BMJ Open

Clinical efficacy and safety of high-flow nasal cannula (HFNC) in acute hypoxaemic patients with COVID-19: a protocol for a systematic review and meta-analysis

Lei Yang,[1] Weili Wang,[2] Gongjie Ye,[1] Zhouzhou Dong [3]

To cite: Yang L, Wang W, Ye G, *et al*. Clinical efficacy and safety of high-flow nasal cannula (HFNC) in acute hypoxaemic patients with COVID-19: a protocol for a systematic review and meta-analysis. *BMJ Open* 2022;**12**:e057743. doi:10.1136/bmjopen-2021-057743

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-057743).

Received 28 September 2021
Accepted 27 March 2022

Check for updates

© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

[1]ICU, Ningbo Medical Center Lihuili Hospital, Ningbo, Zhejiang, China
[2]Department of Respiratory Medicine, Zhenhai Hospital of Traditional Chinese Medicine, Ningbo, China
[3]ICU, Li Huili Hospital, Ningbo, Zhejiang, China

Correspondence to
Dr Zhouzhou Dong;
NBICUDONG@163.com

ABSTRACT

Introduction When COVID-19 patients develop hypoxaemic respiratory failure, they often undergo early intubation. Such a potentially aerosol-generating approach places caregivers at increased risk of contracting COVID-19. This protocol aims to evaluate the clinical efficacy and safety of a high-flow nasal cannula (HFNC) for the treatment of COVID-19 patients with acute hypoxaemic respiratory failure.

Methods and analysis We intend to search MEDLINE, Embase, Web of Science and Cochrane Library to identify all randomised controlled trials (RCTs) on the use of HFNC in COVID-19 patients with acute respiratory failure. We will screen the RCTs against eligibility criteria for inclusion in our review. Two reviewers will independently undertake RCT selection, data extraction and risk of bias assessment. Primary outcome will be the rate of intubation, and secondary outcomes will be intensive care unit (ICU)/hospital mortality, ICU/hospital length of stay and risks of infection transmission. We will conduct meta-analyses to determine the risk ratio for dichotomous data and the mean difference (MD) or standardised MD for continuous data. Subgroup analyses will be performed based on the different quality of studies, different levels of disease severity, and the age and sex of participants.

Ethics and dissemination Ethical approval is not required for this study considering this is a systematic review protocol that uses only published data. The findings of this study will be disseminated through peer-reviewed publications and conference presentations.

PROSPERO registration number CRD42021236519.

Strengths and limitations of this study

- This systematic evidence review of high-flow nasal cannula (HFNC) will be limited to studies evaluating acute hypoxaemic patients who were diagnosed with COVID-19.
- We will compare HFNC with conventional oxygen therapy.
- The protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guidelines.
- The methodological quality of included trials will be assessed using Cochrane's updated risk of bias 2.0 tool.
- Meta-analysis may not be possible for certain outcomes due to a limited number of eligible studies.

INTRODUCTION

The novel SARS-CoV-2 causes COVID-19, which has swept through much of the world and affected tens of millions of people.[1 2] Approximately, 5% of the patients who contract COVID-19 require admission to intensive care units (ICUs).[3] The rate of intubation and mechanical ventilation among patients admitted to the ICU has been reported to vary from 71% to 90%.[4 5] When these patients develop hypoxaemic respiratory failure, they are often on a fast track to proceed from low-flow oxygen supplementation via nasal cannula to a non-rebreather face mask and then directly to intubation and mechanical ventilation. However, intubations are well-known generators of considerable amounts of aerosol, which place caregivers at increased risk of infection transmission (OR 6.6, 95% CI 2.3 to 18.9).[6] In addition, invasive mechanical ventilation has been associated with various adverse events, such as ventilator-associated pneumonia and barotrauma.

High-flow nasal cannula (HFNC) refers to high-flow oxygenated gas heated and humidified to body conditions that is delivered via nasal cannula at maximum flows ranging from 40 to 80 L/min.[7] HFNC is not only an oxygen supplement but is a very well-tolerated ventilatory assist device with multiple potentially advantageous physiological attributes.[8 9] Several studies on reducing intubation rates have compared HFNC with conventional oxygen therapy. While a few randomised studies demonstrated that HFNC therapy

did not result in significantly different intubation rates compared with conventional oxygen therapy in patients with hypoxaemia, there was a significant difference in favour of HFNC in 90-day mortality.[10]

A systematic review in May 2020 commissioned by WHO found that HFNC applied to patients with respiratory failure may substantially reduce the need for invasive ventilation and escalation of therapy to non-invasive ventilation or intubation, with no apparent effect on mortality or patient-reported symptoms, but none of the identified studies directly involved with evidence on COVID-19.[11] Consequently, as for patients due to COVID-19-induced acute respiratory failure, whether HFNC is an optimal choice to reduce the rate of intubation compared with conventional oxygen therapy is unknown. Based on the findings of HFNC therapy in non-COVID-19 patients, as mentioned above, we propose a hypothesis that in terms of the rate of intubation, HFNC therapy might be more effective than conventional oxygen therapy in acute hypoxaemic patients with COVID-19. Furthermore, considering COVID-19 spreads through respiratory droplets and fomites, there is concern that airborne transmission may occur during procedures such as the application of HFNC. Notwithstanding the Surviving Sepsis Campaign COVID-19 guidelines provide a weak recommendation for the preferential use of HFNC in patients refractory to conventional oxygen therapy, studies directly evaluating the risk of disease transmission among patients with COVID-19 are warranted.[2 12] We will conduct a meta-analysis of all published trials and aim to identify the impact of HFNC therapy on improving the outcomes of COVID-19 patients with acute respiratory failure.

METHODS

Registration

The study was conceived and started preliminary searches on February 2021 and planned to be completed in December 2022. The protocol is reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines.[13] The completed checklist can be found in online supplemental appendix 1.

Inclusion criteria

In this systematic review and meta-analysis, we will include clinical trials satisfying the following criteria: (1) the subjects enrolled in each study included COVID-19 patients with acute respiratory failure; (2) COVID-19 patients were divided into an experimental group, in which HFNC oxygen therapy was applied, and a control group, in which patients were assigned to receive conventional oxygen therapy; (3) outcomes included but were not limited to the rate of intubation, ICU/hospital mortality, ICU/hospital length of stay and risks of infection transmission; (4) the diagnosis of COVID-19 was reliable and had high accuracy, and the severity of COVID-19 ranged from mild to critical conditions based on staging from the WHO; (5) the study design was a randomised controlled trial (RCT). We will not limit the language.

Exclusion criteria

We will exclude studies performed on animals or patients under 18 years old or published as protocols, editorials, meeting abstracts, reviews or case reports.

Patient and public involvement

Given that participant recruitment is not necessary, patients will not be involved in the design of this study protocol.

Search strategy

The systematic review process will be guided by the Cochrane Collaboration of Systematic Reviews and the PRISMA-P statement. We will search MEDLINE, Embase, Web of Science and Cochrane Library from December 2019 to August 2022. COVID-19-related studies were not widely commenced before December 2019. The literature search will be updated before the preparation of the final report. The detailed search strategy can be found in online supplemental appendix 2. We will also review the references listed in each identified article and manually search the related articles to identify all eligible studies and minimise potential publication bias. No language restriction will be applied.

Study selection

Two reviewers (LY and WW) will independently review the titles and abstracts based on the inclusion criteria. We will download the texts of the potential records to review them for inclusion further. Where necessary, further information will be sought from the authors of the studies. Reasons for excluding articles will be recorded. Disagreements will be resolved by discussion or through consultation with a third reviewer (ZD). Study selection will be summarised in a PRISMA flow diagram.

Data extraction

Two reviewers (LY and WW) will extract data independently using a standardised data collection form. We will collect the following data: the name of the first author, publication year, study location, study design, sample size, interventions used, and outcomes listed above. In addition, data concerning study participants, such as gender, age, oxygenation index (arterial oxygen tension/fractional inspired oxygen), Sequential Organ Failure Assessment (SOFA), Acute Physiology and Chronic Health Evaluation (APACHE II), time from admission/deterioration, time from HFNC/intubation (including the timing of intubation), sorts of personal protective equipment used by medical staff (surgical/medical mask, fitted respirator masks or helmet), will also be collected. For any missing information, the corresponding author of the study will be contacted to request missing information. For studies appearing in more than one published article, we will consider the most recent and comprehensive publication

with the largest sample size. Disagreement will be solved by discussing or consulting a third person (ZD).

Risk of bias assessment

The methodological quality of the included studies will be assessed by two independent reviewers (LY and WW) using the Cochrane collaboration's updated risk of bias 2.0 (RoB 2.0) tool,[14] in which the RoB of each included trial will be assessed based on the following domains: (1) randomisation process; (2) deviations from intended interventions; (3) missing outcome data; (4) measurement of the outcome and (5) selection of the reported result. Each domain will be rated as 'low', 'high' or 'some concerns'. The overall RoB for a single trial will also be classified as 'low' (RoB is low for all domains), 'some concerns' (some concerns in at least one domain) and 'high' (high RoB for at least one domain or some concerns for multiple domains). Disagreement will be solved by discussing or consulting a third person (ZD).

Data synthesis

The primary outcome is the intubation rate, and secondary outcomes include risks of infection transmission, ICU/hospital mortality and ICU/hospital length of stay. Statistical analysis of our study will be accomplished by an independent statistician using Cochrane systematic review software Review Manager (RevMan; V.5.3.5; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014) and Comprehensive Meta-Analysis software packages.[15] A $p<0.05$ will be considered statistically significant, and the results will be displayed in forest plots. For continuous data, we will calculate the mean difference and 95% CI. For dichotomous data, we will calculate the risk ratio and 95% CI. We will examine the clinical, methodological and statistical heterogeneity by using the I^2 statistic (classified as low (<40%), moderate (40%–60%) or high (>60%)). An I^2 statistic of 60% or greater will be considered as having substantial heterogeneity. A random-effects model will be applied in the presence of statistical heterogeneity; otherwise, a fixed-effects model will be used.

Subgroup analysis

We will conduct a subgroup analysis to explore potential sources of heterogeneity. The subgroup analysis will be based on the different quality of studies (classified by RoB 2.0 as 'low', 'some concerns' or 'high'), different levels of disease severity (indicated by oxygenation index, SOFA and APACHE II), and the age and sex of participants.

Assessment of publication bias

We will use Egger's test to evaluate publication bias and small-study effects, and a $p<0.1$ in the test confirms the bias and small study effect.[16 17]

Quality of evidence of included reviews

We will rate the evidence as 'high', 'moderate', 'low' or 'very low' in a conclusive table using the Grading of Recommendations Assessment, Development and Evaluation system.[18]

DISCUSSION

Acute hypoxaemic respiratory failure is among the leading causes of ICU admission in adult patients, often leading to endotracheal intubation and invasive mechanical ventilation. A recent systematic review and meta-analysis conducted by *Ferreyro et al* revealed that treatment with non-invasive oxygenation strategies compared with standard oxygen therapy was associated with lower risk of death and endotracheal intubation and thus may be more effective than standard oxygen therapy alone.[19] The current COVID-19 pandemic has further highlighted the importance of understanding the best approach to providing respiratory support for patients with respiratory failure. A randomised, open-label clinical trial conducted in emergency and ICUs in three hospitals in Colombia indicated that among patients with severe COVID-19, use of HFNC through a nasal cannula significantly decreased need for mechanical ventilation support and time to clinical recovery compared with conventional low-flow oxygen therapy.[20] However, another large multicentre RCT showed no significant difference between an initial strategy of HFNC compared with conventional oxygen therapy.[21] In patients due to COVID-19-induced acute respiratory failure, whether HFNC is a reliable method to reduce the rate of intubation without increasing the likelihood of infection transmission compared with conventional oxygen therapy is unknown. This protocol defines a systematic review with meta-analysis of RCTs to evaluate the clinical efficacy and safety of HFNC for reducing intubation rate in COVID-19 patients.

Considering that disease severity might be highly associated with indications for the applications of HFNC, we will conduct a subgroup analysis based on different levels of disease severity (indicated by oxygenation index, SOFA and APACHE II) to explore potential sources of heterogeneity. It is also worth noting that the methodological quality of each included RCT will be assessed using Cochrane's updated RoB 2.0 tool, which is a well-established and reliable method. Despite these strengths, we must admit a possible limitation of this study: clinical trials with low number of participants lead to wide CIs and thus high uncertainty of the estimated effects that compromise the level of evidence generated in this meta-analysis.

The current available systematic reviews mentioned above are not specific because of the lack of direct evidence on the effectiveness and safety of HFNC in people diagnosed with COVID-19. The results of this study are expected to provide new insight into the potential effects of HFNC in adults infected with this new coronavirus and thus eliminate uncertainties about the treatment that persist despite some related published studies.

ETHICS AND DISSEMINATION

Ethical approval will not be required for this study, as this is a systematic review protocol that uses only published data and the study findings will be shared with the public either through peer-reviewed publication or abstract presentation at conferences and possible submission to the relevant regional/global health policy-making bodies.

Contributors ZD conceived the idea of research. LY developed the first draft of the manuscript. WW and GY revised several versions of the manuscript.

Funding This work was supported financially by grants from the Natural Science Foundation of Ningbo (2019A610276). No external assistance was provided for the design, delivery or writing of this review.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD

Zhouzhou Dong http://orcid.org/0000-0002-8634-4052

REFERENCES

1 Raoof S, Nava S, Carpati C, *et al*. High-Flow, noninvasive ventilation and awake (nonintubation) proning in patients with coronavirus disease 2019 with respiratory failure. *Chest* 2020;158:1992–2002.
2 Alhazzani W, Møller MH, Arabi YM, *et al*. Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Intensive Care Med* 2020;46:854–87.
3 Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China. *JAMA* 2020;323:1239–42.
4 Grasselli G, Zangrillo A, Zanella A, *et al*. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA* 2020;323:1574–81.
5 Bhatraju PK, Ghassemieh BJ, Nichols M, *et al*. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. *N Engl J Med* 2020;382:2012–22.
6 Tran K, Cimon K, Severn M, *et al*. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One* 2012;7:e35797.
7 Spoletini G, Alotaibi M, Blasi F, *et al*. Heated humidified high-flow nasal oxygen in adults: mechanisms of action and clinical implications. *Chest* 2015;148:253–61.
8 Ni Y-N, Luo J, Yu H, *et al*. Can High-flow Nasal Cannula Reduce the Rate of Endotracheal Intubation in Adult Patients With Acute Respiratory Failure Compared With Conventional Oxygen Therapy and Noninvasive Positive Pressure Ventilation?: A Systematic Review and Meta-analysis. *Chest* 2017;151:764–75.
9 Lee CC, Mankodi D, Shaharyar S, *et al*. High flow nasal cannula versus conventional oxygen therapy and non-invasive ventilation in adults with acute hypoxemic respiratory failure: a systematic review. *Respir Med* 2016;121:100–8.
10 Frat J-P, Thille AW, Mercat A, *et al*. High-Flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015;372:2185–96.
11 Agarwal A, Basmaji J, Muttalib F, *et al*. High-Flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission. *Can J Anaesth* 2020;67:1217–48.
12 Bem RA, van Mourik N, Klein-Blommert R, *et al*. Risk of aerosol formation during high-flow nasal cannula treatment in critically ill subjects. *Respir Care* 2021;66:891–6.
13 Moher D, Shamseer L, Clarke M, *et al*. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015;4:1.
14 Higgins JPT, Sterne JAC, Savovic J. Cochrane methods. *Cochrane Database Syst Rev* 2016;10:S29–31.
15 Borenstein MHL, Higgins J, Rothstein H. *Comprehensive meta-analysis version 2*. Biostat, Englewood, 2005.
16 Macaskill P, Walter SD, Irwig L. A comparison of methods to detect publication bias in meta-analysis. *Stat Med* 2001;20:641–54.
17 Egger M, Davey Smith G, Schneider M, *et al*. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
18 Guyatt GH, Oxman AD, Vist GE, *et al*. Grade: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924–6.
19 Ferreyro BL, Angriman F, Munshi L, *et al*. Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure: a systematic review and meta-analysis. *JAMA* 2020;324:57–67.
20 Ospina-Tascón GA, Calderón-Tapia LE, García AF, *et al*. Effect of high-flow oxygen therapy vs conventional oxygen therapy on invasive mechanical ventilation and clinical recovery in patients with severe COVID-19: a randomized clinical trial. *JAMA* 2021;326:2161–71.
21 Perkins GD, Ji C, Connolly BA, *et al*. Effect of noninvasive respiratory strategies on intubation or mortality among patients with acute hypoxemic respiratory failure and COVID-19: the RECOVERY-RS randomized clinical trial. *JAMA* 2022;327:546–58.