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RESEARCH PROTOCOL

The sevoflurane concentration for light sedation in critically ill patients: A protocol for experimental study

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ABSTRACT:

Background: Deep-inhaled sedation is increasingly used in Thai ICUs. However, there is a lack of information regarding the level of end-tidal sevoflurane concentration during light sedation.

Objectives: The study aims to determine the effective dose (ED50 and ED95) of sevoflurane concentration for light sedation (RASS score -1 to 0) in mechanically ventilated critically ill patients.

Methods: This is a prospective experimental single-center study. Mechanically ventilated patients with RASS ≥ 1 who required sedation in the medical and surgical intensive care unit were enrolled. Using an up-and-down sequential allocation technique, the inhaled sevoflurane level of each patient was allocated based on the previous patient's response. RASS score and hemodynamic parameters were monitored. The primary outcome was the ED50 and ED 95 of end-tidal sevoflurane concentration. The secondary outcomes included the length of intensive care unit stay, duration of ventilator day, the incidence of delirium, hemodynamic status, and respiratory variables changed during the study period.

Hypothesis: There exist specific end-tidal sevoflurane concentrations (ED50 and ED95) that will reliably induce a target RASS score of -1 to 0 in critically ill patients who are mechanically ventilated.

Conclusion: This study will provide an effective dose of inhaled sevoflurane sedation for achieving targeted light sedation levels in critically ill patients, which may have minimal effects on hemodynamics.

Ethics and dissemination: This study has been approved by the Office of Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand, on 22nd May 2023 (COA.MURA2023/390).

Trial registration: TCTR20230825001

Keywords: Sevoflurane; Sedation; Light sedation; Inhaled sedation; Critical illness; Critical care

INTRODUCTION

Over the past decade, critical care units have witnessed a significant increase in inhaled volatile anesthesia used alongside various sedation procedures for mechanically ventilated patients. Sedation in critically ill intubated patients targets several purposes, in particular, reducing anxiety, stress, and discomfort and minimizing complications. By keeping patients calm and cooperative, sedation helps prevent agitation-related injuries and promotes better synchrony with the ventilator, which is crucial for recovery [1]. In 2018, the clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU (PADIS guideline) defined light sedation as a Richmond Agitation-Sedation Scale (RASS) score between -2 to +1 [2]. According to current guidelines, light sedation is highly recommended since it promotes patient comfort, reduces agitation, and shortens ventilator use and intensive care unit stay [2-5]. Whereas deep sedation can have negative consequences, which can lead to higher mortality, delayed extubation, risk of ICU-acquired weakness, myocardial depression and hemodynamic instability, and inactivity-induced diaphragm dysfunction [6,7].

Presently, benzodiazepine sedatives, non-benzodiazepine sedatives, and inhaled volatile anesthetics are commonly used in the ICU setting. Compared to benzodiazepine, non-benzodiazepine sedatives are preferred due to patients' shortened ICU stay and mechanical ventilation duration while also reducing delirium incidence [8-11]. In recent years, the use of volatile anesthetics, such as sevoflurane and isoflurane, has grown in the ICU, particularly during the COVID-19 pandemic. These volatile agents have several advantages, including rapid onset and offset of action, no significant risk to tolerance or withdrawal, clearance via pulmonary exhalation, low hepatic metabolism, and no active metabolite [12,13]—conversely, dose-dependent side effects like cerebral vasodilation, hypotension, and increased serum fluoride levels [12,14,15]. However, there is no evidence of nephrotoxicity. The benefits of inhaled sedatives used in the ICU are shorter wake-up times, decreased extubation time and mortality, and reduced bronchospasm and opioid requirements [16-21]. Despite the mentioned benefits, volatile anesthetics have drawbacks: malignant hyperthermia in high-risk patients, the unfamiliarity of ICU personnel with devices, infrequent access, and cost [22]. Environmental concerns regarding air pollution are mitigated by AnaConDa® devices, an aesthetic conserving device (ACD), which absorb and recycle a significant portion of the inhaled anesthetics [23]. Studies show that isoflurane and sevoflurane environmental levels are below two ppm according to the safe level recommended by the National Institute for Occupational Safety and Health (NIOSH, USA) [24,25].

Previous studies have explored using volatile anesthetics for sedation in critically ill patients, especially deep sedation levels, in situations like COVID-19 ARDS requiring prone positioning or ARDS with paralyzed patients [26]. Jung et al. investigated the optimal initial sevoflurane concentration for RASS -2 to -3 sedation in post-operative head and neck surgery with tracheostomy [27]. The ED 50 and ED 95 are the doses required to achieve the desired effect in 50% and 95% of the population, respectively. They found the ED50 end-tidal sevoflurane concentration by Dixon's method, and the isotonic regression method was 0.40% ± 0.16% and 0.36% (83% CI, 0.26% to 0.54%: 95% CI, 0.20 to 0.60%), respectively. In another study, Jerath et al. showed that the minimum alveolar concentration of sevoflurane and isoflurane was 0.1-0.3 under RASS score -1 to +1 in cardiac surgical patients [17].

Currently, no data is available on the effective dose (ED50 and ED95) of end-tidal sevoflurane concentration for achieving light sedation target RASS -1 to 0 in critically ill patients. Therefore, this study aims to determine the ED50 and ED95 of sevoflurane concentration that induce a RASS score of -1 to 0 in mechanically ventilated critically ill patients.

KEY MESSAGES:

- Deep sedation level in critically ill patients is associated with adverse outcomes.
- Volatile anesthetic sedation can enhance multimodal sedation in an ICU setting.

OBJECTIVES

Primary objective

The primary objective is to determine the ED50 and ED95 of end-tidal sevoflurane concentration for light sedation in critically ill patients who are mechanically ventilated.

Secondary objective

The secondary objectives included the length of stay in the intensive care unit, duration of ventilator day, incidence of delirium, hemodynamic status during the study period (30 minutes), and respiratory variables changed during the study period (30 minutes).

MATERIALS AND METHODS

Study design

A prospective experimental single-center study was conducted and approved by the Office of Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand, on 22nd May 2023 (COA.MURA2023/390), clinicaltrial.gov number TCTR20230825001 on 25th August 2023. Informed consent was obtained from each patient and/or patient representative in the study.

Setting and population

Eligibility criteria require adult patients (>18 years) on a mechanical ventilator for at least 12 hours with a RASS score of 1 or more and in need of sedation at the medical and surgical intensive care unit of Ramathibodi Hospital

in Thailand. Patients were excluded if they had a history or family history of malignant hyperthermia, evidence of raised intracranial pressure, low tidal volumes (<200 ml) and one-lung ventilation, persistent bronchopleural fistula despite chest tube drainage, or pulmonary disease who have a PF ratio<200. Additionally, exclusion criteria included APACHE scores ≥ 20, epidural or regional analgesia, on vasopressor ≥ 0.1 mcg/kg/min of norepinephrine-equivalent dose, lack of commitment to ongoing critical care treatment, cannot inform consent, medication requiring nebulizer, and pregnancy.

Research procedure

All patients admitted to the medical and surgical ICU are considered for participation. Adult patients on mechanical ventilation requiring sedation were enrolled after informed consent. Before starting sevoflurane sedation with the ACD (AnaConDa-S, Sedana Medical AB, Uppsala, Sweden), all patients achieved adequate pain control with a target behavioral pain scale<6 or a number rating scale < 3. Fentanyl 0.7-5 mcg/kg/h is infused to achieve the analgesic goal. In the first step, the ACD (AnaConDa-S) will be applied to deliver the sevoflurane. The end-tidal CO_2 and sevoflurane concentrations are tracked on the gas monitor, and the correct operation of the ACD (AnaConDa-S) is monitored. An initial sevoflurane bolus of 1.5 mL primed the system, followed by an infusion rate adjusted to reach a target end-tidal sevoflurane concentration of 0.5% within 30 minutes, as recommended by the manufacturer. Vital signs and a RASS score were monitored every 5 minutes throughout the process until completion, for a total of 30 minutes. According to Dixon's method, the end-tidal sevoflurane concentration will be adjusted by 0.1% for each subsequent patient based on the response of the previous patient (Figure 1). For the first patient, the initial target sevoflurane concentration will be 0.5%. If the first patient achieves a successful sedation level (RASS score of -1 to 0) or a deeper sedation level below RASS score -1, we will reduce the target end-tidal sevoflurane by 0.1%. Conversely, if the first patient does not reach a successful sedation level (RASS score ≥ +1), we will increase the target end-tidal sevoflurane by 0.1%. The second patient's end-tidal sevoflurane target will be set at 0.4% or 0.6% based on the outcome of the first patient. This sequence will continue until we have completed 20 patients. The patient's sedation level was estimated at 30 minutes. Sedation is successful when the patient reaches a RASS score of –1 to 0. If the target sedation level had a RASS score ≥ +1 for 30 minutes, no further medications were administered. After 30 minutes of investigation, patients may receive an intravenous sedative agent, possibly in combination with sevoflurane inhalation sedation, depending on the intensivist's decision. The maximum end-tidal sevoflurane concentration target is 1.4%, according to the manufacturer's recommendations. During sedation, vasopressors or inotropic agents were administered to maintain mean arterial pressure above 65 mmHg if hypotension occurred during sedation. We will stop the study if patients' mean arterial pressure (MAP) falls below 20% of baseline, if they experience severe hypotension, or if they have cardiovascular compromise.

OUTCOME MEASUREMENT

The primary outcome was the ED50 and ED 95 of end-tidal sevoflurane concentration. The secondary outcomes included the length of intensive care unit stay, duration of ventilator day, the incidence of delirium, hemodynamic status during the study period (30 minutes), and respiratory variables changed during the study period (30 minutes).

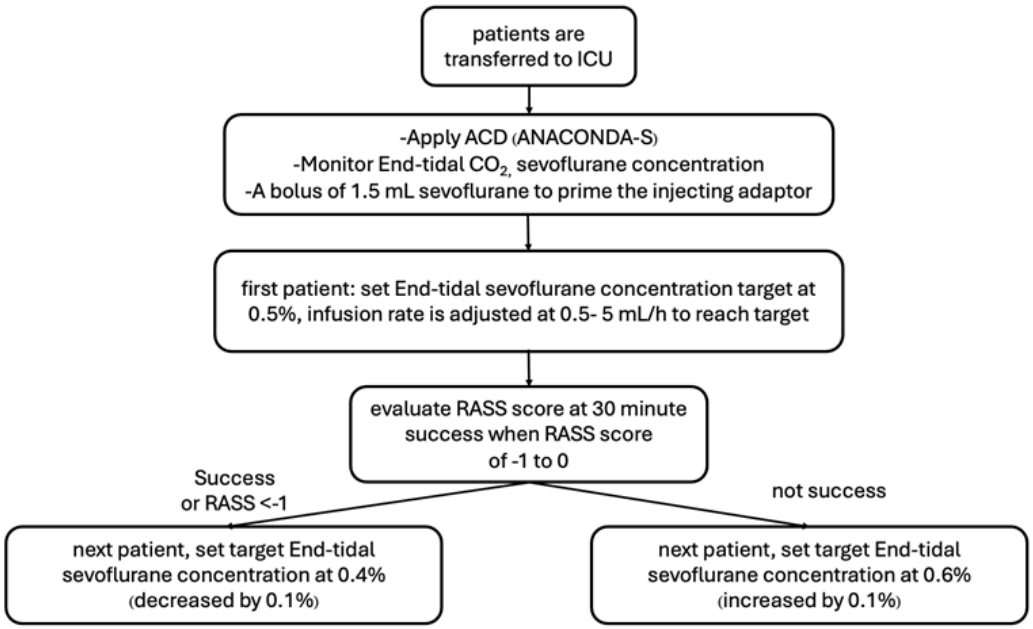

Figure 1. Study flow diagram.

DATA ANALYSIS PLAN

Sample size

According to Pace NL et al., in order to determine the appropriate sample size for an experiment, the study should include 20-40 patients and at least six crossover points [28]. The target dose can be estimated using the Dixon up-and-down method. Therefore, the sample size for this study is 20.

Statistical analysis

The SPSS software would perform all statistical analyses. Categorical variables will be demonstrated as percentages and proportions, while continuous variables will be described using both mean and standard deviation (SD) for normally distributed data and median with interquartile range (IQR) for non-normally distributed data. The ED50 and ED95 were calculated using Dixon's up-and-down method. The Wilcoxon signed-rank test will be used to evaluate changes in hemodynamic and respiratory variables. A p-value less than 0.05 ($p<0.05$) was considered statistically significant.

DATA MANAGEMENT AND DATA MONITORING

Data collection

We will collect a range of data, including demographic information, APACHE II score, type of ICU admission, end-tidal sevoflurane concentration, RASS score, as well as hemodynamic and respiratory parameters during the study. Additionally, we will document the incidence of delirium, hypotension events, opioid use, pain control medication, vasopressor administration, duration of ventilator use, and length of stay in the ICU.

Input data and monitoring method

Patient's characteristics (Supplementary materials Table 1)

Hemodynamic parameters change during the study period (Supplementary materials Table 2)

Respiratory variables change during the study period (Supplementary materials Table 3)

Sequences of individual patients according to Dixon's Up-and-Down method (Figure 2)

DISCUSSION

This prospective experimental study aimed to determine the ED50 and ED95 of sevoflurane concentrations for mechanically ventilated critically ill patients that would induce a RASS score of -1 to 0. The ED50 represents the sevoflurane concentration required for the desired sedation level in 50% of patients, whereas the ED95 indicates the concentration needed for sedation in 95% of patients. Jung et al. investigated the appropriate initial sevoflurane concentration for moderate sedation (RASS -3 to -2) in postoperative head and neck surgery with tracheostomy patients in a surgical ICU [27]. Their study found that the ED50 for initial end-tidal sevoflurane concentration was 0.40% ± 0.16% using Dixon's method. Our study may have had a lower sevoflurane concentration observed because we studied at a lighter sedation level.

Consistent with previous studies, our study may have minimal hemodynamic changes during the 30-minute study period, aligning with findings from other studies [18,29,30]. Consequently, our study will suggest that the administration of sevoflurane concentration may have a minimal effect on hemodynamics in critically ill patients. Additionally, previous studies report that volatile anesthetic sedation in postoperative cardiac surgery patients is associated with significantly lower postoperative troponin concentrations [31,32].

In our study, we will find that it may increase respiratory compliance, similar to the study by Dikmen et al. [33]. Sevoflurane causes relaxation of smooth airway muscles, reduces resistance, and improves lung homogenization, which results in increased compliance [34-36]. Whereas the Turktan et al. study showed no significant change in these lung mechanics, they suggested sevoflurane can be used for sedation in ICU patients with pulmonary disease without compromising lung function, similar to the

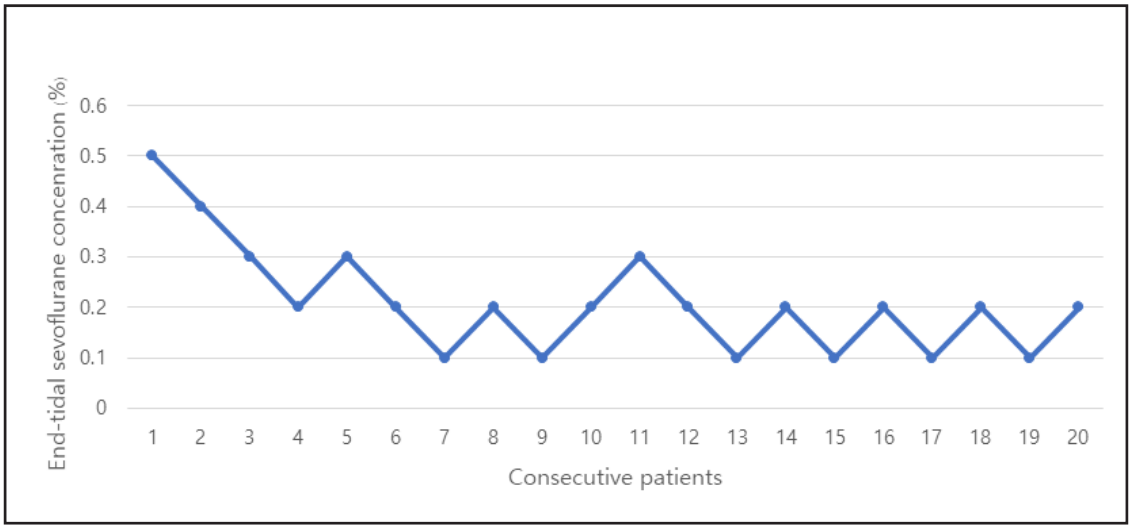

Figure 2. Illustrates the probable sequences of individual patients according to Dixon's Up-and-Down method.

Migliari et al. study [29,37]. In a recent study, Pellet et al. found that inhaled sedation devices substantially increased mechanical power significantly by more than 50% ($p<0.05$) [38].

The length of ICU stays and duration of mechanical ventilator use in our study may be slimmer in the Jung et al. study despite differences in the patient population.

The strength of our study is that it is the first study to determine the effective dose of end-tidal sevoflurane for providing light sedation (RASS score of -1 to 0) in mechanically ventilated critically ill patients. However, a limitation is the lack of familiarity with ACD devices among our personnel.

CONCLUSION

This study will provide an effective dose of inhaled sevoflurane sedation for achieving targeted light sedation levels in critically ill patients, which may have minimal effects on hemodynamics.

CONFIDENTIALITY

The researchers obtain informed consent only in the isolated private medical and surgical ICU room. Patients' data are encrypted with the hospital-based healthcare personnel passcode-locking system in the database. All participants will not be specifically identified. A code number represents the patient's information rather than the patient's name/hospital number/admission number. All data are recorded only in the case record form and on the investigator's personal computer. After the trial, all data will be eliminated from all computers or physical documents.

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ABBREVIATIONS

ACD: Anesthetic conserving device; APACHE II: acute physiology and chronic health evaluation II; ARDS: Acute respiratory distress syndrome; BPS: behavioral pain scale; DBP: diastolic blood pressure; ED: Effective dose; $EtCO_2$: end-tidal of carbon dioxide; EtSevoflurane: end-tidal of sevoflurane; GABA: Gamma-aminobutyric acid; ICU: Intensive care unit; MAC: Minimum alveolar concentration; MAP: Mean arterial pressure; mcg: microgram; mg: milligram; NRS: numerical pain rating scale; NSAIDs: non-steroidal anti-inflammatory drugs; P 0.1: airway occlusion pressure at 0.1 second; $PaCO_2$: Partial pressure of carbon dioxide; PaO_2: Partial pressure of oxygen; PEEP: positive end-expiratory pressure; PF ratio: ratio of arterial oxygen partial pressure to fractional inspired oxygen; RASS: Richmond Agitation and Sedation Scale; SBP: Systolic blood pressure; SD: Standard deviation; SpO_2: Peripheral oxygen saturation.

AUTHORS' CONTRIBUTIONS

(I) Conceptualization, Data curation: Jitpakdee W, Pisitsak C; (II) Formal analysis: Pisitsak C; (III) Funding acquisition: Jitpakdee W; (IV) Methodology: Jitpakdee W, Pisitsak C; (V) Project administration, Visualization, Writing- original draft, Writing -review & editing: Jitpakdee W, Pisitsak C.

ETHICS APPROVAL

The study was conducted and approved by the Office of Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand, on 22nd May 2023 (COA.MURA2023/390), clinicaltrial.gov number TCTR20230825001 on 25th August 2023.

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SUPPLEMENTARY MATERIALS

Table 1. Patient characteristics.

Variables	Patients (N=)
Age; years	
Gender	
Male	
Female	
BMI; kg/m^2	
APACHE II	
Co-morbidities	
Diabetes mellitus	
Hypertension	
Cerebrovascular disease	
Cardiovascular disease	
Congestive heart failure	
Chronic kidney disease	
Chronic obstructive pulmonary disease	
Type of ICU	
Medical ICU	
Surgical ICU	
Postoperative case (<48 h)	
Sepsis	
Drug use	
Opioids; mcg	
Hypotension	
Vasopressor use	
Sevoflurane start rate	
Ventilator days	
ICU stay days	

Values are expressed as mean ± SD or number(proportion) or median (IQR).

Table 2. Hemodynamic variables changed during the study.

	T0	T5	T10	T15	T20	T25	T30	P value
[a]SBP (mmHg)								
[a]DBP (mmHg)								
[a]MAP (mmHg)								
[a]HR (bpm)								

[a] Data are presented as mean ± SD. **Abbreviations:** T0: time at the start; T5: time at 5 minutes; T10: time at 10 minutes; T15: time at 15 minutes; T20: time at 20 minutes; T25: time at 25 minutes; T30: time at 30 minutes.

Table 3. Respiratory variables.

[a]Tidal volume	T0	T30	P value
[a]Respiratory rate			
[a]Respiratory compliance			
[a]Resistance			
[a]AutoPEEP			
[a]P 0.1			
[a]Oxygen saturation			
[a]PF ratio			
[a]pH			
[a]PaO_2			
[a]$PaCO_2$			
[a]HCO_3			

[a] Data are presented as median (interquartile range). **Abbreviations:** T0: time at the start; T30: time at 30 minutes.