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RESEARCH PROTOCOL

Comparison of guiding sedation level by respiratory effort versus usual care in mechanically ventilated patients: A randomized controlled trial protocol

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ABSTRACT:

Background: Critically ill patients relying on mechanical ventilation often require excessive sedation, aiming to address asynchrony and prevent ventilator-induced lung injury (VILI). Unintentionally, there may be more suppression of respiratory efforts. It is well-established that improper respiratory efforts during mechanical ventilation can cause unfavorable outcomes.

Methods: Researchers conducted a single-center randomized control trial, parallel 2 groups (1:1 ratio), with 164 participants. One intervention group employed the optimal respiratory effort (predicted ΔP_L, $P_{0.1}$), and the other control group, employed usual care to guide the adjustment of sedative levels.

Hypothesis: To compare 28-day ventilator-free day (VFD) and mortality between measuring respiratory effort as opposed to usual care and adjusting sedative level during mechanical ventilation.

Conclusions: This study will evaluate the disparity in 28-day VFD and mortality between sedative level guidance by respiratory effort and usual care.

Ethics and dissemination: The study protocol received approval from the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University (COA No. MURA2023/642)

Trial registration: NCT06242236

Keywords: Respiratory effort; Acute respiratory distress syndrome; Dynamic transpulmonary driving pressure swing; Sedation protocol

INTRODUCTION

Encountering excessive respiratory effort despite the use of more assisted mechanical ventilation is a frequent occurrence among critically ill patients, particularly in intensive care units (ICUs). This high degree of respiratory effort results in numerous patients requiring sedative drugs, including neuromuscular blocking agents (NMB). Furthermore, current research has revealed more adverse effects from overused sedation. The interesting thing is that the effect of improper respiratory effort also has more negative ICU outcomes, as will be discussed further.

In critically ill patients, various factors can stimulate an increase in respiratory drive and effort. A study by Mauricio Orozco-Levi and colleagues[1] reported on the impact of excessive respiratory effort. Using electron microscopy of the diaphragm muscle, they identified injuries to the sarcomeres in patients with chronic obstructive airway disease (COPD). The severity of these injuries was correlated with the degree of obstruction and the sudden increase in inspiratory loading. This phenomenon was explained by the occurrence of high-intensity inspiratory loading.

Consistent with Scott et al.[2], who conducted a comparative study using light microscopy of the diaphragm and respiratory muscle in post-mortem bodies from individuals with airway obstruction compared to normal individuals, they observed muscle death, accumulation of disorganized layers, and collagen in the diaphragm, along with dispersed and unevenly distributed cytoplasm. Additionally, there was an accumulation of lipofuscin and features of hypereosinophilia in lung lavage.

Another condition of lung injury inflicted by the excessive effort of patients themselves during mechanical ventilation is known as patient self-inflicted lung injury (P-SILI). This theory was first discussed by Leo Lobe in 1928[3], emphasizing the importance of increased negative intrathoracic pressure during inhalation, which may lead to the movement of fluid from the pulmonary capillaries into the alveoli, causing pulmonary edema. This is supported by the observational reports of Moore and Binger [4], who state that significant negative pressure during inhalation in patients with obstructed airways may result in pulmonary edema. In 1936, Barach et al. [5] confirmed this hypothesis. Subsequent studies, including those by Dreyfuss and Mascheroni in 1988 [6,7], further supported this phenomenon. These findings align with those of Yoshida and colleagues [8], suggesting that it may be explained by an increase in transpulmonary pressure (P_L) and the occurrence of the pendelluft phenomenon [9]. Additionally, patient-ventilator asynchrony (PVA) may also aggravate lung injury.

Simultaneously, insufficient effort can adversely affect the diaphragm and lung function. In 30 percent of patients using mechanical ventilators, there is a development of thinning in the diaphragm muscles, leading to difficulties in the weaning process and requiring prolonged ventilator support. This aligns with the research by Goligher et al.[10], which suggests that changes in diaphragm muscle thickness measured by the diaphragm thickness fraction method, decreasing by more than 10 percent in the first week of intubation, are associated with a prolonged duration of mechanical ventilation, increased bed occupancy time in ICUs, and higher complications from various treatments.

KEY MESSAGES:

- Researchers introduce a novel protocol for sedation adjustment aimed at "lung and diaphragm protective sedation protocol", which utilizes personalized sedation levels based on a patient's respiratory effort.
- Using a proper level of respiratory effort during mechanical ventilators may be the optimal choice for sedation guidance aiming to improve clinical outcomes.
- Minimizing and reasonable sedative use reduces the duration of ventilator dependency and ventilator-associated complications.

The study's conclusion also indicates that an appropriate change in diaphragm muscle thickness fraction, ranging from 15-30 percent in the initial 3 days, correlates with the shortest duration of mechanical ventilation. Therefore, monitoring respiratory effort during assisted ventilation is crucial to finding a balancing point, aiming to adjust the proper respiratory effort level that is neither excessive nor insufficient. This may be related to appropriately adjusting sedative dosages and optimizing mechanical ventilators.

A widely used method to assess patient consciousness is the Richmond Agitation-Sedation Scale (RASS) [11]. This scale assigns scores ranging from -5 to +4, with the target range being -1 to 0 for critically ill patients requiring mechanical ventilation and sedative drug adjustment. Research on RASS in mechanical ventilation patients [12] has shown that using RASS for sedative dosage adjustments, compared to not using it, results in a significantly reduced duration of mechanical ventilation. Additionally, the assessment outcomes are comparable to the Bispectral Index (BIS) when evaluating sedative drug administration in mechanically ventilated critically ill patients. However, the latest study by Dzierba AL et al. [13] reported a lack of correlation between RASS and variables measuring respiratory effort parameters.

The measurement of respiratory effort can be conducted using various methods. Researchers introduce an airway occlusion pressure (ΔP_{occ}), which is particularly interesting in measuring because it can be easily assessed at the bedside and used to calculate the pressure generated by respiratory muscles (P_{mus}) and predicted ΔP_L. Previous studies have demonstrated a strong correlation between ΔP_{occ} and the pressure-time product of P_{mus} per breath (PTP_{mus}), considered a gold standard according to the study by Bertoni et al.[14]

Physiological studies [15] have suggested suitable values to prevent lung and diaphragmatic injuries, as well as avoiding disuse atrophy. These values include P_{mus} between 5-10 cmH_2O, $\Delta P_{occ} < 15$ cmH_2O, $P_{0.1}$ between 1.5-3.5 cmH_2O, and predicted $\Delta P_L \leq 20$ cmH_2O. Unpublished research by Phruet et al., 2023, investigated the clinical impact of these respiratory effort values. They found that a predicted $\Delta P_L > 20$ cmH_2O significantly affected 28-day VFD (P=0.002) and 28-day mortality (OR 8.52, 95% CI 1.45-49.93, P=0.018). Given these findings, the researchers hypothesized that adjusting medication doses based on respiratory effort may provide greater benefits to patients compared to usual care.

OBJECTIVES

Primary objective

The primary objective was to compare the number of ventilator-free days at 28 days between the intervention group, which used respiratory effort to guide sedative levels, and the usual care group.

Secondary objective

The secondary objective encompassed comparing 28-day mortality, duration of mechanical ventilation, duration of ICU stay, duration of hospital stay, in-hospital mortality, assessing respiratory effort levels and BIS correlation, evaluating treatment complications, and measuring cumulative sedative drug administration at 48 hours and 1 week between both groups.

MATERIALS AND METHODS

Study design

This single-center, analytical randomized controlled trial was conducted between October 2023 and October 2025. The study protocol received approval from the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University (COA No. MURA2023/642) and was registered internationally (ClinicalTrials.gov Identifier: NCT06242236).

Participants

Researchers enrolled acute respiratory failure patients requiring mechanical ventilation, who were hospitalized in both medical and surgical ICUs at Ramathibodi Hospital, Mahidol University. In total, 164 participants were enrolled, with 82 participants allocated to each group, considering an estimated 5% data loss error.

The inclusion criteria were as follows: 1) acute respiratory failure patients requiring mechanical ventilation; 2) P/F ratio above 150; 3) age between 18-75 years old. The exclusion criteria included no informed consent, a history of prior hospitalization within the last month, reintubation in the same admission, pregnancy, end-stage cancer/illness, acute myocardial ischemia, and cerebral ischemia within 1 month before enrollment, active neuropsychiatric conditions, comatose status, status epilepticus, uncontrolled thyroid disease, severe ARDS with uncorrected hypoxia (P/F ratio below 150, requiring prone positioning or extracorporeal membrane oxygenation (ECMO), requiring neuromuscular blocking agent), post-thoracic and abdominal surgery, or requiring intercostal tube drainage. Patients who were extubated before 48 hours after enrollment will be excluded, as they do not exhibit the full effort over 48 hours on mechanical ventilation. This could introduce confounding factors unrelated to the effort-guided strategy.

All participants were recorded with demographic data, vital signs, SOFA score, APACHE II score, comorbidity, acute respiratory failure etiologies, history of smoking, ICU arrival date/time, intubation date/time, chest radiographic characteristics, fundamental laboratory data, and gas exchange. The patients were ventilated with a Hamilton or Puritan Bennett ventilator with a built-in negative inspiratory pressure function. The ventilator was set in volume-controlled ventilation (VCV) mode for the entire 48 hours of the study. The peak inspiratory flow rate, inspiratory time, inspiratory flow wave pattern, airway pressure, minute ventilation, tidal volume (Vt) per kg, positive end-expiratory pressure (PEEP), and driving pressure were recorded. Respiratory mechanics were recorded to describe their properties, including measurements of airway resistance and respiratory system compliance. Gas exchange parameters, such as the P/F ratio, were also recorded.

Randomization and allocation concealment

The randomization involves creating equally distributed tokens for both groups, Eligible patients were randomly assigned in a 1:1 ratio to either respiratory effort guidance the sedative level during mechanical ventilator (intervention group) or usual care guidance the sedative level during mechanical ventilator (control group), with a total of 164 participants to be included in the study from 5 ICUs and 82 participants per arm. A 3-digit randomization number will be generated. This randomization number will be reported on the CRF. A copy of the randomization list will be sent to the Human Research Ethics Committee, Faculty of Medicine, Ramathibodi Hospital, Mahidol University.

To minimize selection and confounding biases, researchers implemented allocation concealment through the following steps: First, researchers performed 164 pieces of black paper, which documented the label of 82 pieces of paper for the intervention participant and 82 pieces of paper for the control participant. Secondly, researchers placed these labeled black papers in sealed letters. Thirdly, these letters were placed in a blinded random box for the randomization process and kept with a third party uninvolved in the trial. Fourthly, upon confirming the eligibility of each participant, the investigator called the third party to draw a sealed letter to identify which group the participant belonged to. Finally, in the identification process, participants were assigned as an intervention group or control group according to the concealment letter document, which was ongoing during the process until the final analysis.

Following the enrollment of participants (acute respiratory failure requiring mechanical ventilation and sedation), the investigators proceeded to randomize participants into two groups. The intervention group, employed the optimal respiratory effort parameters (predicted ΔP_L, $P_{0.1}$) to guide the adjustment of sedative levels. The control group employed usual care to guide the adjustment of sedative levels.

Study protocol

After a patient was determined to be eligible, a stabilization period within 24 hours was mandated after intubation, and sedations were given. Inclusion in the study was confirmed only at the end of this period, as shown in Figure 1. Randomization and allocation were performed by a third party, ensuring impartiality. Standard ICU beds were used for all participants.

Intervention group

Patients assigned to the intervention group underwent assessments of respiratory effort through $P_{0.1}$ and predicted ΔP_L within the initial hour post-randomization, and subsequently at least every 8 hours in serial records. Sedative levels for these patients were guided by optimal respiratory effort, with $P_{0.1}$ ranging from -1.5 to -3.5 cmH_2O and a predicted ΔP_L less than 20 cmH_2O. Participating centers were provided with guidelines for adjusting sedative levels to ensure uniformity in sedative administration.

Control group

Patients assigned to the control group underwent assessments of their usual care through an investigator, attending doctor, or nurse adjustment. All control patients used the RASS score (the RASS targeted was 0 to -1) to adjust the sedative level at least every 8 hours as a basic protocol. However, some attending doctors needed to use BIS monitoring for difficult-to-observe patients for greater accuracy and precision. In cases of ventilator asynchrony despite adequate RASS suppression, the doctor was allowed to adjust the sedation as needed. This approach ensures comparability with real practice in usual care patterns. based on the same sedation protocol and practitioner schedule in all ICUs as the intervention sedation protocol within the initial hour post-randomization, and subsequently at least every 8 hours in the same way. Sedative levels for these patients were guided by usual care. Also, the respiratory effort parameters in this group were collected for analysis together.

Configuring ventilator settings upon participants' enrollment in the research involves the following steps:

Selecting the ventilator mode as volume assist–control, adjusting initial Vt to 6-8 ml/kg of predicted body weight, setting the plateau pressure to ≤32 cmH_2O and the driving pressure to <15 cmH_2O, establishing the oxygenation goal as PaO_2 55–80 mmHg or SpO_2 88–95%, fine-tuning positive end-expiratory pressure (PEEP) to optimize oxygen delivery based on the best lung compliance or using a FiO_2 and PEEP table, employing incremental/decremental PEEP titration, or utilizing P_L with an esophageal balloon in cases of impaired chest wall compliance. Additionally, setting the pH goal for arterial blood gas within the range of 7.20–7.45.

In the event that, following the initiation of mechanical ventilation, the plateau pressure persists above 32 cmH_2O for a minimum of 10 minutes, the attending physician should contemplate the following measures:

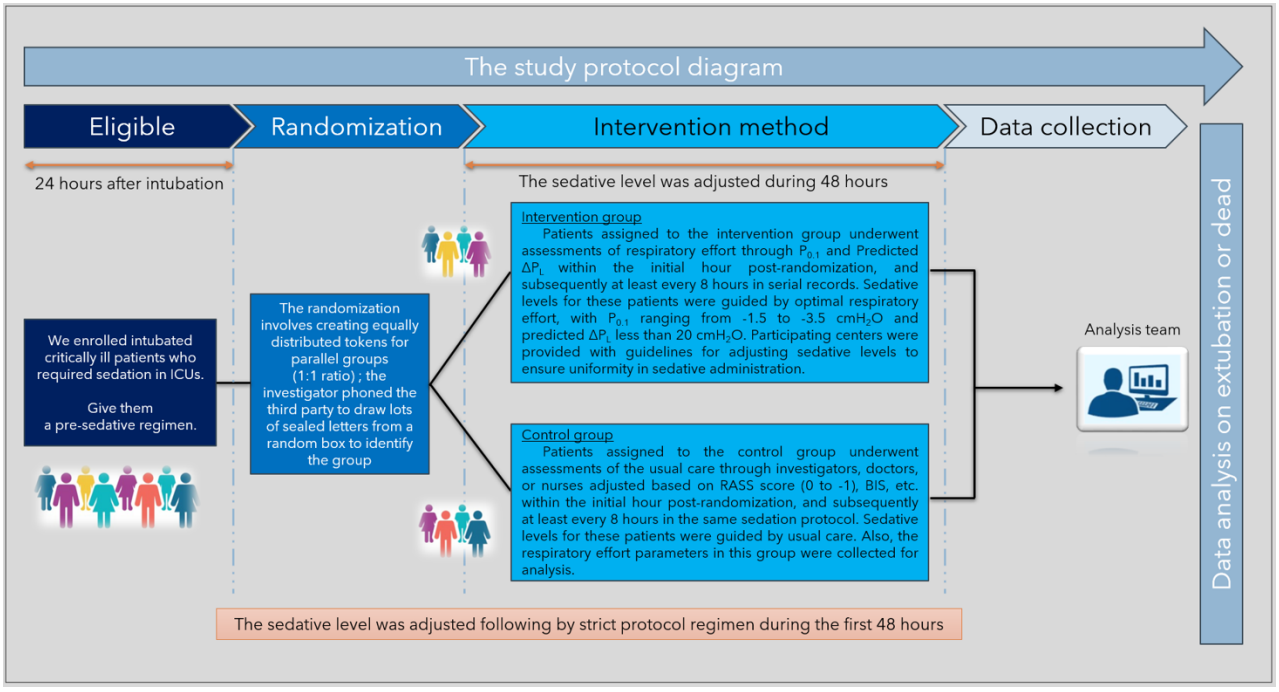

Figure 1. This protocol diagram illustrates the flow of participants through the study. It begins with eligibility screening, followed by concealed randomization to either the intervention or control arm. After randomization, participants receive sedation adjustments based on their assigned group (intervention-guided or usual care). The data was collected and statistical analysis was performed by analysis team.

First, consider a 25-50% increase in sedative dosage if the anticipated change in dynamic-transpulmonary pressure swing (predicted ΔP_L) exceeds 20 cmH_2O or the $P_{0.1}$ exceeds 3.5 cmH_2O. Secondly, gradually reduce Vt by 2 ml/kg or contemplate a decrement in PEEP using a titration of 2 cmH_2O, ensuring compliance and oxygenation goals (PaO_2 55–80 mmHg or SpO_2 88–95%) are not significantly compromised. Thirdly, if there is a potential risk of elevated abdominal pressure or compromised chest wall compliance, as seen in cases of obesity, chest wall restrictions, circumferential chest wall burns, or kyphoscoliosis, consider the use of an esophageal balloon for PEEP titration guidance. Utilize an end-inspiration transpulmonary pressure limit of <25 cmH_2O instead of a plateau pressure exceeding 32 cmH_2O to mitigate the risk of VILI.

In situations where $PaCO_2$ levels are notably elevated beyond 60 in conjunction with an ABG pH below 7.20, take the following actions: Attach a Y-piece to the endotracheal tube or temporarily disconnect the endotracheal tube from the ventilator to assess dynamic air trapping. Consider an increase in respiratory rate, ensuring it does not surpass 35 breaths per minute or exceed the mechanical power of 14.4 J/min. Consider raising the maximum Vt to 10 ml/kg and maintaining a plateau pressure below 32 cmH_2O. If the peak-plateau pressure gradient exceeds 10 cmH_2O at an inspiratory flow rate of 60 L/m (normal is 4 cmH_2O), indicating elevated airflow resistance, address the underlying cause by utilizing bronchodilators, checking for endotracheal tube obstruction, or examining for ventilator circuit blockage or pneumothorax.

The process of sedative level adjustment

Adjusting sedative medications during the first 48 hours of participation in the research involves a stepwise process, with additional details outlined in the upcoming Figure 1. Both groups of patients will undergo minimal sedation adjustments every 8 hours, on a minimum of three times a day, conducted by the researcher team, doctors, and nurses. Researchers held a conference before starting the protocol to implement a standardized sedation protocol and minimize variations between patients in different ICUs. The research team explained the protocol and ensured understanding with representatives of the ICU team involved. To maintain consistency, both the control group and the intervention group will follow the same sedation protocol as described in the safety outcomes section. However, suppose there is a need to increase the sedative dose beyond this frequency. In that case, it can be done based on necessity, such as when the patient's RASS is ≥ 2, there is agitation, or there is a breath-stacking asynchrony index >10%.

Patient assessments will be conducted separately according to the specific intervention or control group. In the intervention group, utilizing the predicted ΔP_L and $P_{0.1}$ methods, the assessment includes

1. Measuring the end-occlusion maneuver using the NIF function to obtain the P_{occ} value.

2. The P_{occ} value is used to calculate the predicted ΔP_L by using the formula [14]

$$\text{Predicted } \Delta P_L = (\text{Peak airway pressure-PEEP}) - (\frac{2}{3}\Delta Pocc)$$

Researchers provide $P_{0.1}$ and ΔP_{occ} five times, with intervals of 30 seconds between each repetition. Select the three values that are closest to each other from the total of five values to calculate the average as a representative value of $P_{0.1}$ and ΔP_{occ} (then calculate to predict ΔP_L) during that time. The goal is to achieve predicted $\Delta P_L \leq$ 20 cmH_2O and maintain the targeted $P_{0.1}$ within the range of 1.5-3.5 cmH_2O with a method of sedation adjustment. The other group (the control group) follows the usual care method.

The sedation adjustment in the intervention arm is categorized into three groups:

1. If targeted $P_{0.1}$ is between 1.5-3.5 cmH_2O and predicted ΔP_L is ≤ 20 cmH_2O, maintain the sedative dose unchanged and reassess every 8 hours.

2. If targeted $P_{0.1}$ is < 1.5 cmH_2O and predicted ΔP_L is ≤ 20 cmH_2O, consider reducing the sedative dose by 10-25% every hour until the target $P_{0.1}$ reaches 1.5-3.5 cmH_2O, and reassess every 8 hours.

3. If targeted $P_{0.1}$ is > 3.5 cmH_2O and predicted ΔP_L > 20 cmH_2O, assess CAM-ICU (use the ICU delirium protocol) and the Critical Care Pain Observation Tool score (CPOT). Consider increasing the sedative dose by 10-25% every hour until the targeted $P_{0.1}$ is reached 1.5-3.5 cmH_2O and the predicted ΔP_L is reached at ≤ 20 cmH_2O, reassessing every 8 hours.

Safety outcomes

How to select sedation and manage the risks associated with sedation.

Overdose or complications resulting from drug interactions, simultaneous use of multiple sedative drugs (drug overdose/side effect/multiple sedative drug use). The planned sedative drug selection is as follows:

1. Consider initiating fentanyl as the first option for analgosedation (following PADIS 2018 guidelines to control the pain first) until reaching the step-up dosage range or the dose at which side effects begin, as outlined in the paragraph below. If side effects occur, the investigators decrease the dose and step up to second-line sedation, provided the research participant has no contraindications or allergies.

Fentanyl Bolus : 25-50 mcg IV bolus dose then

Continuous drip: 0.7- 1.5 mcg/kg/h but not over 100 mcg/h

2. If reaching the step-up dose or experiencing complications with the first drug, consider selecting the second option as appropriate. This decision should be concerned with the efficacy, the risk of complications that may arise in that specific case, and any contraindications. Options for the second drug may include dexmedetomidine and propofol.

Dexmedetomidine IV : drip 0.2 - 1 mcg/kg/h

And/or Propofol IV : drip 0.3 - 2 mg/kg/h

3. Finally, the third-line drug is midazolam, an option for some patients who have no risk of developing delirium due to factors such as old age (>60 years old), prior dementia, an increased APACHE score, and be-

ing restricted to using shorter periods not exceeding 48 hours.

Midazolam IV : drip 0.05 - 1 mg/kg/h

Serious Side Effects: Unexpected individual adverse events related to the administration or increased dosage of sedative drugs as outlined in the research may occur. In the event of an immediate correlation with drug administration or dosage adjustment, consider discontinuing medication and investigating other potential contributing factors.

1. Hypotension:

a. If there is a significant drop in systolic blood pressure (>25%) and/or mean arterial pressure (MAP) < 65 mmHg, reduce the sedative dosage by 25% every 5 minutes until blood pressure returns to the previous normal range.

b. If MAP remains < 65 mmHg after reducing the sedative by more than 50% of the previous dose or discontinuing the drug, assess fluid status and consider low-dose vasopressor administration while investigating additional contributing factors.

2. Bradycardia:

a. If the heart rate decreases by more than 25% and/or falls below 60 beats per minute, reduce the sedative dosage by 25% every 5 minutes until the heart rate returns to the previous normal range.

b. If the heart rate remains < 60 beats per minute after reducing the sedative by more than 50% of the previous dose or discontinuing the drug, or if MAP < 65 mmHg, discontinue the drug and investigate other potential causes, especially electrolyte imbalance and other medications.

c. In the case of unstable bradycardia, consider atropine/inotropic drug therapy following the ACLS Bradycardia Algorithm while awaiting further investigation of potential contributing factors.

3. Gut Hypomotility:

a. If gastric residual volume is between 200-400 ml, reduce the sedative causing the issue by 25% every 4-6 hours, administer prokinetic drugs, and evaluate for other potential causes of gut hypomotility.

b. If gastric residual volume exceeds 400 ml, stop all medications contributing to gut hypomotility.

4. Propofol Infusion Syndrome: In cases of suspected propofol infusion syndrome, discontinue propofol infusion, correct metabolic acidosis, and assess fluid and kidney/liver function.

Measurement

The $P_{0.1}$ values were measured using a built-in function, while the P_{occ} value was measured using the NIF function. Ultimately, the collected data was transmitted for analysis, wherein the predicted ΔP_L was calculated using the following formulas [16] which include the following steps:

1. If the patient is conscious, the doctor informs them and obtains their permit to temporarily interrupt the air supply from the ventilator, which should not exceed 5-10 seconds.

2. Perform the end-expiratory occlusion (EEO) maneuver procedure to obtain $P_{0.1}$ five times within a 30-second interval during each attempt. Identify three similar readings of from this $P_{0.1}$ session that are comparable to calculate the statistical mean value indicating the respiratory effort during that period. And perform the P_{occ} value via the NIF method in the same step accordingly.

3. In cases of vital sign alterations or instability, such as a heart rate of >130 or <50 beats/min, blood pressure <90/60 mmHg or mean blood pressure lower than 65 mmHg, or a decrease in oxygen saturation by ≥3% from baseline, the procedure should be halted. The underlying reason for the abnormality must be assessed first.

OUTCOME

The primary outcome was the number of ventilator-free days at 28 days. The secondary outcomes were 28-day mortality, duration of mechanical ventilator, duration of ICU stay, duration of hospital stay, in-hospital mortality, determining the level of respiratory effort and BIS correlation, complications of treatment, and comparing the accumulation of sedative drugs administered to participants during 48 hours and 1 week after enrollment.

DATA ANALYSIS PLAN

Sample size calculation

Calculate the sample size using a two-group independent sample t-test based on the mean ventilator-free days, utilizing the G*Power version 3.1.9.4 program. The sample size estimation considers a 95% confidence level, and the values are derived from the data of Phruet and colleagues, who collected information on patients receiving ventilator support in the ICU of Ramathibodi Hospital during the years 2021-2023. The program sets the effect size with a significant difference in ventilator-free days at 5 days.

Mean in group1 (μ_1)	=	19.12 days
SD. in group1 (σ_1)	=	9
Mean in group2 (μ_2)	=	14.43 days
SD. in group2 (σ_2)	=	10
Effect size d	=	0.5255883
α err prob	=	0.05
Power (1-β err prob)	=	0.9
Allocation ratio N2/N1	=	1
Sample size group 1	=	78
Sample size group 2	=	78
Total sample size	=	156

From the aforementioned formula, it is found that a sample of 78 subjects is required for each group, totaling 156 subjects for both groups. Considering a data loss rate from technical errors of 5%, a total of 82 subjects per group, or 164 subjects in total, would be needed. It is anticipated that the enrollment of research participants can be completed within 2 years.

OUTCOME ANALYSIS PLAN

Data analysis

The data were expressed as mean ± SD, median, and interquartile range, or percentages. The difference between 2 sets is expressed as continuous data: a t-test or

a Mann-Whitney U test according to the normality of the normality of the data distribution. Categorical data were analyzed using the Chi-squared or Fisher's exact tests. The difference between 3 sets expressed as continuous data: ANOVA was used to compare the mean data of normal distribution continuous variables, also for non-normal distribution by Kruskal–Wallis test (non-parametric test). The main outcomes analysis of the relationship between the intervention arm and control arms with 28-day ventilator-free days and 28-day mortality was analyzed using Mann-Whitney U test statistics. Researchers determined the correlations between sedative level and respiratory effort with a 28-day VFD using Spearman's correlation (q). Logistic/Cox regression analysis was used with 28-day mortality. A p-value < 0.05 was considered statistically significant. All data will be analyzed using SPSS version 29.

DATA MANAGEMENT AND DATA MONITORING

Data collection

After enrollment, the patient is transferred to the ICU, where data is collected regarding demographic information, height, body weight, underlying diseases, SOFA score, APACHE II score, and etiology of respiratory failure. Laboratory tests such as ABG, lactate, CBC, CRP, and renal and liver function are also performed. The initial mode of ventilation was conducted in VCV mode, and ventilator setting parameters were recorded, including real RR, inspiratory flow, inspiratory time, peak airway pressure, plateau pressure, minute ventilation, tidal volume, PEEP, respiratory compliance, and resistance. Following randomization into the intervention and control groups, sedative levels were tailored according to their designated targets. The respiratory effort values (predicted ΔP_L and $P_{0.1}$), along with the RASS scores, were documented for both groups in each participant from the moment of study enrollment and subsequently every 8 hours until 48 hours post-enrollment. Primary outcomes, until extubation or death, were collected up to 28-day ventilator-free days (VFD). Secondary outcomes, including 28-day mortality, in-hospital mortality, duration of mechanical ventilation, duration of ICU stay, duration of hospital stay, assessment of respiratory effort and BIS correlation, treatment complications, and comparison of cumulative sedative drug administration, were documented. The planed report tables were revealed in supplementary materials

DISCUSSION

Adequate sedation is crucial for mechanically ventilated patients, promoting comfort, minimizing ventilator asynchrony, and optimizing ventilator support. However, the prevalent tendency to overuse sedatives may lead to adverse clinical outcomes and increased costs. Traditionally, clinicians have relied on tools such as the RASS, individual physician judgment, and the BIS to guide sedation adjustments. However, researchers introduce a newer approach utilizing respiratory effort parameters (predicted ΔP_L and $P_{0.1}$) that is emerging as an alternative tool, provides a potentially more objective and reliable way to guide sedation adjustments, assesses and monitors readily at the bedside using advanced ventilators, and promotes a standardized approach to the concept of lung-diaphragm protective sedation protocol. Researchers hypothesize that maintaining appropriate respiratory effort, which reduces sedation and enhances lung mechanics, could result in improved 28-day VFD. Furthermore, this approach may also impact mortality rates, the median length of ICU stay, and other secondary outcomes.

Regarding the effectiveness of using respiratory effort parameters (predicted ΔP_L, $P_{0.1}$) to guide sedation adjustments, In the recent research of Dzierba et al.[13] support for $P_{0.1}$ exhibited a significant, non-linear association with ventilator-free days (unadjusted Poisson model, $p < 0.01$). And low predicted ΔP_L in the intervention group, which is physiology lung protective on harmful length negative swings in alveolar pressure, a mechanism by high effort that potentially induces lung injury on top of high changes in ΔP_L according to a study by Bellani et al.[16]. Moreover, another study by Baedorf Kassis et al.[17] shows that keeping a lower ΔP_L after 24 hours is associated with improved 28-day mortality and demonstrates safety for a lung and diaphragm protective strategy. However, no current study shows the benefit of respiratory effort combined with the sedation protocol.

The question arises as to why researchers cannot rely solely on RASS or BIS for sedation guidance, as these do not demonstrate equal respiratory drive and effort. One observational by study Dzierba et al.[13] identified a weak correlation between RASS scores and $P_{0.1}$. Likewise, recent research by Spinelli et al. [18]. found that the correlation between the RASS category and $P_{0.1}$ did not reach statistical significance (β=0.072, p=0.063). There are several potential explanations for this discrepancy. Firstly, respiratory effort is influenced by multiple factors. While RASS primarily evaluates a patient's level of consciousness, respiratory effort can be influenced by factors beyond sedation level, such as metabolic status, variations in respiratory drive, lung mechanics, and ventilatory support (the degree of unloading the respiratory muscles) [19]. Secondly, RASS relies on subjective observation, which may not always detect subtle changes in respiratory effort.

Another significant hypothesis arising from our study posits that employing a novel approach utilizing respiratory effort to guide sedative usage may lead to a reduction in sedation levels, thereby potentially decreasing the occurrence of mechanical complications associated with prolonged sedation, such as ventilator-associated pneumonia (VAP). This finding aligns with meta-analyses [20] advocating for the minimization of sedative use to mitigate the duration of ventilator dependency and the incidence of VAP.

Trial Limitations

The limitation of this study lies in the fact that the primary respiratory effort measure (predicted ΔP_L) was derived from the calculation of ΔP_{occ} using a formula. While this parameter exhibits a strong correlation with the actual transpulmonary pressure swing, direct measurement of

true pleural pressure guided by esophageal manometry remains the gold standard for potentially attaining the highest accuracy in respiratory effort parameter measurement.

Secondly, to mitigate ascertainment bias, researchers will employ a double-blind study design. This entails conducting a double-dummy procedure, wherein both respiratory effort assessment and adjustment of usual care occur simultaneously. The results of both assessments are then directed to the command center, which assigns a separate group to adjust the masked sedative levels and monitor sedative doses, including side effects. This approach involves three parallel groups: an assessment group, a command group, and a group for adjusting sedative levels. As a result, additional investigators are needed to facilitate this process effectively.

CONCLUSION

This study investigated the impact of guiding sedation level by respiratory effort versus usual care on 28-day VFD in patients with acute respiratory failure requiring mechanical ventilation within the first 48 hours. And demonstrating the main secondary outcome as a 28-day mortality between the groups.

CONFIDENTIALITY

None

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ABBREVIATIONS

PVA: Patient-ventilator asynchrony; VILI: ventilator-induced lung injury; VFD: Ventilator-free days; ICUs: Intensive care units; NMBA: neuromuscular blocking agents; P-SILI: Patient self-inflicted lung injury; COPD: Chronic obstructive pulmonary disease; VIDD: Ventilator-induced diaphragmatic dysfunction; P_L: Transpulmonary pressure; P_{pl}: Pleural pressure; Vt: Tidal volume; ARDS: Acute respiratory distress syndrome; VCV: Volume-controlled ventilation; P_{mus}: Respiratory muscle pressure; PTP_{mus}: Pressure-time product of P_{mus} per breath; ms: Milliseconds; $P_{0.1}$: Airway occlusion pressure at first 100 milliseconds; P_{occ}: Airway Occlusion Pressure; NIP: Negative inspiratory pressure; RASS: Richmond Agitation-Sedation Scale; BIS: Bispectral index; ECMO: extracorporeal membrane oxygenation; PEEP: Positive end-expiratory pressure; CRF: Case-record form; ΔP_L: Dynamic-transpulmonary pressure swing; EEO: End-expiratory occlusion test; MAP: Mean arterial pressure; PHT: Pulmonary hypertension.

AUTHORS' CONTRIBUTIONS

(I) Conceptualization: Phruet Soipetkasem, Pongdhep Theerawit, Detajin Junhasavasdikul, Yuda Sutherasan, Sunthiti Morakul, Vichapat Tharanon, Krongtong Putthipokin; (II) Data curation: Phruet Soipetkasem, Haruethai Partumchart; (III) Formal analysis: Phruet Soipetkasem, Pongdhep Theerawit, Haruethai Partumchart; (IV) Methodology: Phruet Soipetkasem, Pongdhep Theerawit, Detajin Junhasavasdikul, Yuda Sutherasan, Sunthiti Morakul; (V) Project administration: Phruet Soipetkasem, Pongdhep Theerawit; (VI) Visualization: Pongdhep Theerawit; (VII) Writing – original draft: Phruet Soipetkasem, Pongdhep Theerawit.

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SUPPLEMENTARY MATERIALS

Table 1. Demonstrates baseline characteristics between the two groups.

Characteristics	N	Intervention	Control
Sex			
• Male, n (%)			
• Female, n (%)			
Age, mean (SD), years			
BMI, mean (SD), kg/m^2			
Smoker, n (%)			
Obesity, n (%)			
OSA, OHS, n (%)			
COPD/Asthma, n (%)			
Diabetes mellitus, n (%)			
History of TB infection, n (%)			
Pulmonary hypertension, n (%)			
CTEPD, n (%)			
Interstitial lung disease, n (%)			
Bronchiectasis, n (%)			
Atrial fibrilation, n (%)			
Old coronary syndrome, n (%)			
Chronic heart failure, n (%)			
Old cerebrovascular disease, n (%)			
Immunocompromised status, n (%)			
Chronic kidney disease, n (%)			
Cirrhosis, n (%)			
Hypoalbuminemia, n (%)			
pH, mean (S.D.)			
PaO_2, mean (S.D.), mmHg			
$PaCo_2$, mean (S.D.), mmHg			
Lactate, median (IQR), mmol/L			
Hemoglobin, mean (S.D.), g/dL			
White blood cell count, mean (S.D.), x 10^3 cell/ml			
CRP, mean (S.D.), mg/dL			
Albumin, mean (S.D.), g/L			
APACHE-II, median (IQR), score			
SOFA score, median (IQR), score			
Tidal volume, median (IQR), ml/kg			
Minute ventilation, median (IQR), L/min			
PEEP, median (IQR), cm H_2O			
Driving pressure, median (IQR), cm H_2O			
Cause of respiratory failure			
• Hypoxic RF, n (%)			
• Hypercapnic RF, n (%)			
• Shock RF, n (%)			
• Infectious cause, n (%)			
COVID-19, n (%)			
Compliance, mean (SD), ml/cm H_2O			
Resistance, median (IQR), cm-H_2O-sec /L			
PF ratio, median (IQR)			
Predicted ΔP_L, median (IQR), cmH_2O			
$P_{0.1}$, median (IQR), cmH_2O			
RASS, median (IQR), Score			

SD: Standard deviation; IQR: Interquartile range; BMI: body mass index; APACHE: Acute physiologic and chronic health evaluation; SOFA: Sequential organ failure assessment; COPD: Chronic obstructive pulmonary disease; OSA: Obstructive Sleep Apnea; OHS: Obesity hypoventilation syndrome;; TB: Mycobacterium tuberculosis; CTEPH: Chronic thromboembolic pulmonary hypertension; PaO_2: Partial Pressure of Oxygen; $PaCO_2$: Partial Pressure of carbon dioxide; CRP: C-Reactive Protein; ms: Milliseconds; RASS: Richmond Agitation-Sedation Scale; PEEP: Positive end-expiratory pressure; ΔP_L: Dynamic-transpulmonary pressure swing; PHT: Pulmonary hypertension; COVID-19: coronavirus disease starting in 2019.

Table 2. Demonstrates the complicated and overall outcomes between the two groups.

Complications	N	Intervention	Control	P-Value
Ventilator-associated pneumonia, n (%)				
Chronic respiratory failure, n (%)				
Pneumothorax, n (%)				
New hypoxemia, n (%)				
Heart failure / pulmonary edema, n (%)				
Malnutrition, n (%)				
Renal failure, n (%)				
Diaphragm weakness, n (%)				
VILI, n (%)				
Pulmonary embolism, n (%)				
Liver failure, n (%)				
Cytokine storm, n (%)				
Propofol infusion syndrome, n (%)				
Hemoptysis/ Organ bleeding, n (%)				
Arrest, n (%)				
Main outcomes	**N**	**Intervention**	**Control**	**P-Value**
28-day VFD, median (IQR) days				
28-day VFD, mean (SD) days				
Duration of intubation, median (IQR) days				
Length of ICU stay, median (IQR) days				
Hospital length of stay, median (IQR) days				
Tracheostomy before discharge, n (%)				
Reintubation, n (%)				
28-day mortality, n (%)				
Death before hospital discharge, n (%)				

SD: Standard deviation; IQR: Interquartile range; VILI: Ventilator-induced lung injury; VFD: Ventilator free day; ICU: Intensive care unit

Table 3. Demonstrates the accumulative sedative dose used between the two groups.

Sedation	N	Intervention	Control	P-Value
During 48 hours after randomization				
Fentanyl, median (IQR) mcg/kg				
Dexmedetomidine, median (IQR) mg/kg				
Propofol, median (IQR) mg/kg				
Midazolam, median (IQR) mg/kg				
During 7 days after randomization				
Fentanyl, median (IQR) mcg/kg				
Sedation	**N**	**Intervention**	**Control**	**P-Value**
Dexmedetomidine, median (IQR) mg/kg				
Propofol, median (IQR) mg/ kg				
Midazolam, median (IQR) mg/ kg				

Table 4. Demonstrates the Spearman correlation between RASS with predicted ΔP_L during 48 hours.

N = total participants		RASS measurement
Predicted ΔP_L	Correlation Coefficient (q)	
	Significant (2-tailed)	
$P_{0.1}$	Correlation Coefficient (q)	
	Significant (2-tailed)	