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RESEARCH PROTOCOL

The efficacy of $P_{0.1}$-guided sedation protocol in critically ill patients receiving invasive mechanical ventilation: A randomized controlled trial

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ABSTRACT:

Background: Mechanical ventilation is a lifesaving treatment in patients with acute respiratory failure. Despite optimal support, some patients still exhibit excessive respiratory drive, leading to patient self-inflicted lung injury (P-SILI) and diaphragmatic dysfunction. Sedation and muscle relaxants are commonly used to reduce respiratory efforts and manage patient-ventilator asynchrony (PVA). Conventionally, sedative drugs are adjusted based on the sedation level assessed by the Richmond Agitation-Sedation Scale (RASS), which may not correlate with the patient's respiratory drive. Drop in airway pressure at the first 100 milliseconds of the beginning of the inspiration after the end-expiratory occlusion ($P_{0.1}$) is a simple and reliable method of respiratory drive monitoring by mechanical ventilation at the bedside and may be the more suitable sedation target.

Objectives: To assess the efficacy of a sedation protocol targeting optimal $P_{0.1}$ and RASS score compared to conventional sedation strategy in patients requiring invasive mechanical ventilation in the medical intensive care units in terms of successful extubation.

Methods: This is an open-labeled, single-center, randomized controlled trial conducted in medical intensive care units at a tertiary care hospital in Bangkok, Thailand. We randomly allocated mechanically ventilated patients in a 1:1 ratio to receive a sedation protocol targeting both optimal respiratory drive measured by $P_{0.1}$ (intervention group) and light sedation (RASS 0 to -2) or standard of care (control group targeting RASS alone). The primary outcome is the rate of successful extubation within 14 days after randomization.

Hypothesis: We hypothesize that sedation protocol targeting optimal $P_{0.1}$ and light sedation will increase the rate of successful extubation at 14 days in mechanically ventilated patients compared to conventional sedation strategy.

Conclusions: This study aims to evaluate the efficacy of a sedation protocol using $P_{0.1}$ measurement to monitor and target optimal respiratory drive, in conjunction with sedation scores, in critically ill patients receiving invasive mechanical ventilation.

Ethics and dissemination: This study protocol was approved by the Human Research Protection Unit of the Faculty of Medicine, Siriraj Hospital, Mahidol University (Certificate of Approval no. Si 915/2023).

Trial registration: NCT06203405

Keywords: Acute respiratory failure; Mechanical ventilation; $P_{0.1}$; Respiratory drive; Sedation

INTRODUCTION

Mechanical ventilation is considered one of the essential and potentially lifesaving supportive treatments in critically ill patients suffering from acute respiratory failure. However, inappropriate mechanical ventilation can lead to ventilator-induced lung injury (VILI). In the preceding years, the concept of patient self-inflicted lung injury (P-SILI) has emerged and become an interesting subject for researchers, aiming to understand the underlying pathophysiology and establish options for prevention and treatments [1]. Recent studies have demonstrated that P-SILI is related to excessive and vigorous inspiratory efforts when superimposed mechanical ventilation, which may be more injurious to the lungs and could facilitate the progression of lung injury [2,3]. Several mechanisms could explain these effects, including increased transpulmonary pressure and lung stress, the pendelluft phenomenon, and increased transmural pulmonary vascular pressure, which causes a negative pressure pulmonary edema.

Despite optimal support by mechanical ventilation, some patients still exhibit excessively high respiratory drives, leading to patient-ventilator asynchrony, which can potentiate lung injury and worsen outcomes [4,5]. Sedatives/analgesics and neuromuscular blocking agents are currently used in clinical practices [6,7]. Sedative drugs are conventionally titrated based on sedation levels assessed by commonly used validated tools such as the Richmond Agitation-Sedation Scale (RASS), Riker Sedation-Agitation Scale (SAS), or Ramsay Scale. These tools were designed to assess the level of arousal but not the patient's effort. A study by Dzierba et al. found no correlation between sedation depth assessed by RASS and respiratory drive measured by airway occlusion pressure; as a result, suboptimal sedation may occur [8]. Excessive sedation leads to several complications, including drug-induced hypotension, delirium, cognitive impairment, ventilator-associated pneumonia, weaning failure, and prolonged duration of mechanical ventilation [9,10], while undersedation results in more P-SILI and diaphragmatic dysfunction [2]. A new strategy for sedation in mechanically ventilated patients called "lung-protective sedation" is proposed [11]. This strategy involves targeting synchrony, facilitating safe levels of the patient's drive and effort, and balancing the risk/benefit of sedation, which may require more advanced monitoring techniques for respiratory drive and effort beyond the depth of sedation.

In the last few years, numerous techniques have been developed and studied for monitoring respiratory drive and breathing efforts to detect excessive drive and efforts and provide guidance on treatments to prevent P-SILI [7,12]. These techniques include end-expiratory occlusion maneuver and airway occlusion pressure measurement, esophageal pressure monitoring, electrical activity of the diaphragm, and diaphragmatic ultrasonography. Drop in airway pressure at the first 100 milliseconds of the beginning of the inspiration after the end-expiratory occlusion or $P_{0.1}$ is a simple and reliable method of respiratory drive monitoring that can be automatically measured and displayed by modern mechanical ventilation at the bedside. A proposed optimal value of $P_{0.1}$ value is 1.5 to 3.5 cmH_2O [13-15]. This method also has good diagnostic performance in detecting abnormal respiratory drive during mechanical ventilation. A cut-off $P_{0.1}$ value of >3.5 cmH_2O for excessive respiratory drive had a sensitivity of 80-92% and specificity of 77-89%, while <1.5 cmH_2O indicated low respiratory drive [16]. Moreover, de Vries et al. found a correlation between $P_{0.1}$ and lung stress and diaphragmatic effort measured by transpulmonary and transdiaphragmatic pressure changes [17]. This study also showed a decent accuracy of $P_{0.1}$ in detecting high lung stress (defined as changes in transpulmonary pressure of >20 cmH_2O) with AUROC of 0.88 (0.84 to 0.92), sensitivity of 89%, and specificity of 74% [17]. A prior study also demonstrated that the $P_{0.1}$ value continuously displayed on the mechanical ventilation accurately reflects the standard $P_{0.1}$ measurement maneuver [14]. Therefore, $P_{0.1}$ can be a promising technique to monitor respiratory drive and guide the adjustment of sedation and neuromuscular blocking agents in mechanically ventilated patients in the intensive care unit (ICU).

KEY MESSAGES:

- Controlling patients' respiratory drive and efforts with sedations, is an essential component of caring for mechanically ventilated patients to prevent further lung injury from excessive drive and effort, known as patient self-inflicted lung injury or P-SILI.
- Currently, sedation is adjusted based on sedation level, such as RASS, which does not include monitoring respiratory drive and effort and may lead to suboptimal sedation use and adverse outcomes.
- To date, studies evaluating of the lung and diaphragm protective sedation strategy involving respiratory drives and effort monitoring are limited. This study aimed to evaluate the efficacy of sedation protocol targeting optimal respiratory drive using $P_{0.1}$ measurement and light sedation in mechanically ventilated patients, compared to conventional sedation strategy.

OBJECTIVES

This study aims to assess the efficacy of titrating sedation targeting optimal $P_{0.1}$ (1.5 to 3.5 cmH_2O) with RASS score compared with a conventional sedation strategy, targeting RASS score alone, in patients requiring mechanical ventilation in the medical intensive care unit.

MATERIALS AND METHODS

Trial design and setting (Figure 1 and 2)

This study is an open-labeled, single-center, randomized controlled trial conducted in the medical ICU at Siriraj

Hospital, Mahidol University, Bangkok, Thailand. The study protocol was approved by the Human Research Protection Unit of the Faculty of Medicine, Siriraj Hospital, Mahidol University (Certificate of Approval no. Si 915/2023). This trial was already registered on ClinicalTrials.gov (NCT06203405). Patient recruitment was started in December 2023 after obtaining a certificate of ethics approval.

Population

Inclusion criteria

1) Patients aged ≥18 years admitted to the medical ICU at Siriraj Hospital, Mahidol University, Bangkok, Thailand

2) Receiving invasive mechanical ventilation due to acute respiratory failure within 72 hours before enrollment

Exclusion criteria

1) Receiving mechanical ventilation due to indications other than acute respiratory failure, such as postoperative procedures or airway protection in comatose patients

2) Receiving mechanical ventilation for >72 hours before enrollment

3) Receiving neuromuscular blocking agents before enrollment

4) Impaired secretion clearance or upper airway obstruction anticipating a tracheostomy

5) Severe metabolic acidosis (arterial pH <7.2) who do not have a plan for renal replacement therapy

6) Intubated for neurological conditions, including intracranial hypertension, intracranial hemorrhage, ischemic stroke, status epilepticus, or neuromuscular diseases

7) Post-cardiac arrest without regaining full consciousness within 24 hours after the return of spontaneous circulation

8) Severe liver dysfunction, including acute fulminant liver failure or cirrhosis with the Child-Pugh score B or C

9) Previous allergy to any of the opioid, sedation, or neuromuscular blocking drugs

10) Pregnancy

11) Do-not-resuscitate (DNR) orders

12) Refuse to participate in the study or cannot identify legally authorized representatives (LAR) within 24 hours after enrollment.

Study procedures

Enrollment, obtaining informed consent, randomization, and blinding

All mechanically ventilated patients admitted to the medical ICU will be screened daily for eligibility. Informed consent will be obtained from the patients or legally au-

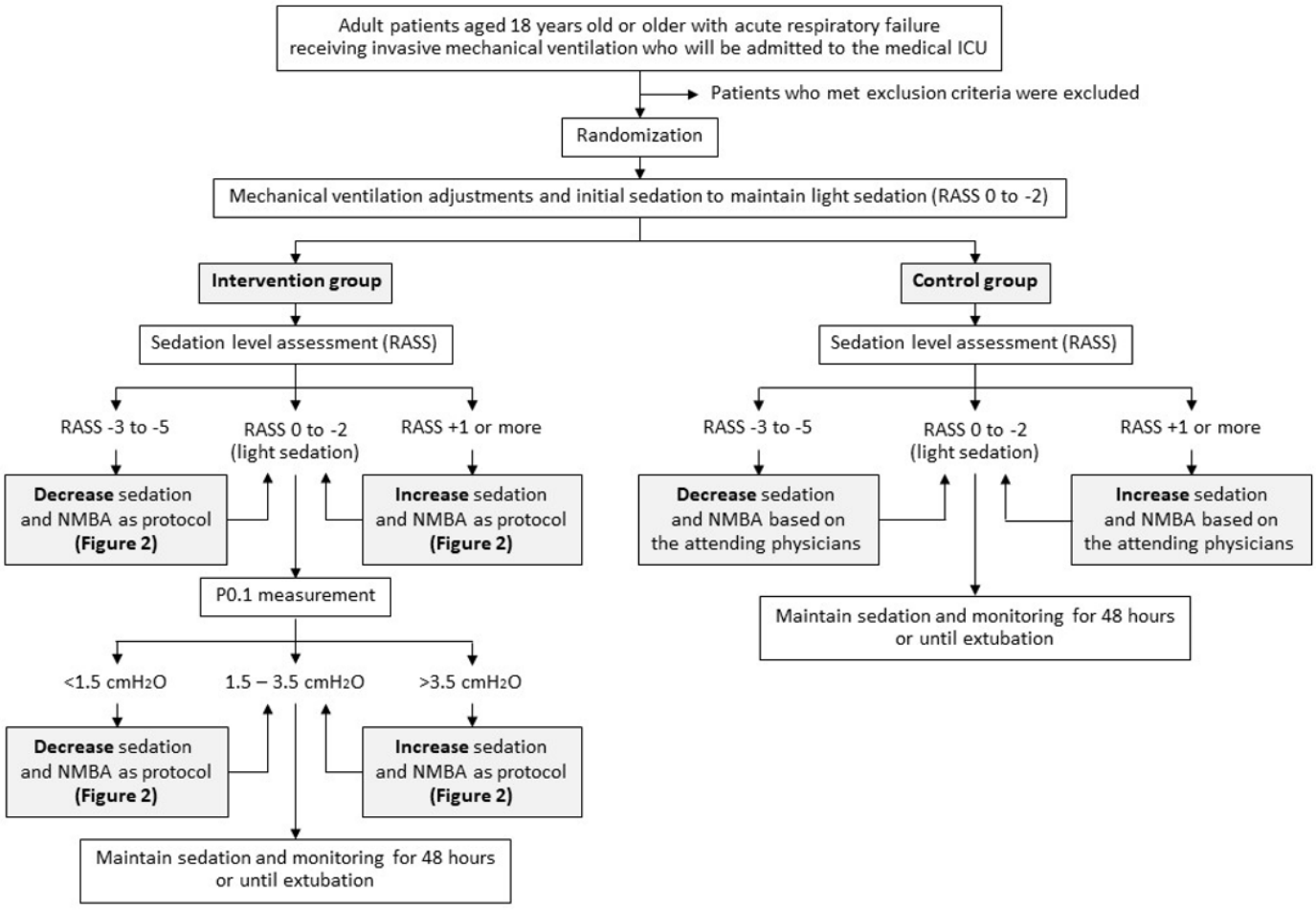

Figure 1. Diagram for study procedures.

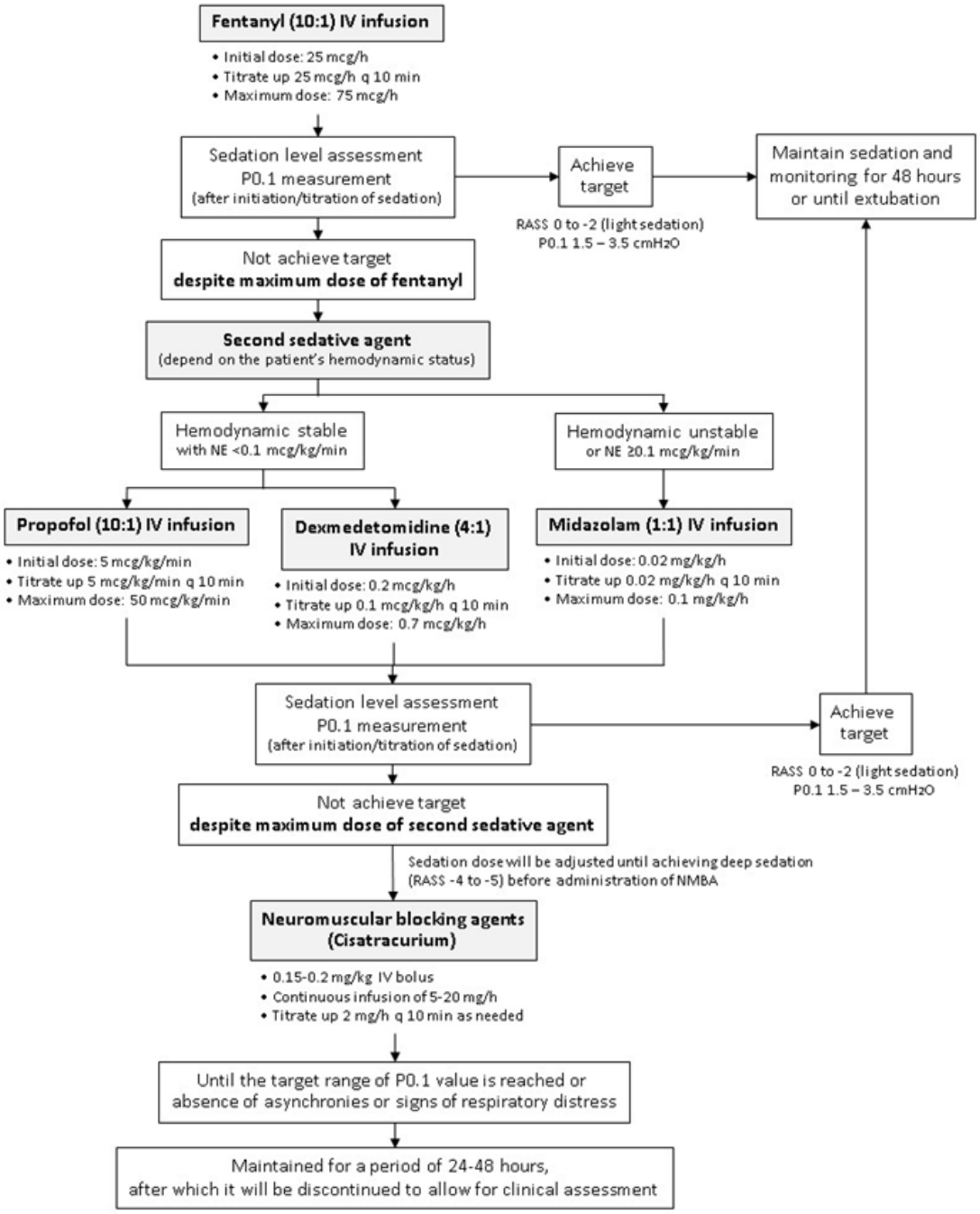

Figure 2. Diagram for administration and adjustment of sedation and neuromuscular blocking agents in the intervention group.

thorized representatives (LAR). Then, patients will be randomly allocated in 1:1 ratio to receive a sedation protocol targeting both optimal respiratory drive and sedation level (intervention group) or standard of care (control group targeting sedation level alone) according to the allocation table generated from a computerized random number sequence generator (www.random.org).

Owing to the nature of the trial intervention, which involves monitoring and adjusting of sedation and neuromuscular blocking agents, it is impossible to blind the investigators, attending physicians, participants, and their relatives. So, we use the rate of successful extubation at 14 days after randomization, an objective measurement, as the primary outcome for this study to reduce the risk of bias arising from an unblinded design.

Mechanical ventilation strategies

Mechanical ventilation will be set according to the clinical judgment of the attending physicians except for the mechanical ventilation setting, which will be changed from a flow trigger of 2 liters/minute, the standard trigger setting in our situation, to a pressure trigger of -2 cmH_2O in both intervention and control groups to enable $P_{0.1}$ measurement during the study period. For patients diagnosed with acute respiratory distress syndrome (ARDS), the mechanical ventilation settings will be adjusted according to the current standard guideline for managing ARDS patients [18]. Only mechanical ventilation devices with $P_{0.1}$ measurement will be used in the study.

Sedation level assessment and $P_{0.1}$ measurement

Patients in both study groups will be monitored for level of arousal using the Richmond Agitation-Sedation Scale (RASS) and respiratory drive using $P_{0.1}$ value measured from the mechanical ventilation during the 48-hour study period after randomization. The RASS score will be assessed routinely by trained ICU nurses and recorded every 8 hours for this study.

$P_{0.1}$ values will be automatically measured by the no occlusion maneuver technique and continuously displayed on the Hamilton-G5 and S1 ventilators (Hamilton Medical: Graubünden, Switzerland), the most available ventilators in our medical intensive care units [19]. For other mechanical ventilation devices without continuous $P_{0.1}$ measurement, including Puritan BennettTM 980 (Medtronic: Minnesota, USA) and CarescapeTM R860 (GE Healthcare: Illinois, USA), $P_{0.1}$ will be measured by expiratory occlusion maneuver and recorded at 2-hour intervals during the study period.

Titration of analgesia, sedation, and neuromuscular blocking agents

At the start of the study, analgesia and sedation will be initially adjusted to achieve light sedation targeting a RASS score of 0 to -2 in both intervention and control groups according to standard practice guidelines for managing pain and agitation for patients receiving mechanical ventilation in the ICU [20-22].

Available analgesia and sedative drugs in the study include intravenous fentanyl 25-75 micrograms/hour, midazolam 0.02-0.1 milligrams/kg/hour, propofol 5-50 micrograms/kg/minute, and dexmedetomidine 0.2-0.7 micrograms/kg/hour.

Propofol or dexmedetomidine is preferred in patients with stable hemodynamics without vasopressors or those treated with low-dose norepinephrine (<0.1 micrograms/kg/minute). Midazolam is preferred in patients who require norepinephrine of ≥0.1 micrograms/kg/minute to maintain hemodynamics.

Deep sedation (RASS -3 to -5) and neuromuscular blocking agents are allowed to facilitate mechanical ventilation in patients with refractory hypoxemia or severe obstructive lung diseases, according to the clinical judgment of the attending physicians. The dose recommendation for cisatracurium is 0.15-0.2 milligrams/kg intravenous bolus injection, then continuous infusion at 5-20 milligrams/hour.

After initial management, sedation will be adjusted according to the group to which patients are assigned.

Intervention group

After achieving a light sedation target, further sedation adjustment in the intervention group will be guided by $P_{0.1}$ measurement as follows:

If a $P_{0.1}$ value of 1.5-3.5 cmH_2O is achieved, no further adjustment is required.

If the $P_{0.1}$ value >3.5 cmH_2O, sedation will be increased to achieve the $P_{0.1}$ target. We acknowledge that this adjustment may lead to deeper sedation levels. After that, if the $P_{0.1}$ value is still >3.5 cmH_2O, indicating high respiratory drive and effort despite deep sedation, cisatracurium will be allowed and titrated until the target is achieved.

If the $P_{0.1}$ value <1.5 cmH_2O, sedative drugs, including propofol, midazolam, or dexmedetomidine, will be reduced first. Then, the dose of fentanyl will be reduced. Cisatracurium, if used, will be stopped in case of $P_{0.1}$ value <1.5 cmH_2O and can be resumed if $P_{0.1}$ value >3.5 cmH_2O despite deep sedation.

Control group

Sedation adjustment after initial management will depend on the clinical judgment of the attending physicians.

The study protocol will be continued for 48 hours after randomization or until the patients are considered ready for weaning. If the patient is not ready for weaning from mechanical ventilators after 48 hours, sedation adjustment will depend on the clinical judgment of the attending physicians.

Other treatments in the intensive care unit and the weaning process

Definite treatment of the primary cause of acute respiratory failure, general critical care management, and other respiratory interventions, including prone positioning, esophageal pressure monitoring, or the use of venovenous extracorporeal membrane oxygenation (VV-ECMO), will be provided to the patients in both groups as the standard of care in our institution [23].

Patients in both groups will undergo daily evaluations by the attending physicians to determine their readiness for the weaning trial as per the standard weaning protocol. The criteria for readiness to wean: recovery from the current critical illness; temperature <38 °C, mean arterial pressure ≥65 mmHg without vasoactive drugs or with low doses of dopamine (<0.05 mcg/kg/min) or norepinephrine (<0.05 mcg/kg/min), heart rate <120 beats/minute, PaO_2/FiO_2 ratio >150 with FiO_2 ≤0.4, PEEP ≤8 cmH_2O, and arterial pH ≥7.35, no symptoms and electrocardiographic signs of active myocardial ischemia, hemoglobin level ≥7 g/dL, RASS score ≥ -1 without neuromuscular blocking agents used in the last 12 hours [24,25].

Patients fulfilling these criteria are considered ready for a weaning trial. They will undergo a spontaneous breathing trial (SBT) using either low-level pressure support (≤8 cmH_2O) or a T-tube oxygen for 30-120 minutes. The patients will be evaluated for airway patency, risk of post-extubation laryngeal edema, respiratory secretions, and level of consciousness before extubation [26,27]. Then, the patients will be extubated if they can tolerate SBT without meeting any of the criteria for failure of SBT according to standard weaning protocol. The criteria for failure of SBT: agitation, depressed mental status, cyanosis, increased accessory muscle activity, PaO_2 ≤50-60 mmHg or SpO_2 ≤90% with FiO_2 ≥50%, $PaCO_2$ ≥50 mmHg or an increase in $PaCO_2$ >8 mmHg, pH <7.32 or a decrease in pH ≥0.07, respiratory rate >35 breaths/min or increase more than 50%, heart rate >140 beats/minute or increase more than 20%, systolic blood

Table 1. Definition

Keyword	Definition
Successful extubation within 14 days	Successful liberation from mechanical ventilation and extubation within 14 days after randomization, without reintubation within 7 days following extubation.
Postextubation respiratory failure [24,25]	Patients who meet at least one of the following criteria within 72 hours after extubation: respiratory rate more than 35 breaths/minute, oxygen saturation less than 90% or PaO_2 less than 80 mmHg despite receiving FiO_2 >50%, respiratory acidosis with pH <7.35 or $PaCO_2$ >50 mmHg or increase of 20% from baseline.
Reintubation	Patients diagnosed with postextubation respiratory failure who experience clinical deterioration despite applications of non-invasive respiratory supports, including NIV or high flow oxygen nasal cannula, and subsequently require reintubation.
Ventilator-associated pneumonia (VAP) [34,35]	Infection of pulmonary parenchyma in patients exposed to invasive mechanical ventilation for at least 48 hours diagnosed with concomitant presence of 3 following criteria: 1) Clinical suspicious of pneumonia (abnormal temperature ≤36 °C or ≥38 °C, WBC ≤ 4,000 or ≥12,000 cells/mm^3, and declining of oxygenation requiring adjustment of PEEP or FiO_2) 2) New or progressive and persistent radiographic infiltrates 3) Positive microbiological cultures from lower respiratory tract specimens, such as endotracheal aspirations or bronchoalveolar lavage
Propofol-related infusion syndrome [36]	A potentially fatal condition caused by prolonged infusion of propofol causing severe cardiorespiratory depression with severe lactic acidosis and hypertriglyceridemia.

pressure >180 mmHg or increase more than 20%, systolic blood pressure <90 mmHg, or new-onset cardiac arrhythmias [24].

High-flow oxygen nasal cannula (Optiflow™ system, Fisher and Paykel Healthcare: Auckland, New Zealand) or non-invasive ventilation (Draeger Carina, Draeger: Lübeck, Germany) with a full facemask will be applied to the patients immediately following extubation for patients with risk factors for post-extubation respiratory failure [25,28]. The decision regarding choices of non-invasive respiratory supports following extubation will be based on the attending physician's judgment.

After extubation, patients who had a respiratory rate of >35 breaths/minute, hypoxemia (oxygen saturation <90% or PaO_2 <80 mmHg despite receiving FiO_2 >50%), or respiratory acidosis (pH <7.35 or $PaCO_2$ >50 mmHg) within 72 hours after extubation and continued to deteriorate while receiving non-invasive respiratory supports will be diagnosed with post-extubation respiratory failure and reintubated immediately [24,25]. Mechanical ventilation, sedation management, and a decision regarding tracheostomy in reintubated patients will depend on the attending physician's judgment.

OUTCOME MEASUREMENT

Primary outcome

The primary outcome was the rate of successful extubation within 14 days after randomization, defined as extubation within 14 days without reintubation until 28 days after ICU admission (Table 1).

Secondary Outcomes

The secondary outcomes were the rate of successful extubation within seven days and 28 days after randomization, ICU and hospital mortality, mortality at 28 days after randomization, ICU and hospital length of stay, duration of mechanical ventilation, ventilator-free days at 28 days after randomization [29], reintubation rate and self-extubation rate within seven days after extubation, post-extubation respiratory failure, tracheostomy, delirium during ICU admission, and maximal infusion dose and duration of sedation and neuromuscular blocking agents use during the study period.

The safety outcomes include ventilator-related complications including ventilator-associated pneumonia and barotrauma (pneumothorax, pneumomediastinum, and subcutaneous emphysema) and medication-related complications including cardiac arrhythmias (severe bradycardia with heart rate <40 beats/minute), serious adverse events (severe allergic reaction or anaphylaxis, and propofol-related infusion syndrome), and severe acidemia (pH <7.20) or requiring renal replacement therapy due to intractable acidemia (Table 1).

DATA ANALYSIS PLAN

Sample size estimation

Based on data from a prior randomized controlled study in the medical ICU at Siriraj Hospital comparing limited driving pressure and conventional low tidal volume ventilation strategies [30], the rate of successful extubation at 14 days was 40%. We anticipated a 20 percent absolute increase in the rate of successful extubation in the intervention group. Therefore, the approximate rate of successful extubation will be 60%. When calculated with a formula for proportion comparison for independent two groups using 80% power and 5% risk of type I error (two-sided alpha of 0.05), a sample size of 97 patients is required in each group. Considering an estimated drop-out rate of 10%, we plan to include a sample size of 214 patients, with 107 patients in each group.

Statistical analysis

We will present the categorized data using numbers and percentages. The chi-square test and Fisher's exact test will be used to compare the variables between each group. We will use the mean and standard deviations for continuous data if the data follows a normal distribution. Alternatively, the median and interquartile range (IQR) will be used if the data is not normally distributed. A t-test or Mann-Whitney U test (Wilcoxon rank-sum test) will be used to compare the data, depending on the data distribution. The intention-to-treat basis will be used for all primary analyses in the study. Primary and secondary outcomes will be reported with between-group differences with a 95% confidence interval to assess the effect of the intervention. We will perform survival analysis using Kaplan-Meier curves with a log-rank test to evaluate the intervention's impact on the successful extubation outcomes, all mortality outcomes, and length of stay outcomes. Additionally, we will use the Cox-proportional hazards model to calculate the hazard ratio and analyze these factors further. Two-sided p-values of less than 0.05 were considered to indicate statistical significance. We plan to conduct an interim analysis when approximately 50% of the estimated sample size has been recruited. The study will be stopped early after an interim analysis based on specific conditions. For futility, if significant differences in the primary outcome or the intervention effect are unlikely to occur. For safety reasons, if notable harm or significant adverse events are observed in either arm of the study. All the statistical data analysis will be performed using R program version 4.3.2 or SPSS version 18.

DATA MANAGEMENT AND DATA MONITORING

Data collection

The following data will be collected during the study period:

1) Baseline characteristics including age, sex, weight, height, body mass index (BMI), principal diagnosis, comorbidities, causes of acute respiratory failure, vital signs, severity of illness using SOFA, APACHE-II score, baseline lung injury score, baseline Glasgow outcome scale (GOS) before admission, and baseline laboratory data,

2) Mechanical ventilation settings and respiratory parameters, including mode of mechanical ventilation, inspiratory pressure, PEEP, actual tidal volume in mL/kg of predicted body weight, actual respiratory rate, peak inspiratory pressure, plateau pressure, minute ventilation, and arterial blood gas analysis (pH, PaO_2, $PaCO_2$, PaO_2/FiO_2 ratio). Mechanical ventilation parameters will be collected on days 1-3 and 7 after randomization or until the patients have been extubated.

3) Level of sedation assessed by RASS and $P_{0.1}$ value during the 48 hours of the study protocol.

4) Number, maximal infusion dose, duration of sedation, and neuromuscular blocking agents used during the study period.

5) Other ICU treatments including prone positioning, vasopressor use, renal replacement therapy, esophageal pressure monitoring, VV-ECMO, and recruitment maneuvers.

6) Weaning process including SBT attempts, cuff leak test, the use of non-invasive ventilation, and high flow oxygen nasal cannula after extubation

7) Outcome variables including the rate of successful extubation within seven days, 14 days and 28 days after randomization, duration of mechanical ventilation, ventilator-free days at 28 days, ICU mortality, hospital mortality, mortality at 28 days after randomization, ICU and hospital length of stay, post-extubation respiratory failure, reintubation rate within seven days after extubation, self-extubation events, tracheostomy, delirium during ICU stay, and GOS at hospital discharge.

8) Complications or adverse events during the study period, including ventilator-associated pneumonia, barotrauma, medication-related complications (cardiac arrhythmia, severe allergic reaction, propofol-related infusion syndrome), and severe acidosis requiring renal replacement therapy.

All patients included in the study will be followed up for at least 28 days after randomization. Summary of all definition and criteria as Table 2.

DISCUSSION

Excessive respiratory drive and effort in patients with spontaneous breathing can potentially lead to patient self-inflicted lung injury (P-SILI) and further worsen outcomes during mechanical ventilation [2,3]. Therefore, monitoring and maintaining respiratory drive within a safe range to minimize patient self-inflicted lung injury are essential components in the care of mechanically ventilated patients. Sedation and neuromuscular blocking agents are commonly used to manage excessive respiratory drive and treatment of asynchronies. In current practices, sedation is adjusted based on sedation scales, for instance, the RASS, the Riker SAS, or the Ramsay Scale [6,7]. However, this approach may not be suitable for mechanically ventilated patients due to the poor correlation between sedation levels and respiratory drive and effort [8], which may lead to suboptimal levels of sedation, resulting in either under- or oversedation.

$P_{0.1}$ is a simple and reliable method that can be measured and displayed by mechanical ventilators at the bedside, and it is well correlated with the patient's respiratory drive [13-17]. Therefore, it can be utilized to monitor respiratory drive, detect abnormal respiratory drive, and guide adjustments of sedation in mechanically ventilated patients. To our knowledge, clinical studies evaluating the efficacy of sedation protocols that include monitoring of respiratory drive are limited. We developed a sedation protocol that implements respiratory drive monitoring using $P_{0.1}$ measurement in addition to sedation level assessments to target optimal respiratory drive and light sedation in mechanically ventilated patients. We hypothesize that this protocol will assist physicians in optimizing sedation management and preventing the inappropriate use of sedation,

Table 2. Summary criteria, measurements and conditions.

***Criteria for failure of spontaneous breathing trial* [24]**

Clinical assessment and subjective indices

1) Agitation and anxiety, depressed mental status, diaphoresis, cyanosis
2) Evidence of increasing efforts (increased accessory muscle activity, facial signs of distress, dyspnea)

Objective measurements

1) PaO_2 ≤50-60 mmHg or SpO_2 ≤90% with FiO_2 ≥50%
2) $PaCO_2$ ≥50 mmHg or an increase in $PaCO_2$ >8 mmHg
3) pH <7.32 or a decrease in pH ≥0.07
4) Rapid shallow breathing index (RSBI) >105 breaths/min/L
5) Respiratory rate >35 breaths/min or increase more than 50%
6) Heart rate >140 bpm or increase more than 20%
7) Systolic blood pressure >180 mmHg or increase more than 20%
8) Systolic blood pressure <90 mmHg
9) Evidence of new-onset cardiac arrhythmias

If the patients can tolerate the SBT without meeting any of the criteria for failure of SBT, they will be evaluated for the airway patency and postextubation laryngeal edema, respiratory secretions, consciousness prior to the extubation process.

Postextubation failure

Evaluation and management of patients at high risk for postextubation laryngeal edema and extubation [26,27,31,32]

Patients with ≥2 risk factors including female, intubation for >3 days, and difficult intubation are classified as high risk for postextubation laryngeal edema and will be assessed for upper airway patency using a cuff-leak test by quantitative method. The patients who are at low risk for laryngeal edema or have a cuff-leak volume of >110 ml will be extubated after passing the SBT. The patients at high risk for laryngeal edema who have a cuff-leak volume of ≤110 ml will be treated with intravenous dexamethasone 10 mg every 12 hours for a total of 2 doses before extubation attempt [33].

Prevention of postextubation respiratory failure

After extubation, patients will be assessed if they are at high-risk of extubation failure to determine if they need noninvasive respiratory supports after extubation such as noninvasive ventilation (NIV) and high flow oxygen nasal cannula (HFNC) for preventing reintubation and postextubation respiratory failure.

Patients with ≥1 of the following criteria will be considered at high-risk for extubation failure [28]:

- Age older than 65 years old
- Heart failure as the primary indications for mechanical ventilation
- Moderate to severe chronic obstructive pulmonary disease
- APACHE II score higher than 12 on extubation day
- BMI more than 30 kg/m2
- Airway patency problems including high risk of developing laryngeal edema
- Inability to deal with respiratory secretions (inadequate cough reflex or suction >2 times within 8 hours before extubation)
- Difficult or prolonged weaning (patients who failed after the first attempt of discontinuation of mechanical ventilation)
- Presence of 2 or more comorbidities
- Mechanical ventilation for more than 7 days

Patients who are at high-risk for extubation failure will be considered for applications of NIV or HFNC after extubation to mitigate the risk of postextubation respiratory failure [25]. The decision regarding the choice of noninvasive respiratory supports following extubation will depend on the attending physician's judgement. We preferred using of NIV over high flow oxygen nasal cannula in patients who are receiving mechanical ventilation due to congestive heart failure, acute exacerbation of COPD, or morbid obesity, provided that they can tolerate the NIV therapy with a well-fitted mask without significant leakage during treatment.

Criteria for postextubation failure and reintubation [24,25]

Patients will be diagnosed with postextubation respiratory failure if at least one of the following criteria are met within 72 hours after extubation: respiratory rate more than 35 breaths/minute, oxygen saturation less than 90% or PaO_2 less than 80 mmHg despite receiving FiO_2 >50%, respiratory acidosis with pH <7.35 or $PaCO_2$ >50 mmHg or increase of 20% from baseline. Patients who meet these criteria and continue to deteriorate despite applications of non-invasive respiratory supports will be reintubated immediately.

High flow oxygen nasal cannula (HFNC)

High flow oxygen (Optiflow™ system, Fisher and Paykel Healthcare: Auckland, New Zealand) will be applied immediately after extubation using a specific nasal cannula. The flow settings will be initially set at 30 L/min and a temperature of 37°C. The flow settings will be adjusted upwards in increments of 5 to 10 L/min steps every 10 minutes until achieve the patient's demand while maintaining arterial pH >7.35 and $PaCO_2$ <60 mmHg. FiO_2 will be initially started at 40% and adjusted to maintain the target of SpO_2 greater than 92%. The high flow oxygen therapy will be continued for the duration of 24 hours and then stopped. If the patients remain clinically stable, the settings will be reduced according to the patients' status.

Noninvasive ventilation (NIV)

NIV (Draeger Carina, Draeger: Lübeck, Germany) with a full facemask will be applied immediately after extubation. The size of interface will be selected to cover the patients' nose and mouth to minimize leakage of air during the therapy. The bilevel positive airway pressure (BiPAP) mode will be used with the initial settings of an inspiratory pressure of 8 cmH_2O and expiratory pressure of 5 cmH_2O. FiO_2 will be initially set at 40% then adjusted to maintain the target of SpO_2 greater than 92%. The inspiratory pressure will be titrated by 2 cmH_2O every 10 minutes until achieve the patients' demand while maintaining arterial pH >7.35 and $PaCO_2$ <60 mmHg. The maximum inspiratory pressure will be limited to 20 cmH_2O. NIV will be maintained for the duration of 24 hours, except during the airway secretion clearance procedures. If the patients remain clinically stable, the NIV settings and duration will be reduced according to the patients' status.

thereby improving clinical outcomes for patients receiving mechanical ventilation compared to conventional sedation strategy in a randomized design. The primary outcome of the study is the rate of successful extubation without reintubation, which is an objective and commonly used outcome in mechanically ventilated patients.

Strengths

he strength of this study lies in its randomized-controlled design. It is the first study to evaluate the implementation of respiratory drive monitoring using $P_{0.1}$ measurement in conjunction with sedation level assessment for adjusting sedation and neuromuscular blocking agents in critically ill mechanically ventilated patients. Moreover, the study protocol is simple and can be performed at the bedside, making it feasible and implementable in daily clinical practices.

Limitations

There are several limitations in this study. First, there is a risk of potential bias due to an unblinded design of the study owing to the nature of the trial intervention, which involves monitoring and adjusting sedation and neuromuscular blocking agents. Second, this study is a single-center study and includes only the patients admitted to the medical ICU. Therefore, the results cannot be generalized for mechanically ventilated patients in other settings, such as the surgical ICU or postoperative patients. Third, patients who have already received neuromuscular blocking agents and are unable to trigger mechanical ventilation were excluded due to the inability to measure $P_{0.1}$. This could lead to the exclusion of a significant number of patients, especially those with severe respiratory distress. Fourth, the duration of the study protocol is only 48 hours; after the study period, sedation will be adjusted according to the attending physician. This limitation may impact the trial intervention's effect, particularly in patients who remain intubated for longer than 48 hours. Finally, parameters related to diaphragm function, such as diaphragmatic excursion or thickness fraction, are not evaluated in this study.

CONCLUSION

In summary, this study plans to evaluate the efficacy of a sedation protocol using $P_{0.1}$ measurement to monitor and target optimal respiratory drive in conjunction with sedation level assessment in critically ill patients with acute respiratory failure who received invasive mechanical ventilation in medical intensive care units.

CONFIDENTIALITY

The data collection process will begin after obtaining a certificate of ethic approval and informed consent from the patients or legally authorized representatives. All the data will be recorded and stored in an electronic database on a personal computer using REDCap software with secure password protection and authorized personal access. Data collected during the study will be retained for at least 10 years following study completion and will be deleted afterward.

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AUTHORS' CONTRIBUTIONS

((I) Study conception and design: Ketdao N, Viarasilpa T; (II) Methodology: Ketdao N, Viarasilpa T; (III) Data collection: Ketdao N, Viarasilpa T; (IV) Data analysis and interpretation of the results: Ketdao N, Viarasilpa T.

SUPPLEMENTARY MATERIALS

None

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