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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

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KEY POINTS

Question: What is the effect of initial noninvasive respiratory strategies using continuous positive airway pressure (CPAP) or high-flow nasal oxygen (HFNO), compared with an initial strategy of conventional oxygen therapy, on the risk of tracheal intubation or mortality among hospitalized adults with acute hypoxemic respiratory failure due to COVID-19?

Findings: In this randomized clinical trial of 1273 patients, the composite primary outcome of tracheal intubation or mortality within 30 days occurred in 36% in the CPAP group compared with 44% in its conventional oxygen therapy comparator group, and in 44% in the high-flow nasal oxygen group compared with 45% in its conventional oxygen therapy comparator group; compared with conventional oxygen therapy, the incidence of the primary outcome was significantly lower with an initial strategy of CPAP and was not significantly different with an initial strategy of high-flow nasal oxygen.

Meaning: Among patients with acute hypoxemic respiratory failure and COVID-19, an initial strategy of CPAP significantly reduced the risk of tracheal intubation or mortality compared with conventional oxygen therapy, but there was no significant difference between an initial strategy of high-flow nasal oxygen compared with conventional oxygen therapy.

ABSTRACT

Importance

Continuous positive airway pressure and high-flow nasal oxygenation have been recommended for acute hypoxemic respiratory failure in COVID-19. Uncertainty exists regarding effectiveness and safety.

Objective

To determine whether either continuous pressure airway pressure or high-flow nasal oxygen, compared with conventional oxygen therapy, improves clinical outcomes in hospitalized patients with COVID-19 acute hypoxemic respiratory failure.

Design, setting and participants

A parallel group, open-label, three-group, adaptive, allocation concealed, randomized clinical trial, of 1273 hospitalized adults with COVID-19 acute hypoxemic respiratory failure. The trial was conducted between 6th April 2020 and 3rd May 2021, across 75 acute hospitals in United Kingdom and Jersey, with final follow-up occurring on 20th June 2021.

Interventions

Participants were randomized to receive continuous positive airway pressure (n=380), high-flow nasal oxygen (n=418), or conventional oxygen therapy (n=475).

Main outcome and measure

The primary outcome was a composite of tracheal intubation or mortality within 30-days.

Results

In 1273 randomized participants (mean age 57 years, 66% male, 65% White ethnicity), primary outcome data were available for 99% participants. The trial stopped prematurely due to declining UK COVID-19 case numbers and the end of the funded recruitment period. Crossover between interventions occurred in 17.1% participants (15.3% in the continuous positive airway pressure group, 11.5% in the high-flow nasal oxygen group, 23.6% in the conventional oxygen therapy group).

The requirement for intubation or mortality within 30-days was significantly lower with continuous positive airway pressure, compared with conventional oxygen therapy (137 of 377 participants (36.3%) vs 158 of 356 participants (44.4%) (P=0.03); mean difference -8%; 95% confidence interval -15%, -1%. There was no statistically significant difference between high-flow nasal oxygen and conventional oxygen therapy (184 of 415 participants (44.3%) vs 166 of 368 participants (45.1%) (P=0.81); mean difference -1%; 95% confidence interval -8%, %6.

Adverse events occurred in 34.2% (130/380), 20.6% (86/418), and 13.9% (66/475) participants in the continuous positive airway pressure, high-flow nasal oxygen, and conventional oxygen therapy groups respectively.

Conclusions and relevance

Among patients with acute hypoxemic respiratory failure due to COVID-19, an initial strategy of CPAP significantly reduced the risk of tracheal intubation or mortality compared with conventional oxygen therapy, but there was no significant difference between an initial strategy of high-flow nasal oxygen compared with conventional oxygen therapy. The study may have been underpowered for the comparison of high-flow nasal oxygen and conventional oxygen therapy. The early termination of the study and crossover between groups should be considered when interpreting the findings.

Trial registration: ISRCTN.com, registration number ISRCTN16912075.

INTRODUCTION

Acute hypoxemic respiratory failure is a key clinical characteristic of COVID-19 pneumonitis. In a study of 63,792 patients with COVID-19 hospitalized in the UK between March and August 2020, 76% required supplemental oxygen and 9% required tracheal intubation and invasive mechanical ventilation.[1] Early in the pandemic, international experiences highlighted the potential risk that intensive care units might become overwhelmed, and high mortality was observed in patients that required invasive mechanical ventilation.[2-4] This drove an urgent public health need to identify strategies to reduce the demand for invasive mechanical ventilation.

In patients with COVID-19 and increasing oxygen requirements, non-invasive respiratory strategies, such as continuous positive airway pressure (CPAP) and high-flow nasal oxygen (HFNO), provide a potentially attractive strategy for avoiding invasive mechanical ventilation. In other respiratory diseases, particularly community acquired pneumonia, both CPAP and HFNO may improve clinical outcomes, although those treated with CPAP experience more adverse events.[5,6] In the context of COVID-19, however, there was concern that these strategies might serve only to delay tracheal intubation due to high failure rates, whilst correspondingly exacerbating lung injury through generation of large tidal volumes.[7-10]

The absence of evidence to support CPAP and HFNO use in patients with COVID-19 led to significant variability both in international guidelines and clinical practice.[9,11] On this basis, there was a need for a trial to determine whether either CPAP or HFNO, compared with conventional oxygen therapy, reduces the need for the composite outcome of tracheal intubation or mortality within 30-days in hospitalized patients with acute hypoxemic respiratory failure due to COVID-19.

METHODS

Study design

Recovery- Respiratory Support was conducted across 75 hospitals in the United Kingdom and Jersey. The trial protocol was approved by the London-Brighton & Sussex Research Ethics Committee and the Health Research Authority, sponsored by the University of Warwick, co-ordinated by Warwick Clinical Trials Unit, and funded by the National Institute for Health Research. An independent Trial Steering Committee and Data Monitoring Committee provided trial oversight. The study was conducted in accordance with Good Clinical Practice guidelines, local regulations, and the ethical principles described in the Declaration of Helsinki.[12] In keeping with regional regulations, consent from patients or agreement from their surrogates was obtained orally, with a written record maintained by the researcher.

The trial protocol has been published previously and is available, alongside the statistical analysis plan, in the online supplement.[13]

The trial was a parallel group, open-label, three-group, adaptive, randomized clinical trial designed to evaluate the clinical effectiveness of CPAP or HFNO, compared with conventional oxygen therapy, in hospitalized patients with acute hypoxemic respiratory failure due to COVID-19. The multi-group design was essentially conducted as two separate trials comparing each of CPAP and HFNO with a common shared control group. A group sequential design allowed early study termination of one or both interventions if they were found to be more effective than conventional oxygen therapy, with the final analysis for each comparison adjusted to control the pairwise alpha value (5%).

Participants

Adult (≥18-years) hospitalized patients with known or suspected COVID-19 were eligible if they had acute hypoxemic respiratory failure, defined as peripheral oxygen saturations (SpO_2) of 94% or

below despite receiving a fraction of inspired oxygen (FiO_2) of at least 0.4, and were deemed suitable for tracheal intubation if treatment escalation was required. We excluded patients with an immediate (<1-hour) need for invasive ventilation, known pregnancy, or planned withdrawal of treatment. A contraindication to one intervention, based on the judgement of the treating clinician, precluded randomization to that specific trial group.

Randomization and masking

Eligible participants were randomized using an internet-based system with allocation concealment. We anticipated that either CPAP or HFNO might be unavailable at sites on a temporary or permanent basis. As such, the randomization system allowed the hospital site to randomize between CPAP, HFNO, and conventional oxygen therapy (on a 1:1:1 basis), or between a single intervention (CPAP/HFNO) and conventional oxygen therapy (on a 1:1 basis). These two systems were integrated and constantly updated to ensure that the allocation ratio was maintained within permitted thresholds. Our planned sample size was inflated to account for minor imbalances in the allocation ratio and, if it had been needed, our system allowed randomisation weightings to be adjusted. Sites could not randomize only between CPAP and HFNO. Randomization was stratified by site, sex, and age, and the allocation was generated by a minimization algorithm, which did not include any random component.

Due to the nature of the trial interventions and context, we were unable to blind patients, treating clinicians, or outcome assessors.

Procedures

Participants randomized to CPAP or HFNO started treatment as soon as possible. Breaks from treatment were permitted for comfort. Participants in the conventional oxygen therapy received oxygen via a standard face mask or low-flow nasal cannula. Those in the HFNO group received

heated humidified HFNO. Those in the CPAP group received CPAP, which did not permit the incorporation of any inspiratory positive airway pressure. Across all groups, local policies and clinical discretion informed decisions regarding device choice and set-up, titration (e.g. FiO_2, flow, positive end expiratory pressure), treatment targets (e.g. SpO_2) and treatment discontinuation. Tracheal intubation was performed when clinically indicated, based on the judgement of the treating clinician. We defined crossover as a participant that received a non-allocated intervention (CPAP or HFNO) for a period of over six-hours, unless used as a bridge to tracheal intubation or for palliative care.

At enrolment, we collected information on demographics (including investigator classified sex and ethnicity), co-morbid state, and physiological observations (including blood pressure, respiratory rate, peripheral oxygen saturations, and blood gas measurements). Collection and reporting of ethnicity was based on fixed categories and mandated by the funder due to the disproportionate effect of COVID-19 infection on non-white populations.[14] Participants were followed up throughout their hospital stay to record intervention use, crossover, adverse events, and outcomes. We undertook data linkage with national datasets to support collection of demographic information and outcomes, Including death after hospital discharge.

Outcomes

The primary outcome was a composite of tracheal intubation or mortality within 30-days of randomization. Tracheal intubation, as an outcome, reflects the need for invasive mechanical ventilation, which is typically delivered in high-resource intensive care units. Secondary outcomes included the individual incidence of tracheal intubation and mortality at 30 days, time to tracheal intubation, duration of invasive mechanical ventilation, time to death, mortality (critical care, hospital), incidence of intensive care unit admission, critical care length of stay and hospital length of stay (from emergency department arrival to discharge).

Sample size calculation

Early COVID-19 data informed the event rate in the conventional oxygen therapy group.[15] Assuming a conservative incidence of 15% for the composite outcome of intubation or mortality (with a two-sided 5% significance level and 90% power), a total of 3,000 participants (1,000 per group across 3 groups) were required. This equated to detecting a reduction of 5% or an odds ratio of 0.625. This minimally important clinical difference aligns with that used in the RECOVERY study.[16,17] We inflated this sample size to 4,002, due to the uncertainties in relation to the disease and event rates.

Efficacy monitoring of each pairwise comparison with conventional oxygen therapy was based on an alpha spending function approach with one-sided pairwise type I error rate of 0.025 and type I error spent at interim analyses proportional to the observed Fisher's information. This allowed the trial to stop early if one or both interventions were more effective than conventional oxygen therapy. Any decision to stop the trial or drop a group due to futility or safety was left to the Data Monitoring Committee. The sample size calculation assumed the conduct of 11 interim analyses, and one final analysis.

Statistical analysis

The primary and secondary analyses were performed for all participants, based on their randomized intervention. Outcome data were compared between each intervention group and conventional oxygen therapy. Participants in the conventional oxygen therapy group were only included in a comparison with HFNO or CPAP, if they had the opportunity to be randomized to that intervention. For the primary outcome, we undertook a post-hoc analysis which compared the CPAP and HFNO groups.

Continuous data were summarized using number of participants, mean, standard deviation (SD), median, and interquartile range (IQR). Categorical data were summarized with frequency count, percentage and missing. Odds ratios (95% confidence interval (CI)) were reported for categorical outcomes using logistic regression models and mean difference (95% CI) reported for continuous outcomes using linear regression models. For time to event analysis, hazard ratios (95% CI) were reported and the proportional odds assumption was assessed using the score test. In accordance with the statistical analysis plan, we planned multiple imputation only if there was substantial missingness (≥20%) in relation to the primary outcome.

Our primary analysis was unadjusted. For adjusted analyses, covariates age, sex, morbid obesity, ethnicity, FiO_2, respiratory rate and treatment phases were used, with site included as a random effect.[18,19] Treatment phases were defined as before July 2020, July 2020 to January 2021, after January 2021, based on the introduction of Dexamethasone and Tocilizumab as standard care in June 2020 and January 2021, respectively.[17,20,21] Due to the non-availability of NHS Digital data, we could not include social deprivation in the adjusted analyses.

We used inverse probability weighting as a secondary exploratory analysis. This method corrects for bias that may be introduced into the treatment effect as a result of the cross-over. Weights were estimated using propensity scores, with the response variable as those participants who did and did not cross-over. These weights were then introduced into the main logistic regression models, to diminish the bias introduced by treatment change. Sub-group analyses were preformed using logistic regression models, with the primary outcome as the response variable and the interaction term of the sub-group and treatment included in the model.

Analyses were conducted using SAS (version 9.4) and R (version 4.0.3) software. No adjustment was made for the multiple comparisons. Thus, the type I error control was the same as if CPAP and HFNO had each been compared with conventional oxygen in separate trials.

Cut-off values for the final P value for the primary analysis were calculated to correct for the type I error spent at the interim analyses performed.[22] The final cut-off values depended on the information available at the interim analyses and are reported in the Results section below. No correction for interim analyses was made to the cut-off values for the secondary endpoints or analyses, with a significance threshold of 0.05 used. Because of the potential for type 1 error due to multiple comparisons, findings for analyses of secondary endpoints should be interpreted as exploratory.

RESULTS

Trial recruitment stopped early. Towards the end of the funded 12-month recruitment period, we observed a rapid decline in hospitalized patients with COVID-19. Over the trial period, trial recruitment had closely tracked the number of UK hospitalized patients (Electronic supplement figure S1). On this basis, the trial management group decided not to seek additional funding and to prioritize the sharing of accumulated data to inform international clinical care. Prior to stopping, three formal interim analyses had been conducted (36, 160, 387 participants) with the trial continuing after each analysis. The results of interim analyses, other than the decision to continue the trial, were not known to the trial management group, trial steering committee, study sponsor or funder. The trial management group's recommendation to stop trial recruitment was agreed by the Trial Steering Committee, and funder. The study sponsor made the decision to stop trial recruitment. The trial closed to recruitment on 3rd May 2021.

Participant recruitment

Between 6th April 2020 and 3rd May 2021, there were 1278 randomizations across 48 hospitals. Five cases underwent double randomisation, leaving 1273 participants (380 CPAP; 418 HFNO; 475 conventional oxygen therapy) (Figure 1). Eight participants withdrew and five patients were lost to follow-up. Primary outcome data were available for 99.0 % (1260/1273) of participants.

We included 733 participants (377 CPAP; 356 conventional oxygen therapy) in the comparison of CPAP with conventional oxygen therapy, and 783 participants (415 HFNO; 368 conventional oxygen therapy) in the comparison of HFNO with conventional oxygen therapy (figure one; Electronic supplement table S1).

Participant characteristics were similar at baseline (table one; electronic supplement table S2). The mean age was 57.4 (95% CI, 56.7 to 58.1) years, 66.3% were male, and 65.3% of White ethnicity. Median time from first COVID-19 symptoms to randomisation was 9 days (IQR, 7.0 to 12.0). Baseline median SpO_2 and FiO_2 were 93% (IQR 91, 95) and 0.60 (IQR 0.40, 0.80) respectively.

The allocated intervention was received by 348/380 (91.6%), 384/418 (91.9%), and 467/475 (98.3%) participants in the CPAP, HFNO, and conventional oxygen therapy groups, respectively (figure one). In the CPAP group, initial positive end expiratory pressure was set at a mean of 8.3 cmH_2O (95% CI, 8.1 to 8.5) (table two). In the HFNO group, initial flow was set at a mean of 52.4 litres/minute (95% CI, 51.4 to 53.5). Pre-intubation vital signs of those that required tracheal intubation are summarised in table two.

Crossover occurred in 58/380 (15.3%) of participants in the CPAP group, 48/418 (11.5%) in the HFNO group, and 112/475 (23.6%) in the conventional oxygen therapy group (figure one; electronic supplement table S3).

Primary Outcome

For the comparison of CPAP and conventional oxygen therapy, the primary outcome occurred in 137/377 (36.3%) participants in the CPAP group and 158/356 (44.4%) participants in the conventional oxygen therapy group (P=0.03), absolute difference -8%, 95% CI -15% to -1% (table three).

For the comparison of HFNO and conventional oxygen therapy, the primary outcome occurred in 184/415 (44.3%) participants in the HFNO group and 166/368 (45.1%) participants in the conventional oxygen therapy group (P=0.83), absolute difference -1%, 95% CI -8%, 6% (table three).

The cut-off values for P values for the primary comparisons of CPAP and HFNO with conventional oxygen therapy corrected for the interim analyses were equivalent to 0.044 for two-sided P values.

Secondary outcomes

Secondary outcomes are summarized in table three and the electronic supplement (figures S2-S4). The decrease in the primary outcome in the CPAP group was driven by a significant decrease in the incidence of tracheal intubation (33.4% v 41.3%; absolute difference 8%, 95% CI -15%, -1%), with no statistically significant difference observed for 30-day mortality (16.7% v 19.2%; absolute difference -3%, 95% CI -8%, 3%). Neither CPAP nor HFNO, compared with conventional oxygen therapy, significantly reduced mortality in critical care or in hospital. In the CPAP group, compared with

conventional oxygen therapy, significantly fewer participants required admission to critical care (55.4% v 62.9%; absolute difference -0.7, 95% CI -15%, -0.3%) and, in those that required tracheal intubation, there was a statistically significant increase in median time to tracheal intubation (2.0 days (IQR 1.0 – 4.0) v 1.0 day (IQR 1.0 – 4.0); absolute difference 1.0, 95% CI 0.2, 1.8). For all other outcomes and comparisons, there was no statistically significant difference between study groups.

Exploratory outcomes

Findings of both our adjusted analyses and our inverse probability weighting analysis were consistent with our primary analysis (table three; electronic supplement table S4). The tests for interaction in sub-group analyses were not statistically significant, except for fraction of inspired oxygen in the comparison of HFNO and conventional oxygen therapy (P=0.02; figure two). Findings were broadly consistent between unadjusted and adjusted sub-group analyses (figure two; electronic supplement figure S5).

Post hoc outcomes

In a post-hoc analysis, which compared CPAP and HFNO, we included 570 participants that were randomized between all three study interventions (electronic supplement). The primary outcome occurred in 91/263 (34.6%) participants in the CPAP group and 136/307 (44.3%) participants in the HFNO group (P=0.02); absolute difference -10%, 95% CI -18% to -2% (electronic supplement table S5).

Adverse events

Adverse events (electronic supplement table S6) occurred most frequently in the CPAP group (CPAP 130/380 (34.2%); HFNO 86/418 (20.6%); conventional oxygen therapy 66/475 (13.9%)). Eight serious adverse events (seven CPAP; one conventional oxygen therapy) were reported. Four were classified

as probably or possibly linked to the trial intervention, with all occurring in the CPAP group (surgical emphysema and pneumomediastinum; pneumothorax and pneumomediastinum (two events); and vomiting requiring emergency tracheal intubation).

DISCUSSION

In this trial of patients with acute hypoxemic respiratory failure due to COVID-19, an initial strategy of CPAP, compared with conventional oxygen therapy, was effective in significantly reducing the composite outcome of tracheal intubation or mortality within 30-days. In contrast, there was no significant difference between an initial strategy of HFNO and conventional oxygen therapy, although given the width of the 95% confidence interval, our trial may have been underpowered to detect small, but clinically important, treatment effects.

This decrease in the incidence of the primary outcome with CPAP was attributable to a significant decrease in the need for tracheal intubation. Neither HFNO nor CPAP reduced mortality, compared with conventional oxygen therapy. More adverse events were reported in the CPAP group.

This pragmatic trial was designed to be deliverable in the context of a pandemic and tested interventions that precluded blinding of either the participant or treating clinician. The decision to perform tracheal intubation, and thereby commence invasive mechanical ventilation, was not standardised .[11] It is possible that the lower tracheal intubation rate in the CPAP group may have been driven by a greater willingness amongst clinicians and patients to delay intubation, and this may be supported by the finding that time to tracheal intubation was longer in the CPAP group. However, physiology at the time of tracheal intubation was similar across groups, suggesting that, irrespective of treatment strategy, clinicians used a similar threshold to determine the need for tracheal intubation. Furthermore, this effect was not observed with HFNO, which should have been susceptible to the same risk of performance bias.

The decision to not standardize escalation to tracheal intubation was driven by clinical uncertainty regarding the optimal timing and threshold of tracheal intubation in patients with COVID-19.[11,23] Whilst rapidly building clinical consensus may be achievable in trials recruiting in a small number of hospitals, such as the HENIVOT trial, the Recovery-RS trial management group determined that any attempt to stipulate specific criteria might influence clinical equipoise and patient acceptability, affect trial recruitment, and, more importantly, reduce trial generalisability.[24] Previous large trials of non-invasive respiratory strategies have differed in their approach to protocolization of tracheal intubation, which likely reflects these specific challenges, even in respiratory conditions where the pathophysiology has been well described.[25-27]

A recent systematic review and meta-analysis of 25 randomized clinical trials (3804 patients) summarised evidence on the clinical effectiveness of non-invasive ventilation (with and without pressure support) and HFNO, compared with conventional oxygen therapy, in acute respiratory failure.[5] Across 14 trials (1275 patients), facemask non-invasive ventilation was significantly associated with a lower risk of both mortality and tracheal intubation. In contrast, HFNO was significantly associated with a lower risk of tracheal intubation (five trials, 1479 patients), but not mortality (three trials, 1279 patients). This trial found that CPAP significantly reduced tracheal intubation, but not mortality, although wide confidence interval precludes the drawing of a specific conclusion about the effect on mortality. The trial further found that HFNO did not significantly reduce the need for tracheal intubation. One explanation for these discordant findings is differences in pathophysiology between COVID pneumonitis and other causes of acute respiratory failure[5,28] Furthermore, in this trial, some hospitals modified care pathways to deliver CPAP and HFNO outside of a critical care unit, which may have influenced the clinical effectiveness of the interventions.

This trial builds on the findings of two other recently published randomized clinical trials that examine the use of non-invasive respiratory strategies in patients with COVID-19.[24,29] The HiFLo-Covid trial compared HFNO with conventional oxygen therapy in 220 adults with severe COVID-19 across three Colombian hospitals.[29] The trial reported that HFNO both reduced the need for tracheal intubation (hazard ratio 0.62, 95% CI 0.39-0.96) and time to clinical recovery. In contrast to this trial and the HiFLo-Covid trial, the HENIVOT trial directly compared two non-invasive respiratory strategies, namely helmet non-invasive ventilation (with pressure support) and HFNO. [24] In 110 patients with COVID-19 recruited across four intensive care units, there was no significant difference for the primary outcome of days free of respiratory support, although significantly fewer patients in the non-invasive ventilation group required tracheal intubation (odds ratio 0.41, 95% CI 0.18-0.89). The protocolized approach to the set-up and weaning of trial interventions and the decision to perform tracheal intubation in both the HENIVOT and HiFLo-Covid trials potentially limits their generalizability.

Limitations

This trial has several limitations. First, the trial did not achieve its planned sample size with the decision to stop recruitment driven by the end of the funded recruitment period, together with declining numbers of patients with COVID-19 in the UK, and an ethical obligation to share accumulated data with the international clinical community. The decision to stop trial recruitment early did not involve the members of the Data Monitoring Committee, which was the only group to have seen interim analyses, such that the risk of bias arising from stopping the trial early is likely to be minimal. However, the trial may have been underpowered to detect small, but clinically important, treatment effects for the comparison of HFNO and conventional oxygen therapy. Second, there was crossover between allocated treatment groups, principally from the conventional oxygen therapy group to one or both interventions. This is a common challenge in trials of non-invasive respiratory strategies and reduces the observed effect size of a clinically effective

treatment.[26,27] Nevertheless, findings from the inverse probability weighting analysis were consistent with the primary analysis. Third, it was determined that it would be impractical to collect screening data, meaning it is not possible to describe the number of non-randomized patients and reasons for non-randomization. Fourth, the trial's definition of acute hypoxemic respiratory failure was based on objective criteria of oxygenation and oxygen use. In clinical practice, the decision to commence non-invasive respiratory strategies may be based both on objective criteria, such as these, and subjective criteria, such as respiratory distress. Fifth, the study population, particularly in terms of ethnic groups, may not be generalizable across all population. Sixth, there were some minor differences between groups at baseline in relation to co-morbid state. Seventh, the trial was rapidly set-up early in the pandemic, prior to the development of a core outcome set for COVID-19 trials.[30] Whilst the outcome list aligns closely to most of the core outcomes subsequently identified, the trial did not capture information on patient recovery following hospital discharge.

CONCLUSIONS

Among patients with acute hypoxemic respiratory failure due to COVID-19, an initial strategy of CPAP significantly reduced the risk of tracheal intubation or mortality compared with conventional oxygen therapy, but there was no significant difference between an initial strategy of high-flow nasal oxygen compared with conventional oxygen therapy. The study may have been underpowered for the comparison of high-flow nasal oxygen and conventional oxygen therapy. The early termination of the study and crossover between groups should be considered when interpreting the findings.

Author contributions

Professor Lall and Dr Ji had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of data analysis.

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The sponsor and funder approved the design of the study and monitored the conduct of the study. They played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Declaration of interests

Professor Perkins is supported as an NIHR senior investigator and through the NIHR West Midlands Applied Research Collaboration. Professor McAuley is programme director for the NIHR Efficacy and Mechanism Evaluation programme. Dr Connolly is a director of research for the Intensive Care Society. Professors Perkins and McAuley were, until recently (term ended June 2021), directors of research for the Intensive Care Society. Professors Dark and De Soyza are NIHR CRN National Specialty Cluster Leads. Professor Dark is supported by the Manchester NIHR Biomedical Research Centre.

Mrs Devrell reports personal fees from the NIHR for patient and public involvement work related to the study. Outside of the submitted work, the following conflicts of interest were declared. Dr Connolly reports grant funding from the NIHR and personal fees from Fisher and Paykel. Dr Dave reports personal fees from Chesei. Professor De Soyza reports grant support, speaker's fees, advisory board fees and conference attendance support from AstraZeneca, Bayer, Chiesi, Gilead, GlaxoSmithKline, Pfizer, Forest labs, Novartis, Insmed, and Zambon. Professor Hart reports grant funding from the NIHR, UK Research and Innovation, with unrestricted grants and equipment from Philips-Respironics, Fisher and Paykel, and Resmed; financial support from Philips for development of the MYOTRACE technology that has patent approved in Europe and US; personal fees for lecturing from Philips-

Respironics, Philips, Resmed, and Fisher and Paykel; and institutional funding for his role on the Philips Global Medical Advisory Board. Dr Messer reports personal fees from Fisher and Paykel. Dr Parekh reports grant funding from the NIHR and Medical Research Council UK Research and Innovation. Professor Steiner reports personal fees from GlaxoSmithKline. Professor McAuley reports personal fees from consultancy for GlaxoSmithKline, Boehringer Ingelheim, Bayer, Novartis, SOBI and Eli Lilly, and from sitting on DMECs for trials undertaken by Vir Biotechnology and Faron Pharmaceuticals. Professor McAuley also reports grant funding to his institution from several funders (NIHR, Wellcome Trust, Innovate UK, Medical Research Council, and Northern Ireland Health and Social Research and Development division) for studies in patients with ARDS and COVID-19, and a patent (US8962032) issued to his institution as a treatment for inflammatory disease. The remaining authors report no conflicts of interest.

Data sharing Statement: See electronic supplement.

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FIGURE LEGENDS

Figure 1: Patient screening, eligibility and enrolment

Figure footnote:

a) Given pandemic circumstances, we did not have hospitals track everyone who was approached or considered but not randomized.
b) Of the 1278 patients randomized, 5 were re-randomized in error (3 to Conventional oxygen therapy and 2 to HFNO) and did not receive initially allocated treatment. These were excluded from the summaries and analysis
c) In those who withdrew or were lost to follow-up (LTFU): in CPAP, 1 withdrawal neither received allocated treatment nor crossed over, 2 were lack of treatment information but did not cross over (1 withdrawal and 1 LTFU); in HFNO, 2 withdrawal neither received allocated treatment nor crossed over, 1 LTFU had insufficient treatment and crossover data; in Conventional oxygen therapy, all 7 received treatment, 6 of them, including 4 withdrawals, did not cross over, and 1 had insufficient cross over data.
d) Of the 1273 patients, 114 and 103 were randomized to CPAP and Conventional oxygen therapy respectively when HFNO was not available; 109 and 113 to HFNO and Conventional oxygen therapy respectively when CPAP was not available; 266, 309 and 259 to CPAP, HFNO and Conventional oxygen therapy when all therapies were available. Comparisons exclude those who did not have an opportunity to be randomized to the alternative intervention based on site availability.

Key: CPAP- Continuous positive airway pressure; HFNO- High-flow nasal oxygen

Figure 2: Unadjusted sub-group analyses: Tracheal Intubation or mortality within 30 days

Upper panel of figure two: Continuous positive airway pressure v conventional oxygen therapy

Lower panel of figure two: high-flow nasal oxygen v conventional oxygen therapy

Figure footnote:

Obese defined as body mass index >35 kg/m^2

The Unknown ethnicity refers to a participant selected category of “not given”.

The p values are calculated using the test for interaction between the sub-group and treatment variables.

Key: BMI- body mass index; CPAP- Continuous Positive Airway Pressure; FiO_2- fraction of inspired oxygen; HFNO- High-flow nasal oxygen

Table 1: Characteristics of participants at baseline

	CPAP (N=380)	HFNO (N=418)	Conventional Oxygen Therapy (N=475)
Treatment period – no. (%)			
Before July 2020	47 (12.4)	44 (10.5)	47 (9.9)
July 2020 - January 2021	262 (69.0)	289 (69.1)	331 (69.7)
After January 2021	71 (18.7)	85 (20.3)	97 (20.4)
Age, mean (SD), years	56.7 (12.5)	57.6 (13.0)	57.6 (12.7)
Sex			
Male	260 (68.4%)	272 (65.1%)	312 (65.7%)
Female	120 (31.6%)	146 (34.9%)	163 (34.3%)
Ethnicity – no. (%)[a]			
Asian	73 (19.2%)	77 (18.4%)	90 (18.9%)
Black	16 (4.2%)	14 (3.3%)	19 (4.0%)
Mixed	3 (0.8%)	4 (1.0%)	6 (1.3%)
White	243 (63.9%)	276 (66.0%)	312 (65.7%)
Other	11 (2.9%)	12 (2.9%)	9 (1.9%)
Not given	33 (8.7%)	34 (8.1%)	35 (7.4%)
Time from symptom onset to hospital admission (days)- Median (IQR) [N]	7.0 (5.5-10.0), [376]	8.0 (5.0-10.0), [407]	7.0 (5.0-10.0), [466]
Time from symptom onset to randomization (days)- Median (IQR) [N]	9.0 (7.0-12.0), [378]	9.0 (7.0-12.0), [414]	9.0 (6.0-12.0), [470]
COVID-19 status – no. (%)	(n=379)	(n=417)	(n=473)
Confirmed	326 (85.8%)	355 (84.9%)	409 (86.1%)
Suspected	53 (13.9%)	62 (14.8%)	64 (13.5%)
Co-morbidities – no. (%)			
None of the below	148 (38.9%)	141 (33.7%)	188 (39.6%)
Hypertension	131 (34.5%)	164 (39.2%)	153 (32.2%)
Diabetes requiring medication	86 (22.6%)	98 (23.4%)	91 (19.2%)
Morbid obesity (BMI >35 kg/m^2)	62 (16.3%)	81 (19.4%)	75 (15.8%)
Chronic lung disease	65 (17.1%)	52 (12.4%)	66 (13.9%)
Coronary heart disease	34 (8.9%)	26 (6.2%)	44 (9.3%)
Uncontrolled or active malignancy	7 (1.8%)	10 (2.4%)	7 (1.5%)
Dementia	4 (1.1%)	1 (0.2%)	3 (0.6%)
ESRF requiring RRT	2 (0.5%)	6 (1.4%)	5 (1.1%)
Congestive cardiac failure	2 (0.5%)	4 (1.0%)	5 (1.1%)
Clinical Frailty Scale (pre-admission) no. (%)[b]			
Very fit to managing well	351 (92.4%)	376 (90.0%)	430 (90.5%)
Very mild frailty to terminally ill	19 (5.0%)	35 (8.4%)	39 (8.2%)

Respiratory rate (breaths per minute)- Median (IQR) [N]	24 (21-30), [377]	24 (20-29), [414]	23 (20-28), [472]
FiO_2- Median (IQR) [N]	0.60 (0.40-0.80), [363]	0.60 (0.40-0.80), [404]	0.60 (0.40-0.80), [459]
SpO_2(%)-Median (IQR) [N]	94.0 (92.0-95.0), [378]	93 (91.0-95.0), [409]	94.0 (92.0-95.0), [470]
SpO_2 to FiO_2 ratio (%)-Median (IQR) [N]	155.0 (110.6-232.5), [363]	156.7 (113.8-232.5), [399]	156.7 (115.0-230.0), [457]
PaO_2 (mmHg)- Median (IQR) [N]	67.5 (60.0-77.3), [238]	66.0 (59.3-74.3), [287]	66.8 (58.5-80.3), [317]
PaO_2 to FiO_2 ratio (mmHg)- Median (IQR) [N]	112.5 (80.0-161.3), [229]	115.0 (80.9-168.4), [284]	113.8 (84.8-150.9), [308]
$PaCO_2$ (mmHg)- Median (IQR) [N]	33.0 (30.0-36.8), [252]	33.0 (30.0-36.0), [306]	33.8 (30.8-36.8), [331]
a- Available categories for ethnicity were: White British, White Irish, White- any other White background, Mixed- White and Black Caribbean, Mixed- White and Black African, Mixed- White and Asian, Mixed- any other Mixed background, Asian- Indian, Asian- Pakistani, Asian- Bangladeshi, Asian- Any other Asian background, Black / African / Caribbean / Black British- African, Black / African / Caribbean / Black British- Caribbean, Black / African / Caribbean / Black British- Any other Black / African / Caribbean / Black British background, Any other ethnic group- Chinese, Any other ethnic group- Any other, Ethnicity not given (recorded in clinical record as not given), not known (no information in clinical record). Categories were based on the National Health data dictionary. b- The clinical frailty score is based on pre-admission functional status and determined through notes review or patient assessment. It is measured on a nine-point score (very fit to terminally ill), with lower scores indicating a lower level of frailty. The categories “very fit” to “managing well” correspond to scores 1 to3, whilst the categories “very mild frailty” to “terminally ill” correspond to scores of 4 to9. Key- BMI- body mass index; CPAP- Continuous Positive Airway Pressure; ESRF- end-stage renal failure; FiO_2- fraction of inspired oxygen; HFNO- High-flow nasal oxygen; $PaCO_2$ -Partial pressure of carbon dioxide; PaO_2 -Partial pressure of oxygen; RRT- Renal replacement therapy; SpO2- Peripheral oxygen saturation.			

Table two: Initial intervention details, prone positioning, and pre-intubation clinical conditions

	CPAP (N=380)	HFNO (N=418)	Conventional Oxygen Therapy (N=475)
Initial intervention details and prone positioning			
CPAP set-up PEEP (cmH_20)- Mean (SD) [N]	8.3 (2.1), [304]		-
CPAP delivery device– no. (%)			
NIV device in CPAP mode	147 (38.7)		
CPAP device	173 (45.5)		
Other[a]	24 (6.3)		
HFNO set-up flow (liters/ minute)- Mean (SD) [N]		52.4 (9.8), [323]	-
Treatment delivery duration (days)- Mean (SD) [N]	3.5 (4.6), [340]	3.7 (4.1), [378]	-
Awake prone positioning – no. (%)- Yes[b]	207/ 327 (63.3%)	243/341 (71.3%)	252/374 (67.4%)
Pre-intubation clinical condition- worst physiology in 60-minutes prior to tracheal intubation[c]	N=126	N=169	N=199
Respiratory rate (breaths per minute)- Median (IQR) [N]	34 (26-39), [73]	28 (24-37), [86]	30 (25-38), [103]
FiO_2- Median (IQR) [N]	0.80 (0.65-0.98), [88]	0.90 (0.70-0.99), [100]	0.90 (0.80-0.98), [117]
SpO_2(%)-Median (IQR) [N]	92.0 (89.0-95.0), [86]	92.0 (88.0-94.0), [100]	92.0 (88.0-93.0), [122]
SpO_2 to FiO_2 ratio (%)-Median (IQR) [N]	118.8 (95.9-146.7), [81]	103.4 (92.6-135.7), [89]	98.0 (92.0-116.3), [109]
PaO_2 (mmHg)- Median (IQR) [N]	66.0 (57.0-81.8), [69]	63.0 (56.3-72.8), [71]	64.5 (54.0-77.3), [94]
PaO_2 to FiO_2 ratio (mmHg)- Median (IQR) [N]	89.0 (69.5-111.0), [65]	75.0 (60.0-98.1), [65]	76.0 (60.0-98.0), [84]
$PaCO_2$ (mmHg)- Median (IQR) [N]	43.1 (34.5-49.5), [70]	36.8 (30.8-46.1), [76]	40.5 (34.5-47.3), [97]
Conscious level– no. (%)- alert	72/80 (90.0)	91/103 (88.3)	112/122 (91.8)
a- CPAP delivery device classified by other as site, included NIV device in CPAP mode (n=17) or specific type of CPAP was missing (n=7). b- Use of prone positioning was recorded during follow-up. and was defined as use at any point during the hospital stay,			

both pre- and post-randomization. The time-point at which it was used was not collected. This did not include use of prone positioning following tracheal intubation. c- Intubated patients only Key- FiO2- fraction of inspired oxygen; HFNO- High-flow nasal oxygen; $PaCO_2$ - Partial pressure of carbon dioxide; PaO2 -Partial pressure of oxygen; PEEP- Positive End Expiratory Pressure; SpO2- Peripheral oxygen saturation.			

Table three: primary and secondary outcomes

CPAP versus Conventional Oxygen Therapy[a]	**CPAP**	**Conventional Oxygen Therapy**	**Absolute difference (95% CI)**	**Unadjusted effect estimate, OR or HR or MD (95% CI)[g]**	**Adjusted effect estimate, OR or HR or MD (95% CI)[g,h]**	**P value (unadj, adj)**
Primary composite outcome						
Tracheal Intubation or mortality within 30 days, n/N(%)[b]	137/377 (36.3%)	158/356 (44.4%)	-8% (-15%- -1%)	0.72 (0.53- 0.96)	0.68 (0.48- 0.94)	0.03, 0.02
Composite outcome components						
Intubation within 30 days, n/N(%)	126/377 (33.4%)	147/356 (41.3%)	-8% (-15%- -1%)	0.71 (0.53- 0.96)	0.67 (0.48- 0.93)	0.03, 0.02
Mortality at 30 days(%), n/N(%)	63/378 (16.7%)	69/359 (19.2%)	-3% (-8%- 3%)	0.84 (0.58 -1.23)	0.91 (0.59 -1.39)	0.37, 0.65
Secondary outcomes						
Tracheal Intubation rate in the study period, n/N(%)	126/377 (33.4%)	147/356 (41.3%)	-8% (-15%- -1%)	0.71 (0.53- 0.96)	0.67 (0.48- 0.93)	0.03, 0.02
Admission to critical care, n/N(%)	204/368 (55.4%)	219/348 (62.9%)	-7% (-15%- -0.3%)	0.73 (0.54- 0.99)	0.69 (0.49- 0.96)	0.04, 0.03
Duration of invasive ventilation (days)- Intubated patients, n/N(%)[c]	15.0 (8.0-25.0), n=126	11.0 (6.0-23.0), n=147	4.0 (0.04- 8.0)	HR: 0.82 (0.61- 1.09)	HR: 0.83 (0.61-1.12)	0.17, 0.22
Time to intubation (days)- median (IQR) [N][c]	2.0 (1.0-4.0), [126]	1.0 (0.0-4.0), [147]	1.0 (0.2- 1.8)	HR: 0.77 (0.61 -0.98)	HR: 0.71 (0.56 - 0.91)	0.03, 0.01
Time to death (days)- median (IQR) [N] [c]	17.0 (11.0-26.0), [74]	17.0 (11.0-24.0), [79]	0 (-3.8- 3.8)	HR: 0.86 (0.61-1.21)	HR: 0.93 (0.65-1.33)	0.38, 0.69
Mortality in critical care, n/N(%)	62/204 (30.4%)	66/219 (30.1%)	0.3%	1.01	1.10	0.95, 0.68

			(-9%- 9%)	(0.67-1.53)	(0.69- 1.75)	
Mortality in hospital, n/N(%)	72/364 (19.8%)	78/346 (22.5%)	-3% (-9%- 3%)	0.85 (0.59 - 1.22)	0.92 (0.62 -1.38)	0.37, 0.69
Length of critical care stay (days), Mean (SD), [N][d]	9.5 (15.6), [368]	9.6 (13.6), [348]	-0.08 (-2.23- 2.07)		MD: -0.16 (-2.30- 1.99)	0.94, 0.88
Length of hospital stay (days), Mean (SD), [N][d]	16.4 (17.5), [364]	17.3 (18.1), [346]	-0.96 (-3.59- 1.67)		MD: -1.14 (-3.84- 1.55)	0.47, 0.41
HFNO versus Conventional Oxygen Therapy[e]	**HFNO**	**Conventional Oxygen Therapy**	**Absolute difference (95% CI)**	**Unadjusted effect estimate, OR or HR or MD (95% CI)[g]**	**Adjusted effect estimate, OR or HR or MD (95% CI)[g,h]**	**P value (unadj, adj)**
Primary composite outcome						
Tracheal Intubation or mortality within 30 days, n/N(%)[b]	184/415 (44.3%)	166/368 (45.1%)	-1% (-8%- 6%)	0.97 (0.73 -1.29)	0.94 (0.68- 1.29)	0.83, 0.69
Composite outcome components						
Intubation within 30 days, n/N(%)	170/415 (41.0%)	153/368 (41.6%)	-1% (-8%- 6%)	0.98 (0.73- 1.30)	0.94 (0.69 - 1.30)	0.86, 0.72
Mortality at 30 days(%), n/N(%)	78/416 (18.8%)	74/370 (20.0%)	-1% (-7%- 4%)	0.92 (0.65-1.32)	0.97 (0.65 - 1.46)	0.66, 0.90
Secondary outcomes						
Tracheal Intubation rate in the study period, n/N(%)[f]	169/415 (40.7%)	154/368 (41.8%)	-1% (-8%- 6%)	0.95 (0.72- 1.27)	0.92 (0.67- 1.27)	0.75, 0.62
Admission to critical care, n/N(%)	252/408 (61.8%)	214/361 (59.3%)	2% (-4%- 9%)	1.11 (0.83- 1.48)	1.04 (0.75-1.45)	0.48, 0.81
Duration of invasive ventilation (days)- Intubated patients- median (IQR) [N][c]	15.0 (8.0-26.0), [169]	12.0 (6.0-23.0), [154]	3.0 (-1.0- 7.0)	HR: 0.92 (0.71 - 1.20)	HR: 1.01 (0.76 - 1.34)	0.56, 0.96
Time to intubation (days) - median (IQR) [N] [c]	1.0 (0.0-3.0), [169]	1.0 (0.0-3.0), [154]	0 (-0.4- 0.4)	HR: 0.98 (0.78 - 1.21)	HR: 0.92 (0.74 -1.16)	0.82, 0.49
Time to death (days)- median (IQR) [N][c]	16.5 (9.0-22.5), [88]	17.0 (11.0-24.0), [85]	0.0 (-3.4- 3.4)	HR: 0.94 (0.68- 1.29)	HR: 0.94 (0.67 - 1.32)	0.69, 0.74
Mortality in critical care, n/N(%)	72/251 (28.7%)	65/214 (30.4%)	-2% (-10%- 7%)	0.92 (0.62-1.38)	0.98 (0.63 -1.54)	0.69, 0.94
Mortality in hospital, n/N(%)	86/405 (21.2%)	80/359 (22.3%)	-1% (-7%- 5%)	0.94 (0.67 -1.33)	0.99 (0.67 -1.47)	0.73, 0.97
Length of critical care stay (days), Mean (SD) [N][d]	10.5 (15.6), [407]	9.6 (14.1), [361]	0.95 (-1.16- 3.07)		MD: 0.47 (-1.57 -2.50)	0.38, 0.65
Length of hospital stay (days), Mean (SD) [N][d]	18.3 (20.0), [405]	17.1 (18.0), [359]	1.21 (-1.50- 3.93)		MD: 0.33 (-2.28 - 2.94)	0.38, 0.80

Table three footnote:

Table legend:

Key- 95% CI- 95% Confidence interval, CPAP- Continuous Positive Airway Pressure; HFNO- High-flow nasal oxygen, HR- Hazard ratio, MD- Mean difference, OR- Odds ratio

The % are based on excluding missing data (i.e. withdrawals and no data provided).

Based on the information available at the interim analyses, the cut-off values for P values for the primary comparisons of CPAP and HFNO with conventional oxygen therapy corrected for the interim analyses were equivalent to 0.044 for two-sided P values. No correction for interim analyses was made to the cut-off values for the secondary endpoints or analyses, with a significance threshold of 0.05 used.

The footnote in figure two provides details on how data were censored for time-to-event analyses.

a- Includes patients randomized between CPAP and conventional oxygen therapy, or between CPAP, HFNO, and conventional oxygen therapy.

b-The final p value for the primary analysis should be compared with the corrected cut-off value equivalent to a two-sided value of 0.044 calculated using the method described by Jennison and Turnbull[22]

c-Proportional hazard assumption was tested in the unadjusted models. The p-values are 0.54, 0.01, and 0.89 for duration of invasive ventilation, time to intubation and time to death, respectively, in the CPAP versus Conventional oxygen comparison. The p-values are 0.32, 0.81, and 0.64 for duration of invasive ventilation, time to intubation and time to death, respectively, in the HFNO versus Conventional oxygen comparison. The only violation (p=0.01) was likely caused by the early cross in the follow-up with the rest of the curves remaining paralleled.

d-Adjusted values reported as mean difference (pairwise comparisons include those with completed critical care/hospital stay. Patients not admitted to critical care were allocated a critical care stay of 0 days)

e-Includes patients randomized between HFNO and conventional oxygen therapy, or between CPAP, HFNO, and conventional oxygen therapy

f- Outcome included tracheal intubation during the index hospital admission- compared with the 30-day analysis, this excluded one patient that was intubated within 30-days, but outside the index hospital admission (HFNO group) and included one patient that was intubated in the

index hospital admission but occurred more than 30-days post-randomization (conventional oxygen therapy group)- both in the HFNO v conventional oxygen therapy comparison.
g- Data are odds ratios unless otherwise specified.
h-Models were adjusted for age, sex, morbid obesity, ethnicity, FiO_2, respiratory rate and treatment phases, with site included as a random effect.