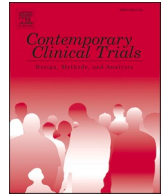




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Rationale and design of the Prone Position and Respiratory Outcomes in Non-intubated COVID-19 PatiEnts: The “PRONE” Study

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ARTICLE INFO

Keywords:

Prone
COVID-19
Awake
Hospitalized
Randomized
Multicenter

ABSTRACT

While benefits of prone position in mechanically-ventilated patients have been well-described, a randomized-control trial to determine the effects of prone positioning in awake, spontaneously-breathing patients with an acute pneumonia has not been previously conducted. Prone Position and Respiratory Outcomes in Non-Intubated COVID-19 PatiEnts: the “PRONE” Study (PRONE) was conducted in non-intubated hospitalized patients with coronavirus disease 2019 (COVID-19) pneumonia as defined by respiratory rate ≥ 20 /min or an oxyhemoglobin saturation (SpO_2) $\leq 93\%$ without supplemental oxygen [1]. The PRONE trial was designed to investigate the effects of prone positioning on need for escalation in respiratory support, as defined by need for transition to a higher acuity level of care, increased fraction of inspired oxygen (FiO_2), or the initiation of invasive mechanical ventilation. Secondary objectives were to assess the duration of effect of prone positioning on respiratory parameters such as respiratory rate and SpO_2 , as well as other outcomes such as time to discharge or transition in level of care.

1. Introduction

Most patients hospitalized with coronavirus disease 2019 (COVID-19) require supplemental oxygen [2]. Many of these patients have severe disease that evolves into acute respiratory distress syndrome (ARDS) characterized by severe hypoxemia, with as high as 20% requiring admission to the intensive care unit (ICU). Of these, more than half require initiation of invasive mechanical ventilation (IMV) and case mortality can reach as high as 40% [3]. In the context of high morbidity, mortality, limited hospital capacity, equipment, and personnel during

the pandemic, there emerged a new imperative to explore ways to mitigate the effect and progression of hypoxemic respiratory failure in early COVID-19.

The first report on prone positioning to improve oxygenation in patients with ARDS appeared in 1976 [4]. Improved gas exchange when prone is the result of optimization in lung recruitment and ventilation-perfusion matching, and it has been hypothesized that prone positioning may also help to prevent ventilator-induced lung injury. Although prone positioning was used for several years to improve oxygenation in patients requiring IMV for management of ARDS, it was

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<https://doi.org/10.1016/j.cct.2021.106541>

Received 21 April 2021; Received in revised form 9 August 2021; Accepted 10 August 2021

Available online 13 August 2021

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not until 2013 that prone positioning was convincingly demonstrated to reduce mortality [5]. While the value of prone positioning in mechanically ventilated patients with moderate-to-severe ARDS is compelling, less is known about its effects in spontaneously breathing, non-intubated patients. Case reports and small retrospective reviews revealed possible improvements in oxygenation in this group; however, effects of prone positioning on respiratory rate, work of breathing, and clinical outcomes were not defined [6,7].

Following the emergence of COVID-19, there have been a number of reports investigating the effects of prone positioning in patients with COVID-19 not requiring IMV. Prone positioning along with high flow nasal cannula (HFNC) and restrictive fluid strategy were prescribed in China's Jiangsu Province during the Wuhan COVID-19 outbreak as attempts at empiric salvage therapy, with reported improvements in oxygenation and reportedly low rates of need for IMV [8]. Several groups thereafter have reported on efforts to study prone positioning in awake COVID-19 patients [8–11]. In a cohort of 10 patients with impending respiratory failure, prone position resulted in a significant improvement in oxygen saturation in as little as one hour [12]. More importantly, prone positioning led to a significant decrease in work of breathing, as evidenced by decreased respiratory rate and patient reports of subjective improvement. Furthermore, a majority of the patients avoided IMV. While this and other reports demonstrate that prone positioning improves oxygenation and respiratory rates [10,13–15], a conclusive change in clinical outcomes has remained elusive, except for a small case series [16]. Further, it remains unknown whether prone positioning produces durable improvements in oxygen requirements, reduced need for escalation to ICU care, or decreases the need for IMV.

Another potential challenge of awake prone positioning is lack of control over tidal volume. It has previously been shown in a meta-analysis that after stratification for tidal volume (V_T), the studies where V_T was not controlled failed to demonstrate a significant decrease in risk of death [17]. In spontaneously breathing patients where tidal volume cannot be controlled, patients may experience what has been referred to as patient self-inflicted lung injury [18]. It is possible that awake prone position could attenuate this process by increasing FRC and reducing transpulmonary pressures. To address these knowledge gaps, a randomized clinical trial was implemented to examine prone positioning in patients with COVID-19 who had not yet progressed to requiring IMV.

2. Methods

2.1. Study design and objectives

A multicenter, randomized control trial in patients hospitalized with COVID-19 pneumonia was initiated at five medical centers including Johns Hopkins University (coordinating center), Duke University, University of North Carolina, University of Miami, and University of Pittsburgh medical centers. This study was registered with www.clinicaltrials.gov (NCT04517123). The primary objective of the PRONE trial was to determine whether prone positioning decreases the need for escalation of respiratory-related care in patients with COVID-19 pneumonia. Secondary objectives included an assessment of whether prone positioning is associated with time to the increase or decrease in respiratory-related care, and changes in oxyhemoglobin saturation, respiratory rate, and work of breathing. The institutional review boards at each of the participating institutions approved the study protocol prior to implementation.

2.2. Recruitment and screening procedures

All patients admitted with COVID-19 pneumonia were eligible for screening through the first day of their hospitalization. The patient's attending physician or study personnel at each site identified patients admitted with COVID-19. The study team then reviewed the medical records to assess eligibility using the inclusion and exclusion criteria

detailed in Table 1. Briefly, inclusion criteria included a documented positive test for SARS-CoV-2 and age ≥ 18 years. Pre-existing advanced lung disease, need for mechanical ventilation, inability to independently change position, or contraindication to prone positioning due to factors such as weakness, recent surgery, severe obesity, or decreased alertness were considered exclusionary. If all the enrollment criteria were met, the patient was approached for informed consent. All participants provided written informed consent prior to enrollment. Screened patients at each site were entered into a password protected database which was maintained by the coordinating center.

2.3. Randomization

After eligibility was confirmed, patients were then randomized to prone positioning on a prescribed schedule versus usual care. The randomization schedule was developed by the coordinating center. The block size was concealed from the recruiting sites, and randomization was performed after informed consent. Eligible patients were assigned to one of the two groups in a 1:1 ratio. Randomization was blocked within each clinical site using block sizes of four. Only the principal investigator at the coordinating center (MD) had access to the randomization table. The coordinating center principal investigator was not involved in recruitment or enrollment.

2.4. Study interventions

Patients who were randomized to the intervention arm were prescribed a schedule of prone positioning summarized in Table 2. Adherence to the schedule was maximized by a wall-posted schedule, nursing reminders, standardized text messaging during hours of wakefulness, or a combination thereof, based on patient preferences and site logistics. Maintenance of the prone position during scheduled hours was not mandated, and patients were not woken to change position. Study participants randomized to the usual care arm were allowed to change position per patient and treating physician preference, including the prone position.

2.5. Data collection

Standard clinical data (including radiological studies, vital signs, laboratory studies) as well as respiratory data (including method of oxygen supplementation, flow rate, and FI_{O_2}) were collected on each patient. Additionally, each enrolled patient had all study related respiratory monitoring as shown in Fig. 1. For the first 24 h after enrollment,

Table 1
Inclusion and Exclusion Criteria.

Inclusion Criteria	
■	Age ≥ 18 years
■	Covid-19 positive by nasopharyngeal swab or serostatus
■	Use of supplemental oxygen or respiratory rate ≥ 20
■	Ability to provide informed consent and speak English
Exclusion Criteria	
■	BMI ≥ 45 kg/m ²
■	Pregnancy (based on the patient's current medical record)
■	Language or hearing impairment
■	Chest tube placement
■	Hemodynamic instability with mean arterial pressure < 60 mmHg
■	Thoracic or abdominal wounds
■	Chest wall deformities (e.g. pectus excavatum and pectus carinatum)
■	Vertebral column deformities that would preclude prone positioning
■	Facial trauma or surgery in the last 30 days
■	Established diagnosis of interstitial lung disease
■	Prior single or double lung transplant
■	Surgery for spine, femur, or pelvis in the last 3 months
■	Thoracic or cardiac surgery in the last 30 days
■	Pacemaker placement in the last 7 days
■	Anything that, in the opinion of the investigator, would increase risk or preclude a participant's full compliance in completing the study

Table 2
Schedule for the Prone Positioning.

Clock time	Position
08:00–10:00	Supine
10:00–12:00	Prone
12:00–14:00	Supine
14:00–16:00	Prone
16:00–18:00	Supine
18:00–20:00	Prone
20:00–22:00	Supine
22:00–08:00	Prone

continuous pulse oximetry monitoring with a Nonin pulse oximeter was conducted, as well as positional and respiratory rate and effort monitoring with a NoxA1 monitor. NoxA1 is a portable digital recording system that allows for continuous monitoring of pulse oximetry (via a wireless sensor) and body position, as well as measurement of respiratory effort based on chest and abdomen movement using RIP bands. Despite adjustments in signal acquisition to optimize battery life, one AA battery for the NoxA1 typically lasted ~19 h.

All patients also underwent position monitoring with a MonBaby wireless sensor that was affixed to the patient’s chest or clothing, starting at enrollment and continuing throughout the hospital admission (Fig. 1). The MonBaby sensor is a small 3-axis accelerometer that monitors body position and can estimate respiratory rate. The de-identified and encrypted data from the MonBaby sensor was wirelessly transmitted to a remote data repository via a host mobile device. The low power consumption allowed utilization of this system to perform extended-duration monitoring of body position on contrast to the NoxA1.

2.6. Outcome variables

The primary endpoint was escalation in respiratory-related care defined as: intubation; transition to HFNC; increase in fraction of inspired oxygen; decision by the primary team to prone patient; and/or transfer from a lower to a higher level acuity of care (e.g. medical floor to intermediate care unit [IMC] or ICU) (Table 3). Secondary endpoints included time from hospital admission to change in respiratory-related

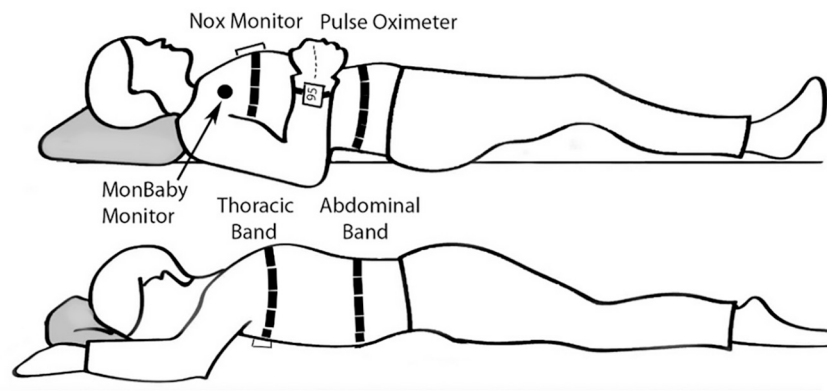
care; amount of change, time to change, and duration of change in respiratory rate, SpO₂ and FiO₂; and time to discharge or transition to lower acuity of care. Missing data will be assumed to be missing completely at random.

2.7. Sample size considerations

The primary endpoint is the composite endpoint of respiratory-related escalation of care. Sample size projections of accrual and ICU transfers were based on early data from New York State, which indicated that nearly 25% of the patients admitted to the hospital with COVID-19 required ICU-level care [19]. Based on these data, it was assumed that the rate of escalation in respiratory-related care as a composite outcome would be higher than 25%. It was assumed that at least 40% of patients in the usual care arm would require some escalation in respiratory-related care. Furthermore, based on data from a case series of 15 patients undergoing noninvasive ventilation that underwent prone positioning [20], it was assumed that 14% of patients in the intervention arm would require some escalation in respiratory-related care. Therefore, assuming type 1 error of 0.05, a total sample size of 100 would provide 80% power to detect an absolute reduction of 26% in the proportion of patients needing an escalation in respiratory-related care (i.e., 40% vs.

Table 3
Control, Intervention, and Outcomes.

Control	Intervention
<ul style="list-style-type: none"> ■ Usual care ■ Does not exclude prone position per patient or provider preference 	<ul style="list-style-type: none"> ■ Alternating 2 h of prone and supine while awake ■ Prone entire time while asleep ■ Deviations allowed as tolerated
Primary Outcomes <ul style="list-style-type: none"> ■ Increase in FiO₂ ■ Transfer to higher level of care 	
Secondary Outcomes <ul style="list-style-type: none"> ■ Time to FiO₂ change ■ Amount of FiO₂ change ■ Time to discharge or transfer 	



		Initial 24h	Up to 10d
NoxA1	SpO ₂	→	→
	RIP	→	→
	RR	→	→
MonBaby	Position	→	→
	RR	→	→

Fig. 1. Data Collection.

Abbreviations: SpO₂ = pulse oximetry; RIP = Respiratory Inductance Plethysmograph; RR = Respiratory Rate.

14% comparing the usual care to the prone arm). We sought to recruit 20% of the patients in each arm and recalculate the sample size based on empirically-derived estimates of event frequency. The results of the first 20% of the data used for the sample size recalculation will be combined with the rest of the data.

2.8. Statistical considerations

The primary analysis will focus on whether the proportion of patients requiring an escalation of respiratory-related care differs between the two groups. Initial analyses will tabulate demographic and baseline characteristics of the participants by randomization group. Primary analysis will be based on intention-to-treat. Baseline characteristics will be compared between treatment groups using Student's *t*-test for continuous variables and χ^2 or Fisher's exact tests for categorical variables as appropriate. Wilcoxon rank-sum tests will also be employed when a nonparametric test of continuous variables is warranted. For the primary endpoint, the proportion of patients requiring escalation of respiratory-related care will be compared. In addition, time-to-event modeling including the Kaplan-Meier product-limit estimator and associated log-rank test will be used to compare the two groups on the time to change in respiratory-related care. Additional post-hoc exploratory analysis will be conducted if differences in baseline characteristics are observed using multivariable regression with the inclusion of baseline variables that are different between the two groups. Statistical analyses will be performed using the SAS Software (SAS institute). A *P* < 0.05 will be used to infer statistical significance.

3. Discussion

Recent evidence demonstrates that prone positioning in intubated patients with ARDS improves oxygenation and decreases mortality [5,21,22]. The physiological changes with prone positioning have been studied extensively in mechanically-ventilated patients. Prone positioning improves lung compliance and reduces the pleural pressure gradient while having little effect on perfusion. The result is a more homogeneous transpulmonary pressure gradient, ventilatory homogeneity, and a reduced shunt fraction [23,24]. Furthermore, prone positioning has previously been shown to improve ventilation, likely through reducing alveolar dead space [24]. Secretion clearance is also significantly enhanced by prone positioning [25].

The understanding of the effects of prone positioning in patients who are not sedated and mechanically-ventilated is limited. The recent data regarding prone positioning as a therapy for COVID-19 pneumonia have demonstrated improvements in oxygenation and respiratory rate but not clinical outcomes. Prone positioning is an attractive early intervention option in COVID-19 patients with hypoxemia because it is a relatively easy therapy to implement, with few contraindications, low cost, and low staff utilization. However, in contrast to the paralyzed ICU patients, prone positioning of awake patients requires patient understanding and adherence, potentially presenting problems with tolerability and monitoring, and thus remains a challenging medical intervention.

The strengths of this study are the randomized clinical design and rigorous data collection, including both comprehensive monitoring in the initial phase and ongoing measurements of position data for the duration of the patient's hospitalization. These have been standardized across the five participating institutions and thus will allow for an assessment of the inherent heterogeneity of the study population as well as the complexities of adherence with the prone positioning regimen. Furthermore, the collected data will provide greater insight into the respiratory-related physiologic changes that occur in patients with COVID-19. The findings from this study will enhance our understanding of the effects of prone positioning and the physiological effects of changes in body position on oxygenation and work of breathing in COVID-19 patients with hypoxemia. This study will provide insight into the temporal dynamics of respiratory indices of non-intubated patients

with COVID-19 pneumonia. These findings will potentially pave the way for future research into factors that can be used to predict decompensation and respiratory failure outside of the highly monitored setting offered by ICUs.

There are a number of limitations to this study. It was conducted during a time of active investigation of possible SARS-CoV-2 treatment options, with rapidly evolving standards of care for hypoxemic respiratory failure in COVID-19 patients. Multiple pharmacological treatment options, including experimental agents under active investigation or under Emergency Use Authorization (EUA) were available. It was thus not practical to standardize patient treatment protocols (either in the control or the intervention group) across time and across the participating centers. The study design is further challenged by the inability to blind patients and care providers due to the nature of the intervention. Studying prone position in awake patients faces additional inherent challenges due to variability in tolerance and adherence. While previous studies showed that measurable improvement in oxygenation may be observed in as little as 1 h after prone positioning [12,21], 16 h daily has previously been recommended for intubated patients [22]. For awake patients, the minimum duration of the intervention required to produce a measurable effect, as well as the durability of these changes, remain to be determined. Therefore, findings from this trial have the potential to impact the current standards of practice in care of patients with respiratory failure due to COVID-19 that does not require mechanical ventilation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

Material support for this research was provided by Nox Medical and MonBaby.

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