Prolonged Prone Positioning for COVID-19-induced Acute Respiratory Distress Syndrome (ARDS): A Pilot Study

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Prolonged Prone Positioning for COVID-induced ARDS

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Introduction:
The Novel Coronavirus has resulted in a pandemic of patients with respiratory failure, the most ill subset of which are experiencing Acute Respiratory Distress Syndrome (ARDS). Few therapies have demonstrated efficacy in treating this novel illness.[1-4] Prone ventilation is one of the few interventions known to decrease mortality in ARDS.[5] Prone positioning has become ubiquitous with the COVID-19 pandemic, expanding to even include non-intubated patients and now getting attention in the lay press.[6-10]

A major limitation to the most impactful implementation of prone positioning is that the ideal duration of prone ventilation is unknown. The landmark study on prone positioning demonstrating a mortality benefit used a 16 hour prone session followed by a supine period.[5] The rationale behind using a 16h strategy was not based on physiologic or outcomes data. There is retrospective, observational data suggesting that improvements in oxygenation may increase with duration of prone positioning extending beyond 16 hours to at least 24 hours. [11, 12] Further, decreasing the number of times position is changed decreases nursing burden and may decrease the rate of inadvertent line or tube displacement, the most feared complication of proning. Other potential risks associated with the act of changing position include transient changes in hemodynamics and oxygenation which would also be expected to occur less frequently with prolonged proning.

Early in the pandemic, we noticed that some patients experienced severe desaturations when returned to the supine position. This led to an alteration in clinical practice where patients were left in the prone position for longer than the standard 16 hours, some up to 72 hours. Given the recent emphasis on prone positioning, the variation in clinical practice and the protracted course of mechanical ventilation experienced by patients with COVID-ARDS, we felt there was equipoise to evaluate prolonged prone positioning in a prospective fashion.

This study was designed as a pilot safety and feasibility study.

Methods
Patient & Public Involvement:
Patient and family information sheets were developed and submitted to the UAB IRB for approval. Upon enrollment, the patient information sheets were given the bedside nurse to be placed with patient belongings. Study authors will disseminate study findings online and via social media in lay person-appropriate language.

Study Design:
The Prolonged Prone Positioning for COVID-19-induced ARDS is a pragmatic, randomized, single-center, parallel-arm study. Patients undergoing prone positioning for COVID-induced ARDS will be randomized to receive either traditional (16 hour) or prolonged (24 hour) prone ventilation sessions. This

study was approved under waiver of informed consent by the UAB IRB in keeping with the federal Office for Human Research Protections guidelines (45 CFR 46.116).

Study Sites:
The Prolonged Prone Positioning for COVID-19-induced ARDS study is being conducted across intensive care units at the University of Alabama at Birmingham Hospital.

Population
This trial includes adults (>=18 years old) located across any ICU at UAB Hospital who are endotracheally intubated in whom the treating physician plans to implement prone positioning imminently. Patients must have a P:F ratio of <=150 on at least 60% FiO2 and at least 10cm H2O of PEEP after ventilator optimization to be included. The primary cause of respiratory failure must be thought to be most likely due to COVID-19 ARDS (e.g. not a patient with a massive aspiration event or an acute heart failure exacerbation who is incidentally found to have COVID-19). This trial excludes patients with pre-existing treatment limitation (i.e. DNR order), prisoners, pregnant females, patients who have been on mechanical ventilation for >=48 hours at the time of screening and any patient in whom there is a contraindication to prone positioning (e.g. open abdomen, severe hemodynamic instability). Finally, patients may be excluded for physician discretion.

Randomization & Treatment Allocation:
Patients were randomized using even numbered blocks in a 1:1 fashion. Treatment allocation was sealed in opaque, sequentially numbered envelopes. After screening was performed and eligibility determined, a member of the treatment team opened the sealed envelope and informed the bedside nurse of the treatment allocation. A sign was then placed on the door of the patient with treatment allocation to inform all staff of the patient's involvement in the study and the treatment allocation.

Study Intervention:
Patients in a UAB ICU who were intubated and in whom the treating physician planned on initiating prone positioning for COVID-induced ARDS were screened for inclusion and exclusion criteria. Inclusion and exclusion criteria were documented on the screening form, and baseline ABG and ventilator settings were documented. Following enrollment, an opaque envelope was opened revealing treatment allocation. The bedside nurse was provided with a form stating the treatment allocation.

If patients are randomized to the traditional proning arm, the patient will be placed in the prone position for 16 hours. Following the 16-hour prone session, the patient will be returned to the supine position. After 4 to 6 hours in the supine position, an ABG is to be drawn. If the P:F ratio is <150 while on 10 cmH2O of PEEP and 60% FiO2, the patient will be returned to the prone position. If the patient is not immediately eligible for reproning at this time but subsequently has a P:F ratio of <150 on requisite ventilator settings, they will be repositioned to the prone position. This process will be continued as long as the patient was eligible. The patient will remain in the same treatment allocation arm.

If randomized to the prolonged proning arm, the patient will be placed in the prone position for 24 hours. Following the 24-hour prone session, the patient will be returned to the supine position. After 4 to 6 hours in the supine position, an ABG will be drawn. If the P:F ratio is <150 while on 10 cmH20 of PEEP and 60% FiO2, the patient will be returned to the prone position. If the patient is not immediately eligible for reproning at this time but subsequently has a P:F ratio of <150 on requisite ventilator settings, they will be repositioned to the prone position. This process will be continued as long as the patient was eligible. The patient will remain in the same treatment allocation arm.

All other care will be directed by the treating team and/or unit/hospital protocols.

Data Collection:
Data collection will be performed through a combination of data collection forms completed by the treatment team and EMR abstraction.

Sample Size Calculation:
This study was designed as a pilot study to evaluate the safety and feasibility. We anticipated an 8h change in duration proned and a standard deviation of 10h along resulting in an initial sample size of 52 patients.

DSMB & Interim Analysis:
Given the pace of enrollment and relatively small sample size, no interim analysis will be performed. This study will be stopped early for poor recruitment if enrollment drops below 8 patients enrolled on a rolling 4-week period.

Statistical Analysis:
Stata 16.1 (StataCorp, College Station, TX) will be used for all statistical analysis. Continuous variables will be presented as means with standard deviation or median with interquartile range. Comparisons will be made with the student's t-test or Mann-Whitney U test, as appropriate. Categorical variables will be reported as frequencies and proportions. Categorical variables will be compared using the Chi^2 test. A p-value of 0.05 will be considered significant.

Handling of Missing Data:
We have planned for no missing data in our power calculation.

Specific Aim 1:
Determine if the protocolized use of prolonged prone positioning results in an increased duration proned in the first 96 hours after proning

Hypothesis:
Patients randomized to receive prolonged prone positioning will spend more hours proned.

Specific Aim 2:
Compare the effect of traditional prone-positioning to prolonged prone-positioning on physiologic data, specifically improvements in P:F ratio and pulmonary mechanics.

Hypothesis: Patients who undergo prolonged prone positioning will have improved physiologic characteristics on day 4 when compared to those in the standard prone duration arm, as measured by P:F ratio and driving pressure.

Research Plan Overview: We propose a pragmatic, open-label, randomized trial of 52 patients in a 1:1 ratio to traditional proning strategy vs. prolonged proning.

Plan for Consent: We will perform this study under waiver of informed consent based on HHS Code of Federal Regulation (45 CFR 46).

IRB Category: Expedited review – Approved

Expected Duration of Study: We expect this study to last approximately 5-6 months at a rate of 8-10 patients enrolled per month.

Expected Results: We expect to find that our study is feasible. We expect to observe a trend towards improved pulmonary mechanics in patients undergoing prolonged proned positioning.

Potential Significance: If successful, this data could provide justification for a large-scale, multicenter randomized controlled trial. The researchers involved in this study have existing relationships with a large, national group capable of performing a multicenter study[13-19]. Ultimately, this research could result in decreased duration of mechanical ventilation and therefore mortality with subsequent increased hospital capacity and cost savings. The potential impact of this study is massive.

Potential Pitfalls: The most obvious potential pitfall for this study is sample size. This is unlikely to be a major issue for multiple reasons: 1) Our UAB MICU has treated a large number of COVID-ARDS patients, many of whom have received prone ventilation 2) Our screening strategy will default to inclusion in the study – given the potential for decreased positioning changes, this will have enthusiastic nursing support to encourage enrollment

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