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

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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 had subsequently spread worldwide, including in 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 medical 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<80% when on evaluation with a FiO_2 of 0.6, 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 (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

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 ^oC. 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_IO_2 > 300mmHg, or SpO_2/F_IO_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 $F_IO_2 \geq 0.8$ 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.

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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