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Supplementary appendix 2

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Ehrmann S, Li J, Ibarra-Estrada M, et al. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. *Lancet Respir Med* 2021; published online August 20. http://dx.doi.org/10.1016/S2213-2600(21)00356-8.

Research protocol

1. Meta-trial protocol (Version 2)

Title

Awake prone positioning of hypoxemic COVID-19 patients: protocol for a randomized controlled open label superiority meta-trial.

Names protocol contributors

Elsa Tavernier[1*], Bairbre McNicholas[2], Ivan Pavlov[3], Oriol Roca[4], Yonatan Perez[5], John Laffey[2], Sara Mirza[6], David Cosgrave[2], David Vines[6], Jean-Pierre Frat[7], Miguel Á Ibarra Estrada[8], Stephan Ehrmann[5], Jie Li[6]

[1]*Universities of Tours and Nantes, INSERM 1246-SPHERE, Tours, France; Clinical Investigation Center, INSERM 1415, CHRU Tours, Tours, France.*

[2]*Anaesthesia and Intensive Care Medicine, School of Medicine, National University of Ireland Galway; Department of Anaesthesia, University Hospital Galway, Saolta Hospital Group, Ireland*

[3]*Department of Emergency Medicine, Hôpital de Verdun, Montréal, Québec, Canada*

[4]*Critical Care Department, Vall d'Hebron University Hospital, Vall d'Hebron Research Institute, Barcelona, Spain ; Departament de Medicina, Universitat Autònoma de Barcelona, Bellaterra, Spain ; Ciber Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain*

[5] *CHRU Tours, Médecine Intensive Réanimation, CIC INSERM 1415, CRICS-TriggerSEP research network, Tours, France ; and INSERM, Centre d'étude des pathologies respiratoires, U1100, Université de Tours, Tours, France*

[6] *Department of Cardiopulmonary Sciences, Division of Respiratory Care, Rush University Medical Center, Chicago, IL.*

[7] *Réanimation Médicale, Centre Hospitalier Universitaire de Poitiers ; Faculté de Médecine et de Pharmacie de Poitiers, Université de Poitiers and INSERM, Centre d'Investigation Clinique-1402, Equipe 5 Acute Lung Injury and Ventilatory Support, Poitiers, France.*

[8] *Unidad de terapia Intensiva, Hospital Civil Fray Antonio Alcalde. Guadalajara, Jalisco, México*

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Abstract

- Introduction: Prone positioning is an effective first-line intervention to treat moderate-severe acute respiratory distress syndrome (ARDS) patients receiving invasive mechanical ventilation, as it improves gas exchanges and reduces mortality. The use of prone positioning in awake spontaneous breathing patients with ARDS secondary to COVID-19 was reported to improve oxygenation in few retrospective trials with small sample size. High-level evidence of awake PP for hypoxemic COVID-19 patients is still lacking.
- Methods and analysis: This meta-trial is a prospective collaborative individual participant data meta-analysis of randomized controlled open label superiority trials. This design is particularly adapted to a rapid scientific response in the pandemic setting. It will take place in multiple sites, among others in USA, Canada, Ireland, France, Spain, and Mexico. Patients will be followed up for 28 days. Patients will be randomized to receive whether awake prone positioning and nasal high flow therapy or standard medical treatment and nasal high flow therapy. Primary outcome is defined as the occurrence rate of tracheal intubation or death up to day 28. An interim analysis plan has been set up on aggregated data from the participating research groups.
- Ethics and dissemination: Ethics approvals were obtained in all participating countries. Results of the meta-trial will be submitted for publication in a peer-reviewed journal. Each randomized controlled trial was registered individually, as follows: NCT04325906, NCT04347941, NCT04358939, NCT04395144, NCT04391140, NCT04477655.

Strengths and limitations of this study

- This pragmatic design will deal with the recruitment difficulties that could occur in the individual trials given the uncertainties of the international dynamics of the COVID-19 pandemic.
- The collaborative interim analysis plan at the level of the meta-trial will enable an earlier data analysis compared to the individual study level or to a retrospective meta-analysis.
- Besides synthesizing the effect size estimates, it also considers the aspect of replication: results being consistent across trials is a strength in favor of a robust treatment effect over different conditions.
- The lack of blinding of trial participants, care providers and outcome assessors is an unavoidable limitation of the study design.

Keywords

COVID-19, Acute Respiratory Distress Syndrome, Respiratory failure, Hypoxemic respiratory failure, high-flow nasal cannula, prone positioning. Research design (MeSH), Therapeutic human experimentation (MeSH), International cooperation (MeSH), Pandemics (MeSH)

Introduction

Background and rationale

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease that was first reported in Wuhan, China, and had subsequently spread worldwide. As of June 6th, 2020, more than six million cases were confirmed globally and close to 0·4 million deaths were reported.[1] Nearly 20% of patients experienced hypoxemia, which was the primary reason for hospitalization.[2] In patients with severe disease who were admitted to the intensive care unit (ICU), mortality rates of up to 42% have been described.[3] As of June 6th, 2020, 51·2% of the 6,128 UK hospitalized patients with COVID-19 that required advanced respiratory support died [3] and 36% mortality was reported for invasively ventilated COVID-19 patients in a single center in Atlanta.[4]

High flow nasal cannula (HFNC) oxygen therapy provides oxygen-rich heated humidified gas to the patient nose at flow rates sufficient to deliver a constant, precisely set high fraction of inspired oxygen (F_iO_2). HFNC washes out the dead space carbon dioxide, provides a low level of positive end expiratory pressure (PEEP), and decreases breathing frequency and work of breathing.[5,6] In hypoxemic respiratory failure, HFNC use is associated with lower mortality, lower rates on endotracheal intubation, and improved oxygenation.[7-9] It has been extensively used early in the COVID-19 outbreak in China.[10]

Prone positioning of mechanically ventilated patients is an effective first-line intervention to treat moderate-severe acute respiratory distress syndrome (ARDS) patients receiving invasive mechanical ventilation, as it improves gas exchanges and reduces mortality.[11,12] There is limited evidence to support awake prone positioning (APP) of patients treated with HFNC. Two small studies showed that APP was feasible in spontaneously breathing patients.[13-14] In one of them, APP combined with HFNC resulted in higher arterial partial pressure of oxygen (P_aO_2) to F_iO_2 ratios than HFNC alone.[13] However, not all hypoxemic COVID-19 patients responded to APP.[15] In a retrospective study of 610 patients from China [16] a multi-pronged intervention that included early and aggressive use of HFNC and noninvasive ventilation (NIV) along with APP for patients resulted in lower overall mortality (3·33%, as compared 4·34% in a nearby province). A very low percentage of patients required mechanical ventilation (<1%, as compared to the national average of 2·3%,[17] in a population that included 10% of critically-ill patients). The authors highlighted that mortality was lower than in a previously reported cohort study of ARDS patients performed at the same institution prior to the pandemic [18] although is not clear if the two populations were comparable in terms of disease severity. Since the outbreak, the use of APP with different oxygen modalities has been described in case series reports by teams from the USA, France, Italy, and China.[19-23] However, none of them provided high-level evidence of the effects on patients' outcome.

Based on the potential beneficial mechanisms of HFNC and APP, early use of APP combined with HFNC to avoid the need for intubation in COVID-19 patients with moderate to severe ARDS needs to be further investigated.

Due to the urgent need to find effective treatments for COVID-19, this meta-trial will gather together several trials launched independently at the beginning of the COVID-19 pandemic. As of May 6, 2020, 8 randomized trials evaluating the efficacy of APP in COVID-19 patients were registered on clinicaltrials.gov. Early in the pandemic, we organized a meeting with the investigators and methodologists of the teams whose trials planned to include similar populations to address the same question of the effects of APP. We have decided to combine our recruitment capabilities, and design an international meta-trial.[24,25] This protocol includes a common analysis plan for the primary endpoint with four interim analysis in order to obtain early evidence.

Objectives

The primary objective is to demonstrate the efficacy of APP combined with HFNC in terms of treatment failure rate at 28 days, defined as a combination of (1) death, (2) intubation, in awake and spontaneously breathing patients with suspected or confirmed COVID-19 infection

Methods and analysis

Trial design

This meta-trial is designed as a collaborative individual participant prospective data meta-analysis of six randomized controlled open label superiority trials with two parallel groups and a primary endpoint of therapeutic failure at day 28.

Study setting

This meta-trial will include patients with severe COVID-19 pneumonia treated with HFNC in the ICU, in emergency departments (ED), in high dependency units, and on medical wards of participating hospitals. A full list of participating institutions is available in each individual trial record on ClinicalTrials.gov.

Eligibility criteria

All adult patients with proven (or clinically suspected, pending microbiological confirmation) COVID-19 pneumonia who require treatment with HFNC are eligible for this trial.

Eligibility criteria for potential trial participants are described in table 1.

Recruitment

Due to the rapidly evolving pandemic situation, we have a strong uncertainty about the pace of enrollment. We anticipate this international collaboration to lead to better recruitment than individual trials studying the same population. Other individual RCTs may be added into this meta-trial study, as long as inclusion criteria, main outcomes, and trial interventions are sufficiently similar.

Interventions

Control group

The patients in the control groups will be treated according to the same standard of care, and receive the same oxygenation support with HFNC as in the intervention groups but they will not be asked to remain in prone position. Details for each trial are presented in table 2.

Intervention description

The patients in the intervention groups will turn in prone position with the help and under the supervision of a caregiver to ensure that they are predominantly on their chest rather than on their side. Patients will be asked to remain in prone position as long as they can and as close as possible to 16 hours or more per day.

Criteria for continuing or modifying allocated interventions

Proning procedure will continue as long as the patient is in the following oxygen conditions:

- P_aO_2/ F_iO_2 below 300 or S_pO_2 (Peripheral oximetry saturation) to F_iO_2 ratio below 340 in the Irish trial
- P_aO_2/ F_iO_2 (or S_pO_2/ F_iO_2) below 300 mmHg (or 315) in the French and Spanish trials
- P_aO_2/ F_iO_2 below 200 mmHg or S_pO_2/ F_iO_2 below 240 in the Canadian and American trial

Proning will be left at the discretion of the clinician in case of intubation.

Proning will be interrupted in case of discharge or death.

The following guidance is provided concerning the need for tracheal intubation to perform invasive mechanical ventilation. Intubation is recommended in case of:[7]

(1) Signs of persisting or worsening respiratory failure, defined by at least two of the following criteria:

-Respiratory rate above 40 breaths/min

-Lack of improvement of the signs of respiratory-muscle fatigue

-Development of copious tracheal secretions

-Hypercapnic respiratory acidosis with a pH below 7·25

-S_pO_2 below 90% at $FiO_2 \geq 0{\cdot}8$ for more than 5 min without technical dysfunction

(2) Hemodynamic instability

(3) Deterioration of neurologic status

For patients who meet the intubation criteria in the HFNC and HFNC+APP groups, a trial of NIV might be allowed according to the physician's preference in patients with signs of persisting or worsening respiratory failure and no other organ dysfunction before performing endotracheal intubation and invasive ventilation. Reasons for intubation will be recorded as well.

Strategies to improve adherence to interventions

The number of sessions and the total time spent in prone position will be collected per 24-hour period, and encouragement will be provided.

Relevant concomitant care permitted or prohibited during the trial

No prohibitions during the trial.

Provisions for post-trial care

Post-trial care will be standard care through the standard healthcare system from each country

Outcomes

The primary outcome is therapeutic failure within 28 days of randomization, defined as intubation or death.

Secondary outcomes:

-Days spent in the hospital (within 28 days of randomization)

-Mortality (within 28 days of randomization)

-Intubation rate

-Duration of invasive ventilation for intubated patients who survive at day 28 in each group

-Mortality of patients who are intubated

-Primary outcome (intubation or death) among patients receiving NIV in each randomization group

-Length of HFNC therapy use in those patients who succeeded with HFNC (efficacy)

-Time to NIV, intubation or death

-Response to prone position: pre and post change of S_pO_2/F_iO_2 ratio, respiratory rate and ROX index (S_pO_2/ (F_iO_2 x respiratory rate). As a practical alternative to PaO_2/F_IO_2, SpO_2/F_IO_2 has been shown to have a strong linear relationship in moderate to severe ARDS.[26,27]

-Daily duration with APP in the first 14 days after enrollment.

-Number of crossovers

-Primary outcome (intubation or death) in both groups of the per-protocol population

Other measures:

In both groups complications will be recorded: complications include skin breakdown, device removal, desaturation, or cardiac arrest in APP or during position change (within 28 days of randomization).

Plans for assessment and collection of outcomes

Protocol explanation will be provident to study sites during a dedicated online or physical meeting. Assessment and collection of outcomes will be performed by investigators, physicians, nurses, research assistants trained and used to deal with hypoxemic patients without additional training required. SpO_2/FiO_2 ratio assessment requires the SpO_2 to be equal of less than 97%. The primary outcome (intubation or death) is easily retrieved from patients' charts. Bedside

sheets are made available to simplify data recording. Each individual study coordinator is responsible for data quality control.

Statistical methods

Sample size

We assume the primary outcome rate to be between 60% and 70% in the control group. The meta-analysis is designed to demonstrate superiority of APP over control with 90% power and a one-sided Type I error rate of 2·5. For a fixed design with no interim analysis and a sample size of 836, the maximum detectable risk ratio will be between 0·847 and 0·814 (a difference of failure rates of about 11% between groups). For the same assumptions, asymmetric two-sided group sequential analysis requires a sample size of 1000, for 5 interim analyses (including the last analysis). Bounds were determined using a Kim-DeMets spending function with parameters 0·75 for efficacy and 3 for futility. This provides an aggressive Pocock-like superiority bound and a conservative O'Brien Fleming-like bound for futility (Figure 1). Sample sizes were computed using the packages epiR and gsDesign in R software.

Randomization

All patients who give consent for participation and who fulfill the inclusion criteria will be randomized. For each trial a professional statistician not involved in patient recruitment will generate the allocation sequence. Participants will be randomly assigned to either control or experimental group with a 1:1 allocation as per a computer-generated randomization schedule stratified by site and using varying block sizes. The American trial will also be stratified by ARDS severity (moderate versus severe), and French and Spanish trial will also be stratified by the therapeutic use of the APP prior to inclusion. In 4 trials, participants will be randomized using an online central randomization system. In the Canadian trial, allocation concealment will be ensured using on site sealed opaque envelopes. By the very nature of the interventions and design, trial participants, care providers, outcome assessors and data analysts could not be blinded to interventions.

Statistical methods for primary and secondary outcomes

We plan a prospective meta-analysis of individual data. Common variables from all datasets will be gathered and combined to conduct the analysis. A detailed analysis plan will be *a priori* defined. The primary analysis will be performed on an intent-to-treat basis. A sensitivity analysis will be performed on a per protocol set described below. Baseline patient characteristics will be presented by country and treatment group. The comparison between intervention arms will be synthesized using mixed-effects models with a random effect on the trial: a mixed-effects logistic regression for the primary outcome and any binary outcome. A survival analysis will be performed on mortality and any other time-to-event outcome, using a gamma-frailty term on each trial in a Cox regression model providing that the assumption of proportional hazards is verified. Regarding adverse events, descriptive statistics (percentages) will be estimated. We plan to assess statistical heterogeneity between countries by visual inspection of the forest plots, which will also present per-country analyses, and by calculating the Q and I^2 statistics.

Interim analyses

We chose a Kim-DeMets alpha-spending approach [28,29] rather than other methods such as a triangular test for its simplicity of implementation and for the continuous stopping boundaries enabling to be more flexible in managing interim analysis if the design of the trial were to change as a result of an unexpected development of the epidemic.

Analyses are planned when the total number of randomized patients with the primary outcome available from the various trials reaches 200 (100 in each arm), 400 (200 in each arm), 600 (300 in each arm), 800 (400 in each arm), and 1000 the last possible analysis. The interim analyses define rules for stopping the trials early for the statistical reasons of established efficacy or futility on the primary outcome. Two professional academic statisticians will conduct all interim analyses (blind duplicates).

At each interim analysis, the Z statistics for a difference of binary endpoints is computed from the data of the two arms and is compared to the efficacy and futility bounds given in Figure 1.

If the value of Z is higher than the interim analysis specific upper bound (or lower than the lower bound), the trials will be considered to be stopped for reasons of demonstrated efficacy (or futility) and data will be published as soon as possible to inform the clinical and scientific community; otherwise the trials will continue.

Methods for additional analyses (e.g. subgroup analyses)

We plan to conduct a subgroup analysis on the severity of ADRS: P_aO_2/F_iO_2 ratio below 150 mmHg (or S_pO_2/F_iO_2 ratio below 190), P_aO_2/F_iO_2 ratio above 150 mmHg (or S_pO_2/F_iO_2 ratio above 190). We will test if the treatment effects differ with severity of ADRS by putting their main effect and interaction terms in the logistic regression.

Adjusted analyses will be nested in the intervention group to evaluate the effect of duration of APP on the risk of intubation or death, as well as the analysis of prognostic factors associated with APP such as co-morbidities, age, body mass index, etc.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

We do not expect any patient to be lost to follow-up. The only missing data could relate to patients who withdraw their consent. In this case, they will be excluded from the intention-to-treat analysis. We will analyze the primary outcome using two analysis sets; the intention-to-treat set, considering all patients as randomized regardless of whether they performed the prone position, and the per protocol analysis set. The per-protocol set will only include patients who spent at least 1 hour in prone position after randomization without intubation or death. Patients in the intervention group who spent less than 1 hour daily in APP, and patients in the control group who remained more than 1h at least one day in APP will be excluded.

Ethics and dissemination

Ethics and consent

Ethics approval was obtained in all 6 participating countries. Informed consent will be obtained according to local regulations in each trial. Local investigators will obtain either verbal or electronic consent. Documentation of consent will be either written or electronic.

Data management, transfer and deposition

The details of data-management procedures can be found in the original protocols (supplementary files). Each investigator is responsible for the confidentiality of the data collected during his or her trial. The data sets will use pseudonymised data. Interim analyses will be performed by centralizing the aggregated data of the primary endpoint per trial. The confidentiality of data will be preserved when the coded, de-personalised data will be transmitted and stored at the location of the statistician in charge of the final analysis.

Steering committee

The steering committee will be responsible for reporting and interpreting the result of the interim analysis and the final analysis. The steering committee will be composed of principal investigators and statistician from all sites and may be completed by independent investigators without any competing interest. This study will be reported in accordance with the CONSORT statement for non-pharmacological trials and published in peer-reviewed journals.

Dissemination strategy

The results of the study will be presented in national and international conferences, and published via a peer-reviewed journal.

Data sharing statement

Deidentified data will be made available upon reasonable request discussed among the steering committee.

Study status

At the time of submitting for publication, the study was collecting data.

Footnotes

Acknowledgements

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research infrastructure network : www.fcrin.org) ; Rice foundation and Irish Critical Care Clinical Trials Network (www.iccctn.org).

Authors' contributions

BM, IP, OR, YP, JL, SM, DC, JPF, MIE, SE, JL conceived the trials. ET provided methodological expertise in the meta-trial design and prepared the first draft of this study protocol. BM, IP, OR, YP, JL, SM, DC, JPF, MIE, SE and JL contributed to the rewriting; all of the authors approved the final protocol and reviewed it for important intellectual content.

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BMJ Open

Awake prone positioning of hypoxaemic patients with COVID-19: protocol for a randomised controlled open-label superiority meta-trial

Elsa Tavernier ,[1,2] Bairbre McNicholas,[3,4] Ivan Pavlov,[5] Oriol Roca,[6,7] Yonatan Perez,[8] John Laffey,[3,4] Sara Mirza,[9] David Cosgrave,[3,4] David Vines,[9] Jean-Pierre Frat,[10] Stephan Ehrmann,[8] Jie Li [9]

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For numbered affiliations see end of article.

Correspondence to
Dr Elsa Tavernier;
elsa.tavernier@univ-tours.fr

ABSTRACT

Introduction Prone positioning (PP) is an effective first-line intervention to treat patients with moderate to severe acute respiratory distress syndrome (ARDS) receiving invasive mechanical ventilation, as it improves gas exchanges and reduces mortality. The use of PP in awake spontaneous breathing patients with ARDS secondary to COVID-19 was reported to improve oxygenation in few retrospective trials with small sample size. High-level evidence of awake PP for hypoxaemic patients with COVID-19 patients is still lacking.

Methods and analysis The protocol of this meta-trial is a prospective collaborative individual participant data meta-analysis of randomised controlled open label superiority trials. This design is particularly adapted to a rapid scientific response in the pandemic setting. It will take place in multiple sites, among others in USA, Canada, Ireland, France and Spain. Patients will be followed up for 28 days. Patients will be randomised to receive whether awake PP and nasal high flow therapy or standard medical treatment and nasal high flow therapy. Primary outcome is defined as the occurrence rate of tracheal intubation or death up to day 28. An interim analysis plan has been set up on aggregated data from the participating research groups.

Ethics and dissemination Ethics approvals were obtained in all participating countries. Results of the meta-trial will be submitted for publication in a peer-reviewed journal. Each randomised controlled trial was registered individually, as follows: NCT04325906, NCT04347941, NCT04358939, NCT04395144 and NCT04391140.

Strengths and limitations of this study

- This pragmatic design will deal with the recruitment difficulties that could occur in the individual trials given the uncertainties of the international dynamics of the COVID-19 pandemic.
- The collaborative interim analysis plan at the level of the meta-trial will enable an earlier data analysis compared with the individual study level or to a retrospective meta-analysis.
- Besides synthesising the effect size estimates, it also considers the aspect of replication: results being consistent across trials is a strength in favour of a robust treatment effect over different conditions.
- The lack of blinding of trial participants, care providers and outcome assessors is an unavoidable limitation of the study design.

INTRODUCTION

Background and rationale

COVID-19 is an emerging infectious disease that was first reported in Wuhan, China, and had subsequently spread worldwide. As of 6 June 2020, more than 6 million cases were confirmed globally, and close to 0.4million deaths were reported.[1] Nearly 20% of patients experienced hypoxemia, which was the primary reason for hospitalisation.[2] In patients with severe disease who were admitted to the intensive care unit (ICU), mortality rates of up to 42% have been described.[3] As of 6 June 2020, 51.2% of the 6128 UK hospitalised patients with COVID-19 that required advanced respiratory support died[3] and 36% mortality was reported for invasively ventilated COVID-19 patients in a single centre in Atlanta.[4]

High flow nasal cannula (HFNC) oxygen therapy provides oxygen-rich heated humidified gas to the patient's nose at flow rates sufficient to deliver a constant, precisely set high fraction of inspired oxygen (FiO_2). HFNC washes out the dead space carbon dioxide, provides a low level of positive end-expiratory pressure and decreases breathing frequency and work of breathing.[5 6] In hypoxaemic respiratory failure, HFNC use is associated with lower mortality, lower rates on endotracheal intubation and improved oxygenation.[7–9] It has been extensively used early in the COVID-19 outbreak in China.[10]

Prone positioning (PP) of mechanically ventilated patients is an effective first-line

intervention to treat patients with moderate to severe acute respiratory distress syndrome (ARDS) receiving invasive mechanical ventilation, as it improves gas exchanges and reduces mortality.[11 12] There is limited evidence to support awake PP of patients treated with HFNC. Two small studies showed that PP was feasible in spontaneously breathing patients.[13 14] In one of them, PP combined with HFNC resulted in higher arterial partial pressure of oxygen (PaO_2) to FiO_2 ratios than HFNC alone.[13] However, not all hypoxaemic patients with COVID-19 responded to awake PP.[15] In a retrospective study of 610 patients from China,[16] a multipronged intervention that included early and aggressive use of HFNC and non-invasive ventilation (NIV) along with PP for awake patients resulted in lower overall mortality (3.33%, as compared with 4.34% in a nearby province). A very low percentage of patients required mechanical ventilation (<1%, as compared with the national average of 2.3%,[17] in a population that included 10% of critically ill patients). The authors highlighted that mortality was lower than in a previously reported cohort study of patients with ARDS performed at the same institution prior to the pandemic,[18] although is not clear if the two populations were comparable in terms of disease severity. Since the outbreak, the use of awake PP with different oxygen modalities has been described in case series reports by teams from the USA, France, Italy and China.[19–23] However, none of them provided high-level evidence of the effects on patients' outcome.

Based on the potential beneficial mechanisms of HFNC and PP, early use of PP combined with HFNC to avoid the need for intubation in COVID-19 patients with moderate to severe ARDS needs to be further investigated.

Due to the urgent need to find effective treatments for COVID-19, this meta-trial will gather together several trials launched independently at the beginning of the COVID-19 pandemic. As of 6 May 2020, eight randomised trials evaluating the efficacy of PP in patients with COVID-19 were registered on ClinicalTrials.gov. Early in the pandemic, we organised a meeting with the investigators and methodologists of the teams whose trials planned to include similar populations to address the same question of the effects of PP. We have decided to combine our recruitment capabilities and design an international meta-trial.[24 25] This protocol includes a common analysis plan for the primary endpoint with four interim analysis in order to obtain early evidence.

Objectives

The primary objective is to demonstrate the efficacy of PP combined with HFNC in terms of treatment failure rate at 28 days, defined as a combination of (1) death and (2) intubation, in awake and spontaneously breathing patients with suspected or confirmed COVID-19 infection.

METHODS AND ANALYSIS

Trial design

This meta-trial is designed as a collaborative individual participant prospective data meta-analysis of five randomised controlled open-label superiority trials with two parallel groups and a primary endpoint of therapeutic failure at day 28.

Study setting

This meta-trial will include patients with severe COVID-19 pneumonia treated with HFNC in the ICU, in emergency departments, in high-dependency units and on medical wards of participating hospitals. A full list of participating institutions is available in each individual trial record on ClinicalTrials.gov. The original protocols are in online supplemental files 1-4).

Eligibility criteria

All adult patients with proven (or clinically suspected, pending microbiological confirmation) COVID-19 pneumonia who require treatment with HFNC are eligible for this trial.

Eligibility criteria for potential trial participants are described in table 1.

Recruitment

Due to the rapidly evolving pandemic situation, we have a strong uncertainty about the pace of enrolment. We anticipate this international collaboration to lead to better recruitment than individual trials studying the same population. Other individual RCTs may be added into this meta-trial study, as long as inclusion criteria, main outcomes and trial interventions are sufficiently similar.

Interventions

Control group

The patients in the control groups will be treated according to the same standard of care and receive the same oxygenation support with HFNC as in the intervention groups, but they will not be asked to remain in prone position. Details for each trial are presented in table 2.

Intervention description

The patients in the intervention groups will turn in prone position with the help and under the supervision of a caregiver to ensure that they are predominantly on their chest rather than on their side. Patients will be asked to remain in prone position as long as they can and as close as possible to 16 hours or more per day or more.

Criteria for continuing or modifying allocated interventions

Proning procedure will continue as long as the patient is in the following oxygen conditions:

- PaO_2/FiO_2 below 200 or SpO_2 (peripheral oximetry saturation) to FiO_2 ratio below 235 in the Irish trial.
- PaO_2/FiO_2 (or SpO_2/FiO_2) below 300 mm Hg (or 315) in the French and Spanish trials.
- PaO_2/FiO_2 below 200 mm Hg or SpO_2/FiO_2 below 240 in the Canadian and American trial.

Proning will be left at the discretion of the clinician in case of intubation.

Proning will be interrupted in case of discharge or death.

Table 1 Eligibility criteria in each trial

	USA and Canada	Ireland	France and Spain
Inclusion criteria	1. COVID-19 pneumonia based on the Ccenters for Disease Control guidelines. 2. Presence of acute hypoxaemic respiratory failure. 3. Acute onset within 7 days of insult or new (within 7 days) or worsening respiratory symptoms. 4. Bilateral opacities on chest X-ray or CT scanner not fully explained by effusions, lobar or lung collapse, or nodules. 5. Cardiac failure not the primary cause of acute respiratory failure. 6. Written informed consent 7. PaO_2/FiO_2 ratio <200 mm Hg or SpO_2/FiO_2 <240 with HFNC at 50 L/min and peripheral capillary oxygen saturation ($SpO_{2)}$ maintained at 92%–95%.	1. Suspected or confirmed COVID-19 infection. 2. Bilateral Infiltrates on chest X-ray SpO_2 <94% on FiO_2 40% by either venturi facemask or HFNC 3. Respiratory rate <40 breath/min. 4. Written informed consent.	1. Adult patient suffering from COVID-19 pneumonia according to the diagnostic criteria in effect at the time of inclusion or very strongly suspected. 2. Patient treated by nasal high flow therapy. 3. Moderate or severe ARDS: bilateral radiological opacities not explained entirely by effusions, atelectasis or nodules; acute hypoxaemia with worsening within the seven previous days, not entirely explained by left ventricular failure; PaO_2/FiO_2 ratio <300 mm Hg (or equivalent SpO_2/FiO_2). 4. Written informed consent in France and oral consent in Spain.
Exclusion criteria	1. Patients with a consistent SpO_2 <80% when evaluated with a FiO_2 of 0.6, or signs of respiratory fatigue (respiratory rate >40/min, partial pressure of carbon dioxide ($PaCO_2$)>50 mm Hg/pH <7.30 and obvious accessory respiratory muscle use). 2. Immediate need for intubation (PaO_2/FiO_2 <50 mm Hg or SpO_2/FiO_2 <90, unable to protect airway or mental status change). 3. Haemodynamic instability (sustained systolic blood pressure <90 mm Hg, sustained mean blood pressure below 65 mm Hg or requirement for vasopressor). 4. Unable to collaborate with HFNC/PP with agitation or refusal of HFNC/PP. 5. Chest trauma or any contraindication for PP. 6. Pneumothorax. 7. Age <18 years. 8. Pregnant. 9. Body mass index >40 kg/m^2.	1. Age <18 years. 2. Uncooperative or likely to be unable to lie on abdomen for 16 hours. 3. Vomiting or bowel obstruction. 4. Palliative care. 5. Multiorgan failure. 6. Standard contraindications to PP including the presence of an open abdominal wound, unstable pelvic fracture, spinal lesions and instability, pregnancy >20/40 gestation and brain injury without monitoring of intracranial pressure.	1. Indication for immediate tracheal intubation. 2. Significant acute progressive circulatory insufficiency. 3. Impaired consciousness, confusion and restlessness. 4. Body mass index >40 kg/m^2. 5. Chest trauma or other contraindication to PP. 6. Pneumothorax. 7. Vulnerable person: safeguard of justice, curatorship or tutorship known at inclusion. 8. Pregnant or lactating woman.

ARDS, acute respiratory distress syndrome; FiO_2, fraction of inspired oxygen; HFNC, high flow nasal cannula; PaO_2, partial pressure of oxygen; PP, prone positioning.

The following guidance is provided concerning the need for tracheal intubation to perform invasive mechanical ventilation. Intubation is recommended in case of[7]:

1. Signs of persisting or worsening respiratory failure, defined by at least two of the following criteria:
   - Respiratory rate above 40 breaths/min.
   - Lack of improvement of signs of respiratory muscle fatigue.
   - Development of copious tracheal secretions.
   - Hypercapnic respiratory acidosis with a pH below 7.25.

Table 2 Standard management in each trial

USA and Canada	Ireland	France and Spain
HFNC will be initiated at 50 L/min (AIRVO2 or Optiflow, Fisher & Paykel Healthcare Limited, Auckland, New Zealand) with temperature set at 37°C. Nasal cannula size will be determined by the patient's nostril size (≤50%). FiO_2 will be adjusted to maintain SpO_2 at 92%–95%. Flow and temperature will be adjusted based on patient's comfort and clinical response.	Control patients will receive full standard care.	HFNC adapted for an SpO_2 of 90%–95%. Except in case of poor tolerance by the patient a minimum gas flow rate of 50 L/min will be set initially. Weaning of the HFNC will first be performed reducing FiO_2 down to 0.4 before reducing the gas flow rate. In clinically stable patients with a FiO_2 less than or equal to 0.4 and a gas flow rate less than or equal to 30 L/min, an attempt will be made to switch to standard oxygen therapy at 4–6 L/min.

FiO_2, fraction of inspired oxygen; HFNC, high flow nasal cannula.

- SpO_2 below 90% at FiO_2 ≥0.8 for more than 5 min without technical dysfunction.

2. Haemodynamic instability.
3. Deterioration of neurological status.

For patients who meet the intubation criteria in the HFNC and HFNC+PP groups, a trial of NIV might be allowed according to the physician's preference in patients with signs of persisting or worsening respiratory failure and no other organ dysfunction before performing endotracheal intubation and invasive ventilation. Reasons for intubation will be recorded as well.

Strategies to improve adherence to interventions

The number of sessions and the total time spent in prone position will be collected per 24-hour period, and encouragement will be provided.

Relevant concomitant care permitted or prohibited during the trial

No prohibitions during the trial.

Provisions for post-trial care

Post-trial care will be standard care through the standard healthcare system from each country.

Outcomes

The primary outcome is therapeutic failure within 28 days of randomisation, defined as intubation (successful or attempted) or death.

Secondary outcomes

- Days spent in the ICU and in the hospital (within 28 days of randomisation).
- Mortality in the ICU and in the hospital (within 28 days of randomisation).
- Primary outcome (intubation of death) among patients receiving NIV in each randomisation groups.
- Time of escalation of therapy (in case of NIV use).
- Length of HFNC therapy use in those patients who succeeded with HFNC (efficacy).
- Length of HFNC therapy in those patients who fail with HFNC (safety).
- Ventilator-free days within the first 28 days.
- Need for rescue treatments in those patients who need to be intubated.
- Need for tracheotomy.
- Organ failure different from respiratory failure.
- Number of protocol violations.
- Time to intubation or death.
- Response to prone position: prechange and postchange of SpO_2/FiO_2 ratio, respiratory rate and ROX index ($SpO_2/(FiO_2 \times$ respiratory rate). As a practical alternative to PaO_2/FiO_2, SpO_2/FiO_2 has been shown to have a strong linear relationship in moderate to severe ARDS.[26 27]
- Duration of participation will be limited to 28 days after randomisation for each patient.
- Daily duration with PP in the first 3 days after enrolment.
- Association between time of onset and outcome.

Other measures

In the PP groups complications will be recorded; complications include skin breakdown, device removal or desaturation during position change (within 28 days of randomisation).

Plans for assessment and collection of outcomes

Protocol explanation will be provident to study sites during a dedicated online or physical meeting. Assessment and collection of outcomes will be performed by investigators, physicians, nurses and research assistants trained and used to deal with patients with hypoxaemia without additional training required. SpO_2/FiO_2 ratio assessment requires the SpO_2 to be equal of less than 97%. The primary outcome (intubation or death) is easily retrieved from patients' charts. Bedside sheets are made available to simplify data recording. Each individual study coordinator is responsible for data quality control.

Statistical methods

Sample size

We assume the primary outcome rate to be between 60% and 70% in the control group. The meta-analysis is designed to demonstrate superiority of PP over control with 90% power and a one-sided type I error rate of 2.5. For a fixed design with no interim analysis and a sample size of 836, the maximum detectable risk ratio will be between 0.847 and 0.814 (a difference of failure rates of about 11% between groups). For the same assumptions, asymmetric two-sided group sequential analysis requires a sample size of 1000, for five interim analyses (including the last analysis). Bounds were determined using a Kim-DeMets spending function with parameters 0.75 for efficacy and 3 for futility. This provides an aggressive Pocock superiority bound and a conservative O'Brien Fleming bound for futility (figure 1). Sample sizes were computed using the packages epiR and gsDesign in R software.

Randomisation

All patients who give consent for participation and who fulfil the inclusion criteria will be randomised. For each trial, a professional statistician not involved in patient recruitment will generate the allocation sequence. Participants will be randomly assigned to either control or experimental group with a 1:1 allocation as per a computer-generated randomisation schedule stratified by site and using varying block sizes. The American trial will also be stratified by ARDS severity (moderate vs severe), and French and Spanish trial will also be stratified by the therapeutic use of the PP prior to inclusion. In four trials, participants will be randomised using an online central randomisation system. In the Canadian trial, allocation concealment will be ensured using on-site sealed opaque envelopes. By the very nature of the interventions and design, trial participants, care providers, outcome assessors and data analysts could not be blinded to interventions.

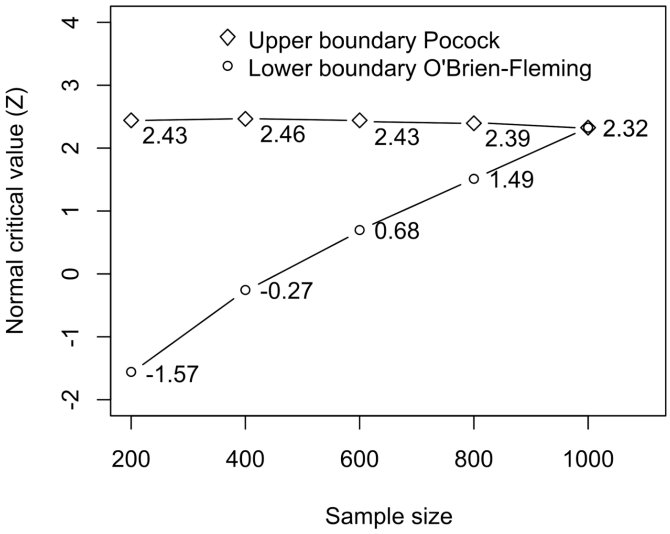

Figure 1 Efficacy and futility stopping boundaries: analyses are planned every 200 patients randomised in the various trials. The interim analyses define rules for stopping the trials early for the statistical reasons of established efficacy or futility on the primary outcome. Bounds were determined using a Kim-DeMets spending function with an aggressive Pocock superiority and a conservative O'Brien Fleming bound for futility.

Statistical methods for primary and secondary outcomes

We plan a prospective meta-analysis of individual data. Common variables from all datasets will be gathered and combined to conduct the analysis. A detailed analysis plan will be a priori defined. The primary analysis will be performed on an intent-to-treat basis. A sensitivity analysis will be performed on a per-protocol set described below. Baseline patient characteristics will be presented by country and treatment group. The comparison between intervention arms will be synthesised using mixed-effects models with a random effect on the trial: a mixed-effects logistic regression for the primary outcome and any binary outcome. A survival analysis will be performed on mortality and any other time-to-event outcome, using a gamma-frailty term on each trial in a Cox regression model providing that the assumption of proportional hazards is verified. Regarding adverse events, descriptive statistics (percentages) will be estimated. We plan to assess statistical heterogeneity between countries by visual inspection of the forest plots, which will also present per-country analyses, and by calculating the Q and I^2 statistics.

Interim analyses

We chose a Kim-DeMets alpha-spending approach[28 29] rather than other methods such as a triangular test for its simplicity of implementation and for the continuous stopping boundaries enabling to be more flexible in managing interim analysis if the design of the trial were to change as a result of an unexpected development of the epidemic.

Analyses are planned when the total number of randomised patients with the primary outcome available from the various trials reaches 200 (100 in each arm), 400 (200 in each arm), 600 (300 in each arm), 800 (400 in each arm) and 1000 the last possible analysis. The interim analyses define rules for stopping the trials early for the statistical reasons of established efficacy or futility on the primary outcome. Two professional academic statisticians will conduct all interim analyses (blind duplicates).

At each interim analysis, the Z statistics for a difference of binary endpoints is computed from the data of the two arms and is compared with the efficacy and futility bounds given in figure 1.

If the value of Z is higher than the interim analysis specific upper bound (or lower than the lower bound), the trials will be considered to be stopped for reasons of demonstrated efficacy (or futility), and data will be published as soon as possible to inform the clinical and scientific community; otherwise the trials will continue.

Methods for additional analyses (eg, subgroup analyses)

We plan to conduct a subgroup analysis on the severity of ARDS: PaO_2/FiO_2 ratio below 150 mm Hg, PaO_2/FiO_2 ratio above 150 mm Hg (or equivalent SpO_2/FiO_2 ratio). We will test if the treatment effects differ with severity of ARDS by putting their main effect and interaction terms in the logistic regression.

Adjusted analyses will be nested in the intervention group to evaluate the effect of duration of PP on the risk of intubation or death, as well as the analysis of prognostic factors associated with PP such as comorbidities, age, body mass index and so on.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

We do not expect any patient to be lost to follow-up. The only missing data could relate to patients who withdraw their consent. In this case, we will perform multiple imputations on the primary outcome. We will analyse the primary outcome using two analysis sets: the intention-to-treat set, considering all patients as randomised regardless of whether they performed the prone position, and the per-protocol analysis set. The per-protocol set will only include patients who spent at least 1 hour in prone position after randomisation without intubation or death. Patients in the intervention group who spent less than 1 hour daily in PP and patients in the control group who remained more than 1 hour at least 1 day in PP will be excluded.

ETHICS AND DISSEMINATION

Ethics and consent

Ethics approval was obtained in all five participating countries. Informed consent will be obtained according to local regulations in each trial. Local investigators will obtain either verbal or electronic consent. Documentation of consent will be either written or electronic.

Data management, transfer and deposition

The details of data management procedures can be found in the original protocols (online supplemental files). Each investigator is responsible for the confidentiality of the data collected during his or her trial. The data sets will use pseudonymised data. Interim analyses will be performed by centralising the aggregated data of the primary endpoint per trial. The confidentiality of data will be preserved when the coded, depersonalised data will be transmitted and stored at the location of the statistician in charge of the final analysis.

Steering committee

The steering committee will be responsible for reporting and interpreting the result of the interim analysis and the final analysis. The steering committee will be composed of principal investigators and statistician from all sites and may be completed by independent investigators without any competing interest. This study will be reported in accordance with the Consolidated Standards of Reporting Trials statement for non-pharmacological trials and published in peer-reviewed journals.

Dissemination strategy

The results of the study will be presented in national and international conferences and published via a peer-reviewed journal.

Data sharing statement

Deidentified data will be made available on reasonable request discussed among the steering committee.

Study status

At the time of submitting for publication, the study was collecting data.

Author affiliations
[1]Clinical Investigation Center, INSERM 1415, CHRU Tours, Tours, Centre, France
[2]Methods in Patients-Centered Outcomes and Health Research, INSERM UMR 1246, Nantes, Loire-Atlantique, France
[3]Department of Anaesthesia and Intensive Care Medicine, School of Medicine, National University of Ireland Galway, Galway, Ireland
[4]Department of Anaesthesia, University Hospital Galway, Saolta University Hospital Group, Galway, Ireland
[5]Department of Emergency Medicine, Hopital de Verdun, Montreal, Quebec, Canada
[6]Critical Care Department, Vall d'Hebron University Hospital, Vall d'Hebron Research Institute, Barcelona, Catalunya, Spain
[7]Departament de Medicina, Universitat Autònoma de Barcelona, Barcelona, Catalunya, Spain
[8]Médecin Intensive Réanimation, CIC 1415, CRICS-TriggerSEP, Centre d'étude des pathologies respiratoires, INSERM U1100, Université de Tours, CHU Tours, Tours, Centre, France
[9]Department of Cardiopulmonary Sciences, Division of Respiratory Care, Rush University, Chicago, Illinois, USA
[10]Réanimation Médicale, CHU Poitiers, Poitiers, France

Twitter David Cosgrave @drdavidc9

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ORCID iDs
Elsa Tavernier http://orcid.org/0000-0003-0798-1182
Jie Li http://orcid.org/0000-0003-0121-1291

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3. Explanations for the protocol revision from version 1

3.1 Removed outcomes

ICU-related outcomes

Overcapacity protocols were activated in some participating hospitals during the pandemic, which led to the creation of intermediate-care units, or high-dependency respiratory units, and prolonged boarding in the emergency department. Correct attribution of outcomes as occurring specifically during the ICU stay, as opposed to those high-dependency units, emergency departments, general units, etc was not obvious and could have led to incorrect interpretations, especially given the fact that the specifics of the set-up varied across participating hospitals. We therefore elected not to report any ICU-related outcomes.

Hospital mortality

We did not report in-hospital mortality within 28 days of enrollment as it appeared redundant with overall 28 mortality, which is a more patient-centered outcome.

Ventilator free days (VFD)

The ventilator-free days are a composite outcome of survival and duration of invasive mechanical ventilation, which interpretation is not straightforward, especially in a study such as the present one, which recruited non-intubated patients in whom intubation could occur at various endpoints. Moreover, in the present meta-trial, only a proportion of patients were indeed intubated. The meta-trial steering committee debated a few possible definitions of VFD that could apply to our population. While debating the "best" definition of VFD in the specific context of this meta-trial, we realized that the readers would likely have various competing definitions of VFD, just as we did. We therefore decided not to report this outcome due to its potential for confusion.

Need for rescue treatments in those patients who need to be intubated; Need for tracheotomy; Organ failure different from respiratory failure
Five countries started the meta-trial project and Mexico joined thereafter. These data were not collected prospectively in Mexico. We decided not to report these outcomes.

3.2 Added outcomes

Duration of invasive mechanical ventilation

Instead of VFD (see above), we decided to report the duration of mechanical ventilation for each group among intubated patients who survived until day 28.

Intubation rate

This outcome was missing from the first version of the protocol due to a clerical oversight.

3.3 Renamed outcomes

Length of HFNC therapy in those patients who fail HFNC (safety)

We felt that the naming of this outcome is confusing. We therefore renamed it to "time to NIV, or intubation or death".

4.1 American protocol

A Multi-Center Randomized Controlled Trial of Early Use of Prone Positioning Combined with HFNC in COVID-19 Induced Moderate to Severe Acute Respiratory Distress Syndrome

Jie Li,[1] Sara Mirza,[1] Tyler Weiss,[1] Ahmad A Elshafei,[1] Andrew Klein,[1] Amanda Miller,[1] Ramandeep Kaur,[1] Brady J. Scott,[1] Lauren J Harnois,[1] Kathleen Posa-Kearney,[2] Flor Cerda,[2] Jacob R Burd,[1] David Vines.[1]

[1] Department of Cardiopulmonary Sciences, Division of Respiratory Care, Rush University Medical Center, Chicago, IL.

[2] Nursing, ICU, Rush University Medical Center, Chicago, IL.

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1. STUDY PURPOSE:

1.1. Introduction

Acute respiratory distress syndrome (ARDS) has a high mortality of 25~40%, even with the improvement of therapies. Previous studies suggest that prone positioning (PP) can increase the average ratio of arterial oxygen tension to the fraction of inspired oxygen (PaO_2/FiO_2) by +35 mmHg, and reduce mortality in moderate to severe ARDS, especially when combined with neuromuscular blocker (NMB) and low tidal volume ventilation, which decrease the risk of ventilator induced lung injury (VILI)[1-5]. However, PP is only recommended in intubated severe ARDS with PaO_2/FiO_2<150mmHg, and the use of PP is still limited in less than 33% of severe ARDS patients[6].

From a theoretical and physiological point of view, HFNC may be beneficial in patients with ARDS. This techniques work via several mechanisms. Firstly, HFNC generates a small positive expiratory pressure. The amount of pressure generated depends on the nasal gas flow and whether the mouth is open or closed. HFNC works mainly by flushing the nasal airspaces, reducing anatomical dead space and providing a high FiO_2. Secondly, HFNC is extremely well tolerated by delivering warm and well-humidified gas through the nostrils and avoiding the discomfort associated with wearing non-invasive ventilation (NIV) masks.[7] Lastly, HFNC can provide constant F_iO_2 by avoiding air entrainment since the gas flow can be set to exceed most patient's inspiratory flow. The major goal of HFNC in treating ARDS is to achieve a sufficient level of oxygenation. However, HFNC may be viewed as a partial support therapy, but it is not totally addressing the underlying pathology of ARDS sufficiently, such as the ventilation–perfusion mismatching caused by alveolar collapse and consolidation in the dependent areas of

the lung as this disease process worsens.[8] In this regard, combination therapy such as PP with HFNC may be considered to get better physiological effects by improving ventilation-perfusion mismatch in ARDS and a better homogeneity of lung mechanics.

The early application of PP with HFNC, especially in patients with moderate ARDS and baseline SpO_2>95%, may help avoid intubation. In a preliminary study, PP was well tolerated with noninvasive respiratory supports, and the efficacy in terms of PaO_2/FiO_2 with HFNC + PP was higher than HFNC alone. Severe ARDS patients were not appropriate candidates for HFNC/NIV+PP, and a risk for delayed intubation should be noticed. A prospective RCT is warranted in the future in non-intubated moderate ARDS patients on the true benefits of PP before intubation.[9]

Coronavirus disease 2019 (COVID-19) is an emerging infectious disease that was first reported in Wuhan, China, and subsequently spread worldwide, including in the United States. Twenty-nine percent of COVID-19 patients may develop ARDS, 30% of these ARDS patients could be successfully supported with HFNC or NIV, and 60% of the ARDS patients needed intubation and invasive mechanical ventilation, or even ECMO support[10].

Based on the potential beneficial mechanisms of HFNC and PP mentioned above, early use of PP combined with HFNC to avoid the need for intubation in COVID-19 patients with moderate to severe ARDS needs to be further investigated.

1.2. Hypothesis / Key Questions

We hypothesize that early use of PP combined with HFNC can avoid the need for intubation in moderate to severe ARDS patients. The purpose of this RCT will be to evaluate the effects of PP combined with HFNC for improving oxygenation and reducing the need for intubation compared with HFNC support alone, as well as the safety of the PP therapy in non-intubated COVID-19 induced ARDS patients.

1.3. Primary Objectives

The primary outcome for the efficacy of PP combined with HFNC will be the treatment failure rate and intubation rate of HFNC or HFNC+PP support and clinical requirement for advanced respiratory support including NIV, invasive ventilation or ECMO.

1.4. Secondary Objectives

The secondary outcomes for the efficacy of PP combined with HFNC will be the improvement of SpO_2/F_IO_2 or PaO_2/FiO_2 from HFNC alone to HFNC+PP. SpO_2/F_IO_2 will be utilized to substitute PaO_2/FiO_2 as a means for evaluating oxygenation.[11-14] As a practical substitute to PaO_2/ F_IO_2, SpO_2/F_IO_2 has been shown to have a strong linear relationship in moderate to severe ARDS[14] and was recommended as a diagnostic tool for early enrollment in clinical trial.[13] F_IO_2 will be titrated to maintain SpO_2 at 90-95%. Other secondary outcomes including the time duration for PP therapy, patients' comfort with PP, PP complications including skin break down, tube/I.V. dislodgement, and the threshold of SpO_2/F_IO_2 for successful PP in COVID-19 induced ARDS cases, HFNC duration, ICU length of stay and ICU mortality rate.

2. STUDY METHODS

This is a multi-center randomized controlled trial, which will be approved by the Ethic Committees of all the participant hospitals. This trial is registered with ClinicalTrials.gov (NCT04325906).

2.1. Inclusion criteria

The diagnostic criteria for COVID-19 pneumonia will be based on the CDC guidelines. .The diagnosis of ARDS will be assigned to patients who meet the Berlin definition criteria [15]:

1) Presence of acute hypoxemic respiratory failure;

2) Acute onset within 7 days of insult, or new (within 7 days) or worsening respiratory symptoms;

3) Bilateral opacities on chest x-ray or CT not fully explained by effusions, lobar or lung collapse, or nodules;

4) Cardiac failure not the primary cause of acute respiratory failure.

Patients are categorized into 2 mutually exclusive classes of ARDS severity using previous definitions based on degree of hypoxemia:

1) Moderate: 100mmHg $\leq PaO_2/F_iO_2 <$ 200mmHg, or 140 $\leq SpO_2/F_iO_2 <$ 240;

2) Severe: $PaO_2/F_iO_2 \leq$ 100mmHg, or $SpO_2/F_iO_2 <$ 140.

COVID-19 induced adult ARDS patients admitted to the adult ICU will be enrolled when their PaO_2/FiO_2 is less than 200mmHg or $F_iO_2 \geq 0.4$ is required to maintain SpO_2 at 88–93% on HFNC treatment.

2.2. Exclusion criteria

The exclusion criterion are

1) If the patients have a consistent SpO_2<90% when on evaluation with a FiO_2 of 0.9, or signs of respiratory fatigue (RR > 40/min, $PaCO_2$> 50mmHg / pH<7.30, and obvious accessory respiratory muscle use);

2) Immediate need for intubation (PaO_2/FiO_2< 50mmHg or SpO_2/FiO_2<100, unable to protect airway or mental status change);

3) Hemodynamic instability (sustained SBP<90mmHg, sustained MBP below 65 mmHg or requirement for vasopressor);

4) Unable to collaborate with HFNC/PP with agitation or refuse HFNC/PP.

5) Chest trauma or any contraindication for PP

6) Pneumothorax

7) Age < 18 years

8) Pregnant

9) Unable to communicate

10) Severe obese (BMI ≥ 40)

11) Patient self-proned for more than an hour

12) Patient with moderate or severe ILD

13) Patient with stage IV lung cancer

14) Patient requiring long term oxygen therapy

3. PROCEDURES INVOLVED

3.1. Recruiting and consent

All patients admitted with COVID-19 will be screened and patients with ARDS who will be selected by the inclusion and exclusion criteria are included.

All participating subjects provide electronic informed consent or telephone consent before randomization.

3.2. Randomization and masking

Randomization will be stratified on ARDS severity (moderate and severe) performed by permuted block methods using Fisher and Yates tables of random permutations using a centralized interactive contact system is used for randomization. The random block length is 4, and random numbers are generated by computer. All of the centers participating in this study are

immediately put in contact with the central unit (Rush University Medical Center) to obtain a randomization number if a patient fulfills the inclusion criteria. Within 6 hr of fulfilling inclusion criteria, a patient will be randomly allocated either to the prone positioning group or the control group (HFNC alone with no prone positioning therapy).

3.3. Blinding and Quality Control

The trial will be overseen by a steering committee, and data quality control will be completed by independent data monitoring board. Clinicians and epidemiologists of above organization are not members of participating in our research group. Research coordinator will timely verify database and regularly monitored all the centers on site to ensure the accuracy of the data recorded. An investigator at each center is responsible for enrolling patients in the study, ensuring adherence to the protocol, and completing the electronic case-report form. Although the individual study assignments of the patients could not be blinded, the coordinating center and all the investigators will remain unaware of the study group outcomes until the data are unlocked. All the analyses are performed by the study statistician not involved in study recruitment, and blind of randomization group until database lock.

3.4. Prone positioning implementation

PP will be performed before or 1 hour after meal. Before PP, all the I.V. lines and nasal cannula will be checked by clinicians. PP will be performed by patient under the supervision of clinicians. Assistance will be offered if needed. If tolerated, PP will be maintained for at least 30

minutes, until the patients feel tired to keep that position. PP will be performed minimum twice a day for the first 3 days after the patient's enrollment. Patients will be informed to maintain prone position as long as they can. F_iO_2 will be adjusted to maintain SpO_2 at 92-95%.

Protocol for sedation and comfort evaluation during PP: No sedation will be used during the PP. The patients are monitored by bedside respiratory therapist and nurses for their comfort and tolerance for the PP at 5mins, 30 minutes after PP for the first PP in each day.

3.5. HFNC treatment

HFNC will be initiated at 50 L/min (AIRVO2 or Optiflow, Fisher &Paykel Health care Limited., Auckland, New Zealand) with temperature set at 37 °C. Nasal cannula size should be ≤ 50% of the patient's nostril size. F_iO_2 will be adjusted to maintain SpO_2 at 90% to 95%. Flow and temperature will be adjusted based on patient's comfort and clinical response. Patients' vital signs, SpO_2, oxygen device and F_iO_2 before HFNC will be recorded, Patients' vital signs, SpO_2, HFNC flow and F_iO_2 at 30 mins, and 2 hour of HFNC will also be recorded for both groups. HFNC will be continuously delivered after enrollment in the study for ≥16 hours a day in the first 3 days. Patient comfort to HFNC, will be assessed by means of a scale used and validated in previous studies that is defined as follows: 1, bad; 2, poor; 3, sufficient; 4, good; 5, very good. Patients' vital signs, SpO_2, HFNC flow and F_iO_2, as well as patient comfort will be documented every 4-6 hours. In order to prevent virus transmission, all the patients with HFNC treatments will wear a surgical mask over the face. [16]

3.6. Withdraw criteria

1) Patients cannot tolerate HFNC or prone position for 30 mins

2) Patients experience any side effects during prone position, including vomit, dizzy, hypotension, etc.

3.7 Weaning criteria

1) Patients' PaO_2/F_1O_2 > 300mmHg, or SpO_2/F_1O_2 > 340

3.8 Treatment Failure Criteria

Failure criteria: treatment failure is defined as one of the following criteria [17]:

(1) Signs of persisting or worsening respiratory failure, defined by at least two of the following criteria:

- Respiratory rate above 40 cycles/min

-Lack of improvement of signs of respiratory-muscle fatigue

-Development of copious tracheal secretions

-Respiratory acidosis with a pH below 7.35

-SpO_2 below 90% at $F_1O_2 \geq 0.8$ for more than 5 min without technical dysfunction

(2) Hemodynamic instability defined by a SBP below 90 mmHg, MBP below 65 mmHg or requirement for vasopressor;

(3) Deterioration of neurologic status (with a Glasgow coma scale below 12 points).

For patients who meet the failure criteria in the HFNC and HFNC+PP groups, a trial of NIV might be allowed according to the physician's preference in patients with signs of persisting or worsening respiratory failure and no other organ dysfunction before performing endotracheal intubation and invasive ventilation. Reasons for intubation will be recorded as well.

3.8 Primary endpoint

28 days after randomization. If patient is discharged earlier before 28 days of enrollment, a follow-up phone call will be made to record patient's status (alive or decease or intubation) at 28 days of enrollment.

3.9 Comprehensive therapy

The treatment of COVID-19 is followed by the CDC protocol. Comprehensive therapy is provided by the ICU attending physicians based on published ARDS guidelines. Antivirus treatment and the use of steroids will be recorded as well.

4. CHARACTERISTICS OF DATA/SPECIMENS TO BE ANALYZED

4.1. Data collection

The following information of all patients is collected in a data file: patients' characteristics, including age, gender, medical history, diagnosis for COVID-19, the laboratory and microbiology findings, treatment and outcome. Complications including skin breakdown, IV line or nasal cannula dislodgement or desaturation during position change. The respiratory assessments before, during the treatments of HFNC or HFNC with prone position.

4.2. Statistical analysis

Definition of the two groups: The patients who receive the prone positioning are classified as prone positioning group. The patients who receive HFNC alone are classified as HFNC group.

Comparisons between the two groups: Quantitative continuous variables are given as either means (±SDs) or medians (with inter-quartile ranges) are compared using the unpaired Student's t test or the Mann-Whitney test. Qualitative or categorical variables are compared with the chi-square test or the Fisher's exact test. ANOVA for paired tests to compare the same variables collected at different time points are used. The cumulative probability of remaining on spontaneous breathing are compared with the Kaplan-Meier estimate of survival and the log-rank test to compare the two groups. Univariate and multivariate analyses of risk factors for PP failure are performed with logistic regression. All analyses are in intention to treat, and the level of significance is set at 0.05.

4.3. Sample size calculation

Sample size estimation: Base on the intubation rate for COVID-19 induced ARDS patients reported in previous studies from 40% to 77% [18-20], we estimate at least a total of 346 subjects with an expected intubation rate of 60% in the moderate to severe ARDS patients with HFNC support,

and of 45% [80% * (1-0.25)=45%, a 25% reduction] in the PP patients in our cases, with a confidence level (1-α)=95% and power level(1- β)=80%.

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4.2 Canadian protocol

A Multi-Center Randomized Controlled Trial of Early Use of Prone Positioning Combined with HFNO in severe COVID-19 Pneumonia

By: Ivan Pavlov, Patrice Plamondon

Version: 2020-06-30

1.1. Introduction

COVID-19 is a novel and evolving disease. No firm estimates of case fatality rates are available right now; published estimates vary from 1.38% (Verity, 2020) to 3.8% (Report of the WHO–China Joint Mission on coronavirus disease 2019 2020). In patients with severe disease, who require hospitalization, mortality rates of up to 28% have been described (Zhou, 2020); mortality in patients treated with mechanical ventilation can be inferred ≥ 40% from published data (Yang, 2020).

High flow nasal oxygen systems (HFNO) provide oxygen-rich heated humidified gas to the patient nose at flow levels sufficient to deliver a constant, precisely set high FiO2. HFNO reduces dead space, provides low levels of PEEP, and decreases breathing frequency and work of breathing (Nishimura, 2016; Baker, 2019). In hypoxemic respiratory failure, HFNO use was associated with lower mortality, lower rates on endotracheal intubation, and improved oxygenation (Frat, 2015; Rochwerg, 2019; Li, 2020).

Prone positioning of mechanically ventilated patients is an effective first-line intervention to treat moderate-severe acute respiratory distress syndrome (ARDS) patients receiving invasive

mechanical ventilation, as it improves gas exchanges and lowers mortality (Guérin, 2013; Scholten, 2016; Guérin, 2018). There is limited evidence in favour of awake prone positioning of patients treated with HFNO. In a small recent study, prone positioning was well tolerated with HFNO by patients with pneumonia mainly due to influenza, and the efficacy in terms of PaO2/ FiO2 with HFNO + prone positioning was higher than HFNO alone (Ding, 2020). In a retrospective study of 610 patients from China (Sun, 2020), a multi-pronged intervention that included early, and aggressive, use of high-flow nasal cannula (HFNO), and proning of awake patients resulted in lower overall mortality (3.33%, as compared 4.34% in a nearby province), very low percentage of patients requiring mechanical ventilation (<1%, as compared to the national average of 2.3 (Guan, 2020), in a population that included 10% of critically-ill patients. The authors highlight that mortality was lower than in a previously reported cohort study of ARDS patients performed at the same institution prior to the pandemic (Liu, 2018), although is not clear if the two populations were comparable in terms of disease severity.

Based on the potential beneficial mechanisms of HFNO and PP mentioned above, early use of PP combined with HFNO to avoid the need for intubation in COVID-19 patients with moderate to severe ARDS needs to be further investigated.

1.2. Hypothesis / Key Questions

We hypothesize that early use of PP combined with HFNO can avoid the need for intubation in severe COVID-19 pneumonia. The purpose of this RCT will be to evaluate the effects of PP combined with HFNO for improving oxygenation and reducing the need for intubation compared

with HFNO support alone, as well as the safety of the PP therapy in non-intubated COVID-19 patients.

1.3. Primary Objectives

The primary outcome for the efficacy of PP combined with HFNO will be the treatment failure rate at 28 days, defined as a combination of (1) death, (2) intubation.

1.4. Secondary Objectives

The secondary outcomes for the efficacy of PP combined with HFNO will be the improvement of SpO_2/F_IO_2 or PaO_2/FiO_2 from HFNO alone to HFNO+PP. SpO_2/F_IO_2 will be utilized to substitute PaO_2/FiO_2 as a means for evaluating oxygenation (Rice, 2007; Chen, 2015). As a practical substitute to PaO_2/ F_IO_2, SpO_2/F_IO_2 has been shown to have a strong linear relationship in moderate to severe ARDS (Rice, 2007). F_IO_2 will be titrated to maintain SpO_2 at 90-94%.

Other secondary outcomes including the time duration for PP therapy, PP complications including skin break down, tube/I.V. dislodgement, and the threshold of SpO_2/F_IO_2 for successful PP in severe COVID-19 cases, HFNO duration, ICU length of stay and hospital length of stay, mortality at 28d.

Subgroup analyses according to the severity of hypoxemia, will also be performed (two subgroups: $SpO_2/F_IO_2 < 190$ and $SpO_2/F_IO_2 \geq 190$, which corresponds to the usual threshold for moderate-severe ARDS).

2. STUDY METHODS

This is a multi-center randomized controlled trial, which has been approved by Ethics Committee of CIUSSS-Centre-Sud-de-l'Île-de-Montréal for all participating hospitals in Québec. Hospitals outside Québec, if any, will pursue their own local IRB approval.

2.1. Inclusion criteria

1. COVID-19, either microbiologically confirmed, or clinically suspected and pending confirmation
2. Lung infiltrates documented on any imaging modality (POC-US, RXP, CT-scan)
3. Respiratory distress that requires support with HFNO in treating physician judgment. At Verdun Hospital, the usual criteria for HNFO initiation are : (1) SpO2<94 with on 4L/min O2 via conventional nasal cannula, OR (2) RR > 26 despite O2 supplementation at 4L/min. These criteria may be adjusted according to local custom.

2.2. Exclusion criteria

The exclusion criteria are

1) Consistent SpO_2<80% with a FiO_2 of 0.8, or signs of respiratory fatigue (RR > 40/min, $PaCO_2$> 50mmHg / pH<7.30, and obvious accessory respiratory muscle use);

2) Immediate need for intubation (PaO_2/FiO_2< 50mmHg or SpO_2/FiO_2 <90, unable to protect airway or mental status change);

3) Hemodynamic instability that requires vasopressor support

4) Unable to collaborate with HFNO/PP

5) Chest trauma or any contraindication for PP

6) Pneumothorax

7) Age < 18 years

8) Pregnancy

9) Unable to consent.

10) severe obesity (BMI > 40) that precludes PP

11) End-of-live care

3. PROCEDURES INVOLVED

3.1. Recruiting and consent

All patients admitted with severe COVID-19 that requires treatment with HFNO will be screened for inclusion and all consenting patients fulfilling the inclusion and exclusion criteria will be included.

All participating subjects provide verbal informed consent before randomization. Due to infection control practices, written consent will be recorded by research assistant or respiratory therapist, after verbal discussion with the patient.

3.2. Randomization and masking

A randomized sequence will be generated for each participating hospital. Sealed envelopes contained the allocation will be provided to each hospital. The sequence will be generated in R, using a random block allocation, with variable block size.

3.3. Blinding and Quality Control

The trial will be overseen by the PI and the research coordinator. Local PIs at each participating center are responsible for enrolling patients in the study, ensuring adherence to the protocol, and completing the case-report form. Although the individual study assignments of the pa-

tients could not be blinded, the coordinating center and all the investigators will remain unaware of the study group outcomes until the data are unlocked. All the analyses are performed by the study statistician not involved in study recruitment, and blind of randomization group until database lock.

3.4. Prone positioning implementation

PP will be performed before or 1 hour after meal. Before PP, all the I.V. lines and nasal cannula will be checked by clinicians. PP will be performed by patient under the supervision of clinicians. Assistance will be offered if needed. If tolerated, PP will be maintained for at least 30 minutes, until the patients feel tired to keep that position. PP will be performed minimum twice a day for the first 3 days after the patient's enrolment. Patients will be informed to maintain prone position as long as they can. F_IO_2 will be adjusted to maintain SpO_2 at 90-94%. PP is not protocolized once the patient has been weaned off HFNC.

No sedation will be used during the PP. The patients will be monitored by bedside respiratory therapist and nurses for their comfort and tolerance for the PP at 5mins, 30 minutes after PP for the first PP session, and at least once for each subsequent session.

3.5. HFNO treatment

HFNO will be initiated at 50 L/min (AIRVO2 or Optiflow, Fisher &Paykel Health care Limited., Auckland, New Zealand) with temperature set at 37 ^{o}C. Nasal cannula size should be ≤ 50% of the patient's nostril size. F_IO_2 will be adjusted to maintain SpO_2 at 90% to 94%. Flow and temperature will be adjusted based on patient's comfort and clinical response. Patients' vital signs, SpO_2, oxygen device and F_IO_2 before HFNO will be recorded, Patients' vital signs, SpO_2, HFNO flow and F_IO_2 at 30 mins, and 2 hour of HFNO will also be recorded for both groups. HFNO will be continuously delivered after enrolment in the study until weaning. The precise criteria for weaning are at the discretion of the treating physician and local protocols.. Patients' vital signs, SpO_2, HFNO flow and F_IO_2, as well as patient comfort will be documented at least every 6 hours. In order to prevent virus transmission, all the patients with HFNO treatments will wear a surgical mask over the face (Whittle, 2020).

3.6. Withdrawal criteria

1) Patients cannot tolerate HFNO or prone position for >30 mins

2) Patients experience any significant side effects during prone position

3.7 Suggested HFNC weaning criteria

HFNO may be weaned once the following settings are maintained for at least 4 hours: F_IO_2<35% and normal work of breathing. Local variations are allowed.

3.8 Primary endpoint

28 days after randomization.

4. CHARACTERISTICS OF DATA/SPECIMENS TO BE ANALYZED

4.1. Data collection

The following information of all patients is collected in a data file: patients' characteristics, including age, gender, medical history, diagnosis for COVID-19, the laboratory and microbiology findings, treatment and outcome. Complications including skin breakdown, IV line or nasal cannula dislodgement or desaturation during position change. The respiratory assessments before, during the treatments of HFNO or HFNO with prone position. See enclosed case report form.

4.2. Statistical analysis

Definition of the two groups: The patients who receive the prone positioning are classified as prone positioning group. The patients who receive HFNO alone are classified as HFNO group.

Comparisons between the two groups: Quantitative continuous variables are given as either means (±SDs) or medians (with inter-quartile ranges) are compared using the unpaired Student's t test or the Mann-Whitney test. Qualitative or categorical variables are compared with the chi-square test or the Fisher's exact test. ANOVA for paired tests to compare the same variables col-

lected at different time points are used. The cumulative probability of remaining on spontaneous breathing are compared with the Kaplan-Meier estimate of survival and the log-rank test to compare the two groups. Univariate and multivariate analyses of risk factors for PP failure are performed with logistic regression. All analyses are in intention to treat, and the level of significance is set at 0.05.

4.3. Sample size calculation

Sample size estimation: Base on the intubation rate for COVID-19 induced ARDS patients reported in previous studies from 40% to 77% (Yang 2020; Wang 2020; Wu 2020), we estimate at least a total of 346 subjects with an expected intubation rate of 60% in the moderate to severe ARDS patients with HFNO support, and of 45% [80% * (1-0.25)=45%, a 25% reduction] in the PP patients in our cases, with a confidence level (1-α)=95% and power level(1- β)=80%.

5. Participating centres

The list of participating centres and local PIs will be updated on the ClinicalTrials.gov record dedicated to the trial: https://clinicaltrials.gov/ct2/show/NCT04395144

6. ACKNOWLEDGMENTS

This protocol borrows heavily from the Rush University and CHRU Tours study protocols.

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4.3 French protocol

SPONSOR	Tours Regional University H 2 Boulevard Tonnellé 37044 Tours cedex 9
Non-health product clinical trial protocol **RIPH I**	
IDRCB (French Health Authority biomedical research) number	2020-A01121-38
STUDY CODE	DR200125
FULL TITLE	Evaluation of prone positioning in conscious patients undergoing high-flox nasal oxygen therapy in the context of acute respiratory distress syndrome induced by COVID-19 disease
ACRONYM	HIGH-PRONE-COVID-19
COORDINATING INVESTIGATOR	Prof. Stephan Ehrmann Intensive Care Medicine, Tours Regional University Hospital
SCIENTIFIC COORDINATOR	Dr. Yonatan Perez Independent intensivist
PROTOCOL VERSION	3
PROTOCOL DATE	03/11/2020
ANSM	File reference: HPSAEC1-2020-04-00003 Authorisation date: 20/04/2020
CPP	Committee: CPP SUD MEDITERRANEE III File reference (IS): 20.04.16.89134 Notice date: 23/04/2020
CNIL	Commitment to the MR-001 Reference Methodology by the Sponsor

SUBSTANTIAL CHANGES (SCs)

Version number (after SC)	**Date**	**Rationale for the SC**
Version 2	21/07/2020	Added secondary endpoints Details of a non-inclusion criterion 12-month study extension Change of investigator for the Brest University Hospital Added new centres
Version 3	03/11/2020	Increased the number of subjects Change of investigator at the Tours and Bordeaux centres Added new centres

PROJECT TEAM

Coordinating investigator: Prof. Stephan Ehrmann Intensive Care Medicine, Tours Regional University Hospital 2, Boulevard Tonnellé 37044 TOURS Cedex 9 Tel.: +33(0)2 47 47 38 55 Email: s.ehrmann@chu-tours.fr	**Scientific coordinator:** Dr. Yonatan Perez Independent intensivist Email: yonatperez@gmail.com
Sponsor: Tours Regional University Hospital 2, Boulevard Tonnellé 37044 TOURS Cedex 9 Mr Julien Le Bonniec Director of Research and Innovation Tel.: +33(0)2 18 37 08 01 EMail: recherche.clinique@chu-tours.fr	**Methodology, biostatistics and data management and health economics** Biometrics component, INSERM CIC-P 1415, Tours Regional University Hospital Manager: Prof. Bruno Giraudeau Methodologist: Dr Elsa Tavernier Tel.: +33(0)2 47 47 47 11 Email: elsa.tavernier@univ-tours.fr Health economics: *not applicable*
Coordination and monitoring Promotion and Quality Control team, Tours Regional University Hospital Manager: Mohamed Ait Amer Meziane Tel.: +33(0)2 47 47 70 07 Email: M.AITAMERMEZIANE@chu-tours.fr	**Vigilance** Biomedical Research Vigilance Unit, Tours Regional University Hospital Manager: Prof. Annie-Pierre Jonville-Bera Vigilance officer: Marie-Sara Agier Tel.: +33(0)2 47 47 80 37 Email: uvrb@chu-tours.fr
Scientific committee: Stephan Ehrmann, Intensive Care Medicine & Resuscitation, Tours Regional University Hospital, France Jie Li, Rush University Medical Center, Cardiopulmonary Sciences, Division of Respiratory Care, Chicago, USA Yonatan Perez, independent intensivist, France Jean-Pierre Frat, Medical Intensive Care Unit, Poitiers University Hospital, France Elsa Tavernier, CIC-P 1415, Tours Regional University Hospital, France	**Partner:** Fisher & Paykel Healthcare SAS. 10, Avenue du Québec - Bâtiment F5 BP 512 Villebon-Sur-Yvette 91946 Courtaboeuf CEDEX, France

Study title

Evaluation of prone positioning in conscious patients undergoing high-flox nasal oxygen therapy in the context of acute respiratory distress syndrome induced by COVID-19 disease (*HIGH-PRONE-COVID-19)*

Sponsor

Tours Regional University Hospital
2, Boulevard Tonnellé 37044 TOURS Cedex 9

Tours,
Sponsor's signature

Julien Le Bonniec
Director of Research and Innovation

Coordinating investigator

Prof. Stephan Ehrmann
Intensive Care Medicine, Tours Regional University Hospital

Tours,
Coordinator's signature

Prof. Stephan Ehrmann

ABSTRACT

TITLE	Evaluation of prone positioning in conscious patients undergoing high-flow nasal oxygen therapy in the context of acute respiratory distress syndrome induced by COVID-19 disease
SPONSOR	TOURS REGIONAL UNIVERSITY HOSPITAL
COORDINATING INVESTIGATOR	Prof. Stephan Ehrmann Intensive Care Medicine, Tours Regional University Hospital
BACKGROUND / RATIONALE	Acute Respiratory Distress Syndrome (ARDS) induces high mortality, particularly in the context of COVID-19 disease. In patients with ARDS, invasively mechanically ventilated through a tracheal tube, prone positionning significantly reduced mortality. Moreover, the implementation of high-flow nasal cannula therapy, a non-invasive respiratory assistance and oxygenation technique, reduced the use of tracheal intubation and reduced mortality in the most severe patients with hypoxic acute respiratory failure. High-flow nasal cannula treatment is a therapeutic modality adopted by international guidelines for the management of COVID-19 patients (Alhazzani 2020). In a pilot study of 20 patients with ARDS, positioning patients receiving nasal high flow treatment in the prone position was found to be feasible and associated with an increase in the PaO_2/FiO_2 ratio. Preliminary data from patients with ARDS-related COVID-19 appear to show significant efficacy of prone positionning in intubated patients in terms of oxygenation as well as high-flow nasal cannula therapy before intubation. Thus, nearly half of the critically ill patients described in the original cohort of Wuhan City, Hubei Province in China had received high-flow nasal cannula therapy; high-flow nasal cannula therapy combined with prone positionning has been incorporated into the care protocols of some Chinese hospitals. We hypothesise that the combined application of high-flow nasal cannula therapy and prone positionning significantly improves the

	fate of patients with COVID-19 by reducing the use of tracheal intubation and associated therapies such as sedation and muscle relaxants administration, resulting in both individual and collective benefit in terms of critical care resource use. This is a completely original approach to ventilatory care, as prone positioning has not been tested on a large scale and is particularly well-suited to the COVID context given the constraints on ventilators.
PRIMARY OBJECTIVE	To evaluate the clinical benefit of prone positioning in patients with COVID-19 and treated with high-flow nasal cannula therapy in terms of reducing the use of heavier oxygenation techniques and reducing mortality.
SECONDARY OBJECTIVES	To evaluate efficacy in terms of oxygenation, progression of pneumonia and patient outcome. To evaluate feasibility and safety in terms of patient comfort and occurrence of complications.
STUDY OUTLINE	Multi-centre randomised controlled open-label trial conducted in 2 parallel groups.
PRIMARY ENDPOINT	Therapeutic failure within 14 days of randomisation: death or intubation or use of non-invasive ventilation with two pressure levels.
SECONDARY ENDPOINTS	- Therapeutic failure within 28 days of randomisation: death or intubation or use of non-invasive ventilation with two pressure levels. - Time to intubation or death - Time to onset of treatment escalation (in case of use of non-invasive ventilation with two pressure levels) - Progression of oxygenation over the 14 days following randomisation (PaO2/FiO2 ratio, SpO2 (pulse oximetry with SpO2 ≤97%)/FiO2 and ROX index) - Progression of the SpO2/FiO2 ratio (SpO2 ≤97%) and of the ROX index during the first proning session - Progression of the WHO COVID disease severity score - Patient comfort before, during and after the first proning session - Occurrence of skin lesions on the anterior surface of the body

	- Displacement of intravascular devices during turnovers - Duration of use of high-flow nasal cannula therapy in the general population, in both non-intubated and intubated patients - Length of stay in intensive care and hospital - Mortality in intensive care and in hospital - Number of days living without ventilation in the 28 days following randomisation
PARTICIPANTS	<u>Inclusion criteria:</u> - Adult patient known to be or very strongly suspected of suffering from COVID-19 pneumonia according to the diagnostic criteria in force at the time of inclusion - Patient treated with high-flow nasal cannula therapy - Mild, moderate or severe ARDS: bilateral radiological opacities not fully explained by effusions, atelectasis or nodules; acute hypoxaemia with deterioration in the previous 7 days, not fully explained by left ventricular failure; PaO_2/FiO_2 ratio <300 mmHg (or equivalent SpO_2/FiO_2 ($SpO2 \leq 97\%$)) - Beneficiary of or affiliated to a social security scheme - Informed consent <u>Non-inclusion criteria:</u> - Indication of immediate tracheal intubation - Significant progressive acute circulatory compromise - Impaired alertness, confusion, agitation - Body mass index> 40 kg/m^2 - Chest trauma or other contraindication to prone position - Pneumothorax with single anterior chest drain and persistent bubbling - Vulnerable person: known legal guardianship, curatorship or tutorship at inclusion - Pregnant or breast-feeding women
INTERVENTION	<u>Experimental group:</u> - High-flow nasal cannula treatment adapted for 90-95% SpO_2 <u>- Proning:</u> depending on the patient's tolerance, the objective is to

	spend as much time as possible, up to 16h and beyond, in prone position per 24-hour period. At least two sessions of at least 30 minutes each must be performed daily. - Usual care otherwise
	<u>Control group:</u> - High-flow nasal cannula treatment adapted for 90-95% SpO_2 - Usual care otherwise
COURSE OF THE STUDY	Screening of all patients with confirmed or suspected COVID and undergoing oxygen therapy ≥4 L/min D1: inclusion visit and randomization Initiation of randomization arm therapies within 6 hours of inclusion D1-Dx: implementation visits D14: primary endpoint evaluation D28/discharge from hospital: last follow-up
RANDOMISATION AND BLINDING	Individual randomization after inclusion of the patient, secure centralised computer system. Open-label study as blinding was not possible.
NUMBER OF SUBJECTS	404 patients, i.e. 202 per group.
STUDY DURATION	19 months: 18 months of recruitment and 1 month of follow-up.
FEASIBILITY	Several preliminary studies have validated the feasibility of placing awake patients in the prone position with high-flow nasal cannula therapy. All of the centres possess significant expertise in the prone positioning technique for patients under invasive mechanical ventilation. In the interventional group, the planned duration of proning sessions allows a wide adaptation according to the patient's tolerance and team availability for maximum feasibility.
EXPECTED BENEFITS	Emergency implementation of this research protocol is likely to bring immediate individual and collective benefits in the face of the global COVID-19 pandemic. The implementation of optimised non-invasive ventilation support by combining the expected benefits of high-flow nasal cannula therapy and prone decubitus is likely to reduce the need for tracheal intubation and mechanical ventilation. This would help ease the tension on the availability of intensive care ventilators. As non-

	invasive management does not require the use of sedative and muscle relaxant drugs, it would also help to alleviate the supply tensions for these drugs. Finally, if it could reduce the length of stay in intensive care, an increase in the supply of intensive care unit beds, also under pressure, would be appreciable.

LIST OF ABBREVIATIONS

ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé (French National Agency for Medicines and Health Products)
CRA	Clinical Research Associate
GCP	Good Clinical Practice
CNIL	Commission Nationale de l'Informatique et des Libertés (French National Commission for Information Technology and Civil Liberties).
CPP	Committee for the Protection of Persons (Institutional review board)
CRF	Case Report Form
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
ICH	International Conference on Harmonization
SRN	State Registered Nurse
INSERM	Institut National de la Santé et de la Recherche Médicale (National Institute for Health and Medical Research)
RM	Reference Methodology
IHP	In-House Pharmacy
GDPR	General Data Protection Regulation
SUSAR	Suspected Unexpected Serious Adverse Reaction
CRT	Clinical Research Technician

CONTENTS

1. Background and rationale

1.1. Background

Acute Respiratory Distress Syndrome (ARDS) induces high mortality, particularly in the context of COVID-19 disease. In patients with ARDS, invasively mechanically ventilated via a tracheal tube and exhibiting a PaO_2/FiO_2 (arterial oxygen partial pressure to inspired oxygen fraction) ratio of less than 150 mmHg, the prone position has been shown to significantly reduce mortality (Guérin 2013).

Moreover, the implementation of high-flow nasal cannula therapy, a non-invasive respiratory assistance and oxygenation technique, has reduced the use of intubation and has reduced mortality in the most severe patients (PaO_2/FiO_{ratio2} ratio less than 200 mmHg) with hypoxic acute respiratory failure (Frat 2015).

Proning patients with ARDS and treated with high-flow nasal cannula therapy was evaluated in 20 patients suffering primarily from viral pneumonia (Ding 2020). Proning was found to be feasible and associated with an increase in the PaO_2/FiO_2 ratio.

Preliminary data from patients with ARDS-related COVID-19 appear to show significant efficacy of prone positioning in intubated patients in terms of oxygenation as well as high-flow nasal cannula therapy before intubation. Thus, nearly half of the critically ill patients described in the original cohort of Wuhan City, Hubei Province, China, had received high-flow nasal cannula therapy (Huang 2020, Yang 2020). It should be noted that in the secondarily affected province of Jiangsu, high-flow nasal cannula therapy combined with prone positioning has been successfully incorporated into care protocols (Sun 2020).

Several potential mechanisms suggest a benefit from early prone positioning of conscious patients under high-flow nasal cannula therapy. First, the improvement in oxygenation observed in many patients can be mediated by two complementary mechanisms: pulmonary vascular redistribution of pulmonary arterial cardiac output and alveolar recruitment of hypoventilated dependent areas. The first mechanism may be predominant in patients with COVID-19, but in all cases, prone positioning is a simple non-pharmacological means of improving ventilation/perfusion ratios (Gattinoni 2020). Improved ventilation/perfusion ratios due to greater efficiency of the pulmonary exchanger may reduce patients' respiratory work and potentially the associated ventilation control. Thus, in conscious patients with high respiratory control causing

significant pulmonary mechanical stress (tidal volume and high respiratory rate), potentially causing so-called "patient self-inflicted lung injury" (PSILI), prone positioning is likely to reduce lung stress. Moreover, similar to what is observed during prone positioning of intubated patients, a homogenisation of pleural pressure gradients is expected, also resulting in a reduction in pulmonary shear stresses.

Prone positioning implementation in awake patients allows to consider all the benefits associated with this technique, without the disadvantages of tracheal intubation, sedation or even neuromuscular paralysis.

We hypothesise that the combined application of high-flow nasal cannula therapy and prone positioning significantly improves the outcome of patients with COVID-19 by reducing the use of tracheal intubation and associated therapies such as sedation and muscle relaxants administration, resulting in both individual and collective benefit in terms of the mobilisation of critical care resources.

The approach is completely novel given the lack of large-scale data on prone positioning during high-flow nasal cannula therapy and is particularly suited to the context of the COVID epidemic given the pressure on critical care beds and ventilators.

1.2. Risk/benefit balance

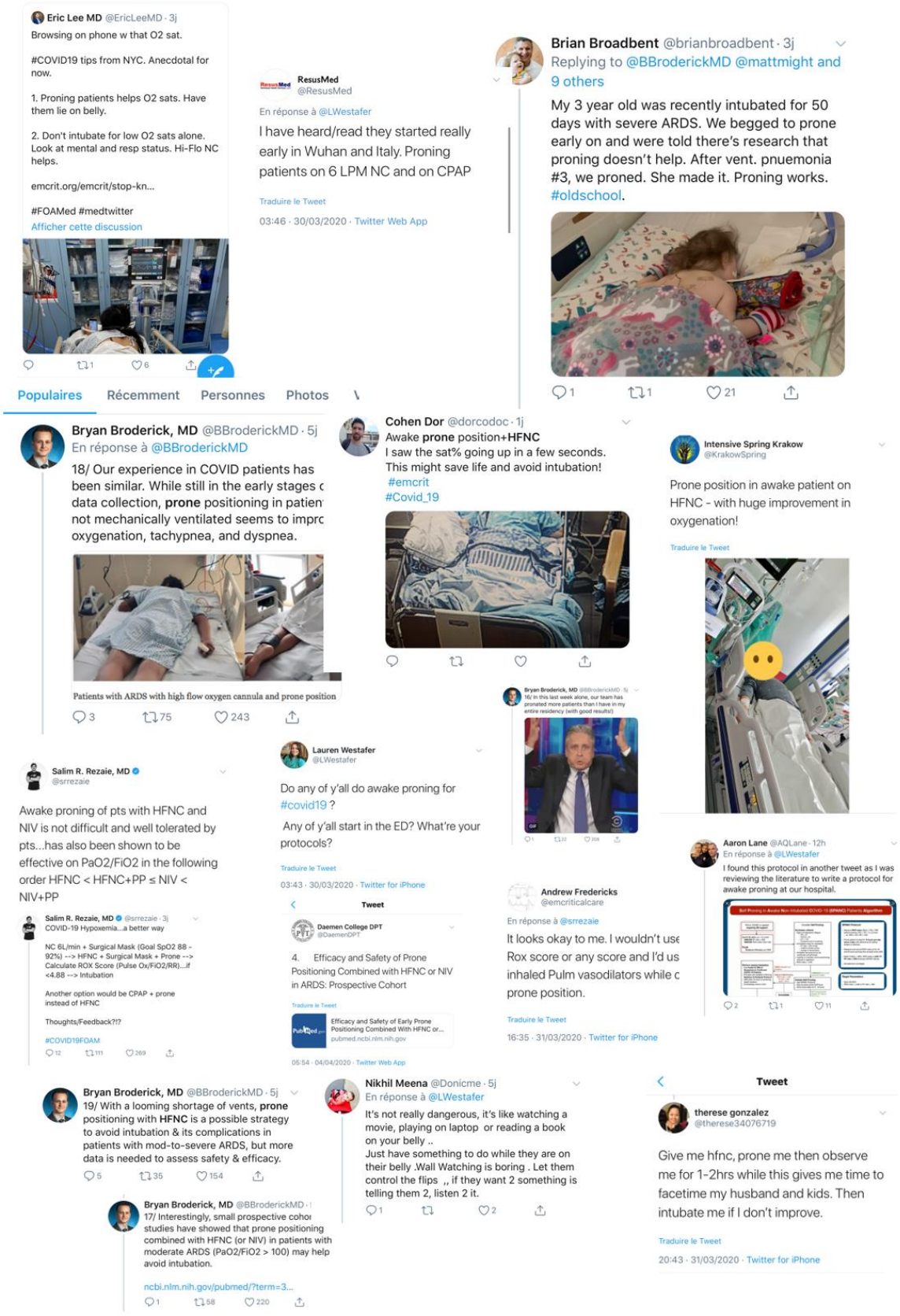
Potential individual benefits:

The primary expected benefit of prone positioning at the individual level is better patient oxygenation to, if the hypotheses underlying this study are confirmed, avoid tracheal intubation and the use of mechanical ventilation and associated sedation techniques. A potential reduction in the length of stay in intensive care and in the hospital is therefore considered.

It should be noted that in the context of the global COVID-19 pandemic, many clinicians are reporting on social networks the practice of prone positioning patients on high-flow nasal cannula therapy outside of any formal assessments (Figure 1).

These accounts, outside the scientific field, are certainly affected by a major selection bias and do not evaluate or report the potential risks associated with the technique. Nevertheless, they constitute testimonies on the potential feasibility and the benefit that some patients seem to derive from the technique. They call for the implementation of a rigorous scientific evaluation of awake prone positioning.

Figure 1: *Excerpts from social networks illustrating the worldwide craze for prone positioning in patients on high-flow nasal cannula therapy, in the absence of formal evaluation through a clinical trial*



Potential collective benefits:

The potential collective benefits of this project are major. Indeed, in the advent that the hypotheses underlying this work would prove to be confirmed, the development of high-flow nasal cannula therapy in prone position would make it possible to avoid the use of tracheal intubation for a large number of patients and would thus mechanically reduce the strain on critical care ventilator needs. Indeed, high-flow nasal cannula therapy in prone position can be administered without the use of a heavy critical care ventilator, whose numbers must be reserved for the most serious patients invasively ventilated through a tracheal tube. The reduction in the length of stay in intensive care and in the hospital would also constitute a major collective benefit during the COVID-19 pandemic: as admission capacities in intensive cares are saturated in several countries, any reduction in length of stay, however modest, would free up a place for new patients.

Potential individual risks:

At the individual level, two main risks can be identified: the possible complications of tracheal intubation in patients in treatment failure and the specific complications associated with prone positioning in patients receiving high-flow nasal cannula therapy.

For patients in treatment failure, despite high-flow nasal cannula therapy and prone positioning, the intubation procedure will be a period at high risk of complication. It should nevertheless be noted that tracheal intubation in intensive care is always a risky situation and that some studies have shown a lower incidence of serious complications (death, cardiac arrest, desaturation below 80%) in the event of pre-oxygenation with the use of high-flow nasal cannula therapy prior to intubation (Guitton 2019). The study will be conducted under conditions allowing immediate use of all the equipment and skills necessary for emergency tracheal intubation in patients who require it. Moreover, the implementation of objective intubation criteria within the protocol makes it possible to avoid any delay in intubation which could be deleterious for the patient.

Complications associated with the prone positiong technique during high-flow nasal cannula therapy are expected to be less than among intubated patients. Indeed, musculocutaneous complications (stiffness, pressure sores), largely favoured by the sedation and muscle relaxation of intubated patients, should be prevented by the natural movements of conscious patients. The same is true for eye complications. The risk of

displacement of the oxygenation device, while it does represent a real risk during prone positioning, is much less serious and very simple to correct in the context of an accidental ablation of high-flow nasal cannula, whereas it is a life-threatening complication in the context of accidental tracheal extubation. The fact that patients will wear a surgical mask over the high-flow nasal cannula reduces the risk of accidental displacement of these cannulas.

Some patients may experience some discomfort in the prone position. Nevertheless, conscious patients can spontaneously adopt the position that is most comfortable for them and the duration of the prone position sessions can be adapted to the patient's tolerance. Accounts by clinicians who have implemented prone positioning in conscious patients under high-flow nasal cannula therapy (Figure 1) seem to indicate that tolerance is good for many patients.

Potential collective risks:

At the collective scale, it is necessary to assess the risk of dissemination into the environment of bioaerosols potentially contaminated with COVID-19 (Ong 2020). Indeed, this dissemination, by exposing the nursing staff, is likely to contribute to the spread of the epidemic. Scientific data show that the risks of bioaerosol dispersion during high-flow nasal cannula therapy in supine position are very limited and comparable to other oxygenation techniques such as simple oxygen mask and bag reserve oxygen mask and possibly lower than that observed with Venturi masks (Li 2020; Hui 2019; Ip 2007; Leung 2019). Thus, the use of high-flow nasal cannula therapy for the management of patients suffering from COVID-19 is part of the international guidelines (Alhazzani 2020) and prompted a health authorities warning message emphasizing the safety of its use (MARS no.2020_27). Placement of a surgical mask over high-flow nasal cannulas as part of the protocol is an additional safety feature (Hui 2012).

To our knowledge, no specific studies on the risk of bioaerosol dispersion in the prone position have been published. There is nothing to suggest that it is significantly different from the risk observed in supine patients.

Thus, the potential collective risk linked to the dispersion of bioaerosols in the context of this project is minimal and quite comparable to that observed for other patients subjected to oxygen therapy in a healthcare setting.

The overall evaluation of the risk/benefit balance is therefore largely favourable both at the individual and collective levels.

2. Objectives

2.1. Primary objective

To evaluate the clinical benefit of prone positioning in patients with COVID and treated with high-flow nasal cannula therapy in terms of reducing the use of heavier oxygenation techniques and reducing mortality.

2.2. Secondary objectives

Evaluate effectiveness in terms of:

- Patient oxygenation
- Clinical course of pneumonia
- Patient clinical outcome

Evaluate the tolerance and safety of the technique at the individual level.

3. Study outline

This is a multi-centre, randomised, open-label, two parallel-group superiority trial with a 1:1 allocation ratio and individual randomization.

4. Endpoints

4.1. Primary endpoint

The primary endpoint is **treatment failure defined by death or intubation or the use of non-invasive ventilation with two pressure levels during the 14 days following randomization**, measured by the investigator on the 14th day after randomization.

Criteria for tracheal intubation: In order to standardise the intubation decision and avoid any delay in intubation, patients meeting one of the following criteria will be intubated (Coudroy 2019, Frat 2015):

- Neurological failure: agitation or altered consciousness, with a Glasgow coma scale of less than 12 points

- Haemodynamic failure: continuous infusion of norepinephrine greater than 0.3 µg/kg/min with signs of tissue hypoperfusion.

- Worsening respiratory failure: two criteria among:

  - Respiratory rate greater than 40 cycles per minute,
  - Occurence or increase in the use of accessory respiratory muscles.
  - Deep hypoxaemia: need for 80% FiO_2 to maintain SpO2 above 92% or $PaO2/FiO_2$ ratio below 100 mmHg
  - Respiratory acidosis with pH <7.35

4.2. Secondary endpoints

- Therapeutic failure within 28 days of randomization: death or intubation or use of non-invasive ventilation with two levels of pressure.

- Time to intubation or death

- Time to onset of treatment escalation (in case of recourse to non-invasive ventilation with two pressure levels)

- Progression of oxygenation in the supine position over the 14 days following randomisation (PaO_2/FiO_2 ratio in the event of arterial blood gas measurement, SpO_2 (pulse oximetry with SpO2 ≤ 97%)/FiO_2, ROX index: SpO_2/FiO_2/Respiratory rate: Roca 2019): 1 daily morning measurement in the supine position. For all substitutions of PaO2 by SpO2, only values of SpO2 ≤97% will be taken into consideration.

- Progression of the SpO2/FiO2 ratio (SpO2 ≤97%) and of the ROX index during the first prone positioning session: difference between the value immediately before proning, the value 30 minutes after proning, the value 2 hours after proning and after returning to supine decubitus.

- Progression of the WHO COVID-19 disease severity score at D7, D14 and D28 after randomisation (WHO 2020): 1. Not hospitalised, normal activities 2. Not hospitalised, unable to perform normal activities, 3. Hospitalised without oxygen therapy, 4. Hospitalised with oxygen therapy, 5. Hospitalised with high flow nasal

oxygen therapy and/or non-invasive ventilation, 6. Hospitalised with invasive mechanical ventilation and/or ECMO, 7. Death

- Patient comfort before, during and after the first proning session (visual analogue scale)

- Occurrence of skin lesions on the anterior surface of the body

- Displacement of intravascular devices during turnovers

- Duration of use of high-flow nasal cannula therapy in the general population, in both non-intubated and intubated patients

- Length of stay in intensive care and hospital

- Mortality in intensive care and in hospital

- Number of days living without ventilation in the 28 days following randomisation

5. Research location

The research sites are public or private, academic or extra-academic health establishments. The list of centres is provided in the appendix.

6. Participants

6.1. Inclusion criteria

- ✓ Adult patient suffering from, or very strongly suspected of suffering from COVID-19 pneumonia according to the diagnostic criteria in force at the time of inclusion
- ✓ Patient treated with high-flow nasal cannula therapy
- ✓ Mild, moderate or severe ARDS: bilateral radiological opacities not fully explained by effusions, atelectasis or nodules; acute hypoxaemia with deterioration in the previous 7 days, not fully explained by left ventricular failure; PaO2/FiO2 ratio <300 mmHg or SpO2/FiO2 <315 (Brown 2017).

  SpO2 must be ≤97% for valid SpO2/FiO2 ratio calculation. The PaO2/FiO2 (or SpO2/FiO2) ratio will be measured with a nasal flow rate of at least 30 L/min.
- ✓ Beneficiary of or affiliated to a social security scheme
- ✓ Informed consent

6.2. Non-inclusion criteria

- ✓ Indication of immediate tracheal intubation
- ✓ Progressive acute circulatory failure: fluid loading of more than 1000 mL, initiation or increase of more than 0.1 µg/kg/min of norepinephrine infusion to maintain systolic blood pressure greater than 90 mmHg in the hour preceding inclusion. Patients stable on a low dose of norepinephrine (<0.3 µg/kg/min), possibly after initial fluid loading not renewed in the hour preceding inclusion, can be included.
- ✓ Impaired alertness, confusion, agitation
- ✓ Body mass index greater than 40 kg/m^2
- ✓ Chest trauma or other contraindication to prone positioning
- ✓ Pneumothorax with single anterior chest drain and persistent bubbling
- ✓ Vulnerable person: known legal guardianship, curatorship or tutorship at inclusion
- ✓ Pregnant or breast-feeding women

6.3. Exclusion period for participation in another study

Persons participating in the research may participate in another study, EXCEPT for studies assessing the prone position combined with high-flow nasal cannula therapy throughout the follow-up period. During the COVID-19 epidemic, gaining extensive knowledge on the best management methods, clinical research evaluating the entire panel of drug and non-drug strategies is a priority at the international level. The analysis of this project will take into account the possible participation of patients in another research protocol as part of the COVID-19 clinical research effort.

7. Non-pharmacological intervention (Excluding health products)

7.1. Experimental group

- High-flow nasal cannula therapy adapted for 90-95% SpO_2. Unless poorly tolerated by the patient, a minimum gas flow rate of 50 L/min will be initially set. Weaning from high-flow nasal cannula therapy will first be performed by FiO2, which will be gradually reduced to 40% before reducing the gas flow. In patients clinically stable at an FiO2 less than or equal to 40% and gas flow less than or equal to 30 L/min, a switch to standard oxygen therapy at 4-6 L/min will be attempted.

FiO2 readings in patients weaned from high-flow nasal cannula therapy will be continued throughout the study using the following calculation formula summarised in

the table below, regardless of the oxygenation interface: FiO2 = 0.21 + (oxygen flow * 0.03)

Débit oxygène (L/min)	FiO2
1	24
2	27
3	30
4	33
5	36
6	39
7	42
8	45
9	48
10	51
11	54
12	57
13	60
14	63
15	66

- Prone position: depending on tolerance, the objective is to spend as much time as possible, up to 16h and beyond, in prone position per period of 24 hours. At least two sessions of at least 30 minutes each must be performed daily.

In connection with TIDieR guidelines ("Template for Intervention Description and Replication": *http://www.equator-network.org/reporting-guidelines/tidier/*), proning will follow the principles specified in **Table 1**.

Proning sessions will be continued daily as long as the PaO_2/FiO_2 ratio or the SpO_2/FiO_2 ratio is below 300 mmHg or 315, respectively.

In the event of weaning from prone positioning following patient improvement, proning sessions will be resumed if the patient again meets the oxygenation criteria (PaO_2/FiO_2 or SpO_2/FiO_2 less than 300 mmHg or 315, respectively), and this until D28 if the patient is still in the unit. In the event of discharge from the unit and readmission, the patient will also be reassigned to their randomization arm and, if necessary, returned to prone position in accordance with the protocol.

- Otherwise usual care: application of national and international guidelines.

7.2. Control group

- High-flow nasal cannula therapy adapted for 90-95% SpO_2. Unless poorly tolerated by the patient, a minimum gas flow rate of 50 L/min will be initially set.

Weaning from high-flow nasal cannula therapy will first be performed by FiO2, which will be gradually reduced to 40% before reducing the gas flow. In patients clinically stable at an FiO2 less than or equal to 40% and gas flow less than or equal to 30 L/min, a switch to standard oxygen therapy at 4-6 L/min will be attempted.

FiO2 readings in patients weaned from high-flow nasal cannula therapy will be continued throughout the study using, whatever the oxygenation interface, the following calculation formula summarised in the table indicated in paragraph 7.1: FiO2 = 0.21 + (oxygen flow * 0.03)

- Otherwise usual care: application national and international guidelines.

In the event of discharge from the unit followed by readmission before the 28th day after randomisation, the patient will be reassigned to their randomization group and thus left in the supine position.

7.3. Changes to the intervention

Minor adaptations to the proning procedure may be considered depending on patient preference and tolerance, as well as in the event of the emergence of new scientific data. In the event of poor tolerance by the patient, in particular during the first session, every effort will be made to try to repeat the sessions with the intention of conducting at least 2 sessions of 30 minutes per day. The aim is to spend as much time as possible per 24-hour period in prone position (up to 16h and beyond over 24 hours).

In the event of medical intolerance to the prone position, the proning session may be interrupted at any time. If intubation criteria appear (see paragraph 4.1), the patient will be placed on their back urgently and intubated if the criteria persist.

7.4. Eligibility criteria for people performing the intervention

Proning will be performed with the help and under the supervision of a registered nurse or a doctor, always under the responsibility of the centre's principal investigator.

7.5. Adherence to the intervention

Compliance with the randomisation group (i.e. intervention for the experimental group or no intervention for the control group) will be checked by the medical and paramedical caregivers as part of routine patient monitoring.

For patients in the experimental group, the number of sessions and the total time spent in prone position will be collected per 24-hour period. Patient comfort will be

assessed before, during and after the first proning session. The prone positiion start and end times will also be noted.

Any deviations (proning of patients in the control group in particular) will be noted. Patients will also be asked not to change their supine/prone position on their own, but to ring the bell and ask a caregiver.

7.6. Concomitant treatments and interventions

All drug and non-drug treatments are authorised.

In particular, right and left lateral decubitus postural interventions are authorised in both trial groups under the responsibility of the physician in charge of the patient.

Prone positioning is not allowed in patients in the control group.

In both trial groups, in the event of tracheal intubation and invasive mechanical ventilation, proning is freely determined by the physician in charge of the patient in accordance with national and international guidelines.

Table 1: Description of the intervention according to TIDieR guidelines		
1. BRIEF PRESENTATION: Provide the name or a phrase that describes the intervention		Proning
2. WHY: Describe any rationale, theory, or goal of the elements essential to the intervention.		The aim is to place the patient in a position opposite to the usual supine position in an inpatient bed in order to reverse the anatomical location of the dependent pulmonary areas such as to induce a redistribution of vascularisation and pulmonary aeration
3. WHAT:	**Materials:** Describe any physical or informational materials used in the intervention, including those provided to participants or used in intervention delivery or in training of intervention providers. Provide information on where the materials can be accessed (for example, online appendix, URL)	Written proning procedure displayed in the room. Demonstration video made available to nursing staff. Monitoring equipment: ECG monitor, pulse oximetry Cushion
	Procedures: Describe each of the procedures, activities, and/or processes used in the intervention, including any enabling or support activities	The patient turns onto their stomach with the help and under the supervision of a caregiver. Continued SpO2 monitoring during the procedure, removal of the anterior electrocardiographic electrodes before the turn-over, return to supine position as soon as the turn-over is performed.
5. WHO PROVIDES: For each category of intervention provider (for example, psychologist, nursing assistant), describe their expertise, background and any specific training given,		Assistance and supervision of a nurse or doctor. Proning is carried out under the responsibility of the investigators.
6. HOW: Describe the modes of delivery (such as face to face or by some other mechanism, such as internet or telephone) of the intervention and whether it was provided individually or in a group		The patient turns onto their stomach individually in the presence and with the help of a caregiver.
7. WHERE: Describe the type(s) of location(s) where the intervention occurred, including any necessary infrastructure or relevant features		The patient's usual hospital room. No movement to carry out the intervention.
8. WHEN and HOW MUCH: Describe the number of times the intervention was delivered and over what period of time including the number of sessions, their schedule, and their duration, intensity or dose		At least 60 minutes per 24-hour period (2 periods of 30 minutes). The aim is to spend as much time as possible in the prone position, up to 16h and beyond over a 24-hour period if the patient tolerates it well. Proning sessions will be continued daily as long as the PaO2/FiO2 ratio or the SpO2/FiO2 ratio is below 300 mmHg or 315, respectively.
9. TAILORING: If the intervention was planned to be personalised, titrated or adapted, then describe what, why, when, and how		The patient will be asked to choose the most comfortable position possible in terms of the position of the arms, rotation of the head and inclination of the bed.
10. HOW WELL-PLANNED: As planned: if intervention adherence or fidelity was assessed, describe how and by whom, and if any strategies were used to maintain or improve fidelity, describe them		The number of sessions and the total time spent in prone decubitus will be collected per 24-hour period.

8. Course of the study

8.1. Selection and recruitment of trial participants

Screening of individuals will be carried out by clinical research technicians, research nurses and investigators in the participating centres. All patients receiving oxygen therapy greater than or equal to 4 L/min and presenting with confirmed or strongly suspected COVID disease will be considered for potential inclusion. Each week, the list of patients assessed for inclusion will be sent to the clinical research associate coordinating the study (screening logs).

8.2. Inclusion

Patients will be included by an investigator after verification of all inclusion and non-inclusion criteria as well as the delivery of information and the collection of consent in compliance with the rules of good clinical practice

Note that patients will keep a copy of the information letter and the signed consent. The original documents will be kept by the investigator.

8.3. Intervention

Upon inclusion, the patient will be randomized as quickly as possible. Patients assigned to the intervention group will be placed in the prone position within no more than 6 hours of inclusion.

8.4. Follow-up

1st proning: the patient's comfort will be evaluated immediately before, during the session (30 minutes to 1 hour and 2 hours after proning) and after recovery in supine position. Oxygenation (SpO_2/FiO_2 ratio, ROX index and PaO2/FiO2 ratio in the event of blood gas production) will be evaluated immediately before, during (30 minutes to 1 hour and 2 hours after placing in prone position) and after return to supine position. Side effects will be noted (secondary endpoints).

Subsequent proning sessions: oxygenation will be assessed daily, in the morning if possible, in supine position. Any side effects will be noted (secondary endpoints).

D14 after inclusion: primary endpoint evaluation.

D28 after inclusion or discharge from hospital if this occurs before D28: end of follow-up, evaluation of secondary endpoints not noted up to this stage. *

Study timeline	**Inclusion**	**Randomization**	**Follow-up**			**End of study**
		T0	D1	D7	D14	D28 or discharge from hospital
Verification of eligibility criteria	X					
Information and consent	X					
INTERVENTIONS:						
Intervention group: Daily proning sessions		♦—	—	—	—	—♦
Control group: No proning sessions						
EVALUATIONS:						
Number of proning sessions and time spent in prone position			♦—	—	—♦	
Daily oxygenation measurement *(PaO_2, SpO2, FiO2, respiratory rate)*	X Description at inclusion		♦—	—	—♦	
Treatment Failure *(death, intubation or use of non-invasive ventilation with two pressure levels)*					X	X
Comfort (1st proning session)			X			
WHO COVID-19 scale				X	X	X
Adverse events *(especially those related to proning)*		♦—	—	—	—♦	X
Permanent withdrawal of high-flow nasal cannula						X
Length of stay (intensive care/hospital)						X
Vital status						X
Number of days alive without ventilation						X

All blood gas samples are collected as part of routine patient care under the responsibility of the physician in charge of the patient.

8.5. Ending the participation of a research subject

All the data must be collected as specified by the protocol, regardless of deviations (e.g.: early termination of the procedure) or changes to the patient's management (e.g.: following the occurrence of an SAE). The only possible reason for stopping data collection is withdrawal of consent. The data will be analyzed by intent to treat (each patient will be analyzed in the group in which they were randomized).

Trial participants will be able to withdraw their consent and request to stop the study at any time and for any reason. The investigator must document the reasons as extensively as possible. In accordance with article L1122-1-1 of the French public health code, and unless expressly requested otherwise, the data obtained until the withdrawal of consent will be used during analyses.

The investigator may temporarily or permanently interrupt the procedure under study for any reason that would serve the best interests of the person participating in the research, in particular in the event of serious adverse events.

8.6. Termination of part or all of the research

The study may be terminated prematurely in the event of the occurrence of unexpected serious adverse events requiring a review of the safety profile of the intervention. Likewise, unforeseen events or new information relating to the intervention, in view of which the objectives of the study or clinical programme are unlikely to be achieved, may cause the sponsor to prematurely discontinue the study. The Tours Regional University Hospital reserves the right to interrupt the study at any time if it turns out that the inclusion objectives have not been achieved.

In the event of premature termination of the study, the information will be sent by the sponsor within 15 days to ANSM and the CPP.

8.7. Study duration

The total duration of participation in the study for the person participating in the research is 28 days from the date of inclusion to the date of the last visit carried out in the context of the study.

The inclusion period is 18 months.

The total study duration is expected to be 19 months.

From the first inclusion, the sponsor must inform, without delay, the competent authority and the CPP of the effective start date of the study (date of consent signature by the first person to take part in the research). The study end date will be sent by the sponsor to the National Agency for the Safety of Medicines and Health Products (ANSM) and to the CPP within 90 days. The research end date corresponds to the end of the participation of the last person to take part in the research, or, if applicable, to the term defined in the protocol.

9. Randomization

9.1. Randomization list generation

Persons participating in the research will be randomized into two groups (experimental group or control group) according to a ratio of 1: 1 using a randomization list generated using SAS©. Randomization will be stratified by centre and by use of proning for therapeutic purposes before inclusion. Variable block sizes will be used. These elements will not be communicated to the sponsor or to the investigators.

9.2. Implementation

The random sequences will be implemented by a statistician from CIC INSERM1415 who is independent of the investigating centres.

9.3. Allocation

The subjects will be randomized centrally via a website (Ennov Clinical©). To ensure secret allocation, the randomization procedure will be possible only if all the inclusion and non-inclusion criteria are met.

10. Blinding

Blinding is not possible for the intervention under study for the patient, investigators, research personnel or caregivers. The study will therefore be conducted in an open-label manner.

11. Other strategy to reduce bias

The endpoint includes tracheal intubation or the use of non-invasive ventilation with two levels of pressure within 14 days of randomization, which is not a fully objective outcome. Intubation criteria were therefore defined in order to standardise the decision for tracheal intubation.

Note that this criterion is being harmonised with a North American project (NCT04325906) with a view to a joint analysis of the results.

Likewise, weaning from proning and high-flow nasal cannula therapy is standardised in the protocol.

12. Data management

12.1. Data collection

12.1.1. Data access

In accordance with Good Clinical Practice (GCP):

- The sponsor is responsible for obtaining the agreement of all parties involved in the research to guarantee direct access to all places where research is conducted, to source data, to source documents and reports for the purposes of quality control and audit by the sponsor.
- The investigators will make available to the persons responsible for monitoring, quality control or auditing research involving the human person, the documents and individual data strictly necessary for this control, in accordance with the legislative and regulatory provisions in force.

12.1.2. Source data

Source documents are defined as any original document or object proving the existence or accuracy of a data or fact recorded during the clinical study.

In the context of this study, the source documents are: the patient's medical file, the reports of the examinations carried, along with the documents used to collect data at the patient's bedside.

12.2. Data collection tool

An electronic data collection tool will be used as part of this study. All the information required by the protocol will be collected in this electronic case report form. It requires only an Internet connection and a browser. The investigators will be issued with a help document for the use of this tool.

12.3. Data confidentiality

In accordance with the legislative and regulatory provisions in force (in particular (EU) Regulation 2016/679 (GDPR) and its transposition into French law LAW 2018- 493 of 20 June 2018, public health code) and the provisions concerning data confidentiality to which the persons responsible for the quality control of research involving the human person have access, in accordance with the provisions relating to the confidentiality of information concerning in particular the nature of the investigational medicinal

products, the tests, the persons who lend themselves to them and the results obtained, the individuals will take all the necessary precautions to ensure the confidentiality of information relating to the devices, the tests, the persons who lend themselves to them and in particular as regards their identity as well as the results obtained. These individuals, like the investigators themselves, are subject to professional secrecy.

During or after the research, the data collected on the persons participating in the research sent to the sponsor by the investigators (or any other specialist participants) will be pseudonymised in compliance with the rules of confidentiality. They must under no circumstances include the full names of the persons concerned or their addresses. Only the first letter of the last name of the person participating in the research and the first letter of their first name will be recorded, accompanied by a coded number specific to the study indicating the order of inclusion. A look-up list will be kept at the centre under the responsibility of the investigator. This list will be kept for the regulatory period provided for this type of research.

The sponsor will ensure that each person taking part in the research has agreed in writing to allow access to their personal data that are strictly necessary for the quality control of the research.

12.4. Data management

The study data will be managed by a CIC INSERM 1415 data-manager. The electronic case report form (eCRF) will be developed using Ennov Clinical® software. Data will be managed according to standard operating procedures (SOP) in force at CIC INSERM 1415. The sponsor's clinical research associate (CRA) in charge of the study will be trained in the use of the eCRF, and will then be in charge of training investigators and CRTs.

The data will be entered at the investigator centres via a secure website, monitored by the CRA, according to the monitoring grade and plan defined according to the risk classification of the study. Queries will be edited by the data manager according to a consistency control plan established during the design of the case report form.

A blind review of the data will be carried out before the database freeze. The database will be frozen according to the SOPs in application at CIC INSERM 1415 and the data will be extracted in the format required for statistical analyses.

13. Statistical analyses

13.1. General

The study data will be analyzed by the CIC Inserm 1415. Analyses will be performed using SAS version 9.4 (or later) and/or R version 3.3.1 (or later). Statistical analysis will be carried out according to a pre-established statistical analysis plan. A statistical analysis report will be drawn up, including all the elements that must be reported as recommended by the consort-statement. A flow diagram will be produced. All statistical tests will be performed with a 5% significance level. In cases where the patient is included but not randomized, this patient will be replaced.

13.2. Definition of analysis populations

The analysis will be carried out according to the intent-to-treat principle: all randomized patients will, whatever happens, be taken into account in the analysis in the arm to which they were allocated.

A subgroup analysis is planned according to the severity of ARDS (mild if the PaO2/FiO2 ratio is between 200-300; moderate if it is between 100-200 and severe if it is ≤100).

13.3. Description of characteristics at inclusion

Patient characteristics at inclusion will be described and compared according to the groups resulting from the randomisation using the following descriptive statistics (no statistical test will be carried out): i) for qualitative variables, population size and percentages, ii) for quantitative variables, mean and standard deviation or median and interquartile range depending on the distribution.

13.4. Primary endpoint analysis

The primary analysis will be based on a mixed logistic regression adjusting for the stratification variable. The intervention effect will be expressed in the form of an odds ratio accompanied by its 95% confidence interval. The intervention effect will also be reported in the form of a difference in proportions (consort 17b).

13.5. Analysis of secondary endpoints

- The treatment failure at 28 days will be analysed by a Cox model or by mixed logistic regression if the assumption of proportionality of the risks is not respected.

- The time to onset of treatment failure and treatment escalation will be analyzed by Wilcoxon tests.

- Oxygenation changes in supine position over the 14 days following randomisation will be analysed in the context of a mixed linear regression model, with the randomisation arm interacting with time in fixed effects, along with a patient-level intercept and random slope.

- Changes in the SpO2/FiO2 ratio and the ROX index during the first proning session will be analyzed as part of a linear regression model

- The WHO COVID disease severity score will be analysed sequentially on D7, D14 and D28 after randomization by chi-square tests.

- Changes in patient comfort before, during and after the first proning session (visual analogue scale) will be analyzed as part of a student test for paired data.

- The duration of use of high-flow nasal cannula therapy will be analyzed in the context of a linear regression model.

- The lengths of stay in intensive care and in hospital will be analyzed in the context of a linear regression model

- The mortality rates in intensive care units and in hospital will be analyzed as the primary endpoint.

- The number of days alive without ventilation during the 28 days following randomization will be analyzed by a Wilcoxon test.

- A sensitivity analysis will be performed on the primary endpoint by considering, in the intervention arm, only those patients who have adhered to the intervention (adherence to the treatment will be defined by the number of sessions performed and their durations).

- A sensitivity analysis will be performed on the primary endpoint in the subgroup of patients who have not participated in any other open-label COVID study and who have been randomised to the intervention arm or other blind COVID study.

13.6. Intermediate analyses

No intermediate analyses will be performed.

13.7. Population calculation

For a primary endpoint occurrence of 40% in the control group and 25% in the intervention group, with a power of 90% and an alpha risk of 5%, we plan to include 404 subjects or 202 patients per group.

14. Study feasibility

All the participating centres are familiar with the technique of placing intubated patients in the prone position; proning awake patients is anticipated to be simpler given the patient's cooperation.

In the specific context of COVID, the feasibility of proning during high-flow nasal cannula therapy appears to be good for a large number of patients, as shown by the numerous positive clinical cases reported and the enthusiasm observed on social networks (Figure 1).

All the centres have significant experience in clinical research and have dedicated research staff.

The data collected are simple and pragmatic, only arterial gas measurements carried out as part of the usual treatment are analyzed, all other variables are collected in a non-invasive manner.

The project has received the support of two international research networks:

- Réseau européen de recherche en ventilation artificielle (REVA - European artificial ventilation research network) - www.reseau-reva.org

- Clinical research in intensive care and sepsis – Trial group for global evaluation and research in sepsis (CRICS-TriggerSEP): www.triggersep.org. FCRIN-labelled research network (French clinical research infrastructure network: www.fcrin.org).

The project leader will be assisted by a scientific committee to conduct the trial. The scientific committee will include national and international experts in artificial ventilation, non-invasive respiratory support and the conduct of large-scale randomised trials.

This study constitutes the French component of an international project (trial in progress in the United States: NCT04325906). The endpoints were harmonised such that the results could be combined in a prospective meta-analysis. This organisation guarantees optimal and rapid recruitment and better external validity, particularly suited to the pandemic crisis situation requiring international optimisation of efforts.

15. Expected benefits

Emergency implementation of this research protocol is likely to bring immediate individual and collective benefits in the face of the global COVID-19 pandemic.

The implementation of optimised non-invasive ventilatory support by combining the expected benefits of high-flow nasal cannula therapy and prone positioning is likely to reduce the need for intubation and mechanical ventilation, helping to relieve pressure on the availability of intensive care unit ventilators. Non-invasive management, not requiring the use of sedatives or muscle relaxant drugs, will also help to ease supply chains and potentially reduce the length of stay in intensive care and therefore increase the intensive care unit bed availability.

Beyond that, the results of this trial will provide important information for the management of patients suffering from acute respiratory distress syndrome other than COVID-19, as well as in the event of a new pandemic involving another virus with a respiratory tropism.

16. Safety evaluation

The terminology used is detailed in the appendix.

16.1. Description of safety parameters

Safety will be evaluated during each proning procedure. In the event of intubation, specific data relating to the complications of the procedure will be collected.

16.2. Procedures in place and schedule for monitoring, collecting and analysing safety parameters

Daily collection of complications related to prone positioning. Specific data collection sheet concerning the peri-intubation period for intubated patients.

16.3. Procedures in place for documentation and notification of serious adverse events

16.3.1. Investigator's responsibilities

16.3.1.1. Notification of serious adverse events

16.3.1.1.1. Information to be sent to the sponsor

Each SAE will be described on the form provided for this purpose ("Initial Serious Adverse Event Declaration" or "Serious Adverse Event Follow-up Declaration"), trying to be as exhaustive as possible. The following information will be submitted:

- Subject identification (number, code, date of birth, date of inclusion, gender, weight, height).
- Severity of the SAE.
- SAE start and end dates.
- Clear and detailed description of the SAE (diagnosis, symptoms, intensity, chronology, actions taken and results).
- Progression of the SAE.
- Subject's current illnesses or relevant history.
- Treatments received.
- Causal relationship of the SAE with the research or other criteria.
- Whenever possible, the investigator must also attach the following to the SAE report:
- A copy of the hospitalisation or prolongation of hospitalisation report.
- Where applicable, a copy of the autopsy report.
- A copy of all the results of additional examinations carried out, including the relevant negative results, with the normal laboratory values.
- Any other documents deemed useful and relevant.

These documents will be pseudonymized and will bear the patient's identification number.

Each adverse event will be monitored until complete resolution (stabilisation at a level deemed acceptable by the investigator or return to the previous state) even if the subject has left the trial.

16.3.1.1.2. Sponsor notification requirements

All SAEs, regardless of their causal relationship with the study or research procedure (except those listed in the protocol as not requiring immediate notification), must be declared by email to uvrb@chu-tours.fr and cpcq@chu-tours.fr. A vigilance officer (Céline Lengellé or Marie-Sara Agier) can be reached by phone at +33(0)2.47.47.80.37 or +33(0)2.47.47.85.92 or by email: uvrb@chu-tours.fr; c.lengelle@chu-tours.fr or marie-sara.marchand@chu-tours.fr.

16.3.1.1.3. Sponsor notification deadline

The investigator must inform the sponsor, without delay from the day on which he/she becomes aware of them, of any SAEs occurring during the study, with the exception of those listed in the protocol as not requiring immediate notification (see § Specific aspects of the protocol).

This initial notification is the subject of a written report and must be followed quickly by one or more detailed written supplementary reports.

16.3.1.1.4. Sponsor notification period

The duration of SAE collection begins on the day the consent is signed and ends 24 hours after the end of the last proning session.

The investigator is responsible for recording and reporting all serious adverse events occurring throughout the study, from the date of signing the consent, and up to 24 hours after the last proning session.

16.3.1.2. Protocol specificities

Certain serious adverse events do not require immediate notification:

a) Certain circumstances requiring hospitalisation do not fall under the "hospitalisation/prolongation of hospitalisation" severity criterion and should not be declared as serious adverse events:

- Hospitalisation predefined by the protocol.
- Admission for social or administrative reasons.
- Transfer to day hospital.
- Hospitalisation for routine treatment or monitoring of the studied disease not associated with a deterioration of the patient's condition.
- Hospitalisation for medical or surgical treatment scheduled before the start of the research.

b) The following expected serious adverse events (related to the condition of the patients) will not require (in agreement with the health authorities) immediate notification, but will be reported in the CRF on the page provided for this purpose:

- Expected complications of COVID-19 disease including intubation, multiple organ failure and death.

- Usual complications of resuscitation: including heart rhythm disorders, arterial hypotension, shock, nosocomial infection, gastrointestinal bleeding.

On the other hand, any cardiac arrest or deep desaturation occurring within 30 minutes before or after intubation (the only potential risks identified) will be immediately notified to the Sponsor.

16.3.1.3. Notification of non-serious adverse events

All other non-serious AEs will be reported on the "adverse event" form in the case report form, specifying the date of occurrence, description, intensity, duration, mode of resolution, aetiology, potential causal relationship and decisions made.

16.3.2. Sponsor's responsibilities

16.3.2.1. Analysis of serious adverse events

The sponsor must evaluate:

- The causation of serious adverse events, in accordance with ICH guidelines. All adverse events for which the investigator or the sponsor considers that a causal relationship with the procedure under study or the research can be reasonably considered are deemed to be suspected adverse reactions. If the sponsor and investigator reach different evaluations, the two opinions are mentioned on the declaration sent to the competent authority if this declaration is necessary.
- The expected or unexpected nature, with the help of the reference document: The protocol (paragraph 1.2).

16.3.2.2. Declaration of suspected unexpected serious adverse reactions

The sponsor declares all suspected unexpected serious adverse reactions (SUSARs) to the French Health Authorities (ANSM), to the Committee for the Protection of Persons (CPP) and to the investigators, within the regulatory deadlines, namely:

- ✓ Without delay* for fatal or life-threatening SUSARs. In this case, relevant additional information must be sought and transmitted within a further 8 days.

- ✓ Within no more than 15 calendar days for all other SUSARs. Likewise, relevant additional information must be sought and submitted within a further 8 days.

*As soon as the Sponsor is aware of the strategy received, the patient identification (number, code, date of birth), the SAE, the notification of the EUDRACT number, and, where applicable, the investigator's imputability. Transmission of DSURs (Development Safety Update Report)

On the anniversary date of the study: (date of first inclusion), or at the request of the Competent Authorities, the sponsor draws up an annual safety report comprising three parts:

- ✓ The analysis of the safety of the people participating in the research.
- ✓ The list of all suspected serious adverse reactions (including suspected unexpected serious adverse reactions) that occurred in the trial concerned in France (and abroad, including in third countries), during the period covered by the report.
- ✓ Summary tables of all serious adverse events and serious adverse reactions that have occurred in the trial concerned since the start of the research.

It is sent to the competent authorities (ANSM) and to the CPP within 60 days of the anniversary date of the study.

16.3.2.3. Declaration of other safety-related data

The sponsor must report, without delay, any new fact to the ANSM and the CPP, along, where applicable, with the measures taken. Additional relevant information must be submitted within a further 8 days.

17. Quality control

A CRA appointed by the sponsor will ensure the proper conduct of the study, the collection of the data generated in writing, their documentation, recording and reporting, in accordance with the SOPs implemented within the Promotion and Quality Control unit of the Tours Regional University Hospital, in accordance with GCPs and with the laws and regulations in force. In the context of the COVID-19 pandemic, quality control will be adapted according to the procedure implemented by the sponsor in the period considered.

The investigator and the members of his/her team agree to make themselves available during Quality Control visits carried out at regular intervals by the CRA. During these visits, the following elements will be reviewed:

- Written informed consent.
- Compliance with the study protocol and the procedures defined therein.
- According to the evaluation of the monitoring level and plan defined according to the risk classification of the study and the requirements relating to the quality of the data collected in the case report form, the following will be checked: accuracy, missing data, consistency of the data with the "source" documents (medical files, appointment books, originals of laboratory results, additional examinations, etc.).

Furthermore, the investigators undertake to accept the quality assurance audits carried out by the sponsor, along with the inspections carried out by the Competent Authorities. All data, documents and reports may be subject to regulatory audits and inspections, notwithstanding any objections based on medical confidentiality.

18. Regulatory and ethical considerations

The investigator undertakes to ensure that the research is carried out in accordance with the legislative and regulatory provisions (Public Health Code) in force concerning research involving human subjects. The investigator also undertakes to work in accordance with GCP and with the Declaration of Helsinki of the World Medical Association.

18.1. CNIL

For this study, the research sponsor will use the reference methodology MR-001 of the French National Commission for Information Technology and Civil Liberties (CNIL).

Data will be collected in accordance with the requirements of EU Regulation 2016/679 (General Data Protection Regulation or GDPR). In the case of data processing necessary for scientific research purposes (article 17.3.d), the right to erase data may not apply. Opposition to processing, however, will always be possible.

The Sponsor, through its Data Protection Officer (DPO), will ensure the compliance of data processing with the GDPR.

18.2. Committee for the Protection of Persons - ANSM

The protocol, information letter and consent form for the study will be submitted to the opinion of the Committee for the Protection of Persons (CPP).

A request for authorisation will be submitted by the Sponsor to ANSM before the start of the study. Prior to implementation of the project, the sponsor must obtain a favorable opinion from the CPP, along with an authorisation from ANSM within the framework of their respective competences.

18.3. Substantive changes

Any substantive changes made to the protocol by the investigator must be approved by the sponsor. This latter must obtain, prior to implementation, a favourable opinion from the CPP and an authorisation from ANSM within the framework of their respective competences. Where applicable, a new consent of the persons participating in the research will be sought and obtained.

18.4. Information and consent

The persons whose participation is requested will be informed in a complete and fair manner, in understandable terms, of the objectives and constraints of the study, of the possible risks incurred, of the necessary monitoring and safety measures, of their right to refuse to participate in the study and of their ability to withdraw at any time.

All this information appears on an information and consent form issued to the person participating in the research. The free, informed and written consent of the person participating in the research will be obtained by the investigator, or a physician representing the investigator, before final inclusion in the study. A copy of the information and consent form signed by both parties will be issued to the patient and, if this latter is under protection, to their legal representative; the investigator will keep the original.

18.5. Insurance

For the duration of the study, the Sponsor will take out insurance guaranteeing its own civil liability as well as that of any physician involved in carrying out the study. It will also ensure full compensation for the harmful consequences of the research for the person participating in it and their beneficiaries, unless it can prove that the damage is not attributable to its fault or to that of any contributor, notwithstanding any objections

involving the actions of a third party or the voluntary withdrawal of the person who had initially consented to participate in the research.

18.6. Registration

The study will be registered on an open access website (ClinicalTrial.gov) prior to the inclusion of the first research person. This registration will be updated regularly.

18.7. Archiving of documents and data at the end of the study

The investigators and the Sponsor are responsible for the conservation of research-related documents and data in accordance with the regulations in force. The means used to preserve these essential documents must allow these documents to remain complete and legible throughout the required storage period, i.e. 15 years after the end of the research.

They must not be moved or destroyed without the sponsor's consent. At the end of this period, the Sponsor will be consulted for destruction. All data, documents and reports may be subject to audit or inspection.

19. Rules of publication

19.1. General

The study data will be analysed by the CIC Inserm 1415. The results of the statistical analyses will be compiled in a written report which will be sent to the study coordinator.

Any written or oral communication of the results of the study must be approved by the study coordinator and, if necessary, by the scientific committee formed in the context of the study.

19.2. Authorship

The “Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals” of the “International Committee of Medical Journal Editors (ICMJE)” will be respected.

Authorship must give rise to a consensus. Any disagreements will be resolved by Yonatan Perez and Stephan Ehrmann.

The authorship will consider the overall contribution to study design, study conduct, analysis, interpretation of data and manuscript writing. All participating centres will be mentioned as contributors to the study with up to 3 contributors per centre listed in the appendix to the manuscript. The centres that included the most patients with a high degree of data quality will be listed in the main authorship. The first, second, third, penultimate and last places are reserved for members of the scientific committee and two centres that included the most patients with a high level of data quality. Membership of the scientific committee does not in itself automatically lead to inclusion in the authorship, which will be determined by effective contribution to the entire project.

19.3. Communication of results to study subjects

In accordance with article L.1122-1 of the Public Health Code, at the end of the research, participating individuals have the right, at their request, to be informed of the overall results of this research, in accordance with the terms and conditions that will be specified in the information document.

19.4. Transfer of data

Data collection and management will be carried out by the Tours Regional University Hospital. The conditions for the transfer of all or part of the database will be decided by the study sponsor and will be the subject of contractual provisions.

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APPENDICES

Associated centres

Investigator's Name	Centre	Email
EHRMANN Stephan	Tours University Hospital	s.ehrmann@chu-tours.fr
TELLIER Anne Charlotte	Tours University Hospital	ac.tellier@chu-tours.fr
REIGNIER Jean	Nantes University Hospital	jean.reignier@chu-nantes.fr
GUITTON Christophe	Le Mans Hospital	cguitton@ch-lemans.fr
NAY Mai-Anh	Orléans Regional Hospital	mai-anh.nay@chr-orleans.fr
PRAT Gwenaël	Brest University Hospital	gwenael.prat@chu-brest.fr
THILLE Arnaud	Poitiers University Hospital	arnaud.thille@chu-poitiers.fr
DELLAMONICA Jean	Nice University Hospital	dellamonica.j@chu-nice.fr
PLANTEFEVE Gaëtan	Argenteuil Hospital	gaetan.plantefeve@ch-argenteuil.fr
ROUX Damien	APHP Colombes	damien.roux@aphp.fr
DELBOVE Agathe	Vannes Hospital	agathe.delbove@ch-bretagne-atlantique.fr
VOIRIOT Guillaume	APHP Tenon	guillaume.voiriot@aphp.fr
NSEIR Saadalla	Lille University Hospital	Saadalla.nseir@chru-lille.fr

QUENOT Jean-Pierre	Dijon University Hospital	jean-pierre.quenot@chu-dijon.fr
AUVET Adrien	Dax Hospital	auveta@ch-dax.fr
SEMENT Arnaud	Mont-de-Marsan Hospital	arnaud.sement@ch-mdm.fr
VINSONNEAU Christophe	Béthune Hospital	cvinsonneau@ch-bethune.fr
TERZI Nicolas	Grenoble University Hospital	nterzi@chu-grenoble.fr
BOYER Alexandre	Bordeaux University Hospital	alexandre.boyer@chu-bordeaux.fr
LEVY Bruno	Nancy University Hospital	b.levy@chru-nancy.fr
MAIZEL Julien	Amiens University Hospital	maizel.julien@chu-amiens.fr
JORET Aurélie	Caen University Hospital	joret-a@chu-caen.fr
KLOUCHE Kada	Montpellier University Hospital	k-klouche@chu-montpellier.fr
LEFEBVRE Laurent	Aix-en-Provence hospital	llefebvre@ch-aix.fr
LACHERADE Jean-Claude	Vendée Departmental Hospital, La Roche sur Yon	jean-claude.lacherade@chd-vendee.fr
BOUTELOUP Marie	Valence University Hospital	mtourre@ch-valence.fr
GRILLET Guillaume	Southern Brittany Hospital - Lorient	g.grillet@ghbs.bzh

FELLER Marc	Blois Hospital	fellerm@ch-blois.fr

Definitions

- **Adverse event (AE)**: any harmful manifestation occurring in a person participating in research involving the human person, whether or not this manifestation is related to the research or to the product to which this research relates.
- **Serious Adverse Event (SAE)**: Severity is defined by one of the following findings:
    - Death.
    - Threat to life (immediate threat to life at the time of the event, regardless of the consequences of corrective or palliative therapy).
    - Significant or lasting impairment or disability.
    - Hospitalisation or prolongation of hospitalisation.
    - Congenital malformation/anomaly.
    - Potentially serious event (adverse clinical event or laboratory result of a serious nature or considered as such by the investigator).
- **Adverse reaction (AR)**: any adverse event caused by the research.
- **Severe adverse reaction (SAR)**: a serious adverse event attributable to research.
- **Unexpected adverse reaction**: any adverse reaction whose nature, severity or progression does not agree with the information on the products, procedures performed, or methods used during the research.
- **New safety fact**: any new datum that may lead to a reassessment of the benefits and risks of the research, or the product being researched, changes in the use of this product, in the conduct of the research, or research documents, or to suspend or interrupt or modify the protocol for research or similar research.
- **Imputability**: relationship between the AE and the study. The research-related AE will become an AR. Factors to consider when determining imputability include:
    - chronology of events,
    - disappearance of the AE when the research is stopped and/or reappearance in the event of a repeat intervention,
    - existence of another aetiology.
- **Intensity**: AE intensity is evaluated by the investigator

Imputability rating

In accordance with ICH guidelines on the management of adverse events in clinical studies - ICH E2B(R3), version of 12 May 2005 - an evaluation of imputability is carried out for any declared SAE. The following rating method is used:

- **Unrelated**: the event appears within a time frame incompatible with the research and/or there is a sufficient amount of information showing that the observed reaction is unrelated to the research and/or there is a plausible alternative explanation.
- **Questionable relationship**: the event has a chronology (appearance, progression) that is not compatible with the research and is likely due to factors other than the research, such as the patient's clinical condition or concomitant drug administration.
- **Possible relationship**: the event appears within a compatible time frame after the research and, although this latter's responsibility cannot be ruled, other factors may be onvolved, such as the patient's clinical condition or the concomitant administration of other medications. Information concerning the progression may be missing or inconclusive.
- **Probable relationship**: the event appears within a compatible time frame after the research. It cannot reasonably be attributed to another factor, such as the patient's clinical condition or concomitant medication. Progression must be clinically compatible.
- **Highly probable relationship**: the event appears in a very suggestive time frame after the research. It cannot be explained by any other factor, such as the patient's clinical condition or concomitant medication. Progression following termination must be clinically compatible. The event can be explained on a pharmacological or pathophysiological level.

Adverse events with a questionable, probable or highly probable relationships to the research are considered to be related to the research. If unexpected, they are classified as SUSARS and must be reported by the sponsor.

4.4 Irish protocol

Awake Prone Positioning to Reduce Invasive VEntilation in COVID-19 Induced Acute Respiratory failure (APPROVE-CARE)

Study Summary

The coronavirus disease 2019 (COVID-19) outbreak is a pandemic associated with a pneumonia which can worsen rapidly into respiratory failure known as acute respiratory distress syndrome (ARDS). There is a high rate of mortality in patients with severe respiratory failure requiring mechanical ventilation. Adjunctive therapies constitute an important part of the management of early moderate to severe ARDS. In patients with confirmed moderate-severe ARDs receiving invasive mechanical ventilation, prone position promotes lung homogeneity, improves gas exchange and respiratory mechanics permitting reduction of ventilation intensity, and reducing lung injury. Prone positioning has been demonstrated to save lives and is recommended in evidence-based guidelines for the management of moderate-severe ARDS.

The use of proning outside of mechanically ventilated patients to improve gas exchange and reduce the end for invasive ventilation has not been extensively studied outside of case series. Maintaining self ventilation is associated with increased aeration of dependent lung regions, less need for sedation, improved cardiac filling, and better matching of pulmonary ventilation and perfusion and thus oxygenation.

In this protocol, we outline details for a randomized clinical trial to determine whether placing patients who have hypoxemia related to COVID19 into a prone position can improve oxygenation and reduce the requirement for mechanical ventilation. If effective, this simple intervention could be widely and rapidly implemented, potentially reducing the need for ICU admission and invasive ventilation, and potentially even saving lives.

1. Study team- Galway

Intensive Care Medicine

Principal Investigator: Dr. Bairbre McNicholas

Dr. Camilla Giacommini

Dr. David Cosgrove

Dr. John Laffey

2. Study sponsor

Clinical Research Facility, National University of Ireland, Galway

3. *Background and rationale*

a. *COVID-19 and Hypoxemia*

Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) first appeared in Wuhan China in December 2019. It has since spread and was declared a worldwide pandemic by the World Health Organisation in March 2020.(1) Its main route of infection are respiratory droplets and contact transmission. Many infections will be asymptomatic or mild, but a subset require hospitalization and admission to critical care is associated with a high morbidity and mortality from the disease. Acute respiratory distress syndrome requiring mechanical ventilation is associated with a 40-60% mortality. To date, there are no specific pharmacological therapies currently although many are being trialled.(2)

b. *Prone position physiology*

Prone position is a non-pharmacological treatment used in patients with severe ARDS which has proven mortality benefits in this population. (3) Physiological studies have shown differences in ventilation pressures in distinct regions of the chest depending on whether one is in the prone or supine position. While breathing in a supine position, the ventral chest wall is lifted by a driving pressure driven by the difference between pleural pressure and atmospheric pressure ($P_{pleural}$ - $P_{atmospheric}$): the diaphragm moves caudally (Ppl - Pabdomen), and the dorsal chest wall moves minimally as lying in contact with a rigid surface. In the supine position, there is a reduction in alveolar size from sternum to vertebra in the supine position at the end of the expiration. This phenomenon has also been clearly identified with CT scans (6-9), and leads to a greater expansion of the nondependent regions and lesser expansion of the dependent parenchyma (6-8).

Contrarily while prone, the dorsal chest wall lifts, the diaphragm shifts similarly to supine position, and the ventral chest wall, now in contact with the firm surface of the bed, is impeded from expanding (8). In the prone position the gravitational forces compress the ventral region, but this effect is damped by regional expansion due to shape matching between lung parenchyma and vertebrae. As the lung mass is anatomically greater in dorsal regions (nondependent when prone) than in ventral region (dependent when prone), the increased aeration and recruitment of the dorsal region tends to exceed the decreased aeration and derecruitment of the ventral regions. That generates a more homogenous ventilation across the entire lung(6). Furthermore, when an individual is supine the heart compresses the medial posterior lung parenchyma (10) and the diaphragm compresses the posterior-caudal lung parenchyma, with the abdominal contents displacing the diaphragm cranially (8,10). Compression by either the heart and/or the diaphragm may exaggerate dependent lung collapse in the supine position (9). During prone ventilation, the heart becomes dependent, lying on the sternum, potentially decreasing medial-posterior lung compression (10). In addition, the diaphragm is displaced caudally, decreasing compression of the posterior-caudal lung parenchyma. A further advantage observed in prone position is both an improvement of ventilation/perfusion match and an increase in cardiac output: the latter is thought to be due to the effect of increased lung recruitment and reduction in hypoxic pulmonary vasoconstriction, resulting in increases in right ventricular preload and decreased right ventricular afterload and a decrease in pulmonary vascular resistance (11,12). An important recent study by Guerin et al. showed that prone positioning applied for at least 16 hours per day in patients with ARDS and PaO2/FiO2 < 150 mmHg significantly reduced 28-day mortality (16% vs 32%).(15) From currently available evidence, prone positioning may be of value even if there is no improvement in gas exchange [10-14].

c. ***Experience with awake prone positioning in self-ventilating patients***

Prone position results in improved ventilation and blood flow ratios. In mechanically ventilated and often paralysed patients, proning requires a high nursing input and patients are at risk for pressure sores related to the position. These issues are less pertinent in patients who are self-ventilating. Proning self-ventilating patients is not commonly carried out as patients with reduced oxygenation generally require assisted ventilation. However, avoidance of mechanical ventilation by improving oxygenation may be importance in COVID19 as outcomes for patients who require mechanical ventilation are poor and resources become limited. We have noted improvement with proning in self ventilating patients at both ward level and in the ICU for patients with confirmed COVID19 and in a patient without COVID19 with ARDS.

d. ***Rationale for treating patients with COVID19 pneumonia with awake prone positioning***

Patients with COVID19 that require invasive mechanical ventilation have a high mortality. We hypothesis that early proning for self-ventilating patients with suspected or confirmed COVID19 who have hypoxemia (spO2 <94%) despite high flow nasal cannula (fiO2 40%) will result in improved oxygenation, reduced work of breathing and a reduced the need for invasive mechanical ventilation.

4. ***Study Aims and Objective***
    a. ***Research hypothesis***

In patients that are hypoxic secondary to COVID19, the use of prone positioning will result in a reduction in requirement for invasive mechanical ventilation. Key secondary hypothesis include that prone positioning will result reduced requirement for assisted ventilation, in improved oxygenation as measured by either S/F or P/F ratio, reduced work of breathing.

    b. ***Study aim***

The study aims to assess the effect of prone positioning in patients who have hypoxemia related to COVID19 on:

- need for mechanical ventilation
- Improvement in oxygenation as measured by S/F or P/F ratio
- Patient work of breathing as measured by the respiratory distress observation scale
- tolerability of the position as measured by the total number of hours in prone position

    c. ***Study objectives***

Primary objective

To assess the effect of awake prone positioning on requirement for mechanical ventilation or death in patients with suspected or confirmed COVID 19 infection.

Secondary objective

To assess the effect of prone positioning on:

- Length of time tolerating prone positions measured in minutes from prone to request to return to supine position or emergency repositioning if required
- SpO2: FiO2 ratio (as a surrogate marker of P/F ratio) measured before proning and 1 hours after proning or P/F ratio where arterial line available
- Number requiring increase in ventilatory assistance (CPAP+BIPAP+IMV etc)
- Work of breathing assessment

5. ***Study Details***
    a. ***Study design***

Multi centre open label randomized controlled study in which patients are randomized to awake prone positioning or standard care. This trial is registered with ClinicalTrials.gov (NCT04347941). This trial is part of a prospective meta-trial listed in appendix 1.

    b. ***Study timeline***

Study will begin 5th june 2020 and until 28 days following the last enrolled patient

    c. ***End of study***

Study will continue until 28 days after the last enrolled patient or for 6 months until October 2020, depending on levels of enrolment.

6. ***Study outcome measure***
    a. ***Primary outcome measure***

Requirement for invasive mechanical ventilation or death by 28 days post enrolment

    b. ***Secondary outcome measure***

- Length of time tolerating prone positions measured in minutes from prone to request to return to supine position or emergency repositioning if required
- SpO2 : FiO2 ratio (as a surrogate marker of P/F ratio) measured before proning and 1 hours after proning or P/F ratio where arterial line available
- Number requiring increase in ventilatory assistance (CPAP+BIPAP+IMV etc)

7. ***Patient Eligibility***
    a. ***Study setting***

A monitored ward or ICU in which patients with confirmed or suspected COVID19 are receiving high flow nasal cannula

    b. ***Study population***

Patients who have *suspected or confirmed* COVID19 who have infiltrates on CXR and who have an oxygen requirement of >4L to keep oxygen saturations about 94% using high flow nasal cannula

    c. ***Eligibility criteria***

Inclusion criteria

Suspected or confirmed COVID19 infection
Bilateral Infiltrates on CXR
SpO2 <94% on FiO2 40% by high flow nasal cannula
Able to provide written informed consent

Exclusion criteria

Age <18
RR>40
Uncooperative or likely to be unable to lie on abdomen for 16 hours
Immediate need for intubation
SBP<80
Vomiting or bowel obstruction
Palliative care
Multiorgan failure
Standard contraindications to prone positioning include the presence of an open abdominal wound, unstable pelvic fracture, spinal lesions and instability, pregnancy > 20/40 gestation and brain injury without monitoring of intracranial pressure.

    d. ***Co-enrolment guidelines***

Patients will be eligible for inclusion in other studies

8. ***Patient screening, consent and recruitment***
    a. ***Patient screening***

All patients admitted to a COVID19 ward, COVID ICU or HDU will be screened for inclusion in the study.

    b. ***Informed consent procedure***

As patients will be self-ventilating, written informed consent or witnessed telephone consent to reduce fomite transmission will be obtained for each patient enrolled in the study. A patient information leaflet will be given to all patients screened as eligible. After a period of time to read and consider the information leaflet time will be given for questions, and then if the patient consents to be involved, written consent will be obtained. Due to the risk of fomite result of informed consent will be witnessed and recorded in the patient chart. The original consent form will be disposed of in yellow waste from the patient room, which should be destroyed.

9. ***Assignment of intervention***

Awake prone positioning will be performed before or 1 hour after meal. Call bell will be given to the patient and an oxygen probe will be attached to the patient to monitor spO2 during the procedure. Before PP, all the I.V. lines and nasal cannula will be checked by clinicians. Awake prone positioning will be performed by patient under the supervision of clinicians. Assistance will be offered if needed. If tolerated, PP will be maintained for at least 30 minutes, until the patients feel tired to keep that position. Patients will be informed to maintain prone position as long as they can. FIO2 will be adjusted to maintain SpO2 at 92-95%. Protocol for sedation and comfort evaluation during PP: No sedation will be used during the PP on ward. The patients are monitored by bedside respiratory therapist and nurses for their comfort and tolerance for the PP at 5mins, 30 minutes after PP for the first PP in each day.

    a. ***Withdrawal criteria***

- Patients cannot tolerate HFNC or prone position for 30 mins
- Patients experience any side effects during prone position, including vomit, dizzy, hypotension, etc.

    b. ***Weaning criteria***

- Patients' PaO2/FIO2 > 300, or SpO2/FIO2 > 340

    c. ***Treatment Failure Criteria***

Failure criteria: treatment failure is defined as one of the following criteria:

- Signs of persisting or worsening respiratory failure, defined by at least two of the following criteria:
    - Respiratory rate above 40 cycles/min
    - Lack of improvement of signs of respiratory-muscle fatigue
- -Development of copious tracheal secretions
- -Respiratory acidosis with a pH below 7.35
- -SpO2 below 90% at FIO2 ≥ 0.8 for more than 5 min without technical dysfunction

- Hemodynamic instability defined by a SBP below 90 mmHg, MBP below 65 mmHg or requirement for vasopressor;
- Deterioration of neurologic status (with AVPU to pain). For patients who meet the failure criteria in the standard treatment and PP groups, a trial of NIV will be allowed according to the physician's preference in patients with signs of persisting or worsening respiratory failure and no other organ dysfunction before performing endotracheal intubation and invasive ventilation. Reasons for intubation will be recorded as well.

d. Allocation and Randomisation

Within 6 hr of fulfilling inclusion criteria, a patient will be randomly allocated either to the prone positioning group or the control group (HFNC alone with no prone positioning therapy). Patients will be randomly allocated to either arm of the study at a ratio based on a 1:1 basis using a REDCAP randomisation process. Randomization will be stratified by site using tables of random permutations using the RECAP database for randomization. The random block length is 4, and random numbers are generated by computer.

e. Blinding

It is not feasible to blind staff or patients as to the procedure. Study data will be blinded for the purposes of analyses, assigned as group 1 or group2 rather than prone / not proned.

10. Schedule of assessment

a. Data collection and management

Data will be collected using an electronic case report form hosted in UCD. Details of CRF attached in appendix B. No patient identifiers will leave hospital unit and all data sent to CRF at NUI Galway will be pseudoanonymised. A collaborative data sharing agreement with UCD and NUI Galway has been developed. Aggregated data will be shared with investigators of the Awake Prone Positioning in COVID Meta-Trial for interim analysis and Anonymised data without personal identifying features will be sent for final analysis and co-reporting of outcomes.

b. Data quality

Data quality will be audited by the CRF at NUI Galway as responsibility of the study sponsor.

11. Statistical Considerations

a. Sample size

From ICNARC data on patients admitted to ICU with COVID19, 60% required advanced respiratory support. From this, we propose a 60% intubation rate in this cohort as defined above and that proning will decrease it to 40%. From this, 97 patients per group for a beta of 0.2 and alpha 0.05, requiring the need to recruit 196 patients. Interim analysis of data will be conducted using aggregated data as part of the Awake Prone Positioning in COVID Meta-Trial.

b. Analysis population

Data will be analysed on an intention to treat basis with all data for patients who consented to be involved included in baseline data analysis. Outcome data will be analysed for all patients who were positioned in the prone position for any length of time. A further per protocol analysis will be carried out on all patients who tolerated at least 1 hour of the daytime proning time and at least 2 hours of the night time proning period in any 24 hour period. Patients who were rescue proned will be considered a protocol deviation and will be studies as a group. Definition of the two groups: The

patients who receive the prone positioning are classified as prone positioning group. The patients who receive HFNC alone are classified as HFNC group. Comparisons between the two groups: Quantitative continuous variables are given as either means (±SDs) or medians (with inter-quartile ranges) are compared using the unpaired Student's t test or the Mann-Whitney test. Qualitative or categorical variables are compared with the chis quare test or the Fisher's exact test. ANOVA for paired tests to compare the same variables collected at different time points are used. The cumulative probability of remaining on spontaneous breathing are compared with the Kaplan-Meier estimate of survival and the log-rank test to compare the two groups. Univariate and multivariate analyses of risk factors for PP failure are performed with logistic regression. All analyses are in intention to treat, and the level of significance is set at 0.05.

c. Missing data

Missing data will be completed using last observation carried forward and the percentage of datasets with full or missing data will be reported.

12. *Data monitoring*

a. Data access and Monitoring arrangement

The eCRF has an audit trail in place, participating centres only have accounts available for delegated people and specific login accounts are created to only edit for their own site. External monitors can only view data and enter queries, they cannot change data. No directly identifiable data will be stored in the eCRF, e.g. only year of birth and no date of birth will be captured Audit trail in place (eCRF) compliant with 21 CFR part 11. The database is compliant with the EU Directive on data protection 95/46/EC. eCRF only accessible via site-specific (password-regulated) delegated log-in. (21 CFR part 11 compliance). Also compliant with the EU Directive on data protection 95/46/EC. A Standard contractual clauses for the transfer of personal data from the Community to third countries (controller to controller transfers) has been signed

13. Regulation, Ethics and Governance

a. Regulatory and ethics approval

Study has been approved by Galway University Hospitals Research ethics committee and the National research ethics committee (CA2352, 20-NREC-COV-054).

b. Protocol compliance

A Request for sponsorship from the CRFG at NUI Galway has been sought which will provide the necessary manpower for trial oversight, quality, statistical analysis. Online training on study protocol will be conducted prior to site initiation. Investigators will be available for any data entry queries or clinical concerns.

c. Good clinical practice

All individuals who will participate in conducting this study and have signed a delegation log will require an up to date certificate of good clinical practice.

d. Indemnity

Patients will be covered under the HSE Clinical Indemnity Scheme and by indemnity provided by the National University of Ireland, Galway

e. Patient confidentiality

A Data privacy impact assessment has been filed for the study. Patient confidentiality will be maintained by keeping data collected in the study coded. The key will be at the local study site where patient is included. No Personal details or identifying data will be transferred from the site to the sponsor where the data will be analysed. The coded data will be securely entered via the electronic case report form which will be managed by NUI Galway. The need data controlled will be the principal investigator, associate investigators, biostatisticians affiliated with NUI Galway. The site lead will have received training in regard to the requirements under GDPR that relate to health research. A data protection impact assessment has been completed and submitted to the SAOLTA data protection officer.

f. Data access

The data will be collected using a paper or digital case report form and the data will be collected in a coded form. The key for the data will be at the local study site in which the patient is included. Data will only be stored on protected and accredited servers. No personal details or identifying data will be transferred from the site to the coordinating centre at NUI Galway where the data will be analysed. The data will be retained for 15 years or as long as local legislation requires. Confidentiality will be maintained by sponsor only having access to coded data and the key only available at the local site. Clinical notes will need to be reviewed by the clinical research team on site. No identifiable data will be collected in the process. Information regarding current clinical presentation and clinical trajectory over the course of hospitalization will be collected Information regarding the patient will be taken out of the record and added to the case report form.

g. Record retention

Participants are requested to give consent to store their data for 15 years (without this permission, patient cannot participate). Next, participants are asked whether there coded data can be used for future research in the field of lung infections (data will also be stored 15 years for this purpose, with extra consent as described).

g. Competing interest

The principal investigators have no conflict of interest related to this study.

h. Data safety and Monitoring Board

Independent Investigators to fulfill data safety and monitoring board the study have been selected. This will be performed by Prof. Andrew Smyth, Galway University Hospitals, Dr. Rabia Hussein, Clinical research facility, UCD. A charter outlining the roles and responsibilities of the DSMB has been created. They will meet on-line after first patient has been enrolled.

14. Dissemination

Results of both registry and randomised controlled trial will be published in an international journal following peer review. To incentivise participation in the study, centres that recruit a patient will be permitted to have one author on final publication. For each additional 10 patients recruited, a further author from that centre will be added to the authors list.

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Appendix 1

Chicago: Jie Li, Sara Mirza, David Vines, Ahmad A Elshafei, Hangyong He, Tyler Weiss, Jonathan Brayd Scott, Lauren J Harnois, Ramandeep Kaur, Amnah A Alolaiwat

France: Elsa Tavernier, Stephan Ehrmann, Yonatan Perez, Jie Li, Jean-Pierre Frat (Scientific committee), List of principal investigators among 13 centers (TELLIER Anne Charlotte, REIGNIER Jean, GUITTON Christophe, NAY Mai-Anh, L'HER Erwan, THILLE Arnaud, DELLAMONICA Jean, PLANTEFEVE Gaëtan, ROUX Damien, DELBOVE Agathe, VOIRIOT Guillaume, NSEIR Saadalla)

.

Ireland: Bairbre McNicholas, David Cosgrave, Camille Giacomini, John Laffey, List of investigators among 10 centres

Quebec : Ivan Pavlov, Philippe Rola, Dev Jayaraman, Patrice Plamondon, Alexandra Hamel, Sean Gilman, Vincent Bouchard, Jason Kirkness

Spain: Oriol Roca, Marina García-de-Acilu, Gonzalo Hernández, Joan R Masclans, Sergi Martí, List of investigators among 4 centres.

4.5 Mexican protocol

Prone Positioning in Non-intubated Patients With COVID-19 Associated Acute Respiratory Failure (PRO-CARF)

Protocol version. 1.0 (Feb 15th, 2020)

Protocol Version. 2.0 (May 3rd, 2020)

Protocol version 2.1 (Nov 6th, 2020)

-Miguel Á. Ibarra-Estrada. Intensive Care Unit, COVID-19 Unit, Hospital Civil Fray Antonio Alcalde. Guadalajara, Jalisco.
-Roxana García-Salcido. COVID-19 Unit. Hospital Civil Fray Antonio Alcalde. Guadalajara, Jalisco.
-Sara A. Aguirre-Díaz. Infectious Diseases Department, COVID-19 Unit, Hospital Civil Fray Antonio Alcalde. Guadalajara, Jalisco.
-Miguel Marín-Rosales. Internal Medicine, COVID-19 Unit, Hospital General de Occidente. Zapopan, Jalisco.
-Alexandra Vargas-Obieta. Intensive Care Unit, COVID-19 Unit, Hospital Civil Fray Antonio Alcalde. Guadalajara, Jalisco.
-Quetzalcóatl Chávez-Peña. Intensive Care Unit, COVID-19 Unit, Hospital Civil Fray Antonio Alcalde. Guadalajara, Jalisco. Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Jalisco.
-José A. López-Pulgarín. Intensive Care Unit, COVID-19 Unit, Hospital Civil “Fray Antonio Alcalde”. Guadalajara, Jalisco. Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Jalisco.
-Julio C. Mijangos-Mendez. Intensive Care Unit, COVID-19 Unit, Hospital Civil Fray Antonio Alcalde. Guadalajara, Jalisco.
-Guadalupe Aguirre-Avalos. Intensive Care Unit, COVID-19 Unit, Hospital Civil “Fray Antonio Alcalde”. Guadalajara, Jalisco. Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara, Jalisco.

Background:

On December 2019, many cases of unknown origin pneumonia appeared in Wuhan, Hubei, China, resembling viral pneumonia. Deep sequencing analysis demonstrated the presence of a new beta-coronavirus, termed SARS-CoV-2 (1). Coronavirus-19 disease (COVID-19) is characterized by a rapid progression to respiratory failure after symptom onset. Most patients have criteria for acute respiratory distress syndrome (ARDS), consisting of acute radiographic infiltrates, hypoxemia, and lung edema of non-cardiac or fluid overload origin (2). However, many patients present with a mismatch between severity of hypoxemia and preserved lung mechanics. Therefore, ventilation-perfusion mismatch could predominate, which implies less alveolar collapse than expected, and response to regular therapies for ARDS may not be similar (3).

Despite general mortality of COVID-19 is less than 5%, it can reach up to 62% in critically-ill patients and even higher in patients with mechanical ventilation (4).

A still underused therapy but with proven benefit in patients with ARDS, is the prone positioning therapy, consisting of prone positioning of the patients everyday for prolonged periods, at least of 16 h, however it is only proven in mechanically ventilated patients (5).

There are scarce data regarding prone positioning in awake patients before COVI-19 pandemic. A retrospective study of 15 patients, showed this therapy combined with non-invasive mechanical ventilation significantly improved oxygenation, however this improvement was transient, as oxygenation returned to baseline at 6 h after prone sessions. There was not adverse events (6).

Another preceding study from china was published in 2019, this was a prospective observational trial which included 20 patients with moderate to severe ARDS. Authors found that prone positioning combined with oxygen through high-flow nasal cannula or non-invasive mechanical ventilation, improved significantly the pO2/FIO2 ratio, and half of the patients avoided intubation. However, according to the design of the study and low sample size, this can only be taken as hypothesis-generating data (7).

Regarding to prone positioning in COVID-19 patients, there are two observational reports, one of them with 24 (8) and the other with 15 patients (9), and only found a non-sustained improvement in oxygenation, and both had a short time to follow-up. The largest trial so far, is a feasibility prospective cohort (10), which included 56 patients, and also showed an improvement in pO2/FiO2 ratio, with an increase of 50% after a prone session of 3 hours, the pO2/FiO2 ratio returned to baseline levels in half of the patients; moreover, intubation rate was not different between patients considered as responders (increase in pO2/FiO2 ratio) and non-responders. Therefore the question if this therapy can lower the requirement of mechanical ventilation is still open.

Although prone positioning is a relatively safe therapy, it is not a standard of care and is only recommended for intubated patients with moderate to severe ARDS according to guidelines (11). Therefore, we propose this randomized controlled trial, as the potential benefit is high, and it could help to optimize resource utilization in patients with this COVID-19, as we foresee the maximal peak of the pandemic at our region is still far from now.

Objectives

Primary Objective

The primary outcome will be intubation rate for mechanical ventilation at 28 days.

Secondary objectives

The secondary outcomes will be:

1. Total hours of prone position at day, < at 28 days.
2. All laboratory variables recorded from admission to discharge.
3. Lung ultrasound (LUS) score at admission to COVID- unit
4. Total number of prone sessions at day, at 28 days.
5. Hours of the longest prone session each day, at 28 days.
6. Change in oxygenation 1-hour after first prone session.
7. Change in the ROX-index 1-hour after first prone session.
8. Total days of prone positioning therapy, at 28 days.

9. Adverse effects of prone positioning therapy (ulceration, back pain, intravenous lines dislodgement), at 28 days.
10. Mechanical ventilation days, at 28 days.
11. Intensive care unit length of stay, at 28 days.
12. Hospital length of stay, at 28 days.
13. Hospital mortality, 28 days.

Methods

This is a multi-center, parallel, superiority, open label, randomized controlled trial, registered with ClinicalTrials.gov (NCT04477655). Approved by the Ethic Committees of both participant hospitals. And informed consent will be obtained from all patients.

Inclusion criteria

-Regardless of diagnosis of acute respiratory distress syndrome, all adult patients (<18 y) patients with confirmed COVID-19 by PCR and respiratory distress will be included.
-Requirement of a fraction of inspired oxygen (FiO2) ≥30% through high-flow nasal cannula (HFNC) to maintain a capillary saturation of ≥90%.
-Written informed consent

Exclusion criteria

-Less than 18 years-old
-Pregnancy
-Patients with immediate need of invasive mechanical ventilation (altered mental status, fatigue)
-Vasopressor requirement to maintain median arterial pressure >65 mmHg
-Contraindications for prone positioning therapy (recent abdominal or thoracic surgery or trauma, facial, pelvic or spine fracture, untreated pneumothorax.
-Do-not-resuscitate or do-not-intubate order
-Refusal or disability of the patient to enroll in the study

Recruitment

All patients admitted with COVID-19 to intermediate and/or intensive care unit at

participating hospitals (any oxygen requirement) will be screened at two academic hospitals (Hospital Civil de Guadalajara and Hospital General de Occidente, Guadalajara, Jalisco, México), and patients with requirement of HFNC with FiO2 ≥30% will be approach to participate by on-site critical care physicians. In case of absence of exclusion criteria, written informed consent will be obtained before randomization.

Procedures (arms):

Patients of the control group will be treated with oxygen therapy through high flow nasal cannula (HFNC). Continuous monitoring of vital signs. Inspired fraction of oxygen will be titrated to maintain a capillary saturation of 92%-95%. Prone positioning will be allowed as a rescue therapy.

Patients of the experimental group will be also treated with oxygen therapy through high flow nasal cannula (HFNC). Patients will be asked to remain in prone position throughout the day as long as possible, with breaks according to tolerance. Pillows will be offered for maximizing comfort at chest, pelvis and knees. Monitoring of vital signs will not be suspended. Inspired fraction of oxygen will be titrated to maintain a capillary saturation of 92%-95%.

Staff intensivist will monitor adherence to protocol and patient's status of both groups on a 24/7 basis.

The prone positioning failure criteria will be:

-Worsening respiratory failure, defined as RR ≥40 /min and/or muscle fatigue
-Intolerance for any reason referred by the patient.
-Requirement of vasopressor to maintain MAP ≥65 mmHg
-Altered mental status

The decision for withhold prone positioning and proceed to endotracheal intubation will be left at the discretion of the attending intensivist. (see figure 1)

HFNC therapy will be initiated at 40 L/min and 37 ºC according to patient comfort and tolerance (Vapotherm, Precision flow, Exeter, New Hampshire), with FiO2 titrated to

a capillary saturation ≥92%, and will be continuously delivered until stopping criteria are met. The primary criteria for stopping the prone positioning therapy will be a requirement of a FiO2 ≤40% to maintain a capillary saturation ≥90% for at least 2 hours after the last prone session.

Randomization and data monitoring

Patients will be randomly allocated to either prone positioning or control group at 1:1 ratio. Such randomization will be stratified by center with permuted blocks and length of 4; numbers will be generated by computer and patients will be sequentially numbered. Investigators assistants will recruit patients, will assign allocation groups, and will obtain informed consent from participants.

Blinding

Due to logistic reasons and the nature of the intervention, only investigators and data analysts will be blinded.

Management of data

A steering local committee will monitor the trial, with assessment of inputs to database for consistence and the presence of missing data. Study coordinators at both centers will verify accuracy of database inputs. On-site investigators at each center are responsible for adherence to the protocol, and filling paper and electronic case-report forms (see appendix). All investigators will be blinded regarding patient allocation and outcome measures until database unlock. All personal data will be coded and de-identified, and paper CRF will be stored for at least 5 years into locked cabinets at each center.

This trial is expected to initiate on May and completion is estimated in December 30th. As this study includes only hospitalized patients, lost to follow-up is not expected, however, all analysis will be performed on an intention-to-treat basis in the case of protocol violations.

Data monitoring committee will be composed of all investigators, and they will be responsible for data monitoring at the primary level, whereas the local IRB will monitor the overall conduct of the study.

Adverse effects

All potential adverse effects are expected to be non-serious (ulceration, back pain, intravenous lines dislodgment), however, all related adverse effects will be documented for each patient, and all investigators will be notified monthly. In case of serious harm, the monitoring committee will discuss the termination of the study.

Statistical details

Sample size

With an intubation rate of 60% according to a recent report from some American centers , and assuming a decrease to 40% to be clinically relevant, we calculated at least a total of 96 patients per group, for a beta of 0.2, and alpha of 0.5. Therefore, we planned to recruit 200 patients, accounting for minimal losses to follow up. There are no plan for interim analysis.

At October 28th, after finish of recruitment with complete outcomes at follow up of the calculated sample, we found a lower than expected rate of intubation (38%), therefore, we asked for an expedited extension of the study, which was granted at November 6th, aiming to a new sample size calculated at 234 patients in each arm, for a total of 468.

Analysis

Categorical variables are presented as numbers and percentages, and comparison between groups will be performed with the chi-square test or the Fisher's exact test as appropriate. Continuous variables are given as means (±SD) or medians (inter-quartile ranges) and will be compared using the Student's t test or the Mann-Whitney test, according to Shapiro-Wilk test for distribution. For comparison between variables recorded at multiple time points, ANOVA for repeated measures will be used. The comparison between groups for cumulative probability of avoiding endotracheal intubation will be performed with Kaplan-Meier analysis and log-rank test. Analysis with ROC curve will be performed with prone positioning hours/day, taking endotracheal intubation as an endpoint. All tests will be performed at two-tails and a p value <0.05 will

be considered as significant. All statistical analysis and graphics will be performed with MedCalc statistical software
(Ostend, Belgium).

Ethics approval

This study initiated immediately after the approval from the institutional review boards at each hospital.

Protocol amendments

One of the investigators (GAA) was responsible for documentation of the protocol amendments, and for process the approval from the IRB.

Conflict of interests

All authors hereby declare that they not have any conflict of interest

Access to data

Only investigators and IRB audit tema will have access to data.

Dissemination policy

Relevant clinical data obtained in this study will be published in peer-review journals of critical/respiratory care, without disclosing any individual patient data. All the investigators will be authors in those final publications. Patient level data, could be shared to abroad investigators on a reasonable request, after data sharing agreement is granted from the local IRB. Sharing of statistical code is not planed.

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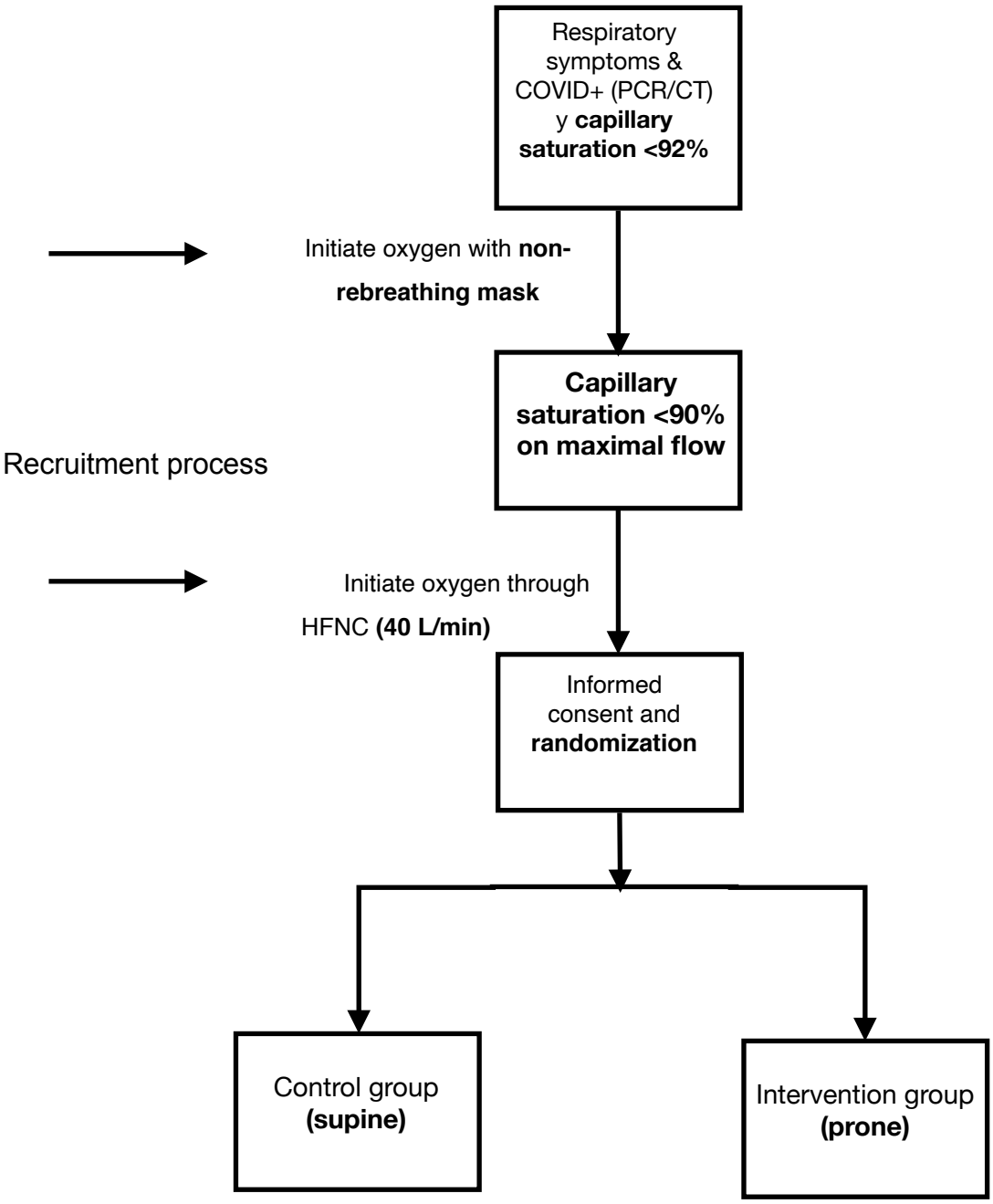

Endotracheal intubation for all patients whose **capillary saturation is ≤80% despite 100% inspired oxygen** and maximal tolerated flow, as well as patients with CO2 retention, **progressive clinical worsening in respiratory distress**, anxiety or altered mental status, regardless the magnitude of oxygen support.

Hospital Civil Fray Antonio Alcalde

Consentimiento Informado

Nombre del Investigador Principal: Dr. Miguel Ángel Ibarra Estrada

Este Formulario de Consentimiento Informado se dirige a hombres y mujeres que son atendidos en los hospitales mencionados en el encabezado, y que se les invita a participar en la investigación clínica Uso de posición prona en pacientes despiertos con síndrome de dificultad respiratoria aguda moderado/ severo y COVID-19

Introducción

Yo soy el Dr. Miguel Ángel Ibarra Estrada, trabajo para el Instituto Jalisciense de Cancerología, el Hospital Civil de Guadalajara, y el Consejo Nacional de Ciencia y Tecnología. Estamos investigando sobre el uso de un método no ventilatorio considerado actualmente como "no convencional" en pacientes con Síndrome de Falla Respiratoria Aguda asociada a COVID-19, una entidad muy común a nivel global actualmente. Le voy a dar información e invitarle a participar de esta investigación. No tiene que decidir hoy si participar o no en esta investigación. Antes de decidirse, puede hablar con alguien con quien se sienta cómodo sobre la investigación.

Puede que haya algunas palabras que no entienda. Por favor, interrúmpame según le informo para darme tiempo a explicarle. Si tiene preguntas más tarde, puede preguntarme a mi, a otros doctores que investigan o a miembros del equipo médico.

Propósito

El Síndrome de Dificultad Respiratoria Aguda asociada a COVID-19 es un estado de gravedad asociado a una alteración severa en los pulmones, que no permite que el oxígeno que se respira se traslade a la sangre. A pesar de las mejoras en el tratamiento especializado en las últimas décadas, aproximadamente 6-8 de cada 10 de los pacientes que son intubados, fallecen. Existe un modo no ventilatorio ya conocido, aunque poco utilizado en nuestro país, que podría favorecer el mejoramiento de este estado de gravedad y potencialmente evitar la intubación y que usted o su familiar tengan que recibir soporte ventilatorio mecánico. El determinar con certeza el beneficio potencial de este método es la razón por la que hacemos este estudio.

Tipo de Intervención de Investigación

Esta investigación incluirá el manejo no ventilatorio llamado "pronación", que consiste en voltearlo a usted o a su familiar 'boca abajo' la mayor parte del día según lo tolere, cuando el equipo médico identifique que se encuentra en riesgo alto de requerir ventilación mecánica, y se llevará a cabo desde la identificación de la alteración pulmonar moderada/severa hasta la resolución o desenlace final.

Selección de participantes

Estamos invitando a todos los adultos con Síndrome de Dificultad Respiratoria Aguda asociada a COVID-19 para participar en la investigación sobre un método no ventilatorio alternativo con potencial para mejorar su pronóstico.

Participación Voluntaria

Su participación (o la de su familiar) en esta investigación es totalmente voluntaria. Usted puede elegir participar o no hacerlo. Tanto si elige participar o no, continuarán todos los servicios que reciba en esta unidad y nada cambiará. Usted puede cambiar de idea más tarde y dejar de participar aún cuando haya aceptado antes.

Información sobre el método de investigación

El método de pronación es un método aplicado desde hace más de 20 años a los pacientes con síndrome de dificultad respiratoria aguda. Se ha probado antes con personas con este tipo de enfermedad pulmonar, aunque solo en los que ya estuvieron recibiendo ventilación mecánica, demostrando resultados favorables al grado de volverse una recomendación ampliamente aceptada en

todo el mundo. Ahora queremos probar este método en personas de nuestro entorno con insuficiencia respiratoria asociada a COVID-19 pero desde antes de ser intubados. A esta investigación se la denomina “Fase 2” de un ensayo clínico.

Debe saber que aunque cualquier tipo de manejo de pacientes graves tiene efectos adversos potenciales, de este método en particular solo se han reportado eventualidades no serias como ulceraciones o edema en cara, o dolor transitorio en brazos o espalda.

Algunos de los participantes en la investigación no serán tratados con dicho método. En su lugar, recibirán el manejo estándar que es básicamente el recomendados actualmente según autoridades internacionales.

Procedimientos y Protocolo

Necesitamos verificar la eficacia y seguridad de la terapia de pronación. Para hacer esto, pondremos a los participantes en dos grupos. Los grupos son seleccionados por azar, al igual como lanzar una moneda al aire.

Los trabajadores de la salud le estarán observando cuidadosamente y también a los otros participantes durante el estudio. Si llega a preocuparnos lo que la pronación hace, podremos realizar cambios inmediatos en el manejo. Si existe algo que le preocupe o que le moleste sobre la investigación, por favor hable conmigo o con alguno de los otros investigadores. Usted recibirá el resto del tratamiento de su condición bajo pautas internacionales.

Duración

El seguimiento que se le dará a usted o a su familiar incluirá toda su estadía en la unidad COVID del Hospital Civil Fray Antonio Alcalde y hasta su egreso.

Efectos Secundarios

Como ya se mencionó, este método ventilatorio no tiene efectos adversos serios. Es posible que pueda también causar problemas que aún no conocemos. Sin embargo, le haremos un seguimiento y mantendremos un registro de cualquier efecto no deseado o cualquier problema. Puede que usemos otros métodos para disminuir los síntomas de los efectos secundarios o reacciones. O puede que dejemos de usar el método experimental. Si esto es necesario, lo discutiremos con usted y siempre se le consultará antes de continuar con el próximo paso.

Beneficios

Si usted o su familiar participa en esta investigación, no se garantiza que obtenga ningún beneficio personal. Puede que no halla beneficio para usted, pero es probable que su participación nos ayude a encontrar una respuesta a la pregunta de investigación. Puede que no haya beneficio para la sociedad en la fase actual de la investigación, pero es probable que generaciones futuras se beneficien.

Confidencialidad

Con esta investigación, se realiza algo fuera de lo ordinario en su comunidad. Es posible que si otros miembros de la comunidad saben que usted participa, puede que le hagan preguntas. Nosotros no compartiremos la identidad de aquellos que participen en la investigación. La información que recojamos por este proyecto de investigación se mantendrá confidencial. La información acerca de usted o su familiar que se recogerá durante la investigación será puesta fuera de alcance y nadie además de los investigadores tendrán acceso a ella. Cualquier información acerca de usted tendrá un número en lugar de su nombre. Solo los investigadores sabrán cual es su número y se mantendrá la información encerrada en cabina con llave. No será compartida ni entregada a nadie.

Derecho a negarse o retirarse

Usted no tiene porque participar en esta investigación si no desea hacerlo, y el negarse a participar no le afectará en ninguna forma a que sea tratado en esta unidad. Usted aún tendrá todos los beneficios que de otra forma tendría. Puede dejar de participar en la investigación en cualquier momento que desee sin perder sus derechos como paciente aquí. Su tratamiento no será afectado en ninguna forma.

A Quién Contactar

Si tiene cualquier pregunta puede hacerlas ahora o más tarde, incluso después de haberse iniciado el estudio. Si desea hacer preguntas más tarde, puede contactar cualquiera de las siguientes

personas: Miguel Ángel Ibarra Estrada, Guadalupe Aguirre Avalos, Quetzalcóatl Chávez Peña (Hospital Civil Fray Antonio Alcalde, Unidad de Terapia Intensiva).

Formulario de Consentimiento

He sido invitado a participar en la investigación de un método no ventilatorio relativamente nuevo llamado pronación, para el manejo del Síndrome de Dificultad Respiratoria Aguda asociada a COVID-19. He sido informado de que los riesgos asociados directamente al manejo son mínimos. Se me ha proporcionado el nombre de uno o más investigadores que pueden ser contactados en caso de requerir mayor información.

He leído la información proporcionada o me ha sido leída. He tenido la oportunidad de preguntar sobre ella y se me han contestado satisfactoriamente las preguntas que he realizado. Consiento voluntariamente participar (o que mi familiar participe) en esta investigación, y entiendo que tengo el derecho de retirarme de la investigación en cualquier momento sin que afecte en ninguna manera mi cuidado médico (o de mi familiar).

Nombre del Participante _____

Nombre y firma del participante o representante legal _____

Fecha (día/mes/año) / /

Iniciales del investigador o asistente:_____

Effect of prone position in awake patients supported by nasal high flow therapy in patients with coronavirus-2 pneumonia

Oriol Roca[1], Andrés Pacheco[1], Marina García-de-Acilu[1], Irene Dot[2], Joan R. Masclans[2].

[1]Servei de Medicina Intensiva, Hospital Universitari Vall d'Hebron, Barcelona, Spain

[2] Servei de Medicina Intensiva, Hospital del Mar, Barcelona, Spain

Acknowlegement

This study protocol is adopted from French trial protocol

Summary

Introduction

Prone position decreases mortality in intubated patients with acute respiratory distress syndrome (ARDS). Nasal high flow may decrease intubation rates in patients with hypoxemic respiratory failure.

Hypothesis

Awake proning may decrease intubation rates and/or mortality in patients with coronavirus infectious disease 2019 (COVID-19).

Objective

To analyze whether the use of awake prone position (APP) decreases intubation rates and mortality in COVID-19 patients. Secondary, the efficacy of APP in terms of oxygenation, progression of pneumonia and patient outcome will be also analyzed.

1. BACKGROUND

Acute Respiratory Distress Syndrome (ARDS) induces high mortality, particularly in the context of COVID-19 disease. In patients with ARDS, invasively mechanically ventilated via a tracheal tube and exhibiting a PaO2/FiO2 (arterial oxygen partial pressure to inspired oxygen fraction) ratio of less than 150 mmHg, the prone decubitus position has been shown to significantly reduce mortality (Guérin 2013).

Moreover, the implementation of high-flow nasal cannula therapy, a non-invasive respiratory assistance and oxygenation technique, has reduced the use of intubation and has reduced mortality in the most severe patients (PaO2/FiOratio2 ratio less than 200 mmHg) with hypoxic acute respiratory failure (Frat 2015).

Proning patients with ARDS and treated with high-flow nasal cannula therapy was evaluated in 20 patients suffering primarily from viral pneumonia (Ding 2020). Proning was found to be feasible and associated with an increase in the PaO2/FiO2 ratio.

Preliminary data from patients with ARDS-related COVID-19 appear to show significant efficacy of prone decubitus in intubated patients in terms of oxygenation as well as high-flow nasal cannula therapy before intubation. Thus, nearly half of the resuscitation patients described in the originator cohort of Wuhan City, Hubei Province, China, had received high-flow nasal cannula therapy (Huang 2020). It should be noted that in the secondarily affected province of Jiangsu, high-flow nasal cannula therapy combined with prone decubitus has been successfully incorporated into care protocols (Sun 2020).

Several potential mechanisms suggest a benefit from early prone decubitus of conscious patients under high-flow nasal cannula therapy. First, the improvement in oxygenation observed in many patients can be mediated by two complementary mechanisms: pulmonary vascular redistribution of pulmonary arterial cardiac output and alveolar recruitment of hypoventilated dependent areas. The first mechanism may be predominant in patients with COVID, but in all cases, prone decubitus is a simple non-pharmacological means of improving ventilation/perfusion ratios (Gattinoni 2020). Improved ventilation/perfusion ratios due to greater efficiency of the pulmonary exchanger may reduce patients' respiratory work and potentially the associated ventilation control. Thus, in conscious patients with high respiratory control causing

significant pulmonary mechanical stress (tidal volume and high respiratory rate), potentially causing so-called "patient self-inflicted" lung damage (PSILI), prone decubitus is likely to reduce lung stress. Moreover, similar to that observed during prone decubitus in intubated patients, a homogenisation of pleural pressure gradients is expected, also resulting in a reduction in pulmonary shear stresses.

Prone decubitus implementation in conscious patients allows us to consider all the benefits associated with this technique, without the disadvantages of tracheal intubation, sedation or even neuromuscular paralysis.

We hypothesise that the combined application of high-flow nasal cannula therapy and prone decubitus significantly improves the outcome of patients with COVID-19 by reducing the use of tracheal intubation and associated therapies such as sedation and curare administration, resulting in both individual and collective benefit in terms of the mobilisation of resuscitation resources.

The approach is completely novel given the lack of large-scale data on prone decubitus during high-flow nasal cannula therapy and is particularly suited to the context of the COVID epidemic given the tension on resuscitation beds and ventilators.

2. REFERENCES

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3. OBJECTIVES

3.1. PRIMARY OBJECTIVE

To evaluate the clinical benefit of prone decubitus in patients with COVID and treated with high-flow nasal cannula therapy in terms of reducing the use of heavier oxygenation techniques and reducing mortality.

3.2. SECONDARY OBJECTIVES

Evaluate effectiveness in terms of:

- Patient oxygenation
- Clinical course of pneumonia
- Patient clinical outcome

Evaluate the tolerance and safety of the technique at the individual level.

4. STUDY OUTLINE

This is a multi-centre, randomised, open-label, two parallel-group superiority trial with a 1:1 allocation ratio and individual randomisation.

5. PARTICIPANTS

5.1. INCLUSION CRITERIA

- Adult patient suffering from, or very strongly suspected of suffering from COVID-19 pneumonia according to the diagnostic criteria in force at the time of inclusion
- Patient treated with high-flow nasal cannula therapy who meet ARDS criteria
- Informed consent

5.2. EXCLUSION CRITERIA

- Indication of immediate tracheal intubation

- Progressive acute circulatory deficit: vascular filling of more than 1000 mL, initiation or increase of more than 0.1 µg/kg/min of noradrenaline infusion to maintain systolic blood pressure greater than 90 mmHg in the hour preceding inclusion. Patients stable on a low dose of noradrenaline (<0.3 µg/kg/min), possibly after initial vascular filling not renewed in the hour preceding inclusion, can be included.
- Impaired alertness, confusion, agitation
- Body mass index greater than 40 kg/m2
- Chest trauma or other contraindication to prone position
- Pneumothorax
- Vulnerable person: known legal guardianship, curatorship or tutorship at inclusion
- Pregnant or breast-feeding women

6. ENDPOINTS

6.1. PRIMARY ENDPOINT

The primary endpoint is treatment failure defined by death or intubation or the use of non-invasive dual-pressure ventilation during the 14 days following randomisation, measured by the investigator on the 14th day after randomisation.

Criteria for tracheal intubation: In order to standardise the intubation decision and avoid any delay in intubation, patients meeting one of the following criteria will be intubated (Coudroy 2019, Frat 2015):

- Neurological failure: agitation or altered consciousness, with a Glasgow coma scale of less than 12 points
- Haemodynamic failure: continuous infusion of norepinephrine greater than 0.3 µg/kg/min with signs of tissue hypoperfusion.
- Worsening respiratory failure: two criteria among:
    - Respiratory rate greater than 40 cycles per minute,
    - Occurence or increase in the use of accessory respiratory muscles.
    - Deep hypoxaemia: need for 80% FiO_2 to maintain SpO2 above 92% or PaO2/FiO_2 ratio below 100 mmHg

- Respiratory acidosis with pH <7.35

6.2. SECONDARY ENDPOINTS

- Therapeutic failure within 28 days of randomization: death or intubation or use of non-invasive ventilation with two levels of pressure.

- Time to intubation or death

- Time to onset of treatment escalation (in case of recourse to non-invasive ventilation with two pressure levels)

- Progression of oxygenation in the supine position over the 14 days following randomisation (PaO2/FiO2 ratio in the event of arterial blood gas measurement, SpO2 (pulse oximetry with SpO2 ≤ 97%)/FiO2, ROX index: SpO2/FiO2/Respiratory rate: Roca 2019): 1 daily morning measurement in the supine position. For all substitutions of PaO2 by SpO2, only values of SpO2 ≤97% will be taken into consideration.

- Progression of the SpO2/FiO2 ratio (SpO2 ≤97%) and of the ROX index during the first prone positioning session: difference between the value immediately before proning, the value 30 minutes after proning, the value 2 hours after proning and after returning to supine decubitus.

- Progression of the WHO COVID-19 disease severity score at D7, D14 and D28 after randomisation (WHO 2020): 1. Not hospitalised, normal activities 2. Not hospitalised, unable to perform normal activities, 3. Hospitalised without oxygen therapy, 4. Hospitalised with oxygen therapy, 5. Hospitalised with high flow nasal oxygen therapy and/or non-invasive ventilation, 6. Hospitalised with invasive mechanical ventilation and/or ECMO, 7. Death

- Patient comfort before, during and after the first proning session (visual analogue scale)

- Occurrence of skin lesions on the anterior surface of the body

- Displacement of intravascular devices during turnovers

- Duration of use of high-flow nasal cannula therapy in the general population, in both non-intubated and intubated patients

- Length of stay in intensive care and hospital

- Mortality in intensive care and in hospital

- Number of days living without ventilation in the 28 days following randomisation

7. NON-PHARMACOLOGICAL INTERVENTION

7.1. EXPERIMENTAL GROUP

High-flow nasal cannula therapy adapted for 90-95% SpO_2. Unless poorly tolerated by the patient, a minimum gas flow rate of 50 L/min will be initially set. Weaning from high-flow nasal cannula therapy will first be performed by FiO2, which will be gradually reduced to 40% before reducing the gas flow. In patients clinically stable at an FiO2 less than or equal to 40% and gas flow less than or equal to 30 L/min, a switch to standard oxygen therapy at 4-6 L/min will be attempted.

FiO2 readings in patients weaned from high-flow nasal cannula therapy will be continued throughout the study using the following calculation formula summarised in the table below, regardless of the oxygenation interface: FiO2 = 0.21 + (oxygen flow *0.03).

Débit oxygène (L/min)	FiO2
1	24
2	27
3	30
4	33
5	36
6	39
7	42
8	45
9	48
10	51
11	54
12	57
13	60
14	63
15	66

Prone position: depending on tolerance, the objective is to spend as much time as possible, up to 16h and beyond, in prone position per period of 24 hours. At least two sessions of at least 30 minutes each must be performed daily.

In connection with TIDieR guidelines ("Template for Intervention Description and Replication": http://www.equator-network.org/reporting-guidelines/tidier/), proning will follow the principles specified in Table 1.

Proning sessions will be continued daily as long as the PaO2/FiO2 ratio or the SpO2/FiO2 ratio is below 300 mmHg or 315, respectively.

In the event of weaning from prone positioning following patient improvement, proning sessions will be resumed if the patient again meets the oxygenation criteria (PaO2/FiO2 or SpO2/FiO2 less than 300 mmHg or 315, respectively), and this until D28 if the patient is still in the unit. In the event of discharge from the unit and readmission, the patient will also be reassigned to their randomization arm and, if necessary, returned to prone position in accordance with the protocol.

Otherwise usual care: application of national and international guidelines.

7.2. CONTROL GROUP

High-flow nasal cannula therapy adapted for 90-95% SpO2. Unless poorly tolerated by the patient, a minimum gas flow rate of 50 L/min will be initially set.

Weaning from high-flow nasal cannula therapy will first be performed by FiO2, which will be gradually reduced to 40% before reducing the gas flow. In patients clinically stable at an FiO2 less than or equal to 40% and gas flow less than or equal to 30 L/min, a switch to standard oxygen therapy at 4-6 L/min will be attempted.

FiO2 readings in patients weaned from high-flow nasal cannula therapy will be continued throughout the study using, whatever the oxygenation interface, the following calculation formula summarised in the table indicated in paragraph 7.1: FiO2 = 0.21 + (oxygen flow * 0.03)

Otherwise usual care: application national and international guidelines.

In the event of discharge from the unit followed by readmission before the 28th day after randomisation, the patient will be reassigned to their randomization group and thus left in the supine position.

7.3. CHANGES TO THE INTERVENTION

Minor adaptations to the proning procedure may be considered depending on patient preference and tolerance, as well as in the event of the emergence of new scientific data. In the event of poor tolerance by the patient, in particular during the first session, every effort will be made to try to repeat the sessions with the intention of conducting at least 2 sessions of 30 minutes per day. The aim is to spend as much time as possible per 24-hour period in prone position (up to 16h and beyond over 24 hours).

In the event of medical intolerance to the prone position, the proning session may be interrupted at any time. If intubation criteria appear (see paragraph 4.1), the patient will be placed on their back urgently and intubated if the criteria persist.

7.4. ELIGIBILITY CRITERIA FOR PEOPLE PERFORMING THE INTERVENTION

Proning will be performed with the help and under the supervision of a registered nurse or a doctor, always under the responsibility of the centre's principal investigator.

7.5. ADHERENCE TO THE INTERVENTION

Compliance with the randomisation group (i.e. intervention for the experimental group or no intervention for the control group) will be checked by the medical and paramedical caregivers as part of routine patient monitoring.

For patients in the experimental group, the number of sessions and the total time spent in prone position will be collected per 24-hour period. Patient comfort will be assessed before, during and after the first proning session. The prone positiion start and end times will also be noted.

Any deviations (proning of patients in the control group in particular) will be noted. Patients will also be asked not to change their supine/prone position on their own, but to ring the bell and ask a caregiver.

7.6. CONCOMITANT TREATMENTS AND INTERVENTIONS

All drug and non-drug treatments are authorised.

In particular, right and left lateral decubitus postural interventions are authorised in both trial groups under the responsibility of the physician in charge of the patient.

Prone positioning is not allowed in patients in the control group.

In both trial groups, in the event of tracheal intubation and invasive mechanical ventilation, proning is freely determined by the physician in charge of the patient in accordance with national and international guidelines.

8. COURSE OF THE STUDY

8.1. SELECTION AND RECRUITMENT OF TRIAL PARTICIPANTS

Screening of individuals will be carried out by clinical research technicians, research nurses and investigators in the participating centres. All patients receiving oxygen therapy greater than or equal to 4 L/min and presenting with confirmed or strongly suspected COVID disease will be considered for potential inclusion. Each week, the list of patients assessed for inclusion will be sent to the clinical research associate coordinating the study (screening logs).

8.2. INCLUSION

Patients will be included by an investigator after verification of all inclusion and non-inclusion criteria as well as the delivery of information and the collection of consent in compliance with the rules of good clinical practice

Note that patients will keep a copy of the information letter and the signed consent. The original documents will be kept by the investigator.

8.3. INTERVENTION

Upon inclusion, the patient will be randomized as quickly as possible. Patients assigned to the intervention group will be placed in the prone position within no more than 6 hours of inclusion.

8.4. FOLLOW-UP

1st proning: the patient's comfort will be evaluated immediately before, during the session (30 minutes to 1 hour and 2 hours after proning) and after recovery in supine position. Oxygenation (SpO2/FiO2 ratio, ROX index and PaO2/FiO2 ratio in the event of blood gas production) will be evaluated immediately before, during (30 minutes to 1 hour and 2 hours after placing in prone position) and after return to supine position. Side effects will be noted (secondary endpoints).

Subsequent proning sessions: oxygenation will be assessed daily, in the morning if possible, in supine position. Any side effects will be noted (secondary endpoints).

D14 after inclusion: primary endpoint evaluation.

D28 after inclusion or discharge from hospital if this occurs before D28: end of follow-up, evaluation of secondary endpoints not noted up to this stage. *

Study timeline	Inclusion	Randomization	Follow-up			End of study
		T0	D1	D7	D14	D28 or discharge from hospital
Verification of eligibility criteria	X					
Information and consent	X					
INTERVENTIONS:						
Intervention group: Daily proning sessions		←	—	—	—	→
Control group: No proning sessions						
EVALUATIONS:						
Number of proning sessions and time spent in prone position			←	—	→	
Daily oxygenation measurement *(PaO_2, $SpO2$, $FiO2$, respiratory rate)*	X Description at inclusion		←	—	→	
Treatment Failure *(death, intubation or use of non-invasive ventilation with two pressure levels)*					X	X
Comfort (1st proning session)			X			
WHO COVID-19 scale				X	X	X
Adverse events *(especially those related to proning)*		←	—	—	→	X
Permanent withdrawal of high-flow nasal cannula						X
Length of stay (intensive care/hospital)						X
Vital status						X
Number of days alive without ventilation						X

All blood gas samples are collected as part of routine patient care under the responsibility of the physician in charge of the patient.

8.5. ENDING THE PARTICIPATION OF A RESEARCH SUBJECT

All the data must be collected as specified by the protocol, regardless of deviations (e.g.: early termination of the procedure) or changes to the patient's management (e.g.:

following the occurrence of an SAE). The only possible reason for stopping data collection is withdrawal of consent. The data will be analyzed by intent to treat (each patient will be analyzed in the group in which they were randomized).

Trial participants will be able to withdraw their consent and request to stop the study at any time and for any reason. The investigator must document the reasons as extensively as possible. In accordance with article L1122-1-1 of the French public health code, and unless expressly requested otherwise, the data obtained until the withdrawal of consent will be used during analyses.

The investigator may temporarily or permanently interrupt the procedure under study for any reason that would serve the best interests of the person participating in the research, in particular in the event of serious adverse events.

8.6. TERMINATION OF PART ALL OF THE RESEARCH

The study may be terminated prematurely in the event of the occurrence of unexpected serious adverse events requiring a review of the safety profile of the intervention. Likewise, unforeseen events or new information relating to the intervention, in view of which the objectives of the study or clinical programme are unlikely to be achieved, may cause the sponsor to prematurely discontinue the study. The Tours Regional University Hospital reserves the right to interrupt the study at any time if it turns out that the inclusion objectives have not been achieved.

In the event of premature termination of the study, the information will be sent by the sponsor within 15 days to ANSM and the CPP.

8.7. STUDY DURATION

The total duration of participation in the study for the person participating in the research is 28 days from the date of inclusion to the date of the last visit carried out in the context of the study.

The inclusion period is 18 months.

The total study duration is expected to be 19 months.

From the first inclusion, the sponsor must inform, without delay, the competent authority and the CPP of the effective start date of the study (date of consent signature

by the first person to take part in the research). The study end date will be sent by the sponsor to the National Agency for the Safety of Medicines and Health Products (ANSM) and to the CPP within 90 days. The research end date corresponds to the end of the participation of the last person to take part in the research, or, if applicable, to the term defined in the protocol.

9. RANDOMIZATION

9.1. RANDOMIZATION LIST GENERATION

Persons participating in the research will be randomized into two groups (experimental group or control group) according to a ratio of 1: 1 using a randomization list generated using SAS©. Randomization will be stratified by centre and by use of proning for therapeutic purposes before inclusion. Variable block sizes will be used. These elements will not be communicated to the sponsor or to the investigators.

9.2. IMPLEMENTATION

The random sequences will be implemented by a statistician from CIC INSERM1415 who is independent of the investigating centres.

9.3. ALLOCATION

The subjects will be randomized centrally via a website (Ennov Clinical©). To ensure secret allocation, the randomization procedure will be possible only if all the inclusion and non-inclusion criteria are met.

10. BLINDING

Blinding is not possible for the intervention under study for the patient, investigators, research personnel or caregivers. The study will therefore be conducted in an open-label manner.

11. OTHER STRATEGY TO REDUCE BIAS

The endpoint includes tracheal intubation or the use of non-invasive ventilation with two levels of pressure within 14 days of randomization, which is not a fully objective outcome. Intubation criteria were therefore defined in order to standardise the decision for tracheal intubation.

Note that this criterion is being harmonised with a North American project (NCT04325906) with a view to a joint analysis of the results.

Likewise, weaning from proning and high-flow nasal cannula therapy is standardised in the protocol.

12. STATISTICAL ANALYSES

12.1. DEFINITION OF ANALYSIS POPULATIONS

The analysis will be carried out according to the intent-to-treat principle: all randomized patients will, whatever happens, be taken into account in the analysis in the arm to which they were allocated.

A subgroup analysis is planned according to the severity of ARDS (mild if the PaO2/FiO2 ratio is between 200-300; moderate if it is between 100-200 and severe if it is ≤100).

12.2. DESCRIPTION OF CHARACTERISTICS AT INCLUSION

Patient characteristics at inclusion will be described and compared according to the groups resulting from the randomisation using the following descriptive statistics (no statistical test will be carried out): i) for qualitative variables, population size and percentages, ii) for quantitative variables, mean and standard deviation or median and interquartile range depending on the distribution.

12.3. PRIMARY ENDPOINT ANALYSIS

The primary analysis will be based on a mixed logistic regression adjusting for the stratification variable. The intervention effect will be expressed in the form of an odds ratio accompanied by its 95% confidence interval. The intervention effect will also be reported in the form of a difference in proportions (consort 17b).

12.4. ANALYSIS OF SECONDARY ENDPOINTS

The treatment failure at 28 days will be analysed by a Cox model or by mixed logistic regression if the assumption of proportionality of the risks is not respected.

The time to onset of treatment failure and treatment escalation will be analyzed by Wilcoxon tests.

Oxygenation changes in supine position over the 14 days following randomisation will be analysed in the context of a mixed linear regression model, with the randomisation arm interacting with time in fixed effects, along with a patient-level intercept and random slope.

Changes in the SpO2/FiO2 ratio and the ROX index during the first proning session will be analyzed as part of a linear regression model

The WHO COVID disease severity score will be analysed sequentially on D7, D14 and D28 after randomization by chi-square tests.

Changes in patient comfort before, during and after the first proning session (visual analogue scale) will be analyzed as part of a student test for paired data.

The duration of use of high-flow nasal cannula therapy will be analyzed in the context of a linear regression model.

The lengths of stay in intensive care and in hospital will be analyzed in the context of a linear regression model

The mortality rates in intensive care units and in hospital will be analyzed as the primary endpoint.

The number of days alive without ventilation during the 28 days following randomization will be analyzed by a Wilcoxon test.

A sensitivity analysis will be performed on the primary endpoint by considering, in the intervention arm, only those patients who have adhered to the intervention (adherence to the treatment will be defined by the number of sessions performed and their durations).

A sensitivity analysis will be performed on the primary endpoint in the subgroup of patients who have not participated in any other open-label COVID study and who have been randomised to the intervention arm or other blind COVID study.

12.5. INTERMEDIATE ANALYSES

No intermediate analyses will be performed.

12.6. POPULATION CALCULATION

For a primary endpoint occurrence of 70% in the control group and 50% in the intervention group, with a power of 80% and an alpha risk of 5%, we plan to include 248 subjects or 124 patients per group.