Does awake prone positioning prevent the use of mechanical respiratory support or death in COVID-19 patients on standard oxygen therapy hospitalised in general wards? A multicentre randomised controlled trial: the PROVID-19 protocol

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ABSTRACT

Introduction COVID-19 is responsible of severe hypoxaemia and acute respiratory distress syndrome (ARDS). Prone positioning improves oxygenation and survival in sedated mechanically patients with ARDS not related to COVID-19. Awake prone positioning is a simple and safe technique which improves oxygenation in non-intubated COVID-19 patients. We hypothesised that early prone positioning in COVID-19 patients breathing spontaneously in medical wards could decrease the rates of intubation or need for noninvasive ventilation or death.

Methods and analysis PROVID-19 is an investigator-initiated, prospective, multicentre randomised, controlled, superiority trial comparing awake prone positioning to standard of care in hypoxaemic COVID-19 patients in 20 medical wards in France and Monaco. Patients are randomised to receive either awake prone position plus usual care or usual care alone with stratification on centres, body mass index and severity of hypoxaemia.

The study objective is to compare the rate of treatment failure defined as a composite endpoint comprising the need for non-invasive ventilation (at two pressure levels) or for intubation or death, between the intervention group (awake prone position plus usual care) and the usual care (usual care alone) group at 28 days.

Ethics and dissemination The protocol and amendments have been approved by the ethics committees (Comité de protection des personnes Ouest VI, France, no 1279 HPS2 and Comité Consultatif d’Éthique en matière de Recherche Biomédicale, Monaco, no 2020.8894 AP/jv), and patients are included after written informed consent. The results will be submitted for publication in peer-reviewed journals.

Trial registration number NCT04363463.

INTRODUCTION

Background and rationale

COVID-19 is responsible of severe hypoxaemia and acute respiratory distress syndrome (ARDS). Among COVID-19 patients who need oxygen therapy and are hospitalised in...
general medical wards, the rate of secondary intensive care unit (ICU) admission to escalate respiratory support is high. The need for tracheal intubation in hospitalised COVID-19 patients is reported as high as 27%–30% in observational studies, with great heterogeneity across studies. The rate of intubation in COVID-19 patients with non-severe respiratory failure who initially need only standard oxygen therapy is difficult to estimate with the available literature.

Among treatment strategies that have been tested or advocated for COVID-19 patients, awake prone positioning is a simple and safe technique which merits further investigations. Prone positioning improves oxygenation through better lung recruitment, reduction of the ventilation-perfusion mismatch and reduction of lung stress and strain, and improves survival in sedated, mechanically ventilated patients with ARDS not related to COVID-19. In non-intubated, spontaneously breathing COVID-19 patients, prone positioning may exert such physiological effects but whether they could translate into better patient-centred outcomes remains uncertain. This has been evaluated mostly in ICU patients with high demand in oxygen flow. One recent meta-trial in ICU patients on high-flow nasal cannula oxygen therapy found that awake prone positioning reduced the need for intubation. In COVID-19 patients who initially need only standard low flow oxygen therapy and still are sufficiently well to allow admission in medical wards, awake prone positioning has been mostly evaluated in observational studies focusing on oxygenation settings and only two small-sized randomised controlled trials. In a cluster randomised controlled trial in 27 COVID-19 patients, oxygen needs in terms of oxygen flow tended to be lower in the prone position group. The second trial was stopped early (30 patients were included) because of lack of patients’ adherence to the scheduled sessions of prone positioning, and did not show improved oxygenation in the intervention group.

We hypothesised that early prone positioning in COVID-19 patients breathing spontaneously in medical wards could decrease the rates of intubation or need for noninvasive ventilation or death.

METHODS AND ANALYSIS

Design
The study is an investigator-initiated, prospective, multicentre randomised, controlled, superiority trial comparing awake prone positioning to standard of care in hypoxaemic COVID-19 patients in medical wards. Our main hypothesis is that awake prone position may reduce the incidence of use of non-invasive ventilation or intubation or death. Two hundred and sixty-eight patients are to be randomised in two parallel groups.

Study setting
The trial is carried out in 20 medical wards in 14 French hospitals and 1 hospital in Monaco. The sponsor (Centre hospitalier régional d’Orléans, France) delivers on-site training and support sessions all along the study on all aspects of the study procedures.

Recruitment, informed consent and study time points
Potentially eligible patients hospitalised in the involved wards are approached by a physician who informs them about the study and hands them the information notice (see online supplemental file 1).

Patients who accept participation sign the written informed consent form (see online supplemental file 2) and are declared enrolled and then are randomised. Date and time of randomisation determine the beginning of the intervention period.

Patients have the right to withdraw their consent and discontinue their participation at any time for any reason.

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

This study respects the Standard Protocol Items: Recommendations for Interventional Trials recommendations and checklist.

Blinding
Blinding of participants, clinical investigators and assessors is not possible due to the nature of the intervention.

Randomisation
A centralised web-based management system (EOL Random, Medsharing, France) is used for randomisation. Patients are assigned to intervention or usual care in a 1:1 ratio with stratification on centres, body mass index (BMI) (<30 kg/m² or not) and severity hypoxaemia (pulse oxygen saturation (SpO₂) <95% or ≥95%). The way the severity of hypoxaemia is estimated is standardised: before randomisation, SpO₂ is measured in all enrolled patients after 5 min of oxygen therapy at a flow of 5 L/min delivered through non-rebreathing face mask or standard nasal cannula. To ease the inclusion process and not to ask for arterial blood gas analysis and add workload on staff members already under pressure during the pandemic, we chose the SpO₂/FiO₂ ratio to stratify randomisation. The cut-off value of an SpO₂ of 95% corresponds to an SpO₂/FiO₂ ratio of 235, assuming that FiO₂ is roughly equal to 0.40 under 5 L/min of standard oxygen. This also corresponds to a PaO₂/FiO₂ ratio of 200 mm Hg, a meaningful threshold that distinguishes mild from moderate COVID-19-related respiratory failure in spontaneously breathing patients, two conditions that have clearly different prognoses (16% vs 48% of in-hospital mortality, respectively).

The group to which the patient is assigned is recorded in the patient’s medical chart and in a dedicated chart gathering the whole randomised patient population of the trial.
Eligibility criteria

Inclusion criteria
Eligible patients should
► Be older than 18 years old and under 85 years old
► Have laboratory-confirmed SARS-CoV-2 infection by PCR.
► Be hospitalised in a medical ward for less than 72 hours.
► Treated by oxygen therapy (nasal cannula, mask or high-flow nasal oxygen therapy).
► Be able to self-position to prone position or with the assistance of one person.
► Have signed the consent form.

Non-inclusion criteria
► Patients on oxygen therapy or continuous positive airway pressure or non-invasive ventilation at home.
► Chronic obstructive pulmonary disease (stage Gold 3 or 4).
► Known chronic interstitial lung disease.
► Chronic neuromuscular disease.
► Contraindication to prone position (recent thoracic trauma, pneumothorax, unstable spine or pelvis fractures).
► Deep vein thrombosis or pulmonary embolism with curative anticoagulation for less than 48 hours.
► Haemodynamic instability (mean arterial pressure under 65 mm Hg) persisting for more than 1 hour.
► Respiratory rate greater than 40 /min, or excessive use of accessory respiratory muscles (as determined by the clinician).
► Indication for curative non-invasive ventilation (acute pulmonary oedema or acute hypercapnic respiratory failure).
► Intestinal occlusive syndrome.
► Patient unable to protect the upper airway.
► Patient discharged from intensive care after having been treated by invasive or non-invasive ventilation for COVID-19.
► Do not intubate order.
► Inability to understand French or to follow instructions to perform awake prone position.
► Patient not affiliated or excluded from social protection, or under law protection (namely minors, pregnant or breastfeeding women, persons deprived of their liberty by court or administrative decision).

Interventions

Figure 1 presents the study outline and interventions.

Intervention group
Patients are encouraged to lie in prone position as frequently and for as long as feasible, as soon as possible after randomisation. They are assisted during positioning and given every necessary accessory to be as comfortable as possible (pillows, cushions, foam wedges) (figure 2).

The patient should lie in prone position for a minimum of two sessions during the daytime period, with an objective of a cumulative time of at least 2 hours and 30 min in prone position during daytime. Each mobilisation (time and duration) during daytime is notified in a notebook by the patient or a staff member. Patients are strongly encouraged to sleep in prone position at night, but this information (time and duration) is not collected. We chose not to record the true duration of prone positioning at night because overloading caregivers, already under pressure during the pandemic, with frequent monitoring and recording of the patients’ position at night seemed to us potentially counterproductive as it entailed the risk of poor adherence of the caregivers to the protocol and could constitute a barrier to recruitment on the part of the investigators.

The call bell is given to the patient so that he/she can call a staff member for assistance before each position change.

Lateral positioning in the bed and movement in the room are allowed outside the prone position periods.

Control group
During the daytime period, the patient is in semisitting position in the bed (minimum 30° inclination not more than 60–70°) or in a chair if he/she wishes. The prone position is not authorised during the daytime. It is allowed at night if it is the patient’s natural sleeping position. The lateral decubitus positioning is allowed and will be collected.

Each mobilisation outside the bed is notified in a notebook by the patient or a staff member.

Outcome measurements
The primary study objective is to compare the rate of treatment failure defined as a composite endpoint comprising the need for non-invasive ventilation (at two pressure levels) or for intubation or death, between the intervention group (awake prone position plus usual care) and the usual care (usual care alone) group at 28 days.

The secondary objectives are to compare between groups:
► The change in the clinical WHO ordinal scale from randomisation to 28 days.
► The rate of endotracheal intubation for invasive mechanical ventilation at 28 days.
► The rate of use of non-invasive ventilation at two pressure levels at 28 days.
The time passed on oxygen therapy from inclusion to day 28.

- The hospital length of stay.
- The mortality at 28 days and during the hospital stay.
- The rate of transfer to ICU at 28 days.
- The rate of use of non-invasive ventilation and intubation over the entire hospital stay.

Study safety, monitoring and data management
For this research that brings minimal risks (in the meaning of the French Law), we did not plan to set up an independent data safety and monitoring board. The study was launched on August 2020. Until now, no serious adverse events (such as cardiac arrest during awake prone position) related to the study procedures have been declared by investigators.

Research assistants appointed by the sponsor regularly monitor all the centres on site to check adherence to the protocol and the accuracy and completeness of the data recorded.

Data management is performed by the Direction de La Recherche, Orléans Hospital. A centralised web-based management system (EOL Random, Medsharing, France) and a centralised electronic case report form (CRF) are used (EOL, Medsharing, France).

A blind review of data will be done prior locking the database.

Sample size
There are few studies in COVID-19 patients in medical wards comparing awake prone position to usual care. In two small studies in hypoxaemic COVID-19 patients in medical wards, the rate of intubation was 0% and mortality was 0% or 3.7% in both groups (prone position and usual care). In a small, cluster randomised study, the rate of transfer to ICU was 0% in the usual care group and 10% in the prone position group. In a randomised controlled trial on prone position versus standard of care, the rate of intubation was 13% in both groups and the rate of mortality was 6.7% in prone position vs 10% in usual care group.

In the above small-sized studies in non-severe COVID-19 patients hospitalised in medical wards, the most useful information was that patients were frequently capable to self-prone positioning. Overall, data on intubation rate in non-severely hypoxaemic COVID-19 patients are scarce. Therefore, despite the progression of the pandemic since the beginning of our project, the calculation of a necessary number of subjects remains highly speculative.

We initially planned to enrol 400 patients (200 in each group) assuming a global treatment failure rate of 15%, an 8% difference in treatment failure rate between groups and a lost to follow-up rate of 10%. In the beginning of October 2021, while the spread of COVID-19 was dramatically slowing down, we anticipated that the targeted number of 400 patients would be difficult to reach in a reasonable time. Therefore, we asked the data manager to let us know the lost to follow-up rate in the 232 included patients on 1 October 2021, for whom outcomes were available in the centralised CRF and to estimate the global rate of treatment failure (without unblinding the group of randomisation), as to recalculate a target number of patients to enrol. Lost to follow-up rate was 0% and the global rate of treatment failure was 12.5%, that is, both lower than anticipated. Based on these new data, we hypothesised that the treatment failure rate will be 4% and 14% in the intervention and usual care group, respectively. With a two-sided alpha risk set at 5% and a statistical power of 80%, 134 patients in each group were needed to demonstrate a difference of 10% in treatment failure rate (use of noninvasive ventilation, intubation or

Figure 2  Picture of prone position.
death) between the two groups with a lost to follow-up rate of less than 2%. This calculation slightly overestimates the necessary sample size because it does not consider the stratified design. This new enrolment target of 268 patients was approved by the ethics committee on 9 November 2021.

Statistical analysis
The patients’ characteristics will be given by group of randomisation as numbers and percentages for the categorical variables and as mean (and SD) or median (25th and 75th percentile) for the continuous variables, depending on their distribution.

The main analysis will be conducted on an intention-to-treat basis. However, patients withdrawing their consent during the study, in accordance with French law, will not be analysed.

The primary endpoint (percentage of patients requiring intubation or treated with non-invasive ventilation at two pressure levels, or who died within 28 days of inclusion) will be compared between groups by a Mann-Whitney U test stratified on stratification variables #2 and #3 (SpO2 and BMI). The effect of the intervention will be expressed in terms of absolute risk difference and its 95% CI. A sensitivity analysis will be conducted by using mixed-effect logistic regression, with the recruiting centre as a random effect, and the study intervention and stratification variables #2 and #3 as a fixed effect. Interaction terms between the stratification variables and the intervention will be introduced into the model and retained only if they show a significant statistical link with the frequency of treatment failure. Logistic regression analysis will be used to estimate the OR and its 95% CI.

The binary secondary endpoints (intubation rate, rate of non-invasive ventilation at two pressure levels, rate of transfer to intensive care, mortality) will be compared between the groups using the same method.

The time to clinical improvement (two points on the WHO scale) will be compared between groups by log rank test and presented as Kaplan-Meier curves. The difference in risk between the groups will be expressed as an HR and its 95% CI. This analysis will be secondarily adjusted for stratification variables, and possibly other covariables that would be misbalanced between groups, using a Cox proportional model provided the proportional assumption is verified.

The durations (of oxygen therapy, of non-invasive ventilation, of hospitalisation), will be compared between groups by a Mann-Whitney U test adjusted for the stratification variables. The differences in durations (of oxygen therapy, non-invasive ventilation, hospitalisation) between groups will be expressed by their median and 95% CI obtained by bootstrapping (2000 unstratified samples).

We will conduct a per-protocol analysis including only patients of the intervention group who laid in prone position for at least 2 hours each day, and patients of the usual care group who never laid in prone position.

The above analyses will be repeated in prespecified subgroups formed according to the stratification variables #2 and #3 (SpO2 and BMI).

We plan no interim analysis.

ETHICS AND DISSEMINATION
Ethics approval
The study protocol and its amendment revising the targeted number of patients to enrol were approved for all centres by the institutional review board of Orléans’ Hospital, as well as by the French ethics committee (Comité de Protection des Personnes Ouest VI, Brest, France, number 1279 HPS2, and number 20.01116.001279-MS05 for the French centres) and the Monegasque ethics committee (Comité Consultatif d’Ethique en matière de Recherche Biomédicale, Monaco, number 2020.8894 AP/jv and amendment submitted on 22 November 2021 and awaiting approval).

The study is conducted in accordance with the current revision of the Declaration of Helsinki, 1996, International Conference on Harmonisation Note for Guidance on Good Clinical Practice and the applicable French regulatory requirements.

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Contributors M-AN, GF and TB designed the study and wrote the study protocol. TB determined the sample size and planned the statistical analysis. M-AN is the coordinating investigator. BP, CP, JC, LP, AS, SD, MM, J-BL, LC, GC, NB, XP-A, AB, LB
and EN include patients. All authors revised the manuscript critically for important intellectual content and approved the final version. All authors gave their agreement to be accountable for all aspects of the work and ensure the accuracy and integrity of any part of the work.

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**Competing interests** M-AN declares personal fees and non-financial support from Fisher & Paykel Healthcare.

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

**Patient consent for publication** Obtained.

**Ethics approval** The study protocol and its amendment revising the targeted number of patients to enrol were approved for all centres by the institutional review board of Orléans’ Hospital, as well as by the French ethics committee (Comité de Protection des Personnes Ouest VI, Brest, France, number 1279 HPS2, and number 20.0116.001279-MSIS for the French centres) and the Monegasque ethics committee (Comité Consultatif d’Ethique en matière de Recherche Biomédicale, Monaco, number 2020.8994 AP IV and amendment submitted on November 22, 2021 and awaiting approval). The study is conducted in accordance with the current revision of the Declaration of Helsinki, 1996, International Conference on Harmonisation Note for Guidance on Good Clinical Practice (ICH GCP) and the applicable French regulatory requirements.

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**REFERENCES**

1. Suleyman G, Fadel RA, Malette KM, et al. Clinical characteristics and morbidity associated with coronavirus disease 2019 in a series of patients in metropolitan Detroit. JAMA Netw Open 2020;3:e2012270.
2. Argenziano MG, Bruce SL, Slater CL, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: retrospective series. BMJ 2020;369:m1996.
3. Wolfsberg S, Gregoriano C, Struja T, et al. Comparison of characteristics, predictors and outcomes between the first and second COVID-19 waves in a tertiary care centre in Switzerland: an observational analysis. Swiss Med Wkly 2021;151:w20569.
4. Pavlov I, He H, McNicholas B, et al. Awake prone positioning in Non-Intubated patients with acute hypoxic respiratory failure due to COVID-19. Respir Care 2021;respcare.09191.
5. Jayakumar D, Ramachandran Dib N, Rabindranaraj Dib E, et al. Standard care versus awake prone position in adults Non-Intubated patients with acute hypoxic respiratory failure secondary to COVID-19 Infection-A multicenter feasibility randomized controlled trial. J Intensive Care Med 2021;36:918–24.
6. Chalmers JD, Crichton ML, Goeminne PC, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19)–a European respiratory Society living guideline. Eur Respir J 2021;57:2100048.
7. Serpa Neto A, Checkley W, Sivakorn C, et al. Pragmatic recommendations for the management of acute respiratory failure and mechanical ventilation in patients with COVID-19 in low- and middle-income countries. Am J Trop Med Hyg 2021;104:60–71.
8. Kallath RH. A comprehensive review of prone position in ARDS. Respir Care 2015;60:1660–87.
9. Guérin C, Reignier J, Richard J-C, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med 2013;368:2159–68.
10. Fan E, Del Sorbo L, Goligher EC, et al. An official American thoracic Society/European Society of intensive care Medicine/Society of critical care medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. Am J Respir Crit Care Med 2017;195:1253–63.
11. Munschli L, Del Sorbo L, Adhikari NKJ, et al. Prone position for acute respiratory distress syndrome. A systematic review and meta-analysis. Ann Am Thorac Soc 2017;14:5280–8.
12. Ding L, Wang L, Ma W, et al. Efficacy and safety of early prone position combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. Crit Care 2020;24:28.
13. Zarantonello F, Andreattta G, Sella N, et al. Prone position and lung ventilation and perfusion matching in acute respiratory failure due to COVID-19. Am J Respir Crit Care Med 2020;202:278–9.
14. Sarma A, Callee CS. Prone positioning in awake, Nonintubated patients with COVID-19: necessity is the mother of invention. JAMA Intern Med 2020;180:1539.
15. Vianello A, Turrin M, Guarnieri G, et al. Prone positioning is safe and may reduce the rate of intubation in selected COVID-19 patients receiving high-flow nasal oxygen therapy: a cluster randomized controlled trial. Eur Respir J 2021;57:2100048.
16. Coppo A, Bellani G, Winterton D, et al. Feasibility and physiological effects of prone positioning in non-intubated patients with acute respiratory failure due to COVID-19 (PRON-CVID): a prospective cohort study. Lancet Respir Med 2020;8:765–74.
17. Ehrmann S, Li J, Ibarra-Extrava M, et al. Awake prone positioning for COVID-19 acute hypoxemic respiratory failure: a randomised controlled, multinational, open-label meta-trial. Lancet Respir Med 2021;9:1387–95.
18. Taboada M, Rodriguez N, Riveiro V, et al. Prone positioning in awake non-ICU patients with ARDS caused by COVID-19. Anaesth Crit Care Pain Med 2020;39:581–3.
19. Etharrar X, Trigui Y, Dols A-M, et al. Use of prone positioning in Nonintubated patients with COVID-19 and hypoxic acute respiratory failure. JAMA 2020;323:2356.
20. Provenhomme E, Trigui Y, Etharrar X, et al. Effect of prone positioning on the respiratory support of Nonintubated patients with COVID-19 and acute hypoxic respiratory failure: a retrospective matching cohort study. Chest 2021;160:85–8.
21. Wormser J, Romanet C, Philippat F. Prone position in wards for spontaneous breathing COVID-19 patients: a retrospective study. Ir J Med Sci 2020;190:1519–22.
22. Caputo ND, Strayer RJ, Levitan R. Early Self-Proning in awake, Non-intubated patients in the emergency department: a single ED’s experience during the COVID-19 pandemic. Acad Emerg Med 2020;27:375–8.
23. Liu X, Liu H, Lan Q, et al. Early prone positioning therapy for patients with mild COVID-19 disease. Med Clin 2021;156:386–9.
24. Dubosh NM, Wong ML, Grossstreuer AV, et al. Early, awake proning in emergency department patients with COVID-19. Am J Emerg Med 2021;46:540–5.
25. Thompson AE, Ranald BL, Wei Y, et al. Prone positioning in awake, Nonintubated patients with COVID-19 hypoxic respiratory failure. JAMA Intern Med 2020;180:1537.
26. Khurat A, Dupuis-Lozeron E, Cariou A, et al. Self-proning in COVID-19 patients on low-flow oxygen therapy: a cluster randomised controlled trial. ERJ Open Res 2021;7:00692-2020–2020.
27. Johnson SA, Horton DJ, Fuller MJ, et al. Patient-directed prone positioning in awake patients with COVID-19 requiring hospitalization (PAPR). Ann Am Thorac Soc 2021;18:1424–6.
28. Chan A-W, Tetzlaff JM, Altman DG, et al. Spirit 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med 2013;158:200.
29. Chan A-W, Tetzlaff JM, Gotzsche PC, et al. Spirit 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ 2013;346:e7586.
30. Wettstein RB, Shellyed DC, Peters Jl. Delivered oxygen concentrations using low-flow and high-flow nasal cannulas. Respir Care 2005;50:604–9.
31. Rice TW, Wheeler AP, Bernard GR, et al. Comparison of the SpO2/FIO2 ratio and the PaO2/FIO2 ratio in patients with acute lung injury or ARDS. Chest 2007;132:410–7.
32. Santus P, Radovanovic D, Saderi L, et al. Severity of respiratory failure at admissions of in-hospital mortality in patients with COVID-19: a prospective observational multicentre study. BMJ Open 2020;10:e043651.
33 Vogelmeier CF, Criner GJ, Martinez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. gold executive summary. *Am J Respir Crit Care Med* 2017;195:557–82.

34 Cao B, Wang Y, Wen D, et al. A trial of Lopinavir-Ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020;382:1787–99.

35 Taylor SP, Bundy H, Smith WM, et al. Awake prone positioning strategy for Nonintubated hypoxic patients with COVID-19: a pilot trial with embedded implementation evaluation. *Ann Am Thorac Soc* 2021;18:1360–8.