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Effective Sevoflurane Concentrations for Light Sedation in Mechanically Ventilated Patients: A Prospective Dose-Finding Study

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Effective Sevoflurane Concentrations for Light Sedation in Mechanically Ventilated Patients: A Prospective Dose-Finding Study

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ABSTRACT

Background: Inhaled anesthetics have traditionally been used to achieve deep sedation and general anesthesia. However, despite increasing interest in their use for sedation in the intensive care unit (ICU), evidence regarding their application at light sedation levels remains limited. This study aimed to evaluate the feasibility of sevoflurane for light sedation and to determine the effective end-tidal concentration required to achieve the target sedation level.

Methods: This prospective, single-center experimental study was conducted in ICU between October 2023 and October 2024. Mechanically ventilated adult patients with RASS ≥1 requiring sedation were enrolled. Dixon's up-and-down sequential allocation method was used to determine the target end-tidal sevoflurane concentration required to achieve light sedation. The primary outcome was the determination of EC50 and EC95 for end-tidal sevoflurane required to achieve the target light sedation level.

Results: Twenty patients were included. The estimated EC50 and EC95 were 0.08% and 0.28%, respectively. Respiratory mechanics did not differ significantly before and after intervention. Hypotension was observed in 3 patients (15%) during the intervention, although no major cardiovascular events occurred.

Conclusion: Very low inhaled sevoflurane concentrations were feasible for light sedation in mechanically ventilated ICU patients without major complications.

Keywords: Anesthetics, Inhalation, Sevoflurane, Conscious sedation, Intensive care units

Trial registration: The study was registered with the Thai Clinical Trials Registry (TCTR20230825001) on August 25, 2023.

Introduction

Sedation in critically ill patients is essential to alleviate anxiety, stress, and discomfort. Current guidelines recommend maintaining light sedation in critically ill patients [1,2]. The 2018 standard guidelines define light sedation as a Richmond Agitation-Sedation Scale (RASS) score between −2 and +1 [2]. Light sedation has been associated with shorter duration of mechanical ventilation and ICU length of stay [2-4]. Traditionally, intravenous sedative agents combined with clinical sedation scale monitoring have been used to achieve and maintain light sedation in critically ill patients [5-6]. However, inhaled sedation with volatile anesthetics, such as sevoflurane and isoflurane, has emerged as an alternative strategy in the ICU, supported by recent randomized controlled trials and systematic reviews. Inhaled sedation has been associated with shorter awakening and extubation times, shorter ICU length of stay, reduced opioid requirements and bronchodilatory effects [7-9]. Despite these advantages, volatile anesthetics have traditionally been used for deep sedation or general anesthesia. In contrast, guidelines increasingly emphasize targeting light sedation in mechanically ventilated patients. However, the application of inhaled sedation at light sedation levels remains controversial. It is unclear whether sevoflurane can be effectively titrated to achieve and maintain light sedation, and what end-tidal concentrations are required. Therefore, this study aimed to evaluate the feasibility of sevoflurane for light sedation and to determine the effective end-tidal concentrations required to achieve this level of sedation.

MATERIALS AND METHODS

Study design and population

This prospective, single-center experimental study was approved by the Office of the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol

University, Thailand, on 22 May 2023 (COA.MURA2023/390) and registered at the Thai Clinical Trials Registry (TCTR20230825001). No important changes to the study protocol, outcomes, or prespecified analyses were made after trial commencement. The study was conducted from October 2023 to October 2024 in the intensive care unit of Ramathibodi Hospital, Bangkok, Thailand.

Eligible participants were adults aged ≥18 years who required mechanical ventilation for at least 12 hours, had a baseline Richmond Agitation–Sedation Scale (RASS) ≥1, and required sedation as determined by the attending physician. Exclusion criteria included a history or family history of malignant hyperthermia; evidence of increased intracranial pressure; low tidal volume ventilation (<200 mL) or one-lung ventilation; persistent bronchopleural fistula despite chest drainage; severe pulmonary dysfunction with a PaO_2/FiO_2 ratio <200; Acute Physiology and Chronic Health Evaluation (APACHE) score ≥20; use of epidural or regional analgesia; requirement for vasopressor support ≥0.1 μg/kg/min (norepinephrine-equivalent dose); lack of commitment to ongoing critical care; inability to obtain informed consent; requirement for nebulized medications; and pregnancy.

Study procedures

All patients were enrolled after obtaining informed consent. Prior to initiation of inhaled sedation, adequate analgesia was ensured, targeting a Behavioral Pain Scale <6 or a Numeric Rating Scale <3. Continuous infusion of fentanyl was administered at 0.7–10 μg/kg/h to achieve the analgesic target.

Inhaled sedation was administered using sevoflurane via an anesthetic-conserving device (AnaConDa-S, Sedana Medical AB, Uppsala, Sweden) integrated into the mechanical ventilator

circuit. The system was primed with an initial bolus of 1.5 mL sevoflurane, followed by continuous infusion titrated to achieve an initial target end-tidal concentration of 0.5% within 30 minutes, in accordance with the manufacturer's recommendations. End-tidal carbon dioxide and sevoflurane concentrations were continuously monitored using a gas analyzer to ensure appropriate device function and drug delivery. Vital signs and sedation depth were monitored throughout the study period. Potential measurement and observer biases were minimized through the use of a standardized analgesia-first sedation protocol and the validated RASS performed by trained personnel. Sedation success was defined as achieving a RASS score between −1 and 0 at 30 minutes.

A sequential allocation design based on Dixon's up-and-down method was applied. The initial patient received a target end-tidal sevoflurane concentration of 0.5%. For each subsequent patient, the target concentration was adjusted in increments of 0.1% based on the prior patient's response: the concentration was increased by 0.1% if the RASS was >0, decreased by 0.1% if the RASS was <−1, and maintained if the target RASS (−1 to 0) was achieved (figure 2). The maximum allowable end-tidal sevoflurane concentration was limited to 1.4% according to manufacturer recommendations. During sedation, vasopressor or inotropic agents were administered as needed to maintain a mean arterial pressure ≥65 mmHg.

Outcomes

The primary outcome was the median effective concentration (EC_{50}) and 95% effective concentration (EC_{95}) of end-tidal sevoflurane required to achieve target light sedation. Secondary outcomes included the incidence of delirium during the ICU stay. Hemodynamic parameters, including mean arterial pressure and heart rate, were recorded during the 30-minute

study period. Respiratory variables, including tidal volume, respiratory rate, and end-tidal carbon dioxide and lung mechanics were also assessed before and after sevoflurane administration during the study period.

Sample size

The sample size was determined based on methodological recommendations for dose-finding studies using the Dixon up-and-down sequential design. According to Pace NL et al., such studies typically require 20–40 patients and at least six independent crossover pairs to provide a reliable estimate of the target dose [10]. Accordingly, a sample size of 20 patients was planned for this study.

Statistical analysis

The EC_{50} was estimated using Dixon's up-and-down method by calculating the mean of the midpoint concentrations of independent crossover pairs, defined as successive patient pairs with opposite responses (i.e., success followed by failure or vice versa) [10-11]. Dose–response relationships were further analyzed using nonlinear regression with a sigmoidal model in GraphPad Prism (version 11.0.0; GraphPad Software, Boston, MA, USA), from which EC_{50} and EC_{95} were derived.

Continuous variables were summarized as mean ± standard deviation or median with interquartile range, depending on data distribution. Categorical variables were presented as frequencies and percentages. Hemodynamic and respiratory variables measured before and after sevoflurane administration were compared using the paired t-test or Wilcoxon signed-rank test, as appropriate.

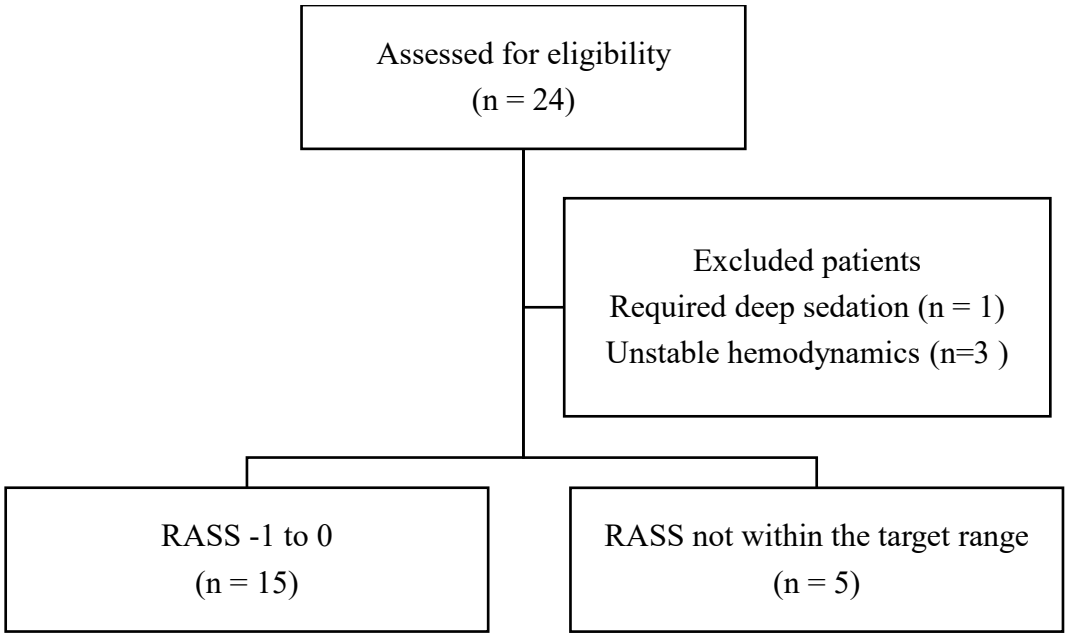
All statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). A two-sided p-value <0.05 was considered statistically significant.

A data analysis and statistical plan was written and filed with a private entity (institutional review board) before data were accessed.

RESULTS

A total of 20 patients were enrolled and completed the study. Of these, five patients had RASS targets outside the recommended range at the end of the study (Figure 1). Complete data were available for all enrolled participants, and no missing data were observed for any study variables. Baseline characteristics are summarized in Table 1. Most patients in this study were elderly, with 14 of 20 patients (70%) being older than 65 years. Patients had relatively low disease severity at enrollment, with only 2 of 20 patients (10%) requiring vasopressor support and a mean APACHE II score of 11 (SD 4). Co-morbidities were heterogeneous, with no single condition predominating among the study population.

Figure 1. Study flow diagram



RASS, Richmond Agitation-Sedation Scale

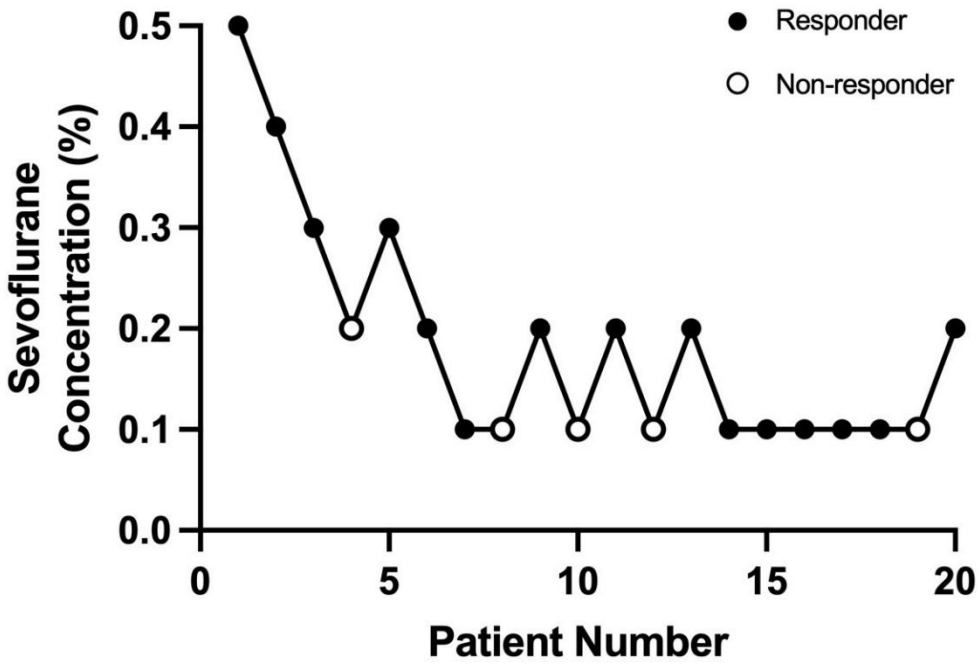
Table 1. Baseline Characteristics

Variables	**Patients (N= 20)**
Age (years), mean (SD)	67 (10)
Male gender	15 (75%)
BMI (kg/m^2), mean (SD)	23 (4)
APACHE II score	11 (4)
Co-morbidities	
Diabetes mellitus, n (%)	5 (25%)
Hypertension, n (%)	8 (40%)
Cerebrovascular disease, n (%)	2 (10%)
Congestive heart failure, n (%)	2 (10%)
Chronic kidney disease, n (%)	4 (20%)

Chronic obstructive pulmonary disease, n (%)	4 (20%)
Postoperative patients within 48 hours, n (%)	9 (45%)
Sepsis, n (%)	10 (50%)
Fentanyl dose (mcg/hour), median (IQR)	25 (0 - 45)
Vasopressor use during enrollment, n (%)	2 (10%)
Initial rate of sevoflurane (ml/hour), mean (SD)	5 (3)

Using Dixon's up-and-down method, 5 independent crossover pairs were obtained (Figure 2). The initial sevoflurane infusion rate required to achieve a mean end-tidal sevoflurane concentration of 0.5% was 5.5 ± 3.8 mL/h, after which the dose was titrated according to the Dixon up-and-down method to achieve the target RASS level.

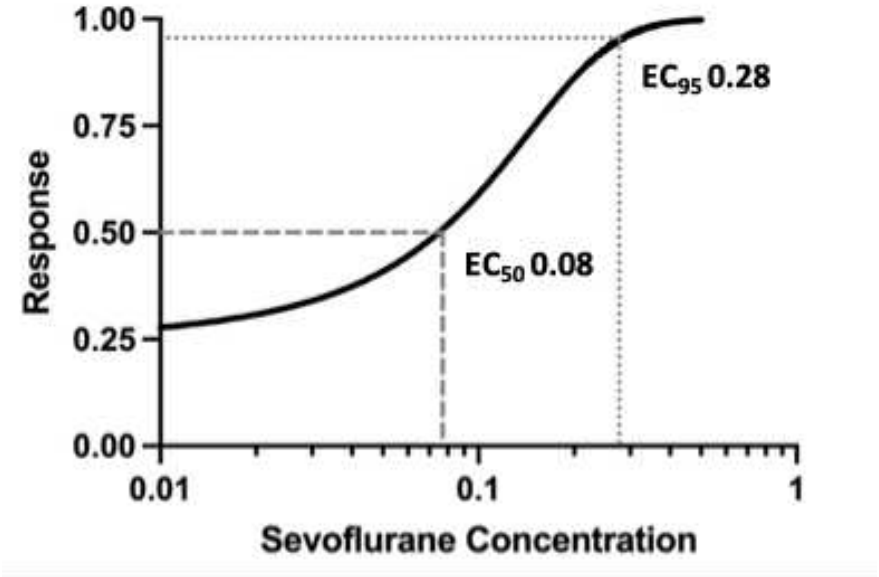
Figure 2. Sequential allocation of end-tidal sevoflurane concentrations using Dixon's up-and-down method.



Closed circles indicate responders and open circles indicate non-responders.

The EC_{50} and EC_{95} of end-tidal sevoflurane were 0.08% and 0.28%, respectively (Figure 3). Fentanyl was administered at a median dose of 25 μg/h. Hypotension occurred in 3 patients (15%), of whom 2 required vasopressor support during the study period. Mechanical ventilation was equally distributed between pressure control ventilation (10 cases, 50%) and pressure support ventilation (10 cases, 50%). The median duration of mechanical ventilation was 3 days, and the median ICU length of stay was 4.5 days. Five cases developed delirium within 7 days after enrollment (25%).

Figure 3. Dose–response curve for end-tidal sevoflurane concentration and achievement of target light sedation



Respiratory mechanics did not differ significantly before and after the intervention including both respiratory system compliance and resistance (Table 2). Similarly, no significant differences were observed in other respiratory or hemodynamic parameters, including systolic blood pressure, diastolic blood pressure, mean arterial pressure, and heart rate (Figure 4).

Table 2. Respiratory variables

	T0	T30	*P*-values
Tidal volume (ml), mean (SD)	545 (213)	511 (156)	0.10
Respiratory rate (breaths/min), mean (SD)	15 (3)	16(2)	0.37
Respiratory compliance (ml/cmH_2O), mean (SD)	56 (16)	60(23)	0.11
Resistance (cmH_2O/L/sec), mean (SD)	13 (3)	13 (3)	0.74
P0.1 (cmH_2O), mean (SD)	-1 (0.8)	-1 (1)	0.64
PaO_2/FiO_2 ratio, mean (SD)	376 (99)	379 (98)	0.91
pH, mean (SD)	7.4 (0)	7.4 (0)	0.70
PaO_2 (mmHg), mean (SD)	129 (48)	127 (38)	0.75
$PaCO_2$ (mmHg), mean (SD)	31 (5)	32 (5)	0.67
HCO_3 (mEq/L), mean (SD)	21 (3)	21 (3)	1.00

T0; time at the start, T30; time at 30 minutes

Figure 4. Hemodynamic variables during study period

Figure 4A

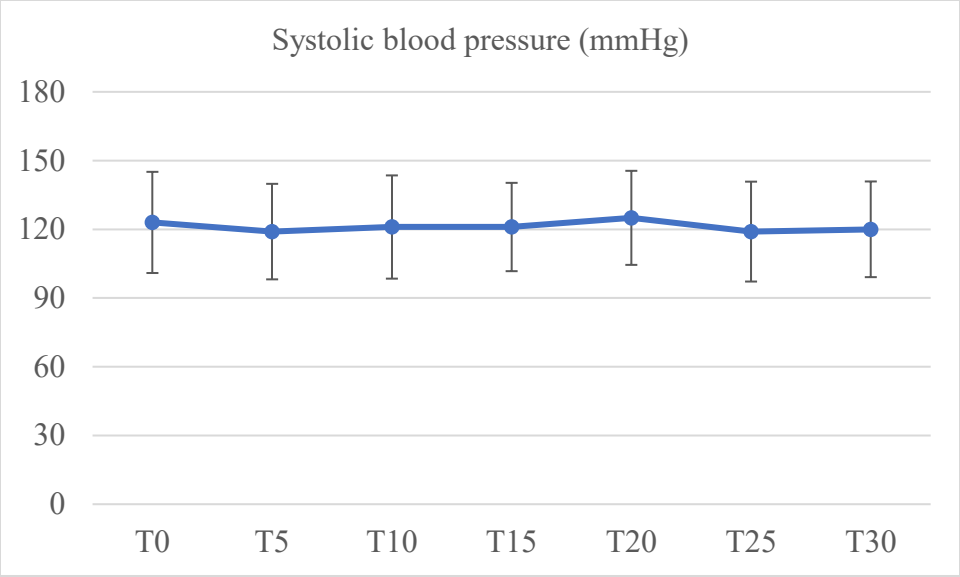


Figure 4B

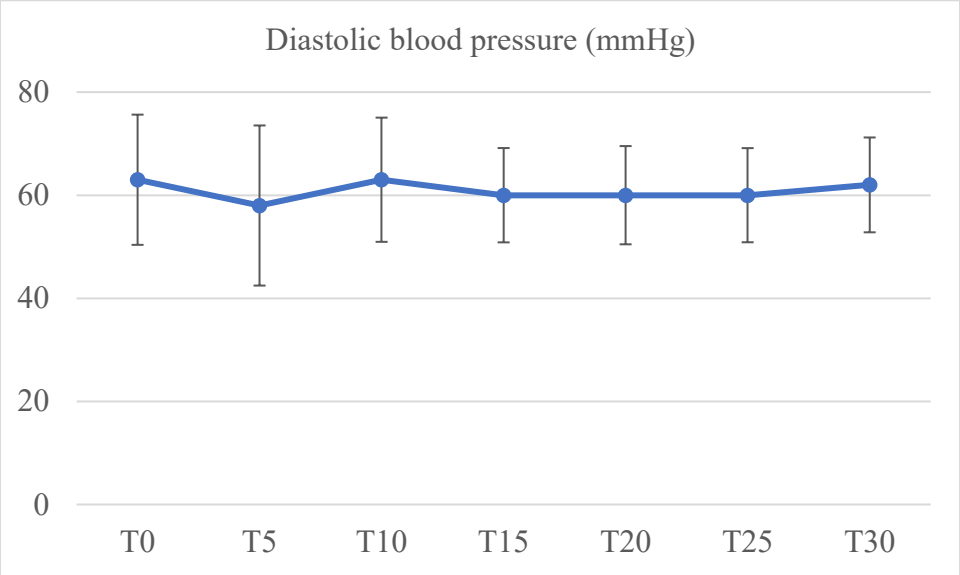


Figure 4C

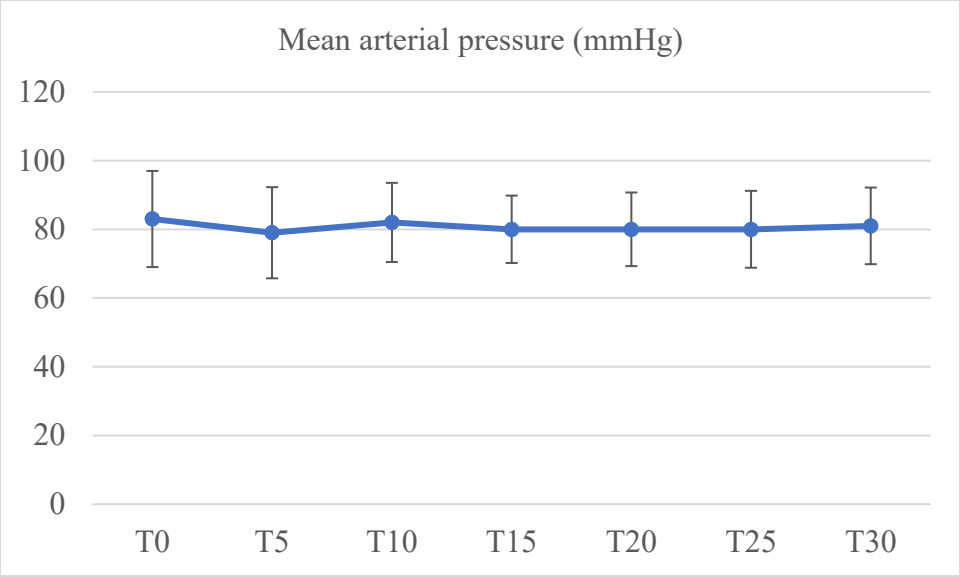
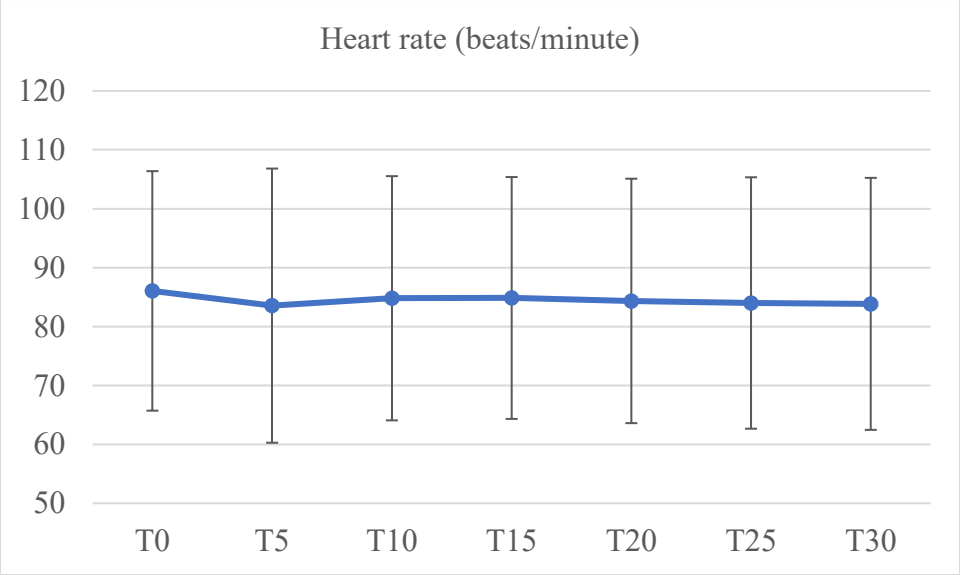


Figure 4D



Data are presented as mean ± SD.

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.

DISCUSSION

In this prospective dose-finding study, we identified that the EC_{50} and EC_{95} of end-tidal sevoflurane required to achieve light sedation (RASS −1 to 0) were 0.08% and 0.28%, respectively. These concentrations are substantially lower than those used in general anesthesia and suggest that light sedation in ICU can be achieved with minimal volatile anesthetic exposure. To our knowledge, this is among the first studies to quantitatively define the dose–response relationship of inhaled sevoflurane specifically for light sedation in mechanically ventilated ICU patients, addressing an important gap in the current literature where prior studies have primarily focused on clinical outcomes rather than dosing thresholds [12-13]. The relatively low effective concentrations observed in this study are likely multifactorial, including the advanced age of the study population, which is associated with increased pharmacodynamic sensitivity to sedatives, the concomitant use of opioid analgesia that may exert synergistic sedative effects, and the predefined target of light sedation, which requires substantially lower hypnotic exposure than deep sedation or general anesthesia. These findings are consistent with contemporary ICU sedation strategies that emphasize maintaining light sedation to reduce delirium, shorten duration of mechanical ventilation, and improve clinical outcomes, as recommended by current clinical practice guidelines [2]. Jung et al. conducted a study in postoperative patients undergoing head and neck surgery with tracheostomy who required sedation and mechanical ventilation in the surgical ICU. The study aimed to determine the effective dose of sevoflurane to achieve a moderate sedation target (RASS −2 to −3), in combination with sufentanil for analgesia. They reported an EC_{50} of 0.36% (83% CI, 0.26–0.54%; 95% CI, 0.20–0.60%) and an EC_{95} of 0.69% (83% CI, 0.62–0.72%; 95% CI, 0.60–0.75%). These findings are consistent with our results, in which lower end-tidal concentrations were required to achieve light sedation (RASS −1 to 0), reflecting the reduced anesthetic requirement at lighter levels of sedation [14].

There is mixed evidence regarding the renal effects of sevoflurane in critically ill patients. Some studies have raised concerns, including polyuria and acute kidney injury [8, 12-13, 15-18], whereas others have reported no significant adverse effects including renal issues associated with its use in ICU settings [7, 19-20]. However, these findings were primarily derived from studies targeting deep sedation, where higher anesthetic exposures were used. In contrast, the present study evaluated sevoflurane for light sedation, resulting in substantially lower end-tidal concentrations. This lower level of exposure may mitigate the risk of renal adverse effects. Nevertheless, further studies are warranted to determine whether light sedation with sevoflurane reduces the risk of acute kidney injury in critically ill patients.

In addition, previous studies have reported increased vasopressor requirements during sevoflurane sedation [12]. In contrast to these findings, we did not observe significant hemodynamic effects following sevoflurane use in our study. This discrepancy may reflect the dose-dependent vasodilatory effects of sevoflurane, which are more pronounced at deeper levels of sedation.

No significant changes in respiratory mechanics were observed following administration of low-dose sevoflurane. This finding is likely attributable to the very low end-tidal concentrations required to achieve light sedation, which may be below the threshold for clinically relevant effects on respiratory drive or airway tone [21]. At these concentrations, sevoflurane is unlikely to reduce tidal volume, increase respiratory rate, or produce bronchodilation reflected by decreased airway resistance. Therefore, the absence of measurable changes in respiratory parameters in this study likely reflects a dose-dependent physiological effect rather than an absence of pharmacologic activity.

Limitations

Although the number of independent crossover pairs (n = 5) was slightly below the conventional recommendation for Dixon's up-and-down method, the response sequence showed clear oscillation around the target concentration, indicating convergence of the allocation process. In addition, dose–response analysis using nonlinear regression yielded EC_{50} and EC_{95} estimates consistent with the Dixon method, supporting the robustness of the results. [10, 22].

The generalizability of our findings may be limited by the use of a standardized analgesia-first protocol with fentanyl. Because opioid administration may reduce sedative requirements, the estimated effective end-tidal sevoflurane concentrations observed in this study may not be directly applicable to settings using different analgesic regimens or opioid doses.

Conclusion

Sevoflurane achieved targeted light sedation at very low end-tidal concentrations (EC_{50} 0.08%, EC_{95} 0.28%) without clinically significant respiratory or hemodynamic effects. These findings support the feasibility of inhaled sevoflurane as a dose-efficient sedation strategy in critically ill patients.

List of abbreviations

APACHE II, acute physiology and chronic health evaluation II

ICU, intensive care unit

RASS, Richmond Agitation-Sedation Scale

EC, Effective concentration

MAP, Mean arterial pressure

SBP, Systolic blood pressure

DBP, Diastolic blood pressure

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

FiO_2 fractional inspired oxygen

SD, Standard deviation

CI, confidence interval

Declarations

Ethics Approval and Consent to Participate

The study was approved by the Office of the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Thailand, on 22 May 2023 (COA.MURA2023/390)**.** The study was performed based on the Declaration of Helsinki. Written informed consents were obtained from all patients.

Consent for publication

Not applicable.

Availability of data and materials

The data of this study could be requested from the corresponding authors.

Competing interests

All authors declare no competing interests.

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Author's Contribution

WJ, CP, SM, TP and ST developed the research idea and designed the overall study framework. WJ, BB and CP conducted the study and collected data. CP, PD and AT analyzed data and created the figures. WJ and CP obtained research funding for the study and wrote the original draft of the manuscript. All authors clinically reviewed, revised and approved the final version of the manuscript.

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