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

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 $\geq$ 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 favor 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.[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%. Conditional to availability of continuous EtCO2, and tcPCO2 at participating hospitals, the variation of calculated V/Q ratio (three-compartment model) will also be reported for the first 72h.

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 (three subgroups: $SpO_2/F_IO_2 < 310$, $SpO_2/F_IO_2 < 240$, $SpO_2/F_IO_2 < 140$, which corresponds to the usual mild, moderate, severe ARDS classifications)

2. STUDY METHODS

This is a multi-center randomized controlled trial, which has been approved by Ethics Committee for all participating hospitals in Québec. Hospitals outside Québec 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

2.2. Exclusion criteria

The exclusion criteria 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 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 is not possible.

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 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 record-

ed. An investigator at each center is 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 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. 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 °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 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 enrollment in the study for ≥16 hours a day in the first 3 days. Patient comfort to HFNO, 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, HFNO 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 HFNO treatments will wear a surgical mask over the face. [16]

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 Weaning criteria

1) Patients' PaO_2/F_IO_2 > 300mmHg, or SpO_2/F_IO_2 > 340

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.

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 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 per-

formed 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 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. ACKNOWLEDGMENTS

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

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