technique in intubation rate and rate of respiratory support in postoperative patients; however, our study has some limitations. Firstly, our meta-analysis showed that use of HFNC affect intubation rate and rate of respiratory support, but those outcomes may be weaken because not all of the included studies have them as the primary endpoint. Secondly, there were differences in the timing and duration of treatment for HFNC in the included trials. Third, the different assess respiratory risks in surgical patients in Catalonia (ARISCAT score) [39] were also different in the included studies, which may affect the outcomes.

Conclusion

In summary, based on available data, our results demonstrate that, compared with conventional oxygen therapy, HFNC might significantly reduce intubation rate and rate of respiratory support in adult postoperative patients, and the results also indicate a trend toward reduced mortality in postoperative patients with HFNC. This meta-analysis provides a good data base for the application of HFNC in postoperative patients.

Footnotes

Contributors: ZL and FG had full access to all the data in the study and take responsibility for its integrity and the accuracy of the data analysis. ZL, SM, and FG performed the systematic review, study selection, statistical analysis, and elaboration of the article for publication. WC, JX and XZ contributed to the data extraction and quality assessment. All the authors participated in the article writing and figure elaboration.

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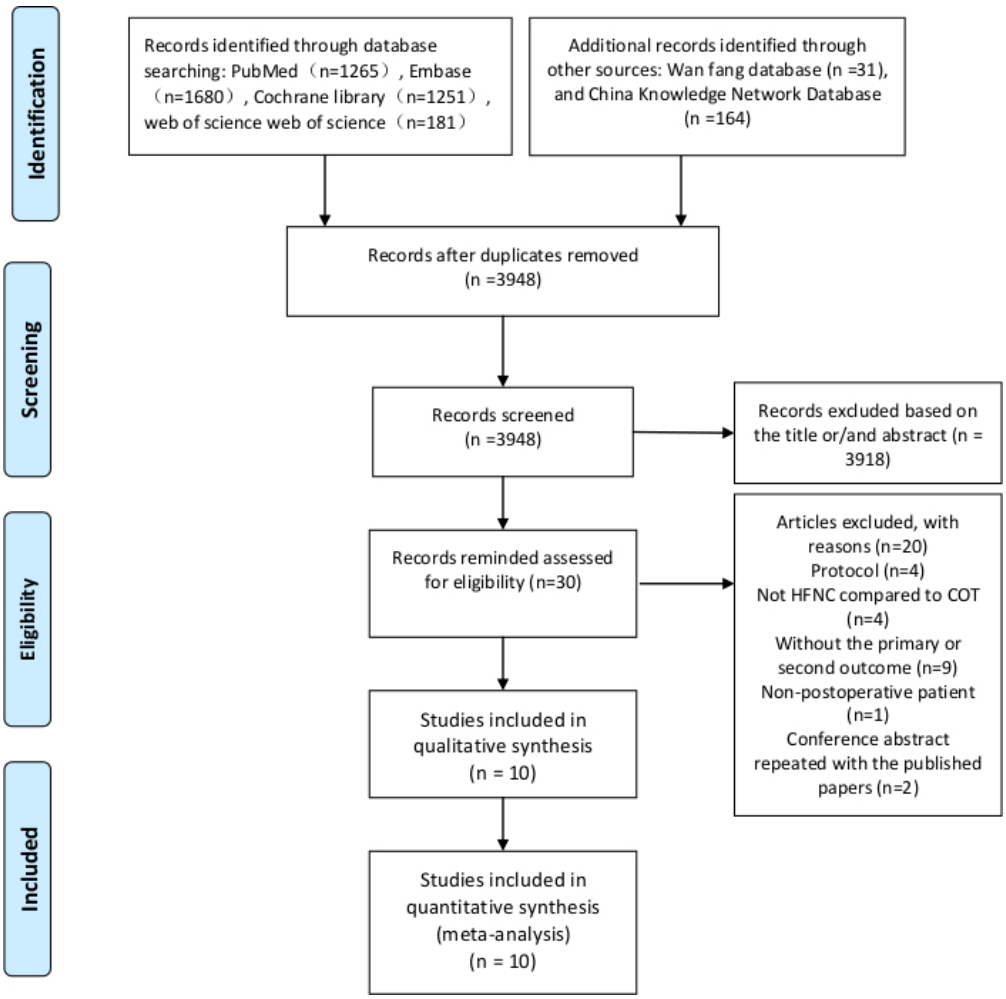
Table 1: Populations and interventions in studies of oxygen therapy in postoperative adults

Table 2: The quality assessment of included studies

Table 3: Summary estimates of effect of high flow oxygen therapy in postoperative adults



Flow diagram of study selection

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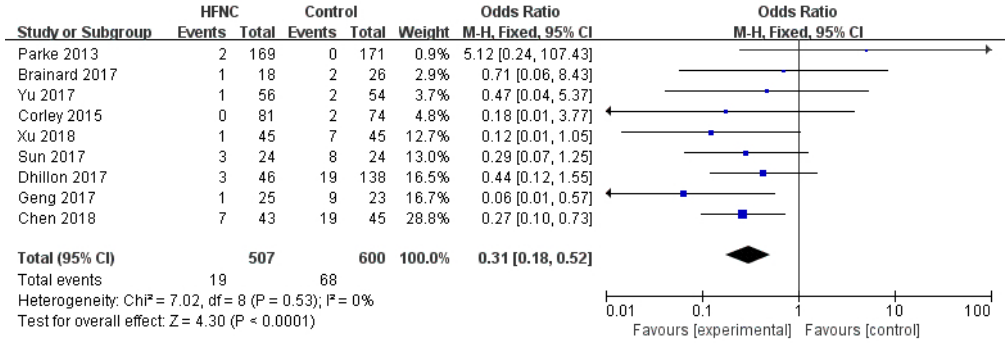

Reintubation rate in post-extubated surgical patients with high-flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT).

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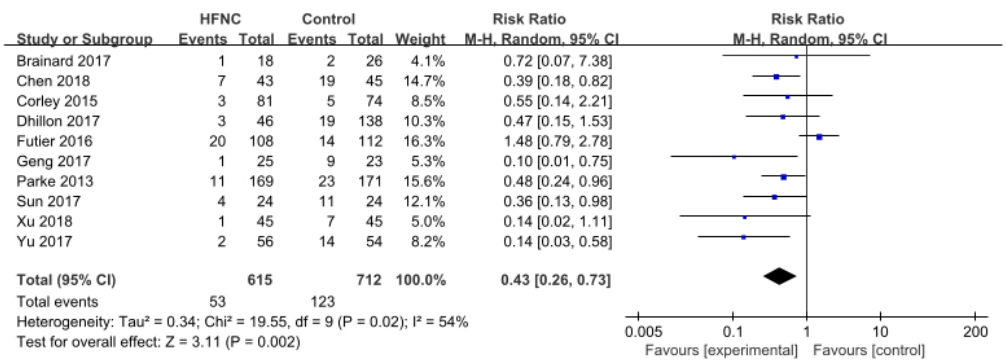

Rate of respiratory support escalation in post-extubated surgical patients with high-flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT).

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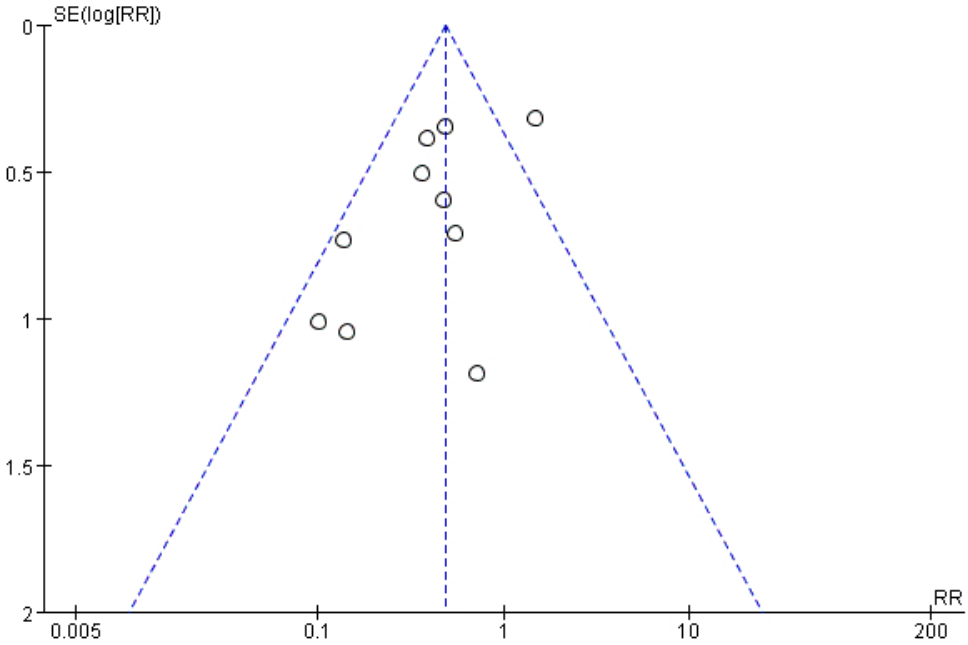

Funnel plot for publication bias of comparing high-flow nasal cannula oxygen therapy (HFNC) with conventional oxygen therapy (COT) for the rate of respiratory support escalation in postoperative patients.

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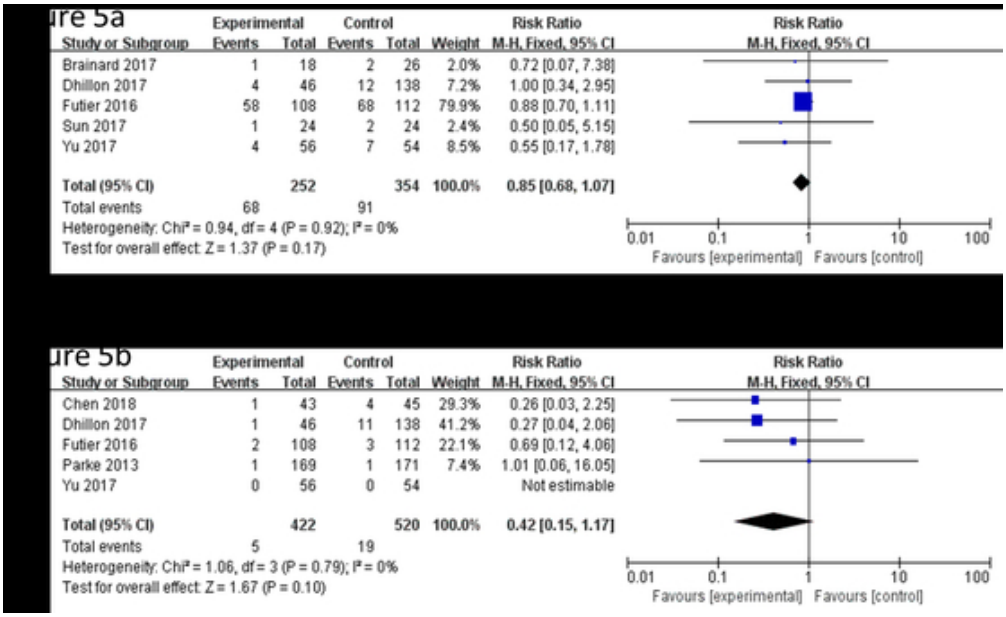

Figure 5a Postoperative pulmonary complications in post-extubated surgical patients with high-flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT).
Figure 5b Hospital mortality in post-extubated surgical patients with high-flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT) .

47x28mm (300 x 300 DPI)

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The effect of high-flow nasal cannula oxygen therapy compared with conventional oxygen therapy in postoperative patients: a systematic review and meta-analysis

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The effect of high-flow nasal cannula oxygen therapy compared with conventional oxygen therapy in postoperative patients: a systematic review and meta-analysis

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Objective: To evaluate the effect of high flow nasal cannula oxygen therapy (HFNC) vs. conventional oxygen therapy (COT) on the re-intubation rate, rate of escalation of respiratory support and clinical outcomes in post-extubation adult surgical patients.

Design: Systematic review and meta-analysis of published literature.

Data sources: PubMed, Embase, the Cochrane Library, Web of Science, China National Knowledge Index (CNKI) and Wan fang databases were searched up to August 2018.

Eligibility criteria: Studies in postoperative adult surgical patients (⩾ 18 years); Receiving HFNC or COT applied immediately after extubation that reported re-intubation, escalation of respiratory support, postoperative pulmonary complications (PPCs), and mortality were eligible for inclusion.

Data extraction and synthesis: The following data was extracted from the included studies: first author's name, year of publication, study population, country of origin, study design, number of patients, patients' baseline characteristics, and outcomes. Associations were evaluated using relative risks (RRs) and 95% confidence intervals (CIs).

Results: This meta-analysis included 10 studies (1327 patients). HFNC significantly reduced the re-intubation rate (risk ratio (RR) 0.38, 95% CI 0.23-0.61, P <0.0001) and rate of escalation of respiratory support (RR 0.43, 95% CI 0.26-0.73, P=0.002) in post-extubation surgical patients compared to COT. There were no differences in the incidence of PPCs (RR 0.87, 95% CI 0.70-1.08, P =0.21) or mortality (RR 0.45, 95% CI 0.16-1.29, P =0.14).

Conclusions: HFNC is associated with a significantly lower re-intubation rate and rate of escalation of respiratory support compared to COT in post-extubation adult surgical patients, but there is no difference in the incidence of PPCs or mortality. More well-designed, large randomized controlled trials are needed to determine the subpopulation of patients who are most likely to benefit from HFNC therapy.

Key Words: high flow nasal cannula; surgical patients; re-intubation; escalation of respiratory support; mortality

Strengths and limitations of this study

- This meta-analysis synthesized data from randomized trials and observational studies to analyze the effect of high flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT) on re-intubation rate, rate of escalation of respiratory support and incidence of PPCs and mortality in post-extubation surgical patients.
- The possible risk of bias for RCTs and case-control and cohort studies were assessed using Cochrane Collaboration methodology or the Newcastle-Ottawa scale.
- Sources of heterogeneity between studies were investigated using random-effects meta-regression. Subgroup analyses were conducted to investigate the subpopulation of patients who were most likely to benefit from HFNC therapy.

INTRODUCTION

Postoperative respiratory failure is associated with perioperative morbidity and mortality in surgical patients, and high costs of healthcare [1] [2]. Causes of early postoperative respiratory failure include hypoxemia, diaphragmatic dysfunction, atelectasis due to postoperative alveolar collapse, or fluid accumulation[3] [4]. Prophylactic strategies such as protective intraoperative mechanical ventilation, postoperative physiotherapy, and noninvasive mechanical ventilation (NIV) may reduce the incidence of postoperative pulmonary complications (PPCs) and improve the prognosis of surgical patients[5]. In particular, some evidence supports the use of NIV for postoperative respiratory failure [6]; however, this technique requires substantial resources and technical expertise, and may cause discomfort to patients [7].

High flow nasal cannula oxygen therapy (HFNC) is increasingly used in the prevention and treatment of respiratory failure in post-extubation non-surgical and surgical patients[6] [8] [9]. The advantages of HFNC compared to conventional oxygen therapy (COT) include improved comfort, delivery of a predictable sustained partial pressure of oxygen due to a reduction of room air entrainment, good humidification, decreased anatomical dead space, and positive end expiratory pressure (PEEP)[3] [4] [10-12] [3] [4] [11] [12] [13] [14]. However, failure of HFNC in patients with pulmonary complications can lead to delayed intubation causing morbidity and mortality[15]. Therefore, the safety and efficacy of HFNC is being increasingly investigated in the literature, but findings are inconsistent [16-18]. In an attempt to provide some clarity, the present systematic review and meta-analysis evaluated the effect of HFNC vs. COT on the re-intubation rate, rate of escalation of respiratory support, and clinical outcomes in post-extubation adult surgical patients.

METHODS

Data Sources and Searches

The PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Index (CNKI) and Wan fang databases were searched from inception to August 31, 2018 using the following keywords: (“high flow” or “high-flow”) and

("operation" or "operative" or "surgery" or "Surgical"). Additional studies were identified by manually searching the reference lists from relevant articles and reviews. No restrictions on language or study design were applied.

Inclusion and Exclusion Criteria

Inclusion criteria were: 1) study population: postoperative adult surgical patients (⩾ 18 years); 2) interventions: HFNC vs. COT; HFNC or COT were applied immediately after extubation; COT was administered via a cool mist/nasal cannula (CM/NC) or face mask; and 3) outcomes: re-intubation, escalation of respiratory support, PPCs and mortality.

Exclusion criteria were: 1) Studies in postoperative surgical patients who did not receive HFNC after extubation; 2) use of a control other than COT; 3) reviews, letters, case reports; or 4) in vitro studies or animal experiments.

Study selection

Two review authors (Z-H.L., S-S.M.) independently assessed titles and abstracts to determine if a study met the inclusion criteria. The full text of potentially relevant studies was retrieved and reviewed. Disagreements about study selection were resolved thorough discussion with a third reviewer (W.C.) until consensus was reached.

Data extraction

Two review authors (Z-H.L., S-S.M.) independently extracted data from the included studies, including first author's name, year of publication, study population, country of origin, study design, number of patients, patients' baseline characteristics, and outcomes.

Primary outcomes were re-intubation rate and rate of escalation of respiratory support. In post-extubation adult surgical patients receiving COT, respiratory support was escalated to HFNC, NIV or invasive mechanical ventilation (IMV) according to the following algorithms: COT→HFNC, COT→NIV, COT→HFNC→IMV, COT→NIV→IMV. In post-extubation adult surgical patients receiving HFNC, respiratory support was escalated to NIV or IMV according to the following algorithms: HFNC

→NIV, HFNC→IMV, HFNC→NIV→IMV. Respiratory therapy was escalated when the patient progressed to acute respiratory failure or due to other causes.

Secondary outcomes were the incidence of PPCs, defined as PPCs identified in the original article, new postoperative pneumonia and atelectasis, and in hospital or 28-day mortality. Disagreements about data extraction were resolved thorough discussion with a third reviewer (W.C.) until consensus was reached.

Assessment of Risk of Bias

Risk of bias in included RCTs was assessed using Cochrane Collaboration methodology[19], which evaluates the following domains: adequacy of sequence generation; allocation sequence concealment; blinding of participants and caregivers; blinding for outcome assessment; incomplete outcome data; selective outcome reporting; and the other sources of bias. Risk of bias was evaluated as 'low risk', 'high risk, or 'unclear risk', Risk of bias in included case-control or cohort studies was assessed using a modified Newcastle-Ottawa scale, which includes three categories: selection, comparability, and exposure or outcome, with each study awarded a maximum of nine stars [20].

Statistical Analysis

Statistical analysis was performed with Review Manager Software 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen Denmark) and STATA 12.0 (Stata Corporation, College Station, TX, USA). Categorical variables are presented as proportions or ratios, and associations were evaluated using relative risks (RRs) and 95% confidence intervals (CIs). A random effects model was used to pool studies to account for the substantial clinical heterogeneity (patients' age, type of surgery, types of controls [CM/NC or face mask], length of follow-up) between studies.

Heterogeneity between studies was quantified by the chi-square and I^2 tests. Heterogeneity between studies was assessed as low (I^2=25%), medium (I^2=50%) or high (I^2=75%)[21]. Univariable random-effects meta-regression was performed to investigate sources of heterogeneity between studies.

Subgroup analyses were conducted to investigate the subpopulation of patients who were most likely to benefit from HFNC therapy. Subgroups were stratified by type of surgery (cardiac, thoracic or mixed surgery), study design (non-RCT or RCT), target SPO2 level (90%-93% or 95%), strategy (prophylactic or therapy), and risk of re-intubation (high risk or low risk: the average values of risk-related parameters for re-intubation were assessed as previously reported [9 10]).

Sensitivity analysis, excluding one study at a time, was performed to explore the impact of study quality on the overall effect estimate of all included studies.

Publication bias was evaluated by Begg's funnel plot with pseudo 95% confidence limits.

The level of evidence of included studies was qualified using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework.

A 2-tailed *P* value <0.05 was considered statistically significant.

Patient and public involvement statement

Patients and the public were not involved in this review.

RESULTS

The searches identified 4572 potentially relevant articles, and 624 duplicates were excluded. After reviewing titles and abstracts, 30 studies were considered potentially eligible for inclusion. After analyzing the full text articles or conference abstracts, 10 studies were included in the final analyses (**Figure 1**)

The characteristics of the included studies are shown in **Table 1**. The studies were published between 2013 and 2018 and were conducted in Oceania, Europe, Asia and American. Seven studies were RCTs, two were case-control studies, and one was a cohort study. The 10 studies included a total of 1327 post-extubation adult surgical patients, of which 615 patients received HFNC, and 712 received COT. Three studies were in patients who had undergone cardiac surgery [17 22 23], 5 studies were in patients who had undergone thoracic surgery [24-28], and 2 studies were mixed, including patients[16,29] who had undergone various types of surgeries. The patients were followed-up until ICU or hospital discharge.

Assessment of Risk of Bias

The results of the quality assessments are shown in **Figure 2A** and **Table 2**. None of the included studies were double blind. In the RCTs, blinding of patients and caregivers was impossible, and most authors regarded this as a limitation associated with their studies. One trial had reporting bias. Four trials were classified as having an unclear risk of bias [24,25,27,28].

All the non-RCTs received seven stars on the modified Newcastle-Ottawa scale, because the assessment of outcomes were self-reported or unstated in the cohort study, and the selection of controls was not described in the case-control studies.

Begg's funnel plot revealed no evidence of publication bias for the primary outcomes, except for one outlier in the analysis of escalation of respiratory support[18] (**Figure 2B, 2C**).

Outcomes

Primary outcomes

Nine studies reported on the re-intubation rate in post-extubation adult surgical patients who received HFNC (n=507) or COT (n=600). The meta-analysis demonstrated that the re-intubation rate was significantly lower in patients who received HFNC compared to those who received COT (RR 0.38, 95% CI 0.23-0.61, *P* <0.0001). There was no evidence of heterogeneity between studies (I^2 = 0%) (**Figure 3**).

Ten studies reported on the rate of escalation of respiratory support in post-extubation adult surgical patients who received HFNC (n=615) or COT (n=712). The meta-analysis demonstrated that the rate of escalation of respiratory support was significantly lower in patients who received HFNC compared to those who received COT (RR 0.43, 95% CI 0.26 to 0.73, *P* =0.002). There was evidence of heterogeneity between studies (I^2 = 54%) (**Figure 4**).

Secondary outcomes

Five studies reported on the incidence of PPCs in post-extubation adult surgical patients who received HFNC (n=252) or COT (n=354). The meta-analysis demonstrated no significant difference in the incidence of PPCs in patients who

received HFNC compared to those who received COT (RR 0.87, 95% CI 0.70-1.08, p=0.21). There was no evidence of heterogeneity between studies (I^2 = 0%) (**Figure 5A**).

Five studies reported on mortality in post-extubation adult surgical patients who received HFNC (n=422) or COT (n=520). 5 patients (1.18%) who received HFNC and 19 patients who received COT, died. However, the meta-analysis demonstrated no significant difference in mortality in patients who received HFNC compared to those who received COT (RR 0.45, 95% CI 0.16-1.29, P =0.14) (**Figure 5B**).

Subgroup analyses

Subgroup analyses stratified by type of surgery (cardiac, thoracic or mixed surgery), study design (non-RCT or RCT), target SPO2 level (90%-93% or 95%), strategy (prophylactic or therapy), and risk of re-intubation (high risk or low risk) showed similar effect estimates for the primary and secondary outcomes as the overall analysis (**Table 3**), except for cardiac surgery, prophylactic strategy and target SPO2 level (90-93%), where there was no significant difference in the re-intubation rate in post-extubation adult surgical patients who received HFNC compared to those who received COT, and target SPO2 level (95%), where there was no significant difference in the rate of escalation of respiratory support in post-extubation adult surgical patients who received HFNC compared to those who received COT.

Random-effects meta-regression

Meta-regression was used to analyze the sources of heterogeneity between studies in the analyses investigating the rate of escalation of respiratory support. Type of surgery (b = 0.262, P = 0.027) and risk factors for intubation (b = 2.358, P = 0.006) were found to be a potential source heterogeneity **(Supplementary Figure 1)**.

Sensitivity Analysis

Sensitivity analyses excluding one study at a time showed similar effect estimates for the primary and secondary outcomes as the overall analysis (**Supplementary Figure 2**).

GRADE

Evidence was qualified using GRADE. Overall, high quality evidence showed that HFNC may have benefit when compared to COT in reducing the re-intubation rate in post-extubation adult surgical patients; however, the level of evidence for the case control study was low (**Supplementary Table 1A**).

Overall, low quality of evidence showed that HFNC may have benefit when compared to COT in reducing the need to escalate respiratory support in post-extubation adult surgical patients. The level of evidence for RCTs was downgraded due to medium heterogeneity between studies, uncertain publication bias, and the level of evidence for the case control group was low due to factors associated with study design (**Supplementary Table 1B**).

DISCUSSION

The results from the present systematic review and meta-analysis of data from 10 studies suggest that HFNC is associated with a significantly lower re-intubation rate and rate of escalation of respiratory support compared to COT in post-extubation adult surgical patients, but there is no difference in the incidence of PPCs or mortality. Subgroup analysis showed that HFNC reduced the re-intubation rate and the rate of escalation of respiratory support compared to COT in both randomized controlled trials and observational studies. These data suggest that the beneficial effects of HFNC, including washout of anatomic dead space, improved gas mixing in large airways, heating and humidification of inhaled gas, increased end-expiratory lung volume, improved oxygenation and reduced respiratory rate and inspiratory effort [30-34] are consistent across healthcare settings and treatment strategies.

Previous studies have investigated the safety and efficacy of HFNC in surgical and non-surgical patients. Two systematic reviews used traditional pairwise comparisons to evaluate the effectiveness of HFNC and COT in post-extubation adult patients [35 36]. In a meta-analysis including 2 studies and 495 cardiac surgical patients, Zhu et al found that HFNC after extubation was associated with a significant reduction in the rate of escalation of respiratory support compared to COT, but did not decrease re-intubation rate or the length of intensive care unit stay [36]. In a

meta-analysis including 7 studies and 2781 adult patients, HFNC after extubation had a similar re-intubation rate compared to either COT or NIV. However, in a subgroup analysis of critically ill patients, HFNC after extubation had a lower re-intubation rate compared to COT [35]. In a study that assessed overall ICU mortality and other hospital outcomes in patients who received HFNC therapy that failed, failure of HFNC resulted in delayed intubation and worse clinical outcomes. Early intubated patients had better overall ICU mortality, extubation success, ventilator weaning, and more ventilator-free days than late intubated patients [15]. Taken together, the findings from the present review and these previous studies suggest that larger, well designed RCTs are required to further investigate the safety and efficacy of HFNC in post-extubation adult surgical patients.

In the present review, there was 'medium' heterogeneity between studies included in the analyses investigating the rate of escalation of respiratory support. This is not surprising, given the differences in type of surgery, study design, target SPO2, therapeutic strategy, and risk of re-intubation between the studies included in the analysis of this outcome. Meta-regression identified type of surgery and the risk factors for re-intubation as the main sources of heterogeneity.

Our subgroup analyses showed no improvement in the re-intubation rate in patients who had undergone cardiac surgery and received HFNC compared to COT post-extubation. Cardiac patients are at high risk for PPCs, and thus many may not benefit from HFNC. The ARISCAT risk score, which predicts the risk of PPCs after surgery, suggests that patients undergoing cardiac surgery have a high risk for PPCs, likely due to the intrathoracic incision and longer duration of surgery, which may be extended by the need for extracorporeal circulation [15].

The subgroup analysis stratified by risk for re-intubation showed HFNC was associated with a lower re-intubation rate and rate of escalation of respiratory support compared to COT in post-extubation patients with a high risk for re-intubation. Consistent with this finding, previous reports show HFNC reduced re-intubation rate compared to COT in critically ill patients with low risk of intubation[10], and was not

inferior to NIV for preventing re-intubation and post-extubated respiratory failure in critically ill patients at high risk of intubation [9].

The present study suggests that when SPO2 is maintained above 90%-93%, HFNC may have benefit compared to COT in reducing the need to escalate respiratory support, but not for decreasing the re-intubation rate. Conversely, when SPO2 was maintained above 95%, HFNC reduced the re-intubation rate but not the rate of escalation of respiratory support. The advantages of reducing the need to escalate respiratory support at the lower SPO2 threshold vs. delaying the time to re-intubation at the higher SPO2 threshold remain to be elucidated. Recent studies show that critically ill patients treated with conservative oxygen therapy (with a slightly lower SPO2 target) vs. conventional therapy had a lower mechanical ventilation time and hospital or ICU mortality [37 38].

In the overall or subgroup analyses in the present review, HFNC did not significantly reduce the incidence of PPCs or mortality compared to COT in post-extubation surgical patients. These data are in contrast to a previous report, which speculated that HFNC may affect the outcomes of postoperative patients by alleviating PPCs[5]

This systematic review and meta-analysis was associated with several limitations. First, not all included studies investigated re-intubation rates and respiratory support escalation as primary endpoints, and most of the included studies were single-center studies. Second, there were differences in the timing and duration of HFNC treatment and length of follow-up in the included studies. Third, the sample size was small; 3 out of 10 studies were non-RCTs, including less than 50 patients each. These limitations represent potential sources of bias and heterogeneity.

Conclusion

Findings from this review suggest that HFNC is associated with a significantly lower re-intubation rate and rate of escalation of respiratory support compared to COT in post-extubation adult surgical patients, but there is no difference in the incidence of PPCs or mortality. More well-designed, large randomized controlled trials are needed to determine the patient population that is most likely to benefit from HFNC therapy.

Footnotes

Contributors: ZL and FG had full access to all the data in the study and take responsibility for its integrity and the accuracy of the data analysis. ZL, SM, JX, HQ and FG performed the systematic review, study selection, and statistical analysis. WC, JX, YY, and XZ contributed to data extraction and the quality assessment. All authors participated in writing the article.

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Patient consent: Not required.

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Data sharing statement: Data are available from the corresponding author on ressonable request fmguo2003@139.com

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Table and Figure legends

Figure 1 Flow diagram of study selection

Figure 2A Risk of bias summary for each included study. Red (–) indicates high risk of bias; yellow (?) indicates unclear risk; and green (+) indicates low risk of bias.

Figure 2B, 2C Funnel plot for publication bias: B) Re-intubation rate; C) Rate of escalation of respiratory support

Figure 3 High-flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT): Re-intubation rate

Figure 4 High-flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT): Rate of escalation of respiratory support

Figure 5 High-flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT): A) Postoperative pulmonary complications; B) Hospital mortality

Table 1 Characteristics of included studies

Table 2 Quality assessment: A) Cochrane collaboration methodology; B) Newcastle-Ottawa scale

Table 3 Subgroup analyses

Supplementary Figure 1 Meta regression: A) Type of surgery; B) Risk factors for intubation

Supplementary Figure 2 Sensitivity Analysis: A) Re-intubation rate; B) Rate of escalation of respiratory support

Supplementary Table 1 GRADE A) Re-intubation rate; B) Rate of escalation of respiratory support

Table1: Characteristics of included studies

Study	Study design	Type of surgery	Patient characteristics (HFNC/COT)			Target SPO2 (%)	Risk of re-intubation
			Patient number	BMI	Age (years)		
Chen, 2018	Case-control study	Thoracic	44/45	NA	66/64	90	High
Xu, 2018	Cohort study	Cardiovascular	45/45	26/27	57/54	95	High
Brainard, 2017	RCT	Thoracic	18/26	26/25	57/59	95	NA
Dhillon, 2017	Case-control study	Mixed	46/138	NA	63/58	NA	NA
Geng, 2017	RCT	Thoracic	25/23	NA	63/63	90	High
Sun, 2017	RCT	Thoracic	24/24	NA	67/65	100	High
Yu, 2017	RCT	Thoracic	56/54	26/25	56/56	95	High
Futier, 2016	RCT	Abdominal or combine thoracic	108/112	25/25	62/661	95	NA
Corley, 2015	RCT	Cardiovascular	81/74	36/35	63/65	95	High
Parke, 2013	RCT	Cardiovascular	169/171	28/29	65/66	93	High

Data are expressed as median (interquartile range), or mean (standard deviation); NA, Not available or not reported

Study	Characteristics of oxygen therapy (HFNC/COT)		escalation of respiratory support#		Strategy	Study center	Follow-up time: primary outcomes
	HFNC Flow rate(L/min)	COT	HFNC	COT			
			NIV/Intubation	HFNC/NIV/Intubation			
Chen, 2018	35-60	Facemask	NA/7	NA/19	Therapy	Single center	2 days
Xu, 2018	35-60	5-10L/min face mask	0/1	0/0/7	Prophylactic	Single center	3 days
Brainard, 2017	40	Nasal cannula or face mask	NA/1	NA/NA/2	Prophylactic	Single center	2 days
Dhillon, 2017	NA	Cool mist/nasal cannula (CM/NC)	NA/NA/3	NA/NA/19	Prophylactic	Single center	NA
Geng, 2017	35-60	Facemask	NA/NA/1	NA/NA/9	Therapy	Single center	NA
Sun, 2017	40-60	8-10L/min atomizing mask	1/3	0/3/8	Therapy	Single center	1 day
Yu, 2017	35-60	Nasal prongs or facemask	2/0	9/5/0	Prophylactic	Multicenter	3
Futier, 2016	50-60	Nasal prongs or facemask	NA/NA(20)*	NA/NA/NA(14)*	Prophylactic	Multicenter	7 days
Corley, 2015	35-50	2–4L/min via nasal cannulae or 6L/min via simple face mask	3/0	1/2/2	Prophylactic	Single center	1 day
Parke, 2013	45	2–4L/min via simple facemask or nasal prongs	9/2	18/5/0	Prophylactic	Single center	2 days

only the final oxygen treatment was recorded; * only get the total number; NA, Not available or not reported

Table 2 Quality assessment: Newcastle-Ottawa scale

Study	Selection				Comparability	Outcome			Overall stars
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Xu, 2018	★	★	★	★	★	-	★	★	7
Chen, 2018	★	★	-	★	★	★	★	★	7
Dhillon, 2017	★	★	★	★	★	-	★	★	7

★ the quality met the criterion of this specific item; - Self-reported or unstated

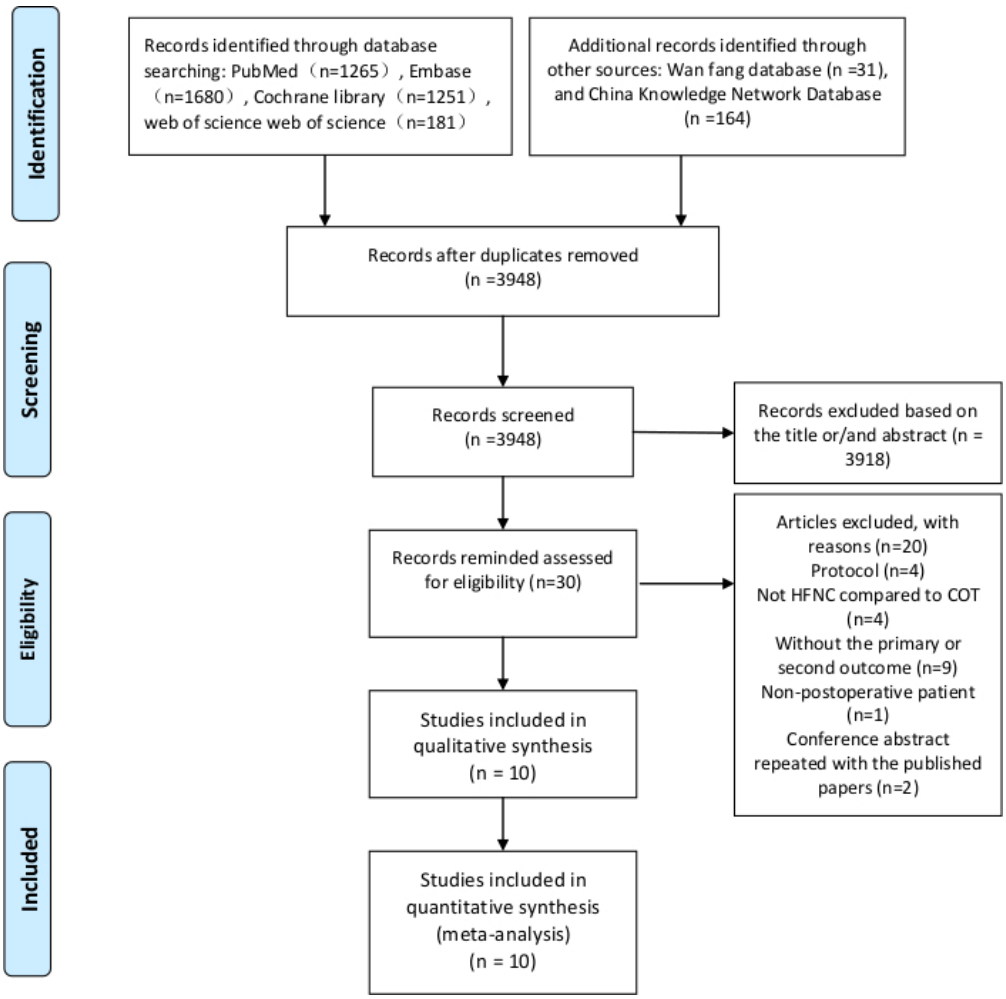
Table 3 Subgroup analyses

Outcome	No studies (No of patients)	Summary estimate (95% CI)	P value (summary estimate)	P value (heterogeneity)	I^2 (%)
Re-intubation	9 (1107)	0.38* (0.23 to 0.61)	0.0001	0.64	0
Cardiac surgery	3 (585)	0. 43* (0.05 to 3.72)	0.44	0.14	49
Thoracic surgery	5 (338)	0. 36* (0.20 to 0.64)	0.0005	0.73	0
RCT	6 (745)	0.39* (0.17 to 0.87)	0.02	0.41	1
Non-RCT	3 (362)	0.37* (0.20 to 0.69)	0.002	0.60	0
Min target SPO2 (90%-93%)	3 (476)	0.41* (0.09 to 1.92)	0.26	0.11	55
Min target SPO2 (95%)	4 (399)	0.31* (0.09 to 1.01)	0.05	0.72	0
prophylactic	7 (1143)	0.46* (0.21 to 1.03)	0.06	0.53	0
Therapy	3 (184)	0.34* (0.18 to 0.62)	0.0005	0.45	0
High risk of re-intubation	7 (879)	0.35* (0.20 to 0.60)	0.0002	0.48	0
Escalation rate of	10 (1327)	0.43* (0.26 to 0.73)	0.002	0.02	54

respiratory support					
Cardiac surgery	3 (585)	0.45* (0.25 to 0.81)	0.008	0.51	0
Thoracic surgery	5 (338)	0.31* (0.18 to 0.53)	0.0001	0.47	0
RCT	7 (965)	0.46* (0.22 to 0.93)	0.03	0.01	64
Non-RCT	3 (362)	0.37* (0.20 to 0.69)	0.002	0.60	0
Min target SPO2 (90%-93%)	3 (476)	0.39* (0.23 to 0.67)	0.0005	0.34	8
Min target SPO2 (95%)	5 (619)	0.46* (0.15 to 1.44)	0.18	0.01	70
prophylactic	7 (1143)	0.50* (0.25 to 1.00)	0.05	0.02	59
Therapy	3 (184)	0.34* (0.19 to 0.60)	0.0002	0.45	0
High risk of re-intubation	7 (879)	0.33* (0.22 to 0.49)	0.00001	0.5	0
PPCs	5 (606)	0.87* (0.70 to 1.08)	0.21	0.92	0
RCT	4 (422)	0.86* (0.69 to 1.086)	0.20	0.83	0

prophylactic	4 (558)	0.86* (0.68 to 1.08)	0.20	0.87	0
Mortality	5 (942)	0.45* (0.16 to 1.29)	0.14	0.79	0
Cardiac surgery	1 (340)	1.01* (0.06 to 16.05)	0.99	-	-
Thoracic surgery	2 (198)	0.26* (0.03 to 2.25)	0.22	-	-
RCT	3 (670)	0.77* (0.17 to 3.41)	0.73	0.82	0
Non-RCT	2 (272)	0.27* (0.06 to 1.18)	0.08	0.98	0
Min target SPO2 (90%-93%)	2 (428)	0.41* (0.08 to 2.09)	0.29	0.45	0
Min target SPO2 (95%)	2 (330)	0.69* (0.12 to 4.06)	0.68	-	-
High risk of re-intubation	3 (538)	0.41* (0.08 to 2.09)	0.29	0.45	0

RCT, randomized controlled trial; PPCs, postoperative pulmonary complications *Relative risk



Flow diagram of study selection

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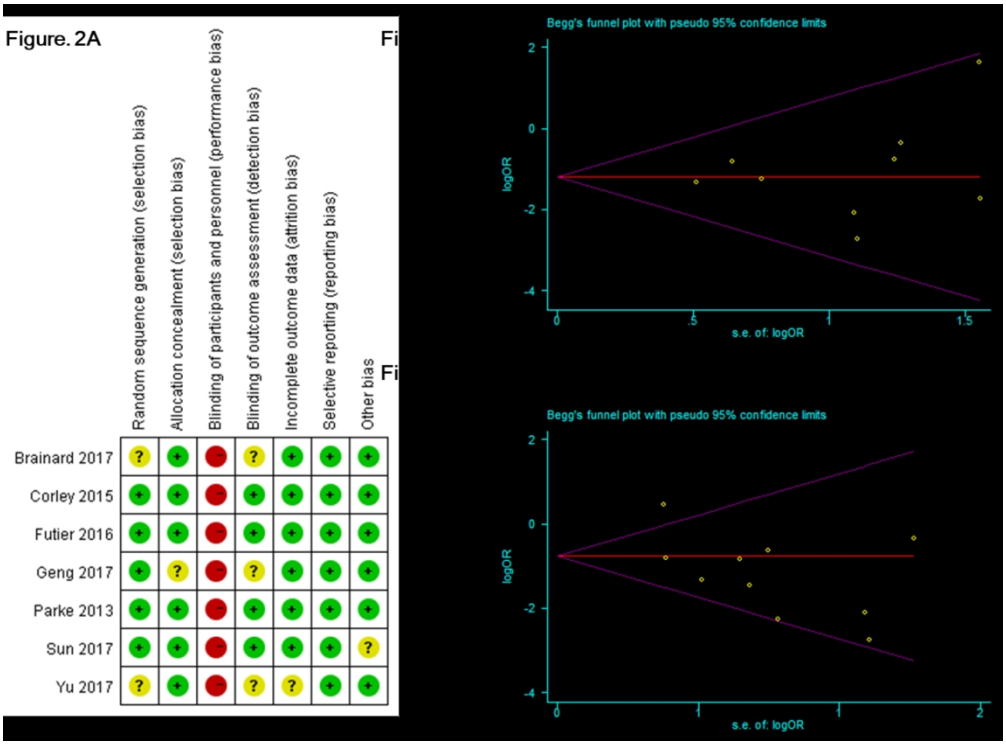
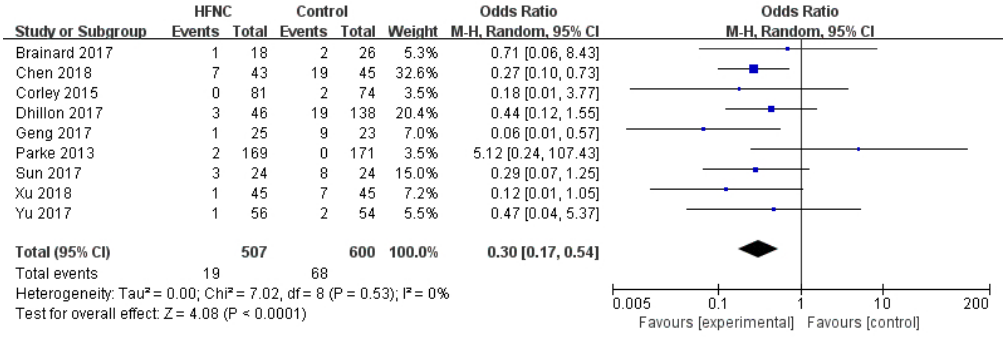


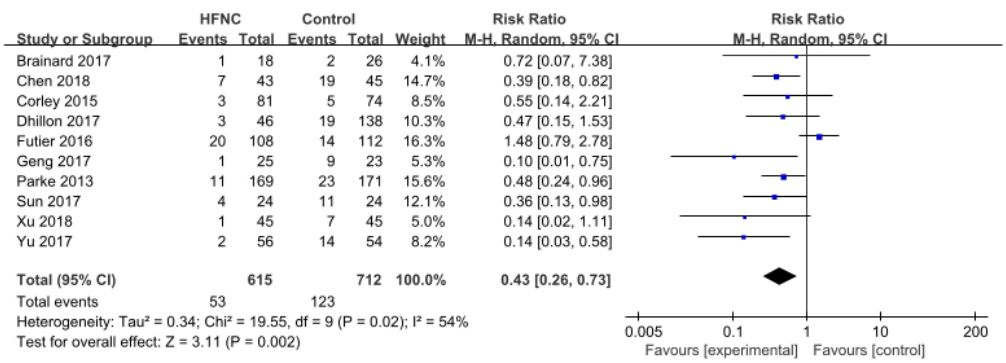
Figure 2A Risk of bias summary for each included study. Red (–) indicates high risk of bias; yellow (?) indicates unclear risk; and green (+) indicates low risk of bias.
Figure 2B, 2C Funnel plot for publication bias: B) Re-intubation rate; C) Rate of escalation of respiratory support

122x90mm (300 x 300 DPI)



High-flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT): Re-intubation rate

67x23mm (300 x 300 DPI)



High-flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT): Rate of escalation of respiratory support

65x22mm (300 x 300 DPI)

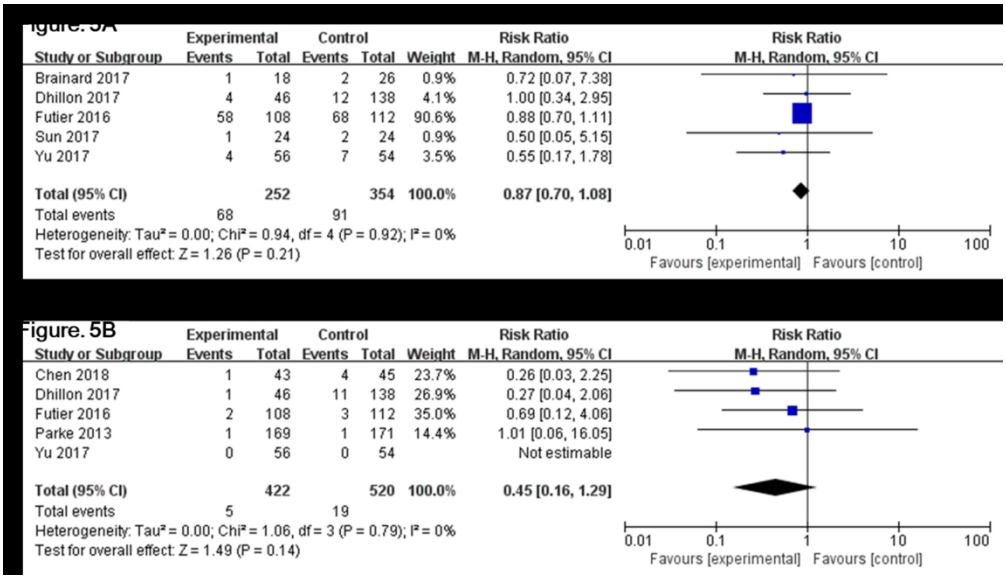
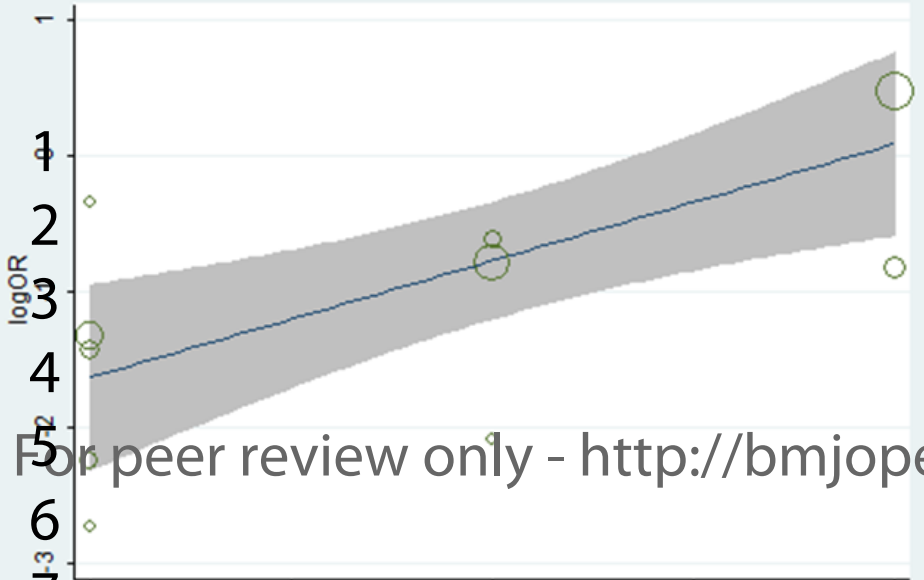


Figure 5 High-flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT): A) Postoperative pulmonary complications; B) Hospital mortality

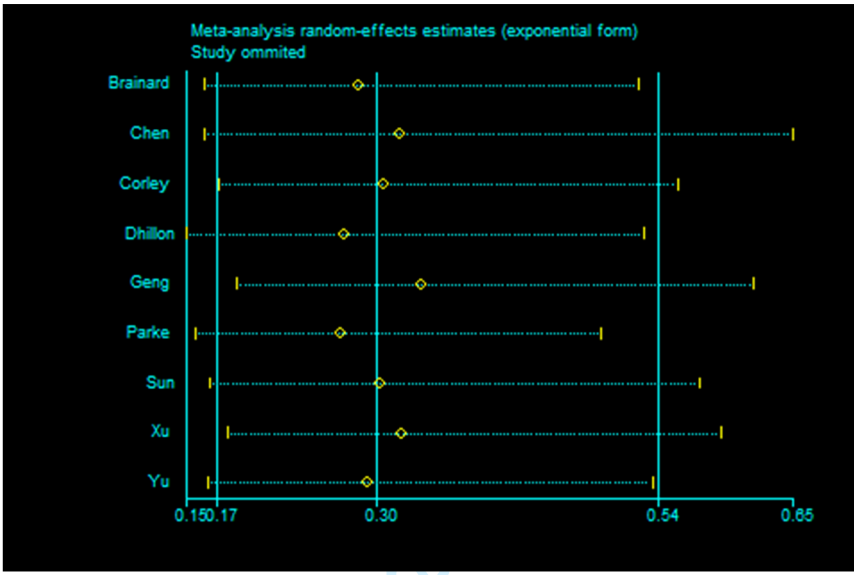
157x90mm (300 x 300 DPI)

Supplementary figure. 1A



Supplementary figure. 1B

Supplementary figure. 2A



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Supplementary figure. 2B

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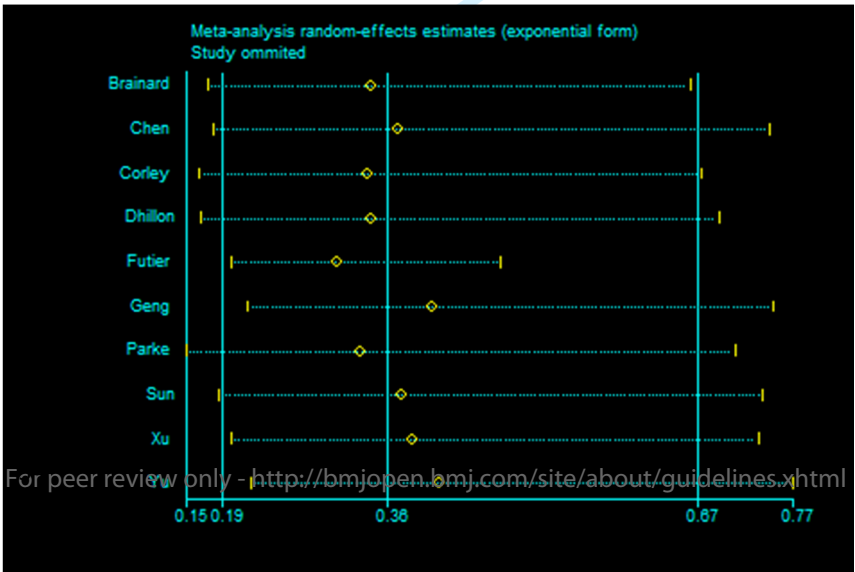

Supplementary Table 1 GRADE A) Re-intubation rate; B) Rate of escalation of respiratory support

A.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reinbutation	Control	Relative (95% CI)	Absolute		
Reintubation-RCT												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/373 (2.1%)	23/372 (6.2%)	RR 0.39 (0.17 to 0.87)	38 fewer per 1000 (from 8 fewer to 51 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								5.7%		35 fewer per 1000 (from 7 fewer to 47 fewer)		
Case control studies												
2	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/89 (11.2%)	38/183 (20.8%)	OR 0.32 (0.15 to 0.71)	130 fewer per 1000 (from 51 fewer to 170 fewer)	⊕OOO VERY LOW	CRITICAL
								28%		169 fewer per 1000 (from 64 fewer to 225 fewer)		
Reintubation- Cohort study												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/45 (2.2%)	7/45 (15.6%)	OR 0.12 (0.01 to 1.05)	134 fewer per 1000 (from 154 fewer to 7 more)	⊕⊕OO LOW	CRITICAL
								15.6%		134 fewer per 1000 (from 154 fewer to 7		

										more)		

[1] High flow nasal cannula oxygen therapy or conventional oxygen therapy based on the individual attending's discretion

B.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Escalation of respiratory support	Control	Relative (95% CI)	Absolute		
Escalation of respiratory support-RCT												
7	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	reporting bias[2]	42/481 (8.7%)	78/484 (16.1%)	RR 0.54 (0.38 to 0.77)	74 fewer per 1000 (from 37 fewer to 100 fewer)	⊕⊕OO LOW	CRITICAL
								13.5%		62 fewer per 1000 (from 31 fewer to 84 fewer)		
Escalation of respiratory support-case control studies												
2	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10 cases 38 controls		OR 0.32 (0.15 to 0.71)	-	⊕OOO VERY LOW	CRITICAL
								38/183 (20.8%)		130 fewer per 1000 (from 51 fewer to 170 fewer)		
								28%		169 fewer per 1000 (from 64 fewer to 225 fewer)		
Escalation of respiratory support- Cohort studies												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/45 (2.2%)	7/45 (15.6%)	OR 0.12 (0.01 to	134 fewer per 1000 (from 154 fewer to 7	⊕⊕OO LOW	CRITICAL

									1.05)	more)		
								15.6%		134 fewer per 1000 (from 154 fewer to 7 more)		

[1] I2=64%, the heterogeneity was high

[2] Funnel plots suggest that there may be publication bias in Futier's research

[3] case-control

[4] High flow nasal cannula oxygen therapy or conventional oxygen therapy based on the individual attending's discretion

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page1,line1-3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page2,line1-27
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page4,line2-21
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page4,line22-24;
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page5,line4-9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page4,line27-30 Page5,line1-3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix Search strategy
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page5,line13-18
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page5,line19-23 Page6,line1-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page5,line24-30 Page6,line1-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page6,line7-16

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page6,line17-25
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page6,line26-29

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page7,line9-10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page6,line28-29; Page7,line1-8;
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page8,line16-26
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page8,line16-26
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2 and Fig2A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Supplementary Figure 1, supplementary Figure 2
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page10,line12-30 Page11,line1-30 Page12,line1-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page12,line18-24

PRISMA 2009 Checklist

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page12,line25-30
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page13,line8-15

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

The effect of high-flow nasal cannula oxygen therapy compared with conventional oxygen therapy in postoperative patients: a systematic review and meta-analysis

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Primary Subject Heading:	Intensive care
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Keywords:	high flow nasal cannula, surgical patients, reintubation, escalation of respiratory support, pulmonary complications

The effect of high-flow nasal cannula oxygen therapy compared with conventional oxygen therapy in postoperative patients: a systematic review and meta-analysis

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Objective: To evaluate the effect of high flow nasal cannula oxygen therapy (HFNC) vs. conventional oxygen therapy (COT) on the re-intubation rate, rate of escalation of respiratory support and clinical outcomes in post-extubation adult surgical patients.

Design: Systematic review and meta-analysis of published literature.

Data sources: PubMed, Embase, the Cochrane Library, Web of Science, China National Knowledge Index (CNKI) and Wan fang databases were searched up to August 2018.

Eligibility criteria: Studies in postoperative adult surgical patients (⩾ 18 years); Receiving HFNC or COT applied immediately after extubation that reported re-intubation, escalation of respiratory support, postoperative pulmonary complications (PPCs), and mortality were eligible for inclusion.

Data extraction and synthesis: The following data was extracted from the included studies: first author's name, year of publication, study population, country of origin, study design, number of patients, patients' baseline characteristics, and outcomes. Associations were evaluated using relative risks (RRs) and 95% confidence intervals (CIs).

Results: This meta-analysis included 10 studies (1327 patients). HFNC significantly reduced the re-intubation rate (risk ratio (RR) 0.38, 95% CI 0.23-0.61, P <0.0001) and rate of escalation of respiratory support (RR 0.43, 95% CI 0.26-0.73, P=0.002) in post-extubation surgical patients compared to COT. There were no differences in the incidence of PPCs (RR 0.87, 95% CI 0.70-1.08, P =0.21) or mortality (RR 0.45, 95% CI 0.16-1.29, P =0.14).

Conclusions: HFNC is associated with a significantly lower re-intubation rate and rate of escalation of respiratory support compared to COT in post-extubation adult surgical patients, but there is no difference in the incidence of PPCs or mortality. More well-designed, large randomized controlled trials are needed to determine the subpopulation of patients who are most likely to benefit from HFNC therapy.

Key Words: high flow nasal cannula; surgical patients; re-intubation; escalation of respiratory support; mortality

Strengths and limitations of this study

- This meta-analysis synthesized data from randomized trials and observational studies to analyze the effect of high flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT) on re-intubation rate, rate of escalation of respiratory support and incidence of PPCs and mortality in post-extubation surgical patients.
- The possible risk of bias for RCTs and case-control and cohort studies were assessed using Cochrane Collaboration methodology or the Newcastle-Ottawa scale.
- Sources of heterogeneity between studies were investigated using random-effects meta-regression. Subgroup analyses were conducted to investigate the subpopulation of patients who were most likely to benefit from HFNC therapy.
- However, the clinical heterogeneity between trials included was relatively high and a patient level meta-analysis might still be needed.

INTRODUCTION

Postoperative respiratory failure is associated with perioperative morbidity and mortality in surgical patients, and high costs of healthcare [1] [2]. Causes of early postoperative respiratory failure include hypoxemia, diaphragmatic dysfunction, atelectasis due to postoperative alveolar collapse, or fluid accumulation[3] [4]. Prophylactic strategies such as protective intraoperative mechanical ventilation, postoperative physiotherapy, and noninvasive mechanical ventilation (NIV) may reduce the incidence of postoperative pulmonary complications (PPCs) and improve the prognosis of surgical patients[5]. In particular, some evidence supports the use of NIV for postoperative respiratory failure [6]; however, this technique requires substantial resources and technical expertise, and may cause discomfort to patients [7].

High flow nasal cannula oxygen therapy (HFNC) is increasingly used in the prevention and treatment of respiratory failure in post-extubation non-surgical and surgical patients[6] [8] [9]. The advantages of HFNC compared to conventional oxygen therapy (COT) include improved comfort, delivery of a predictable sustained partial pressure of oxygen due to a reduction of room air entrainment, good humidification, decreased anatomical dead space, and positive end expiratory pressure (PEEP)[3] [4] [10-14]. However, failure of HFNC in patients with pulmonary complications can lead to delayed intubation causing morbidity and mortality[15]. Therefore, the safety and efficacy of HFNC is being increasingly investigated in the literature, but findings are inconsistent [16-18]. In an attempt to provide some clarity, the present systematic review and meta-analysis evaluated the effect of HFNC vs. COT on the re-intubation rate, rate of escalation of respiratory support, and clinical outcomes in post-extubation adult surgical patients.

METHODS

Data Sources and Searches

The PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Index (CNKI) and Wan fang databases were searched from inception to August 31, 2018 using the following keywords: (“high flow” or “high-flow”) and

("operation" or "operative" or "surgery" or "Surgical") (**Supplementary Figure 1**). Additional studies were identified by manually searching the reference lists from relevant articles and reviews. No restrictions on language or study design were applied.

Inclusion and Exclusion Criteria

Inclusion criteria were: 1) study population: postoperative adult surgical patients (⩾ 18 years); 2) interventions: HFNC vs. COT; HFNC or COT were applied immediately after extubation; COT was administered via a cool mist/nasal cannula (CM/NC) or face mask; and 3) outcomes: re-intubation, escalation of respiratory support, PPCs and mortality.

Exclusion criteria were: 1) Studies in postoperative surgical patients who did not receive HFNC after extubation; 2) use of a control other than COT; 3) reviews, letters, case reports; or 4) in vitro studies or animal experiments.

Study selection

Two review authors (Z-H.L., S-S.M.) independently assessed titles and abstracts to determine if a study met the inclusion criteria. The full text of potentially relevant studies was retrieved and reviewed. Disagreements about study selection were resolved thorough discussion with a third reviewer (W.C.) until consensus was reached.

Data extraction

Two review authors (Z-H.L., S-S.M.) independently extracted data from the included studies, including first author's name, year of publication, study population, country of origin, study design, number of patients, patients' baseline characteristics, and outcomes.

Primary outcomes were re-intubation rate and rate of escalation of respiratory support. In post-extubation adult surgical patients receiving COT, respiratory support was escalated to HFNC, NIV or invasive mechanical ventilation (IMV) according to the following algorithms: COT→HFNC, COT→NIV, COT→HFNC→IMV, COT→NIV→IMV. In post-extubation adult surgical patients receiving HFNC, respiratory support was escalated to NIV or IMV according to the following algorithms: HFNC

→NIV, HFNC→IMV, HFNC→NIV→IMV. Respiratory therapy was escalated when the patient progressed to acute respiratory failure or due to other causes.

Secondary outcomes were the incidence of PPCs, defined as PPCs identified in the original article, new postoperative pneumonia and atelectasis, and in hospital or 28-day mortality. Disagreements about data extraction were resolved thorough discussion with a third reviewer (W.C.) until consensus was reached.

Assessment of Risk of Bias

Risk of bias in included RCTs was assessed using Cochrane Collaboration methodology[19], which evaluates the following domains: adequacy of sequence generation; allocation sequence concealment; blinding of participants and caregivers; blinding for outcome assessment; incomplete outcome data; selective outcome reporting; and the other sources of bias. Risk of bias was evaluated as 'low risk', 'high risk, or 'unclear risk', Risk of bias in included case-control or cohort studies was assessed using a modified Newcastle-Ottawa scale, which includes three categories: selection, comparability, and exposure or outcome, with each study awarded a maximum of nine stars [20].

Statistical Analysis

Statistical analysis was performed with Review Manager Software 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen Denmark) and STATA 12.0 (Stata Corporation, College Station, TX, USA). Categorical variables are presented as proportions or ratios, and associations were evaluated using relative risks (RRs) and 95% confidence intervals (CIs). Random-effects model attempted to generalize findings beyond the included studies by assuming that the selected studies are random samples from a larger population[21], so it was used to pool studies to account for the substantial clinical heterogeneity (patients' age, type of surgery, types of controls [CM/NC or face mask], length of follow-up) between studies.

Heterogeneity between studies was quantified by the chi-square and I^2 tests. Heterogeneity between studies was assessed as low (I^2=25%), medium (I^2=50%) or high (I^2=75%)[22]. Univariable random-effects meta-regression was performed to investigate sources of heterogeneity between studies.

Subgroup analyses were conducted to investigate the subpopulation of patients who were most likely to benefit from HFNC therapy. Subgroups were stratified by type of surgery (cardiac, thoracic or mixed surgery), study design (non-RCT or RCT), target SPO2 level (90%-93% or 95%), strategy (prophylactic or therapy), and risk of re-intubation (high risk or low risk: the average values of risk-related parameters for re-intubation were assessed as previously reported [9 10]).

Sensitivity analysis, excluding one study at a time, was performed to explore the impact of study quality on the overall effect estimate of all included studies.

Publication bias was evaluated by Begg's funnel plot with pseudo 95% confidence limits.

The level of evidence of included studies was qualified using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework.

A 2-tailed *P* value <0.05 was considered statistically significant.

Patient and public involvement statement

Patients and the public were not involved in this review.

RESULTS

The searches identified 4572 potentially relevant articles, and 624 duplicates were excluded. After reviewing titles and abstracts, 30 studies were considered potentially eligible for inclusion. After analyzing the full text articles or conference abstracts, 10 studies were included in the final analyses (**Figure 1**)

The characteristics of the included studies are shown in **Table 1**. The studies were published between 2013 and 2018 and were conducted in Oceania, Europe, Asia and American. Seven studies were RCTs, two were case-control studies, and one was a cohort study. The 10 studies included a total of 1327 post-extubation adult surgical patients, of which 615 patients received HFNC, and 712 received COT. Three studies were in patients who had undergone cardiac surgery [17 23 24], 5 studies were in patients who had undergone thoracic surgery [25-29], and 2 studies were mixed, including patients[16,18] who had undergone various types of surgeries. The patients were followed-up until ICU or hospital discharge.

Assessment of Risk of Bias

The results of the quality assessments are shown in **Figure 2A** and **Table 2**. None of the included studies were double blind. In the RCTs, blinding of patients and caregivers was impossible, and most authors regarded this as a limitation associated with their studies. One trial had reporting bias. Four trials were classified as having an unclear risk of bias [25,26,28,29].

All the non-RCTs received seven stars on the modified Newcastle-Ottawa scale, because the assessment of outcomes were self-reported or unstated in the cohort study, and the selection of controls was not described in the case-control studies.

Begg's funnel plot revealed no evidence of publication bias for the primary outcomes, except for one outlier in the analysis of escalation of respiratory support[18] (**Figure 2B, 2C**).

Outcomes

Primary outcomes

Nine studies reported on the re-intubation rate in post-extubation adult surgical patients who received HFNC (n=507) or COT (n=600). The meta-analysis demonstrated that the re-intubation rate was significantly lower in patients who received HFNC compared to those who received COT (RR 0.38, 95% CI 0.23-0.61, *P* <0.0001). There was no evidence of statistical heterogeneity between studies (I^2 = 0%) (**Figure 3**).

Ten studies reported on the rate of escalation of respiratory support in post-extubation adult surgical patients who received HFNC (n=615) or COT (n=712). The meta-analysis demonstrated that the rate of escalation of respiratory support was significantly lower in patients who received HFNC compared to those who received COT (RR 0.43, 95% CI 0.26 to 0.73, *P* =0.002). There was evidence of statistical heterogeneity between studies (I^2 = 54%) (**Figure 4**).

Secondary outcomes

Five studies reported on the incidence of PPCs in post-extubation adult surgical patients who received HFNC (n=252) or COT (n=354). The meta-analysis demonstrated no significant difference in the incidence of PPCs in patients who

received HFNC compared to those who received COT (RR 0.87, 95% CI 0.70-1.08, p=0.21). There was no evidence of statistical heterogeneity between studies (I^2 = 0%) (**Figure 5A**).

Five studies reported on mortality in post-extubation adult surgical patients who received HFNC (n=422) or COT (n=520). 5 patients (1.18%) who received HFNC and 19 patients who received COT, died. However, the meta-analysis demonstrated no significant difference in mortality in patients who received HFNC compared to those who received COT (RR 0.45, 95% CI 0.16-1.29, P =0.14) (**Figure 5B**).

Subgroup analyses

Subgroup analyses stratified by type of surgery (cardiac, thoracic or mixed surgery), study design (non-RCT or RCT), target SPO2 level (90%-93% or 95%), strategy (prophylactic or therapy), and risk of re-intubation (high risk or low risk) showed similar effect estimates for the primary and secondary outcomes as the overall analysis (**Table 3**), except for cardiac surgery, prophylactic strategy and target SPO2 level (90-93%), where there was no significant difference in the re-intubation rate in post-extubation adult surgical patients who received HFNC compared to those who received COT, and target SPO2 level (95%), where there was no significant difference in the rate of escalation of respiratory support in post-extubation adult surgical patients who received HFNC compared to those who received COT.

Random-effects meta-regression

Meta-regression was used to analyze the sources of statistical heterogeneity between studies in the analyses investigating the rate of escalation of respiratory support. Type of surgery (b = 0.262, P = 0.027) and risk factors for intubation (b = 2.358, P = 0.006) were found to be a potential source statistical heterogeneity **(Supplementary Figure 2)**.

Sensitivity Analysis

Sensitivity analyses excluding one study at a time showed similar effect estimates for the primary and secondary outcomes as the overall analysis (**Supplementary Figure 3**).

GRADE

Evidence was qualified using GRADE. Overall, high quality evidence showed that HFNC may have benefit when compared to COT in reducing the re-intubation rate in post-extubation adult surgical patients; however, the level of evidence for the case control study was low (**Supplementary Table 1A**).

Overall, low quality of evidence showed that HFNC may have benefit when compared to COT in reducing the need to escalate respiratory support in post-extubation adult surgical patients. The level of evidence for RCTs was downgraded due to medium statistical heterogeneity between studies, uncertain publication bias, and the level of evidence for the case control group was low due to factors associated with study design (**Supplementary Table 1B**).

DISCUSSION

The results from the present systematic review and meta-analysis of data from 10 studies suggest that HFNC is associated with a significantly lower re-intubation rate and rate of escalation of respiratory support compared to COT in post-extubation adult surgical patients, but there is no difference in the incidence of PPCs or mortality. Subgroup analysis showed that HFNC reduced the re-intubation rate and the rate of escalation of respiratory support compared to COT in both randomized controlled trials and observational studies. These data suggest that the beneficial effects of HFNC, including washout of anatomic dead space, improved gas mixing in large airways, heating and humidification of inhaled gas, increased end-expiratory lung volume, improved oxygenation and reduced respiratory rate and inspiratory effort [30-33] are consistent across healthcare settings and treatment strategies.

Previous studies have investigated the safety and efficacy of HFNC in surgical and non-surgical patients. Two systematic reviews used traditional pairwise comparisons to evaluate the effectiveness of HFNC and COT in post-extubation adult patients [34 35]. In a meta-analysis including 2 studies and 495 cardiac surgical patients, Zhu et al found that HFNC after extubation was associated with a significant reduction in the rate of escalation of respiratory support compared to COT, but did not decrease re-intubation rate or the length of intensive care unit stay [35]. In a

meta-analysis including 7 studies and 2781 adult patients, HFNC after extubation had a similar re-intubation rate compared to either COT or NIV. However, in a subgroup analysis of critically ill patients, HFNC after extubation had a lower re-intubation rate compared to COT [34]. In a study that assessed overall ICU mortality and other hospital outcomes in patients who received HFNC therapy that failed, failure of HFNC resulted in delayed intubation and worse clinical outcomes. Early intubated patients had better overall ICU mortality, extubation success, ventilator weaning, and more ventilator-free days than late intubated patients [15]. Taken together, the findings from the present review and these previous studies suggest that larger, well designed RCTs are required to further investigate the safety and efficacy of HFNC in post-extubation adult surgical patients.

In the present review, there was 'medium' heterogeneity between studies included in the analyses investigating the rate of escalation of respiratory support. This is not surprising, given the differences in type of surgery, study design, target SPO2, therapeutic strategy, and risk of re-intubation between the studies included in the analysis of this outcome. Meta-regression identified type of surgery and the risk factors for re-intubation as the main sources of heterogeneity.

Our subgroup analyses showed no improvement in the re-intubation rate in patients who had undergone cardiac surgery and received HFNC compared to COT post-extubation. Cardiac patients are at high risk for PPCs, and thus many may not benefit from HFNC. The ARISCAT risk score, which predicts the risk of PPCs after surgery, suggests that patients undergoing cardiac surgery have a high risk for PPCs, likely due to the intrathoracic incision and longer duration of surgery, which may be extended by the need for extracorporeal circulation [15].

The subgroup analysis stratified by risk for re-intubation showed HFNC was associated with a lower re-intubation rate and rate of escalation of respiratory support compared to COT in post-extubation patients with a high risk for re-intubation. Consistent with this finding, previous reports show HFNC reduced re-intubation rate compared to COT in critically ill patients with low risk of intubation[10], and was not

inferior to NIV for preventing re-intubation and post-extubated respiratory failure in critically ill patients at high risk of intubation [9].

The present study suggests that when SPO2 is maintained above 90%-93%, HFNC may have benefit compared to COT in reducing the need to escalate respiratory support, but not for decreasing the re-intubation rate. Conversely, when SPO2 was maintained above 95%, HFNC reduced the re-intubation rate but not the rate of escalation of respiratory support. The advantages of reducing the need to escalate respiratory support at the lower SPO2 threshold vs. delaying the time to re-intubation at the higher SPO2 threshold remain to be elucidated. Recent studies show that critically ill patients treated with conservative oxygen therapy (with a slightly lower SPO2 target) vs. conventional therapy had a lower mechanical ventilation time and hospital or ICU mortality [36 37].

In the overall or subgroup analyses in the present review, HFNC did not significantly reduce the incidence of PPCs or mortality compared to COT in post-extubation surgical patients. These data are in contrast to a previous report, which speculated that HFNC may affect the outcomes of postoperative patients by alleviating PPCs[5]

This systematic review and meta-analysis was associated with several limitations. First, not all included studies investigated re-intubation rates and respiratory support escalation as primary endpoints, and most of the included studies were single-center studies. Second, there were differences in the timing and duration of HFNC treatment and length of follow-up in the included studies. Third, the sample size was small; 3 out of 10 studies were non-RCTs, including less than 50 patients each. These limitations represent potential sources of bias and heterogeneity.

Conclusion

Findings from this review suggest that HFNC is associated with a significantly lower re-intubation rate and rate of escalation of respiratory support compared to COT in post-extubation adult surgical patients, but there is no difference in the incidence of PPCs or mortality. More well-designed, large randomized controlled trials are needed to determine the patient population that is most likely to benefit from HFNC therapy.

Footnotes

Contributors: ZL and FG had full access to all the data in the study and take responsibility for its integrity and the accuracy of the data analysis. ZL, SM, JX, HQ and FG performed the systematic review, study selection, and statistical analysis. WC, JX, YY, and XZ contributed to data extraction and the quality assessment. All authors participated in writing the article.

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Data sharing statement: Data are available from the corresponding author on ressonable request fmguo2003@139.com

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Table and Figure legends

Figure 1 Flow diagram of study selection

Figure 2A Risk of bias summary for each included study. Red (–) indicates high risk of bias; yellow (?) indicates unclear risk; and green (+) indicates low risk of bias.

Figure 2B, 2C Funnel plot for publication bias: B) Re-intubation rate; C) Rate of escalation of respiratory support

Figure 3 High-flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT): Re-intubation rate

Figure 4 High-flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT): Rate of escalation of respiratory support

Figure 5 High-flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT): A) Postoperative pulmonary complications; B) Hospital mortality

Table 1 Characteristics of included studies

Table 2 Quality assessment: A) Cochrane collaboration methodology; B) Newcastle-Ottawa scale

Table 3 Subgroup analyses

Supplementary Figure 1 Search strategies for PubMed and Embase databases

Supplementary Figure 2 Meta regression: A) Type of surgery; B) Risk factors for intubation

Supplementary Figure 3 Sensitivity Analysis: A) Re-intubation rate; B) Rate of escalation of respiratory support

Supplementary Table 1 GRADE A) Re-intubation rate; B) Rate of escalation of respiratory support

Table1: Characteristics of included studies

Study	Study design	Type of surgery	Patient characteristics (HFNC/COT)			Target SPO2 (%)	Risk of re-intubation
			Patient number	BMI	Age (years)		
Chen, 2018	Case-control study	Thoracic	44/45	NA	66/64	90	High
Xu, 2018	Cohort study	Cardiovascular	45/45	26/27	57/54	95	High
Brainard, 2017	RCT	Thoracic	18/26	26/25	57/59	95	NA
Dhillon, 2017	Case-control study	Mixed	46/138	NA	63/58	NA	NA
Geng, 2017	RCT	Thoracic	25/23	NA	63/63	90	High
Sun, 2017	RCT	Thoracic	24/24	NA	67/65	100	High
Yu, 2017	RCT	Thoracic	56/54	26/25	56/56	95	High
Futier, 2016	RCT	Abdominal or combine thoracic	108/112	25/25	62/661	95	NA
Corley, 2015	RCT	Cardiovascular	81/74	36/35	63/65	95	High
Parke, 2013	RCT	Cardiovascular	169/171	28/29	65/66	93	High

Data are expressed as median (interquartile range), or mean (standard deviation); NA, Not available or not reported

Study	Characteristics of oxygen therapy (HFNC/COT)		escalation of respiratory support#		Strategy	Study center	Follow-up time: primary outcomes
	HFNC Flow rate(L/min)	COT	HFNC	COT			
			NIV/Intubation	HFNC/NIV/Intubation			
Chen, 2018	35-60	Facemask	NA/7	NA/19	Therapy	Single center	2 days
Xu, 2018	35-60	5-10L/min face mask	0/1	0/0/7	Prophylactic	Single center	3 days
Brainard, 2017	40	Nasal cannula or face mask	NA/1	NA/NA/2	Prophylactic	Single center	2 days
Dhillon, 2017	NA	Cool mist/nasal cannula (CM/NC)	NA/NA/3	NA/NA/19	Prophylactic	Single center	NA
Geng, 2017	35-60	Facemask	NA/NA/1	NA/NA/9	Therapy	Single center	NA
Sun, 2017	40-60	8-10L/min atomizing mask	1/3	0/3/8	Therapy	Single center	1 day
Yu, 2017	35-60	Nasal prongs or facemask	2/0	9/5/0	Prophylactic	Multicenter	3
Futier, 2016	50-60	Nasal prongs or facemask	NA/NA(20)*	NA/NA/NA(14)*	Prophylactic	Multicenter	7 days
Corley, 2015	35-50	2–4L/min via nasal cannulae or 6L/min via simple face mask	3/0	1/2/2	Prophylactic	Single center	1 day
Parke, 2013	45	2–4L/min via simple facemask or nasal prongs	9/2	18/5/0	Prophylactic	Single center	2 days

only the final oxygen treatment was recorded; * only get the total number; NA, Not available or not reported

Table 2 Quality assessment: Newcastle-Ottawa scale

Study	Selection				Comparability	Outcome			Overall stars
	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Xu, 2018	★	★	★	★	★	-	★	★	7
Chen, 2018	★	★	-	★	★	★	★	★	7
Dhillon, 2017	★	★	★	★	★	-	★	★	7

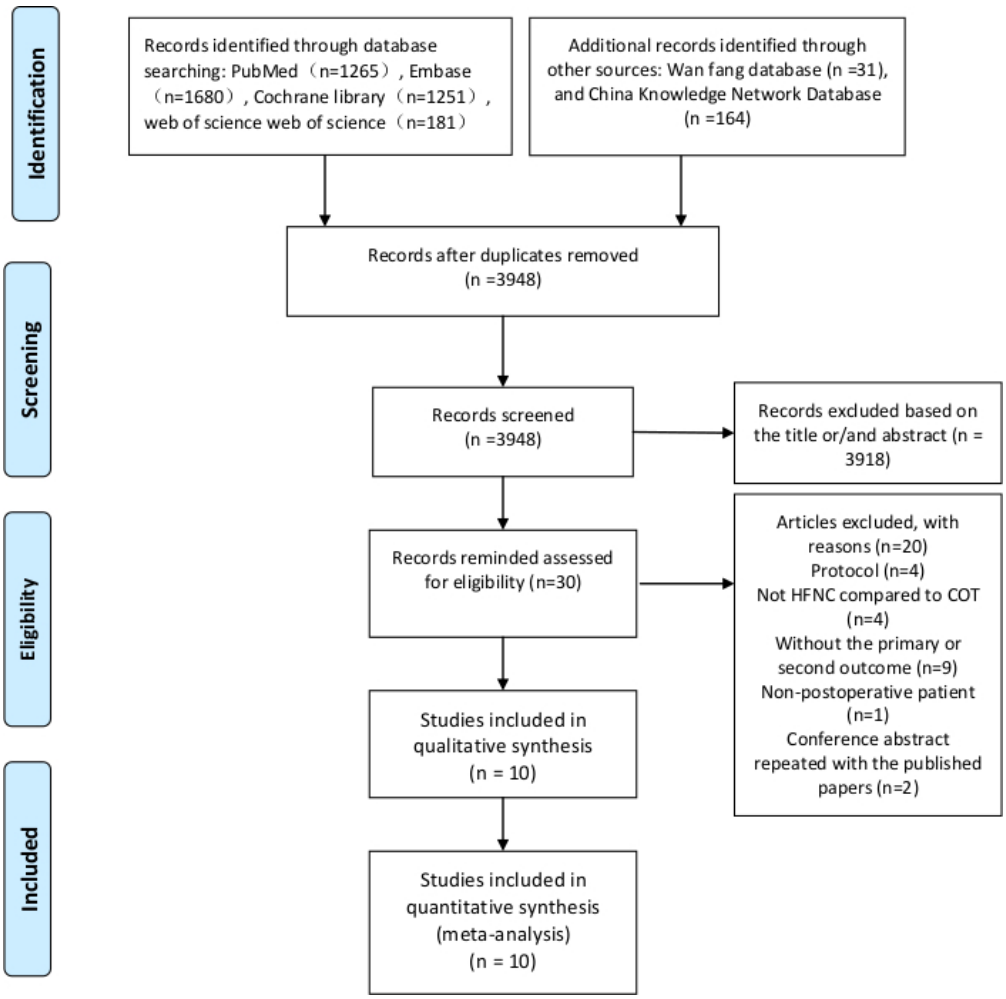
★ the quality met the criterion of this specific item; - Self-reported or unstated

Table 3 Subgroup analyses

Outcome	No studies (No of patients)	Summary estimate (95% CI)	P value (summary estimate)	P value (heterogeneity)	I^2 (%)
Re-intubation	9 (1107)	0.38* (0.23 to 0.61)	0.0001	0.64	0
Cardiac surgery	3 (585)	0. 43* (0.05 to 3.72)	0.44	0.14	49
Thoracic surgery	5 (338)	0. 36* (0.20 to 0.64)	0.0005	0.73	0
RCT	6 (745)	0.39* (0.17 to 0.87)	0.02	0.41	1
Non-RCT	3 (362)	0.37* (0.20 to 0.69)	0.002	0.60	0
Min target SPO2 (90%-93%)	3 (476)	0.41* (0.09 to 1.92)	0.26	0.11	55
Min target SPO2 (95%)	4 (399)	0.31* (0.09 to 1.01)	0.05	0.72	0
prophylactic	7 (1143)	0.46* (0.21 to 1.03)	0.06	0.53	0
Therapy	3 (184)	0.34* (0.18 to 0.62)	0.0005	0.45	0
High risk of re-intubation	7 (879)	0.35* (0.20 to 0.60)	0.0002	0.48	0
Escalation rate of respiratory support	10 (1327)	0.43* (0.26 to 0.73)	0.002	0.02	54
Cardiac surgery	3 (585)	0.45* (0.25 to 0.81)	0.008	0.51	0
Thoracic surgery	5 (338)	0.31* (0.18 to 0.53)	0.0001	0.47	0
RCT	7 (965)	0.46* (0.22 to 0.93)	0.03	0.01	64
Non-RCT	3 (362)	0.37* (0.20 to 0.69)	0.002	0.60	0
Min target SPO2 (90%-93%)	3 (476)	0.39* (0.23 to 0.67)	0.0005	0.34	8
Min target SPO2 (95%)	5 (619)	0.46* (0.15 to 1.44)	0.18	0.01	70
prophylactic	7 (1143)	0.50* (0.25 to 1.00)	0.05	0.02	59
Therapy	3 (184)	0.34* (0.19 to 0.60)	0.0002	0.45	0
High risk of re-intubation	7 (879)	0.33* (0.22 to 0.49)	0.00001	0.5	0
PPCs	5 (606)	0.87* (0.70 to 1.08)	0.21	0.92	0
RCT	4 (422)	0.86* (0.69 to 1.086)	0.20	0.83	0

prophylactic	4 (558)	0.86* (0.68 to 1.08)	0.20	0.87	0
Mortality	5 (942)	0.45* (0.16 to 1.29)	0.14	0.79	0
Cardiac surgery	1 (340)	1.01* (0.06 to 16.05)	0.99	-	-
Thoracic surgery	2 (198)	0.26* (0.03 to 2.25)	0.22	-	-
RCT	3 (670)	0.77* (0.17 to 3.41)	0.73	0.82	0
Non-RCT	2 (272)	0.27* (0.06 to 1.18)	0.08	0.98	0
Min target SPO2 (90%-93%)	2 (428)	0.41* (0.08 to 2.09)	0.29	0.45	0
Min target SPO2 (95%)	2 (330)	0.69* (0.12 to 4.06)	0.68	-	-
High risk of re-intubation	3 (538)	0.41* (0.08 to 2.09)	0.29	0.45	0

RCT, randomized controlled trial; PPCs, postoperative pulmonary complications *Relative risk



Flow diagram of study selection

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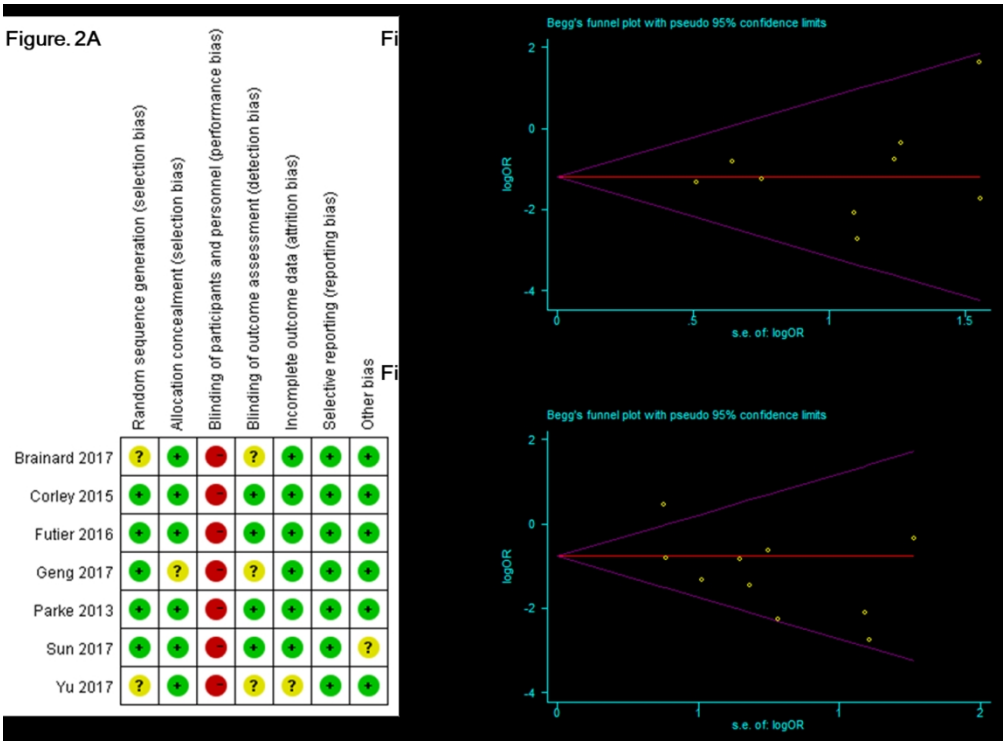

Figure 2A Risk of bias summary for each included study. Red (–) indicates high risk of bias; yellow (?) indicates unclear risk; and green (+) indicates low risk of bias.
Figure 2B, 2C Funnel plot for publication bias: B) Re-intubation rate; C) Rate of escalation of respiratory support

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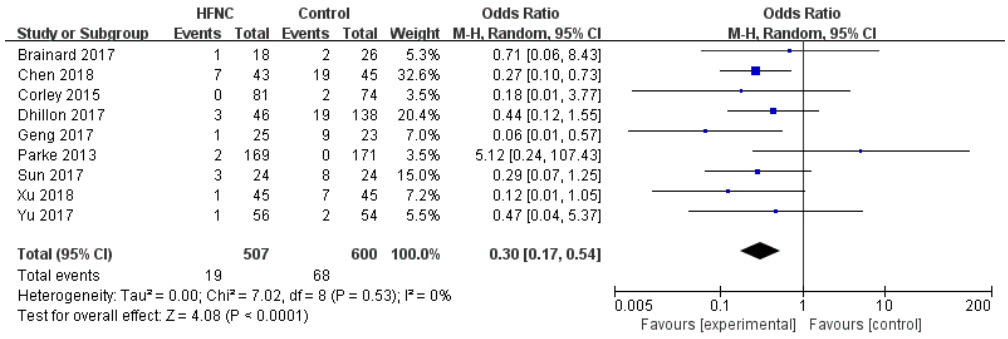

High-flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT): Re-intubation rate

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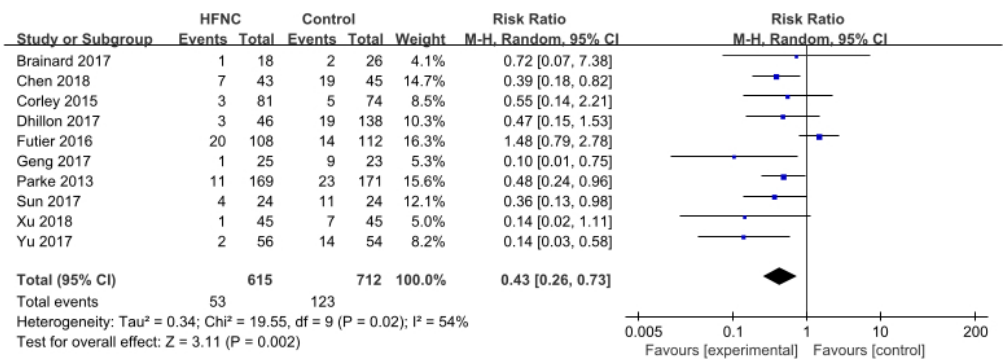

High-flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT): Rate of escalation of respiratory support

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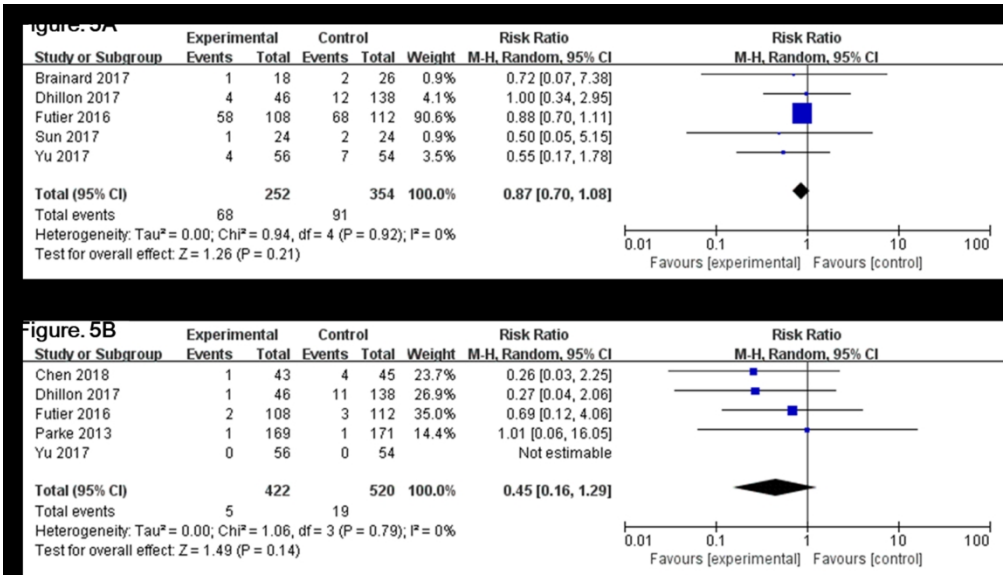


Figure 5 High-flow nasal cannula oxygen therapy (HFNC) versus conventional oxygen therapy (COT): A) Postoperative pulmonary complications; B) Hospital mortality

157x90mm (300 x 300 DPI)

The scope search strategy to identify the trial study being published

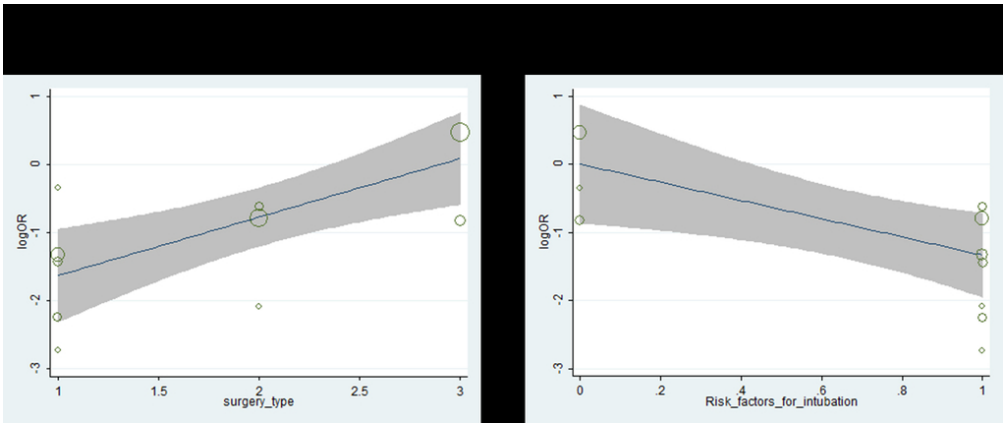
A:PubMed:

((((((Surgically[Title/Abstract]) OR (((((operation[Title/Abstract]) OR operative[Title/Abstract]) OR surgery[Title/Abstract]) OR Surgical[Title/Abstract])))))) AND ((high flow[Title/Abstract]) OR high-flow[Title/Abstract])

B:Embase

#10. #7 AND #8 AND [humans]/lim AND [clinical study]/lim
#9. #7 AND #8
#8. #2 OR #3
#7. #1 OR #4 OR #5 OR #6
#6. 'operation':ab,ti
#5. 'operative':ab,ti
#4. 'surgical':ab,ti
#3. 'high-flow':ab,ti
#2. 'high flow':ab,ti
#1. 'surgery'/exp

52x74mm (300 x 300 DPI)



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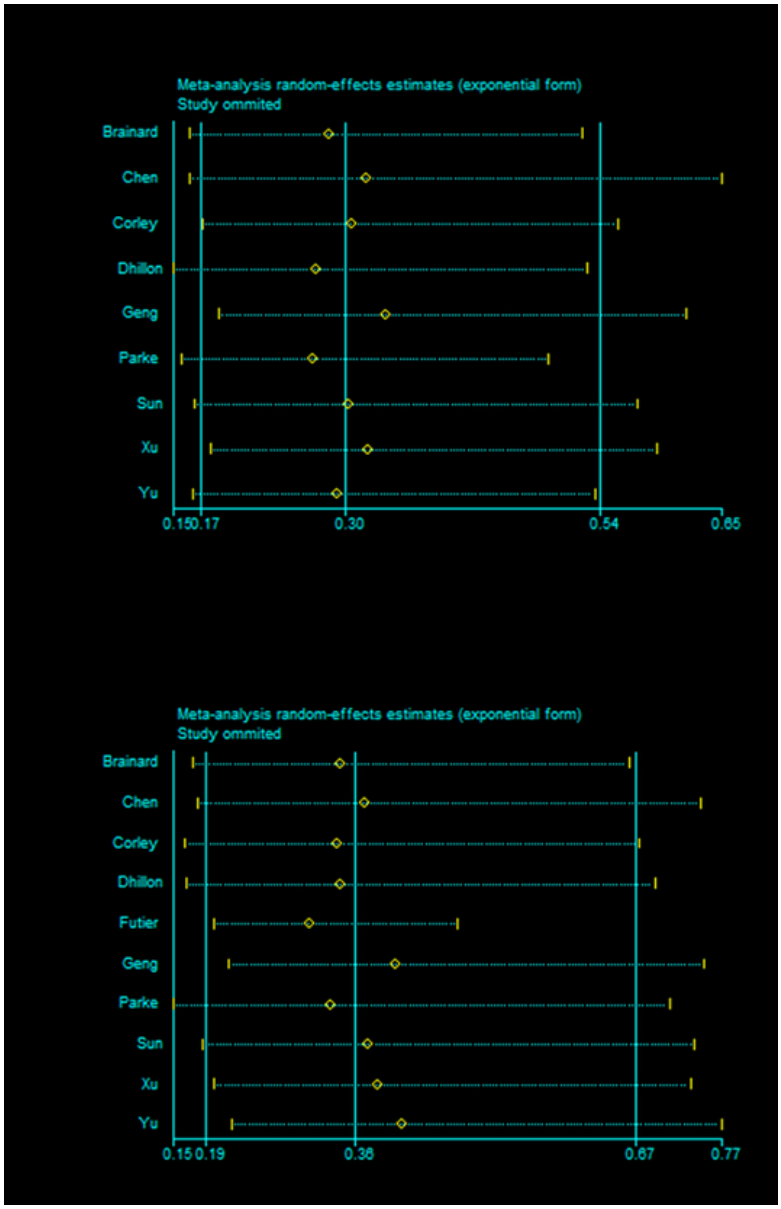

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Supplementary Table 1 GRADE A) Re-intubation rate; B) Rate of escalation of respiratory support

A.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reinbutation	Control	Relative (95% CI)	Absolute		
Reintubation-RCT												
6	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	8/373 (2.1%)	23/372 (6.2%)	RR 0.39 (0.17 to 0.87)	38 fewer per 1000 (from 8 fewer to 51 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
								5.7%		35 fewer per 1000 (from 7 fewer to 47 fewer)		
Case control studies												
2	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/89 (11.2%)	38/183 (20.8%)	OR 0.32 (0.15 to 0.71)	130 fewer per 1000 (from 51 fewer to 170 fewer)	⊕OOO VERY LOW	CRITICAL
								28%		169 fewer per 1000 (from 64 fewer to 225 fewer)		
Reintubation- Cohort study												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/45 (2.2%)	7/45 (15.6%)	OR 0.12 (0.01 to 1.05)	134 fewer per 1000 (from 154 fewer to 7 more)	⊕⊕OO LOW	CRITICAL
								15.6%		134 fewer per 1000 (from 154 fewer to 7		

										more)		

[1] High flow nasal cannula oxygen therapy or conventional oxygen therapy based on the individual attending's discretion

B.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Escalation of respiratory support	Control	Relative (95% CI)	Absolute		
Escalation of respiratory support-RCT												
7	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	no serious imprecision	reporting bias[2]	42/481 (8.7%)	78/484 (16.1%)	RR 0.54 (0.38 to 0.77)	74 fewer per 1000 (from 37 fewer to 100 fewer)	⊕⊕OO LOW	CRITICAL
								13.5%		62 fewer per 1000 (from 31 fewer to 84 fewer)		
Escalation of respiratory support-case control studies												
2	observational studies[3]	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10 cases 38 controls		OR 0.32 (0.15 to 0.71)	-	⊕OOO VERY LOW	CRITICAL
								38/183 (20.8%)		130 fewer per 1000 (from 51 fewer to 170 fewer)		
								28%		169 fewer per 1000 (from 64 fewer to 225 fewer)		
Escalation of respiratory support- Cohort studies												
1	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/45 (2.2%)	7/45 (15.6%)	OR 0.12 (0.01 to	134 fewer per 1000 (from 154 fewer to 7	⊕⊕OO LOW	CRITICAL

									1.05)	more)		
								15.6%		134 fewer per 1000 (from 154 fewer to 7 more)		

[1] I2=64%, the heterogeneity was high

[2] Funnel plots suggest that there may be publication bias in Futier's research

[3] case-control

[4] High flow nasal cannula oxygen therapy or conventional oxygen therapy based on the individual attending's discretion

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Page1,line1-3
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page2,line1-27
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page4,line2-21
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page4,line22-24;
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	No
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page5,line4-9
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page4,line27-30 Page5,line1-3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary Figure 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page5,line13-18
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page5,line19-23 Page6,line1-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page5,line24-30 Page6,line1-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page6,line7-16

PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page6,line17-27
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Page6,line28-29 Page7,line1-2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page7,line11-12
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Page7,line1-10;
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Page8,line3-13
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Page8,line14-29
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2 and Fig2A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Supplementary Figure 2, supplementary Figure 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page10,line16-30 Page11,line1-30 Page12,line1-20
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)	Page12,line21-27

PRISMA 2009 Checklist

Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page12,line28-30 Page13,line1-3
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page13,line11-18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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