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Helmet Non-Invasive Ventilation for COVID-19 Patients (Helmet-COVID): study protocol for a multicentre randomised controlled trial

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ABSTRACT

Introduction Non-invasive ventilation (NIV) delivered by helmet has been used for respiratory support of patients with acute hypoxaemic respiratory failure due to COVID-19 pneumonia. The aim of this study was to compare helmet NIV with usual care versus usual care alone to reduce mortality.

Methods and analysis This is a multicentre, pragmatic, parallel randomised controlled trial that compares helmet NIV with usual care to usual care alone in a 1:1 ratio. A total of 320 patients will be enrolled in this study. The primary outcome is 28-day all-cause mortality. The primary outcome will be compared between the two study groups in the intention-to-treat and per-protocol cohorts. An interim analysis will be conducted for both safety and effectiveness.

Ethics and dissemination Approvals are obtained from the institutional review boards of each participating institution. Our findings will be published in peer-reviewed journals and presented at relevant conferences and meetings.

Trial registration number NCT04477668.

Strengths and limitations of this study

- This trial compares helmet non-invasive ventilation to usual care for respiratory support of patients with acute hypoxaemic respiratory failure due to COVID-19 pneumonia.
- The trial is a multicentre, pragmatic, parallel randomised controlled trial.
- The main limitation is the unblinded design due to the nature of the intervention.

INTRODUCTION

The novel SARS-CoV-2 has led to a pandemic resulting in over 181 million cases and approximately 4.4 million fatalities as of 17 August 2021.[1] The resulting COVID-19 leads to severe pneumonia and acute respiratory distress syndrome (ARDS) among other organ injuries.[2] ARDS may occur in up to 5% of infected patients.[3–5] Early in the pandemic, invasive mechanical ventilation was widely used because of concerns about non-invasive ventilation (NIV) safety and efficacy. However, NIV use increased with time, including mask NIV and helmet NIV.

NIV has been shown to have physiological benefits in patients with acute hypoxaemic respiratory failure (AHRF) secondary to pulmonary oedema, atelectasis or pneumonia.[6] It has been shown to improve arterial oxygenation by increasing functional residual capacity, shifting the tidal volume to a more compliant part of the pressure–volume curve, thus reducing both the work of breathing and the risk of tidal opening and closure of the airways.[7] NIV is commonly provided through nasal or oronasal interfaces. The resulting aerosol generation may increase the risk of transmission of pathogens to healthcare providers, raising concerns about the use of NIV in patients with viral pneumonia.[8] Helmet NIV has been used for AHRF including patients with COVID-19 pneumonia. The helmet surrounds the patient's entire head to provide positive pressure and supply oxygen and is sealed with a soft, airtight collar that wraps around the neck. Due to this design, it has advantages over the nasal and oronasal interfaces. These include less air leaks, no skin or nasal bridge skin injuries, no eye irritation, fitting for different facial contours[9] and hypothetically less dissemination of aerosols in the environment. However, helmet interface may be associated with increase in dead space (especially if the settings are not used appropriately), claustrophobia, discomfort, and difficulty in access for suction and feeding.

Evaluation of helmet NIV as a respiratory support modality started more than two decades ago.[10] Helmet NIV has been investigated as a treatment for different forms of AHRF in adults in various settings, such as prehospital ambulance, emergency department and intensive care unit (ICU).[7 11–15] However, earlier clinical studies are relatively scarce and mostly small in size, and often use improvement in oxygenation and intubation rate as primary outcomes.[6]

However, evidence on helmet NIV for AHRF is growing. A systematic review of randomised controlled trials (RCTs) and observational studies published before June 2016 found 11 studies involving 621 patients.[16] Compared with controls, the use of a helmet was associated with lower hospital mortality, intubation rate and complications.[16] There was no significant difference in gas exchange and ICU stay.[16] A meta-analysis of four RCTs (377 patients) showed that helmet NIV significantly increased the ratio of arterial oxygen partial pressure to fraction of inspired oxygen (PaO_2:FiO_2) and decreased arterial carbon dioxide levels, intubation rate and in-hospital mortality compared with standard oxygen therapy.[17] In a more recent systematic review and network meta-analysis that included 25 studies (published up to April 2020) with 3804 patients with AHRF, mortality and intubation rate were lower with helmet NIV compared with standard oxygen by more than 50%, while the effects of mask NIV and high-flow nasal oxygen were modest compared with those of standard oxygen.[18] Helmet NIV was superior to both mask NIV and high-flow nasal oxygen, while mask NIV and high-flow nasal oxygen were not different in their effects on mortality and intubation rate.[18] One study reported the cost-effectiveness of helmet NIV compared with mask NIV.[19]

Data on helmet NIV in AHRF related to COVID-19 are emerging. A recent RCT conducted in four Italian ICUs on patients with COVID-19 and moderate-to-severe AHRF found that treatment with helmet NIV did not result in significantly fewer days of respiratory support at 28 days from randomisation (primary outcome) as compared with high-flow nasal oxygen alone (mean difference, 2 days; 95% CI −2 to 6; p=0.26).[20] Nevertheless, the intubation rate was significantly lower in the helmet NIV group compared with the high-flow nasal oxygen group (30% vs 51%, p=0.03).[20] Additionally, the median number of days free of invasive mechanical ventilation within 28 days was significantly higher in the helmet NIV group than in the high-flow nasal oxygen group (28 vs 25 days; mean difference, 3 days; 95% CI 0 to 7; p = 0.04).[20] The hospital mortality was 24% in the helmet NIV group and 25% in the high-flow nasal oxygen group.[20]

As the efficacy of helmet NIV to improve outcomes in severe AHRF due to COVID-19 pneumonia has not been clearly established, the aim of this study was to compare helmet NIV with usual care versus usual care alone to reduce 28-day all-cause mortality. We hypothesise that helmet NIV will reduce 28-day all-cause mortality in patients with suspected or confirmed severe COVID-19 pneumonia and AHRF.

METHODS AND ANALYSIS

Trial design

This is an investigator-initiated, pragmatic parallel RCT that will compare helmet NIV with usual care to usual care alone in 1:1 ratio in patients with suspected or confirmed COVID-19 pneumonia and AHRF. Randomisation is performed using a computer-generated schedule using variable block sizes (4 or 6) and is stratified by site. The trial is sponsored by King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, has been registered with ClinicalTrials.gov and is conducted across multiple centres in Saudi Arabia and Kuwait. Training and in-service education on helmet NIV use as well as on protocol implementation are provided to all participating centres. The competency of the bedside respiratory therapists is supervised by experienced respiratory care supervisors and intensivists.

Sample size

In a large observation study of patients with AHRF and ARDS, hospital mortality was 34.9% (95% CI 31.4% to 38.5%) for patients with mild ARDS, 40.3% (95% CI 37.4% to 43.3%) for those with moderate ARDS and 46.1% (95% CI 41.9% to 50.4%) for those with severe ARDS.[21] A systematic review found an overall pooled mortality estimate among 10 815 patients with ARDS due to COVID-19 to be 39% (95% CI 23% to 56%).[22] Considering a mortality rate of 40% in patients with COVID-19 pneumonia and moderate to severe ARDS treated with usual care, we calculated that enrolment of 304 patients (152 in each group) would provide the study with 80% power to demonstrate an absolute difference of 15% in the primary outcome between the usual care group and the helmet NIV group at a two-sided alpha level of 0.05. To account for 5% loss to follow-up, the total number of patients required for the trial is 320 patients.

Participant eligibility

The trial will enrol ICU patients with suspected[23] or confirmed COVID-19 pneumonia who have AHRF. Detailed inclusion and exclusion criteria can be found in table 1.

Table 1 Eligibility criteria

Inclusion criteria	1. Suspected or confirmed COVID-19.* 2. Aged ≥14 years old. ICUs that use other age cut-off for adult patients will adhere to their local standard (16 or 18 years). 3. Acute hypoxaemic respiratory failure based on PaO_2:FiO_2 ratio <200 despite supplemental oxygen with a partial or non-rebreathing mask at a flow rate >10 L/min or higher. 4. Intact airway protective gag reflex. 5. Able to follow instructions.
Exclusion criteria	1. Prior intubation during this hospital admission. 2. Cardiopulmonary arrest. 3. Glasgow Coma Scale score of <12. 4. Tracheostomy. 5. Upper airway obstruction. 6. Active epistaxis. 7. Requirement for more than one vasopressor to maintain mean arterial pressure >65 mm Hg. 8. Pregnancy. 9. Imminent intubation. 10. Patients with do-not-intubate orders (or equivalent). 11. Enrolled in another trial for which coenrolment is not approved, including trials on mechanical ventilation. 12. Patients already treated with helmet. 13. Patients with chronic carbon dioxide retention (PaCO >45). 14. Previous enrolment in this trial. 15. The primary cause of respiratory failure is not heart failure as judged by the treating team.
Eligible non-randomised	1. Patient or substitute decision maker declines consent. 2. ICU physician or other treating clinician declines consent.

*A suspected/probable COVID-19 case is defined as at least *two* of the following symptoms: fever (measured or subjective), chills, rigours, myalgia, headache, sore throat, new olfactory and taste disorder(s) or at least one of the following symptoms: cough, shortness of breath or difficulty breathing, or severe respiratory illness with at least one of the following: clinical or radiographical evidence of pneumonia or ARDS and no alternative more likely diagnosis. A confirmed COVID-19 case is defined as detection of SARS-CoV-2 RNA in a respiratory specimen using a molecular amplification detection test such as RT-PCR (https://wwwn.cdc.gov/nndss/conditions/coronavirus-disease-2019-covid-19/case-definition/2020/).
ICU, intensive care unit; PaO_2:FiO_2, ratio of arterial oxygen partial pressure to fraction of inspired oxygen; RT-PCR, reverse transcription PCR.

Informed consent

Informed consent will be obtained from the potential trial participants or their surrogate decision makers. A hybrid model of consent will be used where a priori consent is obtained, if possible; otherwise, delayed consent model will be obtained as per local approvals. The first patient was enrolled in February 2021. As of 29 June 2021, a total of 199 patients were enrolled from five sites. There are several sites that are processing institutional review board (IRB) and regulatory approvals.

Patient and public involvement

There was no patient or public involvement in the conception, design or conduct of the study, or the writing or editing of this paper. However, patient comfort and experience as well as compliance to the intervention were taken into consideration and data on these were collected.

Trial interventions

Helmet group

A helmet (Subsalve, USA, or its equivalent) which is made of transparent latex-free polyvinyl chloride will be applied to patients randomised to the intervention group as per the study protocol, which considers the manufacturer instructions. It will be connected to an ICU ventilator in pressure support (PS) mode with positive end-expiratory pressure (PEEP) using a conventional respiratory circuit joining two port sites to allow inspiratory and expiratory flows. The starting settings is PS of 8–10 cm H_2O, PEEP of 10 cm H_2O with FiO_2 of 100%, targeting flow rate of ≥50 L/min with an inspiratory rise time of 50 ms and end flow/cycling off of 50% of maximal inspiratory flow. PEEP may be increased by 2 cm every 3 min to achieve oxygen saturation (SpO_2) ≥90% on FiO_2 ≤60%, and PS can be increased by 2 cm every 3 min to achieve respiratory rate of ≤25 breaths/min and disappearance of accessory muscle activity. The maximal allowed PS+PEEP is 30 cm H_2O. Interruptions of helmet should be avoided or kept at minimum at least in the first 48 hours.[20] More details of helmet NIV application, set-up and weaning can be found in online supplemental file 1. Some patients may not tolerate helmet NIV. In that case, the physician or the respiratory therapist explains the procedure to the patient. Dexmedetomidine infusion may be used to improve comfort with the helmet NIV. Other intravenous sedatives such as benzodiazepines or intravenous narcotics should generally not be used. If the patient continues to be intolerant to the helmet, the patient can be managed according to the usual care. Detailed data about helmet NIV tolerance are collected.

Control group

In the control group, patients receive usual care according to the clinical practices of each site. This may include oxygen provided using standard oxygen devices, high-flow nasal oxygen or NIV provided by nasal mask, face mask or total mask.

Endotracheal intubation

The decision to intubate will be at the discretion of the treating team with no involvement from the research team. However, the protocol provides guidance on assessing patients for the need of endotracheal intubation throughout the study period (for both study groups: helmet NIV or usual care) according to the following general principles.

Enrolled patients should be assessed within 4 hours of enrolment (or sooner as required) and at frequent intervals for the following criteria, although the decision is usually not based on a single variable:

- Neurological deterioration (*not attributed to sedation*).
- Persistent or worsening respiratory failure of NIV (manifesting as SpO_2<88%, respiratory rate >36 breaths/min, PaO_2:FiO_2 ratio <100 or persistent requirement of FiO_2 ≥70%).
- Intolerance of face mask or helmet.
- Airway bleeding.
- Copious respiratory secretions.
- Respiratory acidosis with pH <7.25
- Haemodynamic instability.
- Significant radiological worsening.

Cointerventions

Patients who require endotracheal intubation are managed by the primary team with lung protective strategy with tidal volumes of 6 mL/kg of predicted body weight and titration of PEEP to achieve SpO_2 of 88%–95% at the lowest possible FiO_2. Daily interruption of sedation, awakening and breathing trials, and early mobilisation are performed as per the ICU standards.[24] Management of COVID-19 is provided as per local protocols; physicians are advised to follow the clinical practice guidelines set by the Saudi Critical Care Society,[25] the Surviving Sepsis Campaign[26 27] and the WHO.[28] The study protocol does not mandate particular therapies; however, corticosteroids, immune modulators and antiviral therapy are all recorded. Conservative fluid management is recommended where neutral balance should be targeted and intravenous resuscitation should be reserved for shock treatment in both groups and fluid balance is recorded.

Blinding

Due to the nature of the study intervention, blinding is not be possible.

Recruitment schedule and enrolment procedures

Schedule of assessments is detailed in table 2. All non-intubated subjects with suspected or confirmed COVID-19 are screened on admission to the ICU. A screening log will be kept to monitor and report the size of the patient population from which eligible patients have been randomised. Coenrolment in other RCTs is permissible as long as inclusion in the other RCT would not confound the results of this trial and after discussion with the steering committees of the other studies.

Data collection

Baseline data on demographics, admission diagnosis and clinical information are collected. Clinical information include Acute Physiology and Chronic Health Evaluation (APACHE) II score,[29] source of admission, ICU admission category (elective, emergency or non-surgical), ICU admission diagnosis and comorbidities (as defined by the APACHE II severity of illness scoring system). Daily data will be recorded until discharge from the ICU or 28 days after randomisation. We will collect data on the use of helmet including the tolerance of helmet (>1-hour use).

Outcomes

The primary outcome is 28-day all-cause mortality. Secondary outcomes are intubation rate within 28 days, ICU mortality, hospital mortality (censored at day 180), ICU-free days at day 28, invasive ventilation-free days at day 28, renal replacement therapy-free days at day 28 and vasopressor-free days at day 28. Safety outcomes include skin pressure injuries, barotrauma and serious adverse

Table 2 Schedule of assessments in the trial

Task	Screening	Randomisation	Baseline	Days 1–28	180-day follow-up
Assess eligibility to enter study	X				
Assess ability to gain consent and follow-up	X				
Consent	X				
Demographics and eligibility checklist	X	X	X		
Laboratory data			X	X	
Vital signs			X	X	
Vital status up to day 28 in the ICU				X	X
Vital and functional status					X
Discharge date from ICU, from hospital				X	X
Adverse events				X	
Protocol violations				X	

ICU, intensive care unit.

events (including cardiovascular events and device complications).

Additionally, there will be a follow-up of enrolled patients at day 180 about vital status, functional status (EuroQoL-5D-5L) which is planned to be reported separately. For patients who have been discharged from hospital before day 180, follow-up will be conducted by telephone.

Data analysis

A formal statistical analysis plan will be agreed on and placed in the public domain before the study database is locked for the analysis of the primary outcome. The primary outcome will be compared in the intention-to-treat and per-protocol cohorts (effectiveness analysis) using the χ^2 test. Results will be reported as relative risk with 95% CI. Kaplan–Meier curves will be plotted to assess the time from enrolment to death and will be compared by means of the log-rank test. A two-tailed p value of <0.05 will be considered to indicate statistical significance. SAS software V.9.2 will be used for all the analyses.

A priori analysis will be done for the following subgroups:

- Patients with moderate ARDS (Pao_2:FiO_2 ratio 100–200) and patients with severe ARDS (Pao_2:FiO_2 ratio <100).
- Obese patients (body mass index >30 kg/m^2) and patients with body mass index of ≤30.
- Patients aged >65 and ≤65 years.
- APACHE II score higher or lower than the median of enrolled patients.

For the occasional randomised patient who is withdrawn from the trial and allows use of data, the patient's data will be included in the group to which he/she was allocated as per the intention-to-treat principle, and the reason of withdrawal will be documented.

Trial management and monitoring

The study steering committee members will be responsible for overseeing the conduct of the trial, for upholding or modifying study procedures as needed, addressing challenges with protocol implementation, formulating the analysis plan, reviewing and interpreting the data, and preparing the manuscript. This will be achieved through meetings (in-person or by conference calls) at least quarterly.

Several measures are taken to minimise, observe and document any potential safety concerns. First, any unexpected safety concerns will be reported immediately to the steering committee and IRB. Second, an independent data safety monitoring board will be monitoring the safety of the trial. Lastly, interim analyses will be conducted after recruiting one-third and two-thirds of the total patients, and the interim test statistics will be the primary outcome analysis for both safety and effectiveness. The data safety monitoring board will use formal stopping rules based on the primary endpoint of 28-day mortality. The trial may be stopped for safety (p<0.01) or effectiveness (p<0.001). There will be no plans to terminate the trial for futility. We will account for alpha spending by the O'Brien-Fleming method, and the final p value will be considered at 0.048. The principles used in the conduct of safety monitoring and reporting in this trial are those outlined by Cook *et al.*[30]

In this trial, reporting of serious adverse events will be restricted to events that are not captured as study outcome and are considered to be related to the helmet NIV (possibly, probably or definitely).[30] These may include cardiovascular events (ie, cardiac arrest and hypotension with drop in blood pressure to systolic <90 mm Hg) and device complications (ie, helmet deflation).

ETHICS AND DISSEMINATION

The study will be conducted according to the principles of the latest version of Good Clinical Practice and in accordance with all relevant local ethical, regulatory and legal requirements. A manuscript with the results of the primary study will be published in a peer-reviewed journal. Separate manuscripts will be written on secondary aims,

Table 3 List of ongoing registered RCTs on helmet NIV

Trial	Registration	Interventions	Design	Countries	N
Helmet-COVID	NCT04477668	Helmet versus usual care	Multicentre RCT	Saudi Arabia and Kuwait	320
Comparison of High-Flow Nasal Oxygen, Face-Mask NIV and Helmet NIV in COVID-19 ARDS Patients	NCT04715243	High-flow nasal oxygen versus helmet NIV versus mask NIV	Multicentre RCT	Oman	360
Helmet CPAP vs High-Flow Nasal Oxygen in COVID-19	NCT04395807	High-flow nasal oxygen versus helmet CPAP	Single-centre RCT	Sweden	120
High-Flow Nasal Oxygen vs CPAP Helmet in COVID-19 Pneumonia	NCT04381923	High-flow nasal oxygen versus helmet CPAP	Single-centre RCT	USA	200
Early CPAP in COVID-19 Patients with Respiratory failure (EC-COVID-RCT)	NCT04326075	Early helmet CPAP versus usual care	Single-centre RCT	Italy	900

Helmet-COVID, Helmet Non-Invasive Ventilation for COVID-19; NIV, non-invasive ventilation; RCT, randomised controlled trial.

and these will also be submitted for publication in peer-reviewed journals as well.

DISCUSSION

The importance of this study stems from the current pandemic situation as different treatment modalities are being sought to answer important clinical questions. Available literature on the evaluation of helmet NIV as a respiratory support modality in patients with COVID-19 is limited. Table 3 provides a list of ongoing RCTs on helmet NIV. This study aimed to contribute to the existing literature and in turn influence clinical practice.

We planned our pragmatic trial to address whether using helmet NIV as the primary non-invasive respiratory support in patients with severe COVID-19, in addition to the commonly used high-flow nasal oxygen and mask NIV, improves outcome. By nature of this question, there is heterogeneity of the control group, as patients in this group could receive standard oxygen, high-flow nasal oxygen or mask NIV at the decision of the treating team. This approach is supported by a recent network meta-analysis of RCTs that showed only a modest effect of high-flow nasal oxygen and mask NIV on mortality or intubation rate compared with standard oxygen, while patients treated with helmet NIV had more than 50% reduction in mortality and intubation rate compared with the other three modalities.[18] In addition, this approach is likely to be more representative of usual practice in which patients may get oxygen therapy, high-flow nasal oxygen and NIV at different times during their acute illness. Given the fact that the use of helmet NIV has not been widespread across ICUs, we thought that the broader question addressed by our study might be more relevant to deciding whether to introduce this modality or not in a given ICU.

The main limitation to our study is inability to blind the given allocation due to the nature of the intervention.

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