Effects of 45° prone position ventilation in the treatment of acute respiratory distress syndrome
A protocol for a randomized controlled trial study
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Abstract
Background: Acute respiratory distress syndrome (ARDS) is an increasingly common acute respiratory failure that seriously threatens people’s health. ARDS has a case fatality rate of up to 40%. ARDS is a serious threat to the life safety of patients and the quality of life, causing a huge economic burden to individuals, families, and society. ARDS has become a large worldwide public health problem. Prone position ventilation (PPV) is an important auxiliary treatment for ARDS, which could improve oxygenation. However, PPV could cause Pressure injuries (PI) and other complications easily. We found that 45° PPV could reduce the incidence of PI, but lack of robust Evidence-based medicine evidence proving its efficacy. Therefore, we designed a randomized controlled trial to evaluate the efficacy of 45° PPV in the treatment of ARDS.

Methods: A total of 268 patients will be randomly assigned to the control group and the test group (n=134 each) in a ratio of 1:1. The treatment period is 7 days. The primary outcome measure will be the incidence of PI. The secondary outcomes will include APACHE II score, Braden Scale score, heart rate, systolic blood pressure, diastolic blood pressure, central venous pressure, mean arterial pressure, pH of arterial blood, oxygenation index, oxygen partial pressure, and carbon dioxide partial pressure. The evaluation will be performed at baseline, 1 hour, 12 hour, 48hour, 5days, 7days after PPPV.

Results: This study is helpful to evaluate the efficacy of 45° PPV in the treatment of ARDS.

Conclusion: 45° PPV may reduce the incidence of PI and improve oxygenation in patients with ARDS, which has important value in practical application

Trial registration: ChiCTR2000040436, registration time: November 28, 2020.

Abbreviations: ARDS = acute respiratory distress syndrome, PI = pressure injuries, PPV = prone position ventilation, RCT = randomized controlled trial.

Keywords: 45°, acute respiratory distress syndrome, clinical efficacy, prone position ventilation, protocol

1. Introduction
Acute respiratory distress syndrome (ARDS) is an increasingly common acute respiratory failure that seriously threaten people’s health. ARDS has a case fatality rate of up to 40%.1,2 The concept of adult respiratory distress syndrome was first proposed by Ashbaugh et al in 1967.3 With the continuous understanding of ARDS, it was found that ARDS occurs not only in adults but also in children, The American Thoracic Society (ATS) and...
European Society of Intensive Care Medicine have renamed adult respiratory distress syndrome as ARDS.\(^14\)\(^5\) ARDS is a clinical syndrome characterized by acute, progressive dyspnea and intractable hypoxemia, which is caused by various intrapulmonary and/or extrapulmonary causes other than cardiogenic factors. ARDS is an acute respiratory failure caused by diffuse alveolar and interstitial edema following the damage to pulmonary capillary endothelial cells and alveolar epithelial cells. ARDS is characterized by progressive dyspnea and intractable hypoxemia, non-cardiogenic pulmonary edema, opacity of bilateral chest X-ray films and decreased lung compliance. The etiology of ARDS includes shock, severe infection, trauma, severe burn, pancreatitis, pneumonia, drug overdose and poisoning, blood transfusion, etc.\(^16\)\(^9\)

Piehl et al.\(^10\) first reported the efficacy of prone position ventilation (PPV) in ARDS, and he found that PPV can improve oxygenation by recruiting alveoli situated in dorsal dependent regions, which is consistent with the results of subsequent clinical studies.\(^11\)\(^–\)\(^13\) PPV could improve the pulmonary ventilation/blood flow ratio, oxygenation and reduce the mortality by recruiting alveoli situated in dorsal dependent regions and promoting the redistribution of lung gas.\(^14\)\(^–\)\(^17\) One meta-analyses have shown that PPV could reduce mortality in patients with severe ARDS.\(^12\) Guerin et al.\(^13\) found that early application of PPV can significantly reduce the 28-day and 90-day mortality rate mortality in patients with severe ARDS. More than 70% of lung injury patients could clinically improve oxygenation by using PPV.\(^18\)

However, a clinical application of PPV is difficult especially for critically ill patients with various pipelines and obese patients. Even worse, PPV could cause a variety of complications, such as hemodynamic instability, pressure injuries (PI), aspiration, conjunctival edema, as well as the compression, displacement and prolapse of various indwelling catheters caused by postural changes, among which the PI is the most common. Manzano et al.\(^19\) found that the incidence of PI in patients with mechanical ventilation for more than 7 days was as high as 35.6%. Mechanical ventilation time was a risk factor for PI in critically ill patients.\(^20\)\(^21\) Sud S et al.\(^22\) found that the incidence of PI was 42.7% in patients with ARDS using PPV.

We found that 45° PPV could reduce the incidence of PI, but lack of robust Evidence-based medicine evidence proving its efficacy. Therefore, we aim to conduct a randomized controlled clinical trial (RCT) to evaluate the efficacy of 45° PPV in the treatment of ARDS.

2. Methods

2.1. Trial design and registration

This is a randomized controlled clinical trial of 45° PPV (test group) compared to 0° PPV (control group). Participants will be recruited from the Department of Emergency and Intensive Care Medicine, Guangzhou Panyu central hospital. The Figure 1 shows the study design in the flowchart, and the Figure 2 illustrates the time schedule of enrolment, interventions, assessments, and visits of participants. We developed the protocol based on the Standard Protocol Items: Recommendations for Intervention Trials guidelines (Additional file 1).

This protocol has been registered in the Chinese Clinical Trial Registry on November 28, 2020, http://www.chictr.org.cn/showprojen.aspx?proj=64953. And the registration number is ChiCTR2000040436.
researchers directly. We will provide potential participants with detailed information describing the benefits and possible risks of the trial. If they decide to participate, they will sign written informed consent. We will strengthen doctor-patient communication to improve the compliance.

2.8. Patient safety
The adverse events associated with PPV included severe hypoxemia, pneumothorax and intracranial hypertension. Clinicians will record the occurrence of any adverse events and the intervention will be stopped immediately in case of serious adverse event. The independent safety supervision committee composed of three experts from different fields in Guangzhou Panyu central hospital has the right to terminate the study.

3. Interventions
3.1. Basic treatment
All patients will be endotracheally intubated and mechanically ventilated with tidal volume 6ml/kg (ideal body weight),
inspiratory to expiratory ratio 1:2–1:3, respiratory rate less than 20 times/min. And PEEP and FiO2 will be adjusted according to the ARDSnet protocol.

3.2. The control group
The patients in the control will undergo mechanical ventilation in the 0° prone position for 16 hours a day and turning over every 2 hours. We will remove the electrodes in the anterior chest area and paste hydrocolloid dressings on the clavicle and the anterior superior iliac spine. The electrode will be stucked on the back.

3.3. The test group
The patients in the test group will undergo mechanical ventilation in the 0° prone position for 2 hours, then tilted 45° towards prone to the left for 2 hours and tilted 45° towards prone to the right for 2 hours, and returned to 0° prone position finally. This cycle will last for 16 hours.

3.4. The course of treatment
The duration of treatment will be 7 days.

3.4.1. Combined treatment regulations. During study, it is forbidden to use PPV in other positions.

|                      | Baseline | Treatment period |
|----------------------|----------|------------------|
|                      | 1h       | 6h               |
| Enrollment           |          |                  |
| Informed consent     |          | x                |
| Inclusion/exclusion  |          | x                |
| criteria             |          |                  |
| Medical history      |          | x                |
| Allocation           |          | x                |
| Intervention         |          |                  |
| Assessments          |          |                  |
| Concomitant medication |        | x    |
| vital signs          |          | x    |
| APACHE II score      |          | x    |
| Braden Scale score   |          | x    |
| Hemodynamic indexes  |          | x    |
| Oxygenation          |          | x    |
| incidence of PI      |          | x    |
| Adverse event        |          | x    |

Figure 2. Study design schedule.

Table 1. Study design schedule.
3.5. Outcome measures

3.5.1. Primary outcome. The primary outcome will be the incidence of PI. Outcome indicators will be collected at day 7 of PPV.

3.5.2. Secondary outcomes.

(1) APACHE II score: APACHE-II score includes 12 physiological scores, 1 age score, 1 Glasgow scores and 5 chronic disease scores. The APACHE II score ranged from 0 to 71 points and a higher score indicated a worse severity. The APACHE II score will be evaluated at baseline, and 1 hour, 12 hour, 48 hour, 5 days and 7 days post-PI.

(2) Braden Scale score: The Braden Scale score has been widely used for predicting PI risk. The Braden Scale score ranged from 6 to 23 points and a higher score indicated a high PI risk. The Braden Scale score will be evaluated at baseline, and 1 hour, 12 hour, 48 hour, 5 days, and 7 days post-PI.

(3) Hemodynamic indexes: The hemodynamic indexes include HR, systolic blood pressure, diastolic blood pressure, central venous pressure, mean arterial pressure. The hemodynamic indexes will be evaluated at baseline, and 1 hour, 12 hour, 48 hour, 5 days, and 7 days post-PI.

(4) Oxygenation: The Oxygenation include pH of arterial blood, oxygenation index, partial pressure of oxygen and partial pressure of carbon dioxide. The Oxygenation will be evaluated at baseline, and 1 hour, 12 hour, 48 hour, 5 days, and 7 days post-PI.

3.5.3. Safety outcomes. Other complications of PPV include unplanned extubation, catastrophic hypoxemia, pneumothorax, eye complications and intracranial hypertension. Of course, this study also has some shortcomings, including:

4. Discussion

ARDS is characterized by severe and life-threatening acute respiratory syndrome with a high mortality. PPV is an important method to improve the alveolar ventilation in patients with ARDS. PPV can improve oxygenation in patients with ARDS by increasing alveolar ventilation, re-distributing transpulmonary pressure, opening alveoli, reducing the risk of alveolar hyperinflation, reducing the compression of mediastinum on lung tissue, improving the pulmonary ventilation/blood flow ratio, reducing intrapulmonary shunt, clearing the sputum from the trachea easily. However, there are complications in about such as hemodynamic instability, skin and mucous membrane PI, aspiration, conjunctival edema, and various indwelling catheter compression, displacement and prolapse caused by body position change, among which the PI is the most common. We found that 45° PPV could reduce the incidence of PI, but lack of robust Evidence-based medicine evidence proving its efficacy. Therefore, we aim to conduct a RCT to evaluate the efficacy of 45° PPV in the treatment of ARDS.

RCT is the gold standard to evaluate the efficacy and safety of drugs. Of course, this study also has some shortcomings, including:

4.1. Trial status

Protocol version number V1.0, October 10, 2020. The trial is currently in the recruitment phase of participants. Recruitment will be beginning on December 1, 2020 and is expected to end on December 31, 2023.
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Author contributions

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