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Original Contribution

The effect of high-flow nasal cannula in reducing the mortality and the rate of endotracheal intubation when used before mechanical ventilation compared with conventional oxygen therapy and noninvasive positive pressure ventilation. A systematic review and meta-analysis

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ABSTRACT

Background: The effects of high flow nasal cannula (HFNC) on adult patients when used before mechanical ventilation (MV) are unclear. We aimed to determine the effectiveness of HFNC when used before MV by comparison to conventional oxygen therapy (COT) and noninvasive positive pressure ventilation (NIPPV).
Methods: The Pubmed, Embase, Medline, Cochrane Central Register of Controlled Trials (CENTRAL) as well as the Information Sciences Institute (ISI) Web of Science were searched for all the controlled studies that compared HFNC with NIPPV and COT when used before MV in adult patients. The primary outcome was the rate of endotracheal intubation and the secondary outcomes were intensive care unit (ICU) mortality and length of ICU stay (ICU LOS).
Results: Eight trials with a total of 1084 patients were pooled in our final studies. No significant heterogeneity was found in outcome measures. Compared both with COT and NIPPV, HFNC could reduce both of the rate of endotracheal intubation (OR 0.62, 95% CI 0.38–0.99, $P = 0.05$; OR 0.48, 95% CI 0.31–0.73, $P = 0.0006$) and ICU mortality (OR 0.47, 95% CI 0.24–0.93, $P = 0.03$; OR 0.36, 95% CI 0.20–0.63, $P = 0.0004$). As for the ICU LOS, we did not find any advantage of HFNC over COT or NIPPV.
Conclusions: When used before MV, HFNC can improve the prognosis of patients compared both with the COT and NIPPV.

1. Background

Approximately 60% of the patients are reported to receive endotracheal intubation and mechanical ventilation (MV) when admitted to the intensive care unit (ICU) [1]. In spite of the complete respiratory support, the hospital mortality of invasive mechanical ventilation remains as high as 30.7% due to the potential adverse events such as barotrauma and ventilator-associated pneumonia [2-3]. Thus, treatment to avoid or substitute the endotracheal intubation has important clinical values for mortality control.

Noninvasive positive pressure ventilation (NIPPV) and conventional oxygen therapy (COT) are the most common respiratory support techniques [4-9]. However, NIPPV is found to be associated with numerous potential hazards including skin damage, eye irritation, intolerance of interface, and diet and expectoration interruption [10], which to some extent limit the general applications of the NIPPV and lead to 25% of failure in patients with hypoxemic respiratory failure [11]. As for the COT, the inconsistent oxygen concentration and lack of sufficient pressure support also result in up to 52% of endotracheal intubation [11]. Therefore, the limitations of NIPPV and COT continuously intrigue physicians and researchers to explore and refine a new way of oxygen delivery and support system when used before MV to improve the clinical prognosis of patients.

High-flow nasal cannula (HFNC) is a novel technique of oxygen therapy, and it delivers heated and humidified oxygen via special devices at a rate of up to 60 L/min. Based on its widely proved clinical efficacy together with easier application and better patient tolerance in critically ill infants and children, physicians especially practitioners in emergency settings began to focus on the potential roles of HFNC in adult patients when used before MV [12]. However, contradictory conclusions were drawn in spite of large numbers of clinical trials. Frat et al. conducted a multicenter, open-label trial in 310 patients, and found that HFNC could not decrease intubation rate compared with COT or NIPPV (38% vs. 47% vs. 50%, $P = 0.18$) [13], while some studies showed lower rate

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of invasive ventilation in HFNC compared with COT (1.9% vs. 4.2%, $P = 0.02$) and NIPPV(35% vs. 55%, $P = 0.04$) [14-15].

Although hundreds of studies have been performed in the clinical practices of HFNC, specific investigations and evaluations in the subgroup receiving HFNC before MV, which happens frequently in the emergency departments, are still in scarce. In order to identify the roles of HFNC in improving the outcomes of patients when used before MV, a systematic review and meta-analysis of all published trials was conducted.

2. Methods

2.1. Search strategies

From 1946 to October 2016, a comprehensive computer search was conducted in Pubmed, Embase, Medline, Cochrane Central Register of Controlled Trails (CENTRAL) and Information Sciences Institute (ISI) Web of Science using the keywords of "HFNC" or "high-flow nasal cannula" or "high-flow oxygen therapy" or "nasal high-flow oxygen therapy" and "NIPPV" or "non-invasive positive pressure ventilation" or "noninvasive positive pressure ventilation" or "non-invasive ventilation" or "noninvasive ventilation" or "oxygen therapy" or "COT" or "venturi mask" without limitation in the publication type or language. We also reviewed the references listed in each identified article and manually searched the related articles to identify all eligible studies and minimize any potential publication bias.

2.2. Inclusion and exclusion criteria

Eligible clinical trials were identified based on the following criteria: 1) the subjects enrolled in each study did not receive MV or surgery before or at hospital admission; 2) patients were divided into experimental group, in which HFNC oxygen therapy was applied, or control group, in which they were assigned to receive NIPPV or COT; 3) outcomes included but not limited to rate of endotracheal intubation, ICU mortality, length of stay (LOS) in ICU. We excluded studies if they were performed in animals or in patients under 18 years old, or published as reviews or case reports.

2.3. Study selection

Two independent investigators performed the study selection in two phases. First, they discarded duplicated and non-controlled studies by screening titles and abstracts. Second, eligible studies were extracted by reviewing full texts in accordance with the previously designed study inclusion criteria. Any disagreement was resolved by mutual consensus in the presence of a third investigator.

2.4. Data extraction

Independently, the two data collectors extracted and recorded desirable information from each enrolled study in a standard form recommended by Cochrane, [16] which consisted of authors, publication year, study design, country, NCT No., population, demographic characteristics (age, gender, etc.), disease conditions (Acute Physiologic and Chronic Health Evaluation II (APACHE II) and Simplified Acute Physiologic Score II (SAPS II)), outcome measures, and study results. For any missing data information, corresponding authors were contacted by email to request the full original data. Different opinions between the two collectors were determined by reaching a consensus or consulting a third investigator.

2.5. Quality assessment

For the assessment of bias risks in estimating the study outcomes, we used the Cochrane risk of bias tool [16]. Each study was assessed for: 1) random sequence generation (selection bias); 2) allocation concealment(selection bias); 3) blinding of participants and personnel (performance bias); 4) blinding of related outcomes assessment (detection bias); 5) incomplete outcome data (attrition bias); 6) selective reporting (reporting bias); and 7) other biases. Two investigators conducted the quality assessment for the study methodology, independently and separately. Any divergence was resolved by mutual consensus in the presence of a third investigator.

2.6. Statistical analysis

Statistical analysis of our study was accomplished by an independent statistician using Cochrane systematic review software Review Manager (RevMan; Version 5.3.5; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014). We used *Mann-Whitney U* test to verify hypothesis and rendered statistical significance as a *Z*-value and *P*-value <0.05, and the results were displayed in Forest plots.

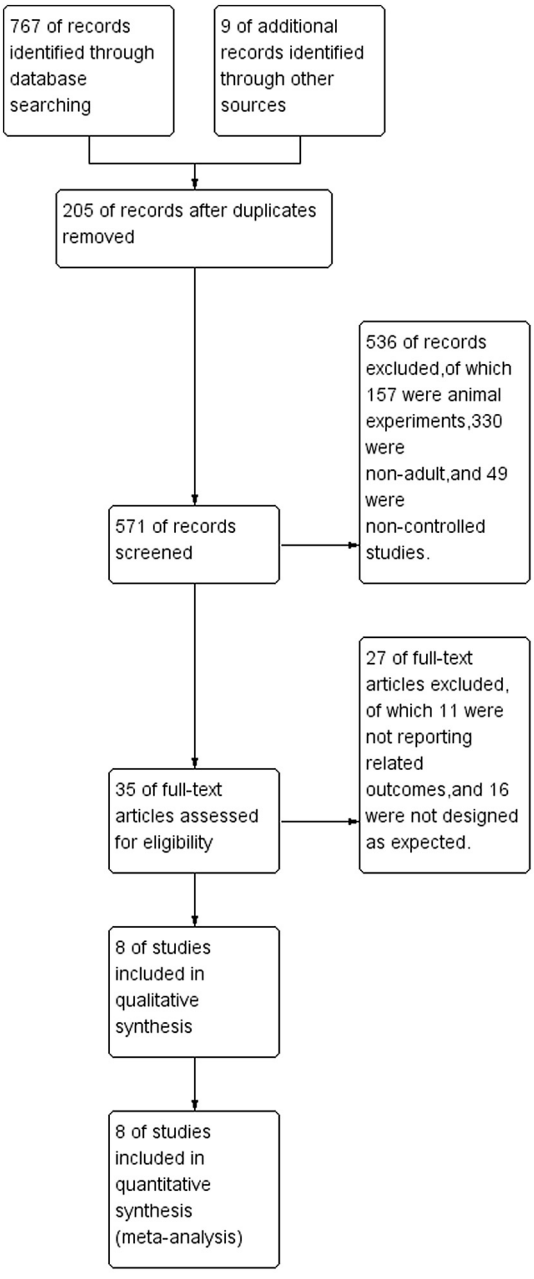

Fig. 1. Study flow diagram.