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High-flow nasal cannula oxygen therapy in acute respiratory failure at Emergency Departments: a systematic review.

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Contributions:

NM drafted the manuscript with the support of AWT and JPF. OM and JG contributed to drafting and critical revisions of the manuscript and for important intellectual content. All authors read and approved the final version of the manuscript.

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LISTS OF ABBREVIATIONS

AHF – Acute Heart Failure

ARF – Acute Respiratory Failure

COPD – Chronic Obstructive Pulmonary Disease

COT – Conventional oxygen therapy

ED – Emergency Department

HFOT – High-Flow Oxygen Therapy

ICU – Intensive Care Unit

LOS – Length of stay

NIV – Noninvasive ventilation

RCT – Randomized Control Trial

ABSTRACT

Objectives: The use of high-flow oxygen therapy (HFOT) through nasal cannula for the management of acute respiratory failure at the emergency department (ED) has been only sparsely studied. We conducted a systematic review of randomized-controlled and quasi-experimental studies comparing the early use of HFOT versus conventional oxygen therapy (COT) in patients with acute respiratory failure admitted to EDs.

Methods: A systematic research of literature was carried out for all published control trials comparing HFOT with COT in adult patients admitted in EDs. Eligible data were extracted from Medline, Embase, Pascal, Web of Science and the Cochrane database. The primary outcome was the need for mechanical ventilation, *i.e.* intubation or non-invasive ventilation as rescue therapy. Secondary outcomes included respiratory rate, dyspnea level, ED length of stay, intubation and mortality.

Results: Out of 1829 studies screened, five studies including 673 patients were retained in the analysis (350 patients treated with HFOT and 323 treated with COT). The need for mechanical ventilation was similar in both treatments (RR=0.75; 95% CI 0.41 to 1.35; $p=0.31$; $I^2=16\%$). Respiratory rate was lower with HFOT (Mean difference (MD)=-3.14 breaths/min; 95% CI = -4.9 to -1.4; $p < 0.001$; $I^2 = 39\%$), whereas sensation of dyspnea did not differ. (MD=-1.04; 95% CI=-2.29 to -0.22; $P=0.08$; $I^2=67\%$). ED length of stay and mortality were similar between groups.

Conclusion: The early use of HFOT in patients admitted to an ED for acute respiratory failure didnot reduce the need for mechanical ventilation as compared to COT. However, HFOT decreased respiratory rate.

Registration: PROSPERO ID CRD42019125696

Key words: respiratory failure, high-flow nasal cannula, emergency department

Background

Dyspnea is one of the chief complaints in emergency departments, involving more than half of patients admitted.[1] The usual first-line strategy of oxygenation is conventional oxygen therapy (COT) delivered through a nasal cannula or nonbreathing mask.[2] However, COT has several limitations especially in control of delivery of high inspired fraction of oxygen (FiO_2). The FiO_2 delivered through standard oxygen devices, even with a non-rebreathing mask, does not exceed 70% and may be lower in case of acute respiratory failure, due to the high inspiratory flow generated by patients leading to the dilution of inhaled oxygen with room air.[3] Moreover, comfort and tolerance may be compromised over a 5 L/min oxygen flow due to cold and dry gas increasing airway resistance.[4]

High-flow nasal cannula oxygen therapy (HFOT) is a recent technique of oxygen supply first used in preterm infants and more recently in adult intensive care units[5] or postoperative patients.[6] HFOT is able to deliver high FiO_2 titrated to 100%, even during acute respiratory failure.[3] The high flow generates a low level of positive pressure in the upper airway and a subsequent positive end-expiratory pressure effect increasing with gas flow.[7,8] The continuous washout of dead space in the upper airways[9–11] and the other physiological effects may also enable HFOT to improve gas exchange, reduce respiratory rate and the work of breathing.[12,13] In patients admitted for acute respiratory failure, several studies have shown better comfort under HFOT than COT of noninvasive ventilation, the comfort being favored by the interface and heated and humidified gas delivered by HFOT.[14–16]

The use of HFOT in EDs has been spreading after the first substantial benefits were reported in patients admitted in an ICU for acute respiratory failure.[5] However, HFOT has been poorly assessed in EDs and its impact is unclear. Two systematic reviews with metanalysis were previously published with conflicting results.[17,18] Therefore, we decided to perform a systemic review of randomized or quasi-experimental trials assessing the early use of HFOT compared to conventional oxygen therapy in the management of patients with acute respiratory failure admitted to EDs.

MATERIALS AND METHODS

Eligibility criteria

Articles were considered for inclusion if they met the following criteria: (1) original research reporting a randomized controlled trial or quasi-experimental study comparing HFOT to COT, (2) including adult human subjects (3) admitted to Emergency Departments and (4) full text published in English or in French. Editorials, case reports, letters, retrospective studies and abstracts were excluded from the study. Reviewers also screened references of relevant articles when considering inclusion.

Data sources and search strategy

A comprehensive and relevant literature search of Medline, Embase, Pascal, Web of Science and Cochrane database (Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register) was conducted using Medical

Subject Heading and Free text terms from January 1st, 2010 to April 30th, 2018. The following key word terms were used to perform the search (“emergency department” or “emergency room” or “emergency unit” or “emergency service” or “ED”) and (“high-flow” or “high flow nasal” or “high flow nasal cannula” or “heated and humidified high-flow” or “high-flow nasal oxygen” or “high-flow oxygen” or “nasal high flow” or “HFOT” or “HHHF” or “HFNC”).

Data Extraction

For each eligible study, two authors (NM and JG) summarised and evaluated the studies and their data. Data were directly extracted using a standardized form including (1) sample size, (2) characteristics of the population, (4) type of interventions and the appropriateness of statistical analyses and (5) main findings and (6) risk of bias.

Data synthesis and analysis

The primary outcome was treatment failure defined by the need for mechanical ventilation, *i.e.* intubation or noninvasive ventilation as rescue therapy. Secondary outcomes were change in respiratory rate, change in dyspnea level after treatment initiation, length of stay (LOS) in EDs, tracheal intubation rates and mortality.

Quantitative data were presented as the mean and standard deviation or as the median and interquartile range if adequate. We calculated a pooled estimate of risk ratio (RR) for qualitative data, and of a mean difference for quantitative data in the individual studies using a random-effects model. The homogeneity assumption was measured by the I^2 . A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. All analyses were conducted with Review Manager 5.3 (The Cochrane Collaboration). For all analyses, a p-value below 0.05 was considered as significant.

Risk of bias

Risk of bias was assessed regarding randomization, allocation sequence concealment, incomplete outcome data, selective outcome reporting and other biases. Blinding could not be implemented due to the nature of these studies.

Registration

The study protocol was registered on the Prospero database (ID CRD42019125696) in March 2019.

RESULTS

Search results and trial characteristics

By screening titles and evaluating the abstracts of 1829 relevant records identified, we deleted reviews, case reports, comments, non-adult, non-randomized studies and duplicate studies resulting in four randomized controlled trials (**Figure 1**). Thus, five studies were included comparing the use of HFOT versus COT at the emergency department.

Included studies

A total of 673 patients were retained in the analysis (**Table 1**), including 350 patients assigned to HFOT group and 323 patients assigned to COT group. Definitions of acute respiratory failure were based on clinical parameters, respiratory rate (\geq 25 breaths per min) and SpO₂ values (equal to or below 92- 94% in room air; Table 1).[19–23] Three studies[19,20,22] included a heterogeneous population of patients with acute exacerbation of chronic obstructive pulmonary disease or asthma (30 to 49%), cardiogenic pulmonary edema (14 to 35%) and pneumonia (19 to 23%), while one study only included patients admitted for cardiogenic pulmonary edema[21] and another included acute hypoxemic respiratory failure mainly due to pneumonia (81%).[23]

All studies compared HFOT with COT alone (Table 2). COT was administered with nasal cannula or non-rebreathing mask and HFOT via specific large nasal cannula, with a gas flow between 35 and 50 L/min. While primary outcomes differed among studies, but all of them reported clinical parameters including respiratory rate, dyspnea measurement (numerical rating/visual analogic scale, or 5-point Likert scale) after treatment initiation and escalation to invasive ventilation, NIV or crossover to high-flow.

The risk of bias in each study is detailed in **Figure 2** and as evaluated according to the methods described in the Cochrane Handbook.

Need for mechanical ventilation

All studies reported findings on treatment failure (Table 2). The pooled results are shown in **Figure 3**. The need for mechanical ventilation including NIV or intubation did not differ between groups: 24 out of 350 patients (7%) treated with HFOT vs. 30 out of 323 patients (9%) treated with COT ($p = 0.25$). No heterogeneity across studies was found ($I^2 = 16\%$; $p = 0.31$). The estimate of the relative risk (RR) for treatment failure with HFOT compared to COT was 0.75 (95% confidence interval 0.41 to 1.35; $p = 0.33$).

Clinical impact on respiratory rate and dyspnea

Respiratory rate was assessed in five studies, while dyspnea level was measured in four. Respiratory rate was lower with HFOT than with COT after initiation in three studies,[19,21,23] whereas it was similar in two others^{18,20}. Two studies reported a lower dyspnea level after HFOT (**Table 2**).[19,22,23]

Only three studies presented data that could be pooled, and results are shown in **Figure 4**. The respiratory rate was lower in the HFOT group (mean difference of -3.14; 95% confidence interval: -4.89 to -1.39; $p < 0.001$). The sensation of dyspnea was similar between treatments (Mean difference = -1.04; 95% confidence interval -2.29 to 0.22; $P = 0.08$).

Length of stay in ED

In the four studies assessing the impact of HFOT on length of stay, there was no difference when compared to COT. [19,21,23] LOS could not be pooled because of a lack of data. (**Table 2**)

Tracheal intubation rate

Five studies reported intubation rate. Tracheal intubation rates between patients treated with HFOT and those treated with COT were 11 out of 350 (3%) and 12 out of 323 (4%) respectively ($p=0.63$). Pooled results are shown in Figure 3. No heterogeneity between studies was found ($I^2 = 0\%$; $P = 0.58$). HFOT was not associated with reduction in the intubation rate (RR =0.87; 95% confidence interval 0.41 to 1.86; $P = 0.72$).

Mortality

Three studies reported on in-hospital, Day-7, Day-28 or Day-90 mortality. In-hospital **mortality** rates **between** patients treated with HFOT and those treated with COT were 22 out of 282 patients deceased (8%) vs. 18 out of 251 (7%), respectively ($p=0.78$). Pooled results are shown in **Figure 3**. No heterogeneity between studies was found ($I^2 = 0\%$; $P = 0.65$). HFOT was not associated with an improvement in the mortality rate, with RR = 1.03 (95% confidence interval 0.57 to 1.86; $P = 0.65$).

Adverse events

No serious adverse events linked with HFOT application were reported in the five selected studies. Minor adverse events associated with HFOT were uncommon and included unpleasant smell, feeling hot, dried-out nose and chest discomfort.

DISCUSSION

Our results suggest that early HFOT did not reduce the need for mechanical ventilation or the mortality rate. While HFOT did not improve dyspnea level when compared with COT, it was associated with a decreased respiratory rate. To our knowledge, only two other reviews have aimed to assess the use of HFOT in an ED setting. However, their results are contradictory, and neither included the most recent study.

HFOT impact on outcomes

Even if recent work has reported that its effects may be limited in immunocompromised patients[24], HFOT has been shown to reduce the mortality rate in acute hypoxemic respiratory failure patients in ICUs and also to lower the intubation rate in the most severely ill patients[5]. Although these benefits are substantial, our results suggest that HFOT did not have a similar effect in EDs. Among selected studies, four did not report any difference between treatments, and one reported a difference but included crossover with HFOT in COT groups.

Several reasons could explain the observed difference between ICU and EDs. First, HFOT was used over longer periods in ICUs than in EDs where HFOT was administered for only a few hours. We assumed the delay was too short and the effect too low to improve important patient such outcomes as intubation or mortality rates. Consequently, studies performed in EDs are insufficiently powered to detect a significant impact on outcomes. In addition, the heterogeneity of the patients included in studies may have limited the observed effect of HFOT. Indeed, three

studies included [acute respiratory failure of all origins](#) that were related to acute exacerbation of chronic obstructive pulmonary disease or acute heart failure in almost half of patients [19–23]. Few data are available in the literature on the impact of HFOT in these two diagnoses, even if it seems to provide benefits[15,25,26]. However, we cannot exclude the hypothesis that the global effect of HFOT is limited in this population by contrast with acute hypoxemic respiratory failure.

Clinical impact of HFOT

Regardless of its effect on outcomes, HFOT must also be assessed on the basis of its clinical impact. HFOT is known to improve clinical parameters and dyspnea in the first hour of treatment in patients with acute respiratory failure[14,27], including patients admitted to EDs. Our results suggest that HFOT provided a higher clinical effect than COT, but this effect was not correlated with improvement in the sensation of dyspnea.

Among studies selected in this meta-analysis, only three provided data sufficient to be pooled in the analysis[21,22]. Jones *et al.* did not report difference in respiratory rate between HFOT and COT [20] or improvement in breathing in patients between treatments. By contrast, Bell *et al.* found more patients with improved respiratory rate and sensation of dyspnoea with HFOT than COT[19]. In addition, in a recent before-after study, we reported that patients with acute hypoxemic respiratory failure treated with HFOT, and compared to COT, had less breathlessness and were more likely to show improved respiratory rate 1 hour after initiation of the treatment[23].

Heterogeneity between studies could be explained by the ventilatory support provided by HFOT through several physiological effects and by the different modalities of HFOT across studies. HFOT generates a low level of PEEP in the upper airways [28,29]. The PEEP effect improves tidal volume and End Expiratory Lung Volume, thereby suggesting alveoli recruitment [30,31]. In addition, experimental and pilot studies have shown that HFOT provides dead space washout of the upper airways[9,10]. Dead space washout is suggested as a key mechanism of respiratory support of HFOT. It prevents the rebreathing of CO₂ and allows functional reduction in physiological dead-space, thereby optimizing minute ventilation[11] and slowing down respiratory rate[9]. PEEP effect and dead-space washout, and ultimately clinical effect, are directly proportional to the delivered flow: the higher the flow, the higher the PEEP and the wash-out[28]. In selected studies, initial flow could vary from 30 [20]to 50 L/min [19,21,23], suggesting various levels of physiological effects, and various clinical impacts.

Length of stay

ED Length of stay is a fundamental determinant of the quality of care in emergency departments. Increased ED length of stay is associated not only with increased overcrowding, but also with aggravation of the mortality rate, regardless of the disease responsible for admission [32,33]. The introduction in an ED of a new treatment, initially developed and assessed in ICU and post-operative room, must be assessed not only in terms of clinical response and impact on outcomes, but also according to its impact on the organization of ED and quality of care, evaluated with LOS. Four of the selected trials measured LOS as a secondary outcome, and none reported any variation as compared to control, suggesting that HFOT could be used without impact on overall quality of care.

Limits and strengths

This review has several limitations. First, we included a small number of studies. Only four randomized controlled and one quasi-experimental trial have been performed to date, and conclusions about the effectiveness of HFOT in EDs remain under discussion.

Another limitation is due to the heterogeneous population included in the different studies. As previously indicated, three of the works assessed HFOT in a heterogeneous and unselected population where most patients were suffering from acute exacerbation of COPD or AHF. This heterogeneity of patients is responsible for a lack of clarity regarding the real effect of HFOT in patients admitted to an Emergency Department with acute respiratory failure. In addition, one study with a before-after design and having included 15% of the total population of the meta-analysis was included in this review. The inherent bias due to the study design may limit the validity of our findings. Finally, included RCTs are from different parts of the world, and were provided in different emergency departments. Standard treatment cannot be considered as equivalent, and results of studies may be less comparable.

The main strength of this review is that it included only studies conducted in Emergency Departments. Most of the published reviews have included various procedures performed in different departments, from intensive care units to post-operative units [34,35]. Although many trials have reported the effectiveness of the HFOT in intensive care, the results are not necessarily similar in an Emergency Department. Two other reviews that specifically included studies performed in an ED were recently published, but neither one included the most recent trial, which mainly included patients with hypoxemic respiratory failure.[17,18] In addition, we considered our primary outcome (requirement for invasive or non-invasive mechanical ventilation) as more relevant than the intubation rates used in previous meta-analyses. Among included studies, several patients required non-invasive ventilation instead of COT as first-line treatment.[36] We assumed the need for mechanical ventilation, including non-invasive ventilation, to be a broader focus of HFOT efficacy. Finally, the two previous meta-analyses did not report the impact of HFOT on respiratory rate, which is the best clinical marker of disease severity, adequate response to treatment and patients' prognosis.[37–39] Our meta-analysis confirms the lack of substantial benefit of HFOT in patients visiting an ED for acute respiratory failure.

Clinical implications

Even if HFOT provides hopeful clinical effects in EDs, this review and metanalysis suggests a low level of evidence that HNFC provides an effect on outcome superior to COT when used in unselected ARF patients. While early use of HFOT in EDs is not associated with less need for mechanical ventilation, it does lead to improved respiratory parameters. Regardless, the use of HFOT in ED should be undertaken with caution and limited to a selected population. Further large-scale RCTs are needed to assess the clinical impact of HFOT as compared to other oxygenation strategies.

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TABLE AND FIGURES LEGENDS

Figure 1: Flow diagram of the study selection process.

Figure 2: Risk of bias summary. Review of authors' judgements about each risk of bias item for each included study.

Figure 3 – Forrest plot of comparison of A – Need for mechanical ventilation, B - Mortality rate, C – Tracheal Intubation rate between High-flow oxygen therapy and Conventional oxygen therapy

HFOT : High-Flow Oxygen Therapy – COT : Conventional Oxygen Therapy – CI : Confidence Interval – RR : Relative Risk – NIV : Noninvasive ventilation

There was a reduction of respiratory failure with HFOT, but we did not report improvement in terms of need for mechanical ventilation (*i.e* NIV or intubation), and mortality rate.

Figure 4 – Forest plot of comparison in reduction in : A – Respiratory Rate B – Dyspnea level, between High-flow oxygen therapy and Conventional oxygen therapy

HFOT : High-Flow Oxygen Therapy – COT : Conventional Oxygen Therapy – CI : Confidence Interval

High flow oxygen therapy was associated with a more pronounced improvement of respiratory rate and dyspnea than conventional oxygen therapy.

Table 1: Description of included studies

Table 2: Evolution of clinical parameters after oxygenation support provided for at least 1h

ACKNOWLEDGEMENTS

We wish to thank Jeffrey Arsham, an American medical translator, for reviewing and editing our original English-language manuscript.

COMPETING INTEREST

NM reports travel expense coverage to attend scientific meetings and payment for lectures from Fisher & Paykel. JPF reports travel expense coverage to attend scientific meetings and personal fees from Fisher & Paykel. AWT reports travel expense coverage to attend scientific meetings and payment for lectures from Fisher & Paykel.

Table 1: Description of included studies

Author, Year	Patients, n	Age (year)	Male (M, %)	Inclusion criteria	Main diagnoses	COT	HFOT	Main outcomes
Rittayamai, 2015	40	65±15	38%	SpO ₂ <94% on room air and RR>24 breaths/min	35% CHF 15% Asthma 15% AE of COPD 23% Pneumonia	COT via nasal cannula or nonbreathing mask to maintain SpO ₂ of 94%. Duration 1 hour.	Gas flow set at 35L/min with FiO ₂ titrated to maintain SpO ₂ ≥94%. Duration 1 hour.	Dyspnea / RR other physiological data
Jones, 2015	303	73±16	48%	SpO ₂ ≤ 92% on room air (≤ 90% if known chronic hypercapnia) and RR≥22 breaths/min	26% AE of COPD 7% Asthma 24% Pneumonia 14% CHF	COT via nasal cannula or non-breathing mask during 24 hours with gas flow adjusted according to clinical need.	Gas flow set at 40L/min with FiO ₂ started at 28% and then titrated according to clinical need, during 24 hours.	Therapeutic escalation/ dyspnea, RR other physiological data
Bell, 2015	100	74±15	44%	Dyspnea and RR> 25 breaths/min and SpO ₂ ≤ 93% on room air	45% AE of COPD 22% CHF 19% Pneumonia	COT via nasal cannula or non-rebreathing mask with flow adjusted according to clinical need. Duration 2 hours.	Gas flow set at 50L/min with FiO ₂ started at 30%, and then titrated according to clinical need. Duration 2 hours.	Decrease in RR or therapeutic escalation/ dyspnea
Makdee, 2017	128	70±15	35%	SpO ₂ <95% on room air and RR>24 breaths/min	100% CHF	COT via nasal cannula or non-rebreathing mask, and flow adjusted to maintain a SpO ₂ ≥ 95%. Duration 1 hour.	Gas flow set from 35 to 60L/min with FiO ₂ titrated for SpO ₂ ≥95%. Duration 1 hour.	RR/ dyspnea other physiological data
Macé, 2019	102	68 [59-85] and 73 [61-84]	61%	RR > 25 breaths/min And/or Signs of increased breathing effort	81% pneumonia 3% asthma	COT via nasal cannula or nonbreathing mask according to severity of patients	Gas flow set at 50L/min with FiO ₂ titrated to, and flow adjusted to maintain SpO ₂ > 92%	Proportion of patients presenting improved signs of respiratory failure Tolerance/dyspnea/Blood oxygenation

*Oxygenation support was provided for at least 1h

CHF, congestive heart failure; RR: Respiratory Rate; AE of COPD: Acute Exacerbation of Chronic Obstructive Respiratory Failure; PEEP, Positive End Expiratory Pressure.

Table 2: Evolution of clinical parameters after oxygenation support provided for at least 1h

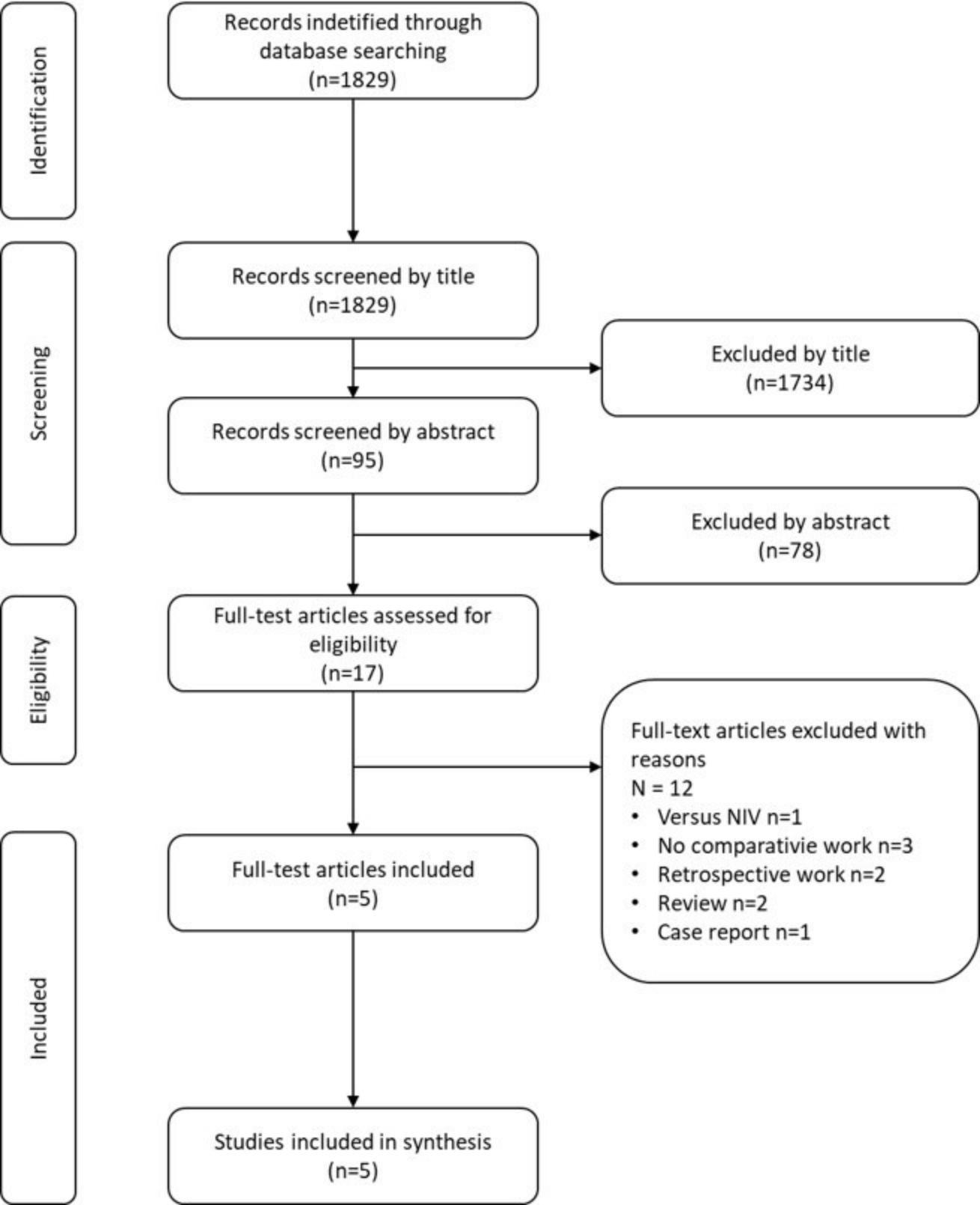
Author, Year	Dyspnea level		P value	Respiratory Rate		P value	SpO2 (%)		P value	ED length of stay, median		p-value
	HFOT	COT		HFOT	COT		HFOT	COT		HFOT	COT	
Rittayamai, 2015 [20]	H1: 2.0±1.8	H1: 3.8±2.3	.01	H1: 26 ± 6	H1: 27 ± 5	.82	H1: 96.8±2.5	H1: 97.6±2.0	.13	-	-	
Jones, 2015 [18]	-	-	-	H1: 27 H2: 26 H3: 24	H1: 27 H2: 26 H3: 24	.92 .74 .93	H1: 92.1 H2: 93.0 H3: 92.9	H1: 94.5 H2: 94.1 H3: 93.7	<.01 .04 .29	4.5	4.9	.32
Bell, 2015 [17]	55.8% ^a	75% ^a	.044	66.7% ^b	38.5% ^b	.005	-	-		4.4	5.0	.29
Makdee, 2017[19]	H1: 3.1±2	H1: 3.6±2.2	NS	H1: 22 ± 4	H1: 25 ± 4	<.01	H1: 99.2±1.2	H1: 98.7±1.5	<.05	6.9	6.0	NS
Macé, 2019[23]	-	-	-	H1: 24 ± 6 ^c	H1: 29 ± 8 ^c	.01	H1: 95 ± 5 ^c	H1 95 ± 3 ^c	0.12	5	8	0.08

Results are expressed as mean±SD unless specified. Respiratory rate was expressed as breaths/min, except for Bell *et al.*

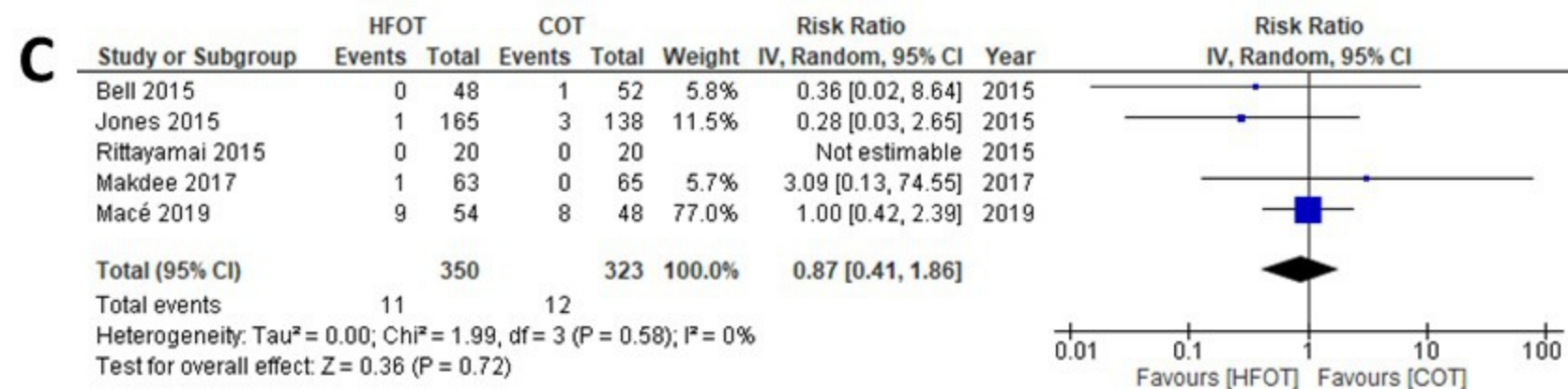
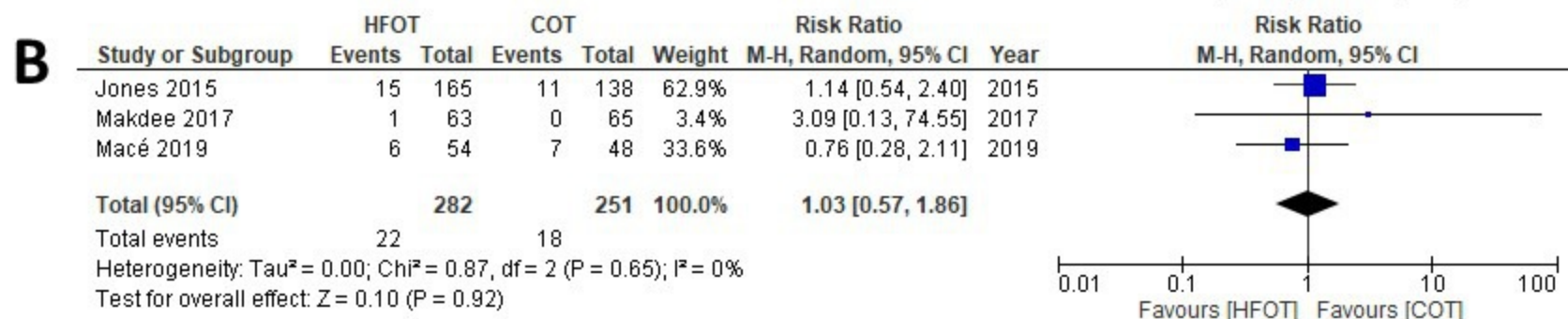
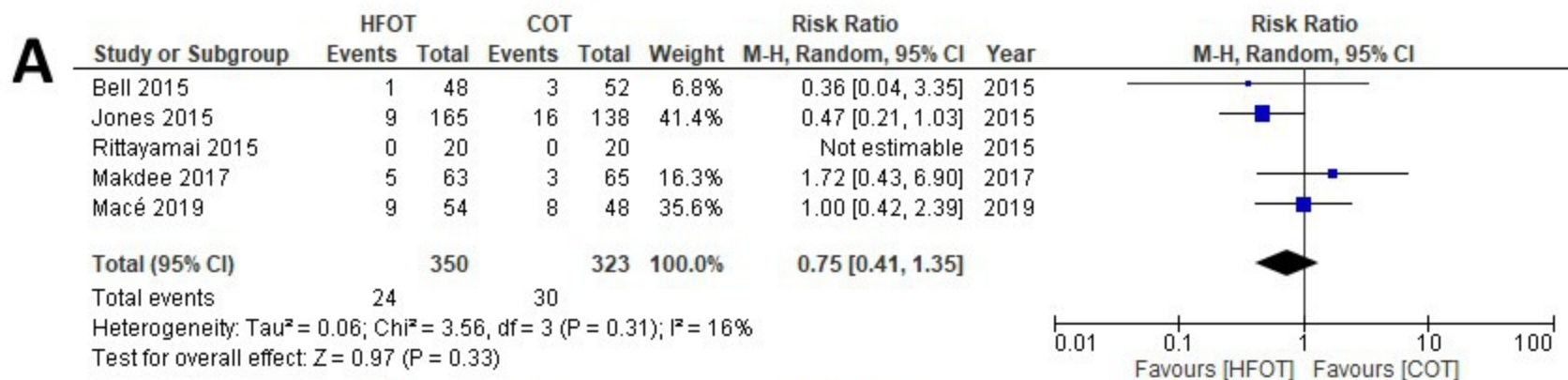
^a Reduction in the self-reported Borg scale value within 2h after treatment started

^b Reduction in respiratory rate >20% within 2h after treatment started

^c Unpublished data



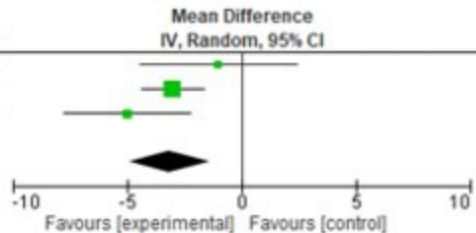
	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bell 2015	+	+	-	?	+	+	?
Jones 2015	+	+	-	?	+	+	?
Macé 2019	-	-	-	?	+	+	?
Makdee 2017	+	+	-	?	+	+	?
Rittayamai 2015	+	+	-	?	+	+	?



A

Study or Subgroup	HFNC			COT			Weight	Mean Difference IV, Random, 95% CI	Year
	Mean	SD	Total	Mean	SD	Total			
Rittayamai 2015	26	6	20	27	5	20	19.7%	-1.00 [-4.42, 2.42]	2015
Makdee 2017	22	4	63	25	4	65	53.6%	-3.00 [-4.39, -1.61]	2017
Macé 2019	24	6	54	29	8	48	26.7%	-5.00 [-7.77, -2.23]	2019
Total (95% CI)			137			133	100.0%	-3.14 [-4.89, -1.39]	

Heterogeneity: $\tau^2 = 0.99$; $\chi^2 = 3.27$, $df = 2$ ($P = 0.19$); $I^2 = 39\%$
 Test for overall effect: $Z = 3.52$ ($P = 0.0004$)

**B**

Study or Subgroup	HFOT			COT			Weight	Mean Difference IV, Random, 95% CI	Year
	Mean	SD	Total	Mean	SD	Total			
Rittayamai 2015	2	1.8	20	3.8	2.3	20	41.5%	-1.80 [-3.08, -0.52]	2015
Makdee 2017	3.1	2	63	3.6	2.2	65	58.5%	-0.50 [-1.23, 0.23]	2017
Total (95% CI)			83			85	100.0%	-1.04 [-2.29, 0.22]	

Heterogeneity: $\tau^2 = 0.56$; $\chi^2 = 2.99$, $df = 1$ ($P = 0.08$); $I^2 = 67\%$
 Test for overall effect: $Z = 1.62$ ($P = 0.10$)

