Systematic Review and Meta-Analysis

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Volatile sedation in the intensive care unit

A systematic review and meta-analysis

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Abstract

Background: Volatile sedation in the intensive care unit (ICU) may reduce the number of adverse events and improve patient outcomes compared with intravenous (IV) sedation. We performed a systematic review and meta-analysis comparing the effects of volatile and IV sedation in adult ICU patients.

Methods: We searched the PubMed, Embase, Cochrane Central Register, and Web of Science databases for all randomized trials comparing volatile sedation using an anesthetic-conserving device (ACD) with IV sedation in terms of awakening and extubation times, lengths of ICU and hospital stay, and pharmacologic end-organ effects.

Results: Thirteen trials with a total of 1027 patients were included. Volatile sedation (sevoflurane or isoflurane) administered through an ACD shortened the awakening time [mean difference (MD), −80.0 minutes; 95% confidence intervals (95% CIs), −134.5 to −25.6; $P = .004$] and extubation time (MD, −196.0 minutes; 95% CIs, −305.2 to −86.8; $P < .001$) compared with IV sedation (midazolam or propofol). No differences in the lengths of ICU and hospital stay were noted between the 2 groups. In the analysis of cardiac effects of sedation from 5 studies, patients who received volatile sedation showed lower serum troponin levels 6 hours after ICU admission than patients who received IV sedation ($P < .05$). The effect size of troponin was largest between 12 and 24 hours after ICU admission (MD, −0.27 μg/L; 95% CIs, −0.44 to −0.09; $P = .003$).

Conclusion: Compared with IV sedation, volatile sedation administered through an ACD in the ICU shortened the awakening and extubation times. Considering the difference in serum troponin levels between both arms, volatile anesthetics might have a myocardial protective effect after cardiac surgery even at a subanesthetic dose. Because the included studies used small sample sizes with high heterogeneity, further large, high-quality prospective clinical trials are needed to confirm our findings.

Abbreviations: ACD = anesthetic conserving device, CI = confidence interval, ICU = intensive care unit, IV = intravenous, LOS = length of stay, MD = mean difference, MV = mechanical ventilation, NT-proBNP = serum N-terminal prohormone of brain natriuretic peptide, OR = odds ratio, PICOS = the Patient, Intervention, Comparator, Outcomes, and Study, PONV = postoperative nausea and vomiting, PRISMA = the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT = randomized controlled trial.

Keywords: anesthetics, critical care, inhalation, meta-analysis, sedation

1. Introduction

Suboptimal sedation in critically ill patients is associated with adverse events, high costs, and increases in morbidity and mortality.[1–3] The current sedation guidelines, which are updated periodically, are based on intravenous (IV) agents.[2] However, the updated sedation practices with IV agents are problematic due to adverse effects such as accumulation, tolerance, withdrawal, delirium, and hemodynamic instability.[4–9]

Volatile anesthetic agents used in general anesthesia have also been used as sedatives due to favorable pharmacokinetics such as rapid elimination via pulmonary exhalation, limited hepatic metabolism, and no accumulation.[10–12] Moreover, the perioperative organ protective effects of volatile anesthetic agents, especially on the heart, have been confirmed through the mechanisms of ischemic pre- and post-conditioning.[13–17] Nevertheless, the use of volatile sedation in the intensive care unit (ICU) has been limited due to intensivists' lack of familiarity with these agents, emergence agitation, postoperative nausea and vomiting (PONV), and nephrotoxicity from inorganic fluoride.[18–22] Most importantly, volatile sedation in the ICU has been limited by technical problems, including the wasting of volatile agents by high-flow ICU ventilators and atmospheric contamination by open ventilator circuits.[23]

Volatile sedation in the ICU is becoming increasingly popular due to fewer technical problems since the development of anesthetic reflectors, such as AnaConDa (SEDANA Medical, Uppsala, Sweden) and Mirus (Pall Medical, Dreieich, Germany), which reduce volatile agent wasting.[24,25] Once these anesthetic reflectors were commercially available, several small randomized controlled trials were published comparing the effects of volatile and conventional IV sedative agents in the ICU.[26–38]

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Therefore, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) using these new anesthetic reflectors (AnaConDa and Mirus) to evaluate whether volatile sedation is associated with improved outcomes compared with IV sedation in adult ICU patients.

2. Materials and methods

2.1. Literature search

This study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses of RCTs.[39] This study did not require ethical approval because it was an analysis of previously published studies. Two independent reviewers (JMK and HYK) separately searched the PubMed, Embase, Cochrane Central Register, and Web of Science of Controlled Trials databases for all studies, regardless of language, published before May 31, 2017. The search terms used were: ("sevoflurane" OR "isoflurane" OR "desflurane" OR "anesthetic conserving device" OR "AnaConDa" OR "Mirus") AND 'sedation" AND ("critical care" OR "intensive care"). Additional studies were identified by manually searching the references of the original studies.

2.2. Study selection

We included RCTs and quasi-RCTs of patients who underwent sedation in the ICU. The inclusion criteria, based on the Patient, Intervention, Comparator, Outcomes, and Study (PICOS) design criteria, were as follows: patient: adult patients (≥18 years) who underwent sedation in the ICU; intervention: patients sedated with volatile sedatives (sevoflurane, isoflurane, or desflurane) via an AnaConDa or Mirus reflector; comparator: patients sedated with IV sedatives; at least 1 primary outcome [awakening time, extubation time, length of stay (LOS) in the ICU, or LOS in the hospital] or secondary outcomes (myocardial effects, renal effects, incidence of delirium, or incidence of PONV); and study design: RCT or quasi-RCT. Observational studies, retrospective studies, case reports, letters, reviews, and abstracts were excluded.

2.3. Data extraction and outcome measurement

The 2 reviewers (JMK and HYK) selected all datasets for this study. Disagreements were resolved by discussion and consensus. Authors of potentially relevant studies were contacted for further information if the relevant data were not published. Among the primary outcomes, awakening time was defined as the time (in minutes) from the termination of sedative administration to awakening. Extubation time was defined as the time (in minutes) from the termination of sedative administration to extubation. The LOS in the ICU and hospital were defined as the hours and the days from admission to discharge. Among the secondary outcomes, myocardial effects were determined by examining serum troponin (μg/L) and serum N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (pg/mL) levels after ICU admission. The serum creatinine (mg/dL) level on the first postoperative day was used as a measure of the renal effects. The incidences of delirium and PONV were recorded as the number of patients who experienced these effects during the post-sedation period. If studies had more than 1 volatile or IV sedation arm, the arms were combined such that there was only 1 volatile and 1 sedation arm.

2.4. Quality assessment

Two reviewers assessed the articles and investigated the risk of bias for RCTs using the Risk of Bias tool from the Cochrane Collaboration.[40] The 7 different domains were as follows: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other bias. The risk of bias for each trial was reported as "low," "unclear," or "high." In the allocation concealment domain, we considered the difficulty in ensuring complete blinding of a caregiver when administering sedation to a patient via anesthetic reflectors or IV. The primary outcomes, such as awakening and extubation times and LOS in the ICU and hospital, were estimated according to the robustness of the study protocol. If the trial had objective criteria, such as a targeted sedation level or plans for stopping sedation and starting ventilator weaning, the risk of bias was rated as low despite the lack of blindness. For PONV and delirium outcomes, we also evaluated whether the method of measurement was objective. In the selective reporting domain, we evaluated bias based on protocols from http://www.clinicaltrials.gov and outcomes that were expressed in the methods. For other bias domains, we considered the influence of sponsors. If the trials received financial assistance from a medical instrument or pharmaceutical company, the risk of bias was rated as "unclear." Review Manager software (RevMan; version 5.3) was used to present the risk of bias.

2.5. Data synthesis and statistical analysis

Data that were reported as median and range were changed to mean and standard deviation.[41] Data that were not reported numerically in the original articles were extracted from the figures. Measurement units were standardized. Troponin I levels were converted to troponin T levels using a conversion factor of 0.65/2, based on the ratio of the upper limit and previous literature.[16] Units of serum creatinine levels were converted to mg/dL. Meta-analyses were performed to calculate the pooled mean difference (MD) for continuous data or the odds ratio (OR) for dichotomous data with 95% confidence intervals (95% CIs) using either a fixed effects or random effects model. Heterogeneity was assessed using the Cochrane Q test and I^2 statistics.[42] The fixed effects model was used for meta-analysis unless at least 4 studies were included and the I^2 exceeded 50, at which point the random effects model was used. In addition, subgroup analyses were performed in primary outcomes showing substantial heterogeneity to identify the influence of sedation duration, patient type, financial support, and type of IV agents. Differences in effect size between subgroups were analyzed with a meta-regression model. Publication bias was evaluated using the Egger regression test and a funnel plot.[43] If the outcomes showed significant publication bias, then the trim and fill method was used for additional analyses. All statistical analyses were performed using the meta-analysis package for R ver. 3.3.2 (metaphor; Vienna, Austria; http://www.R-project.org).[44]

3. Results

3.1. Study selection

A flow chart illustrating the study selection process is shown in Fig. 1. We retrieved 1532 records in our initial search. After removing 459 duplicates, we excluded 1023 other records for the following reasons: non-ICU or nonvolatile sedation studies

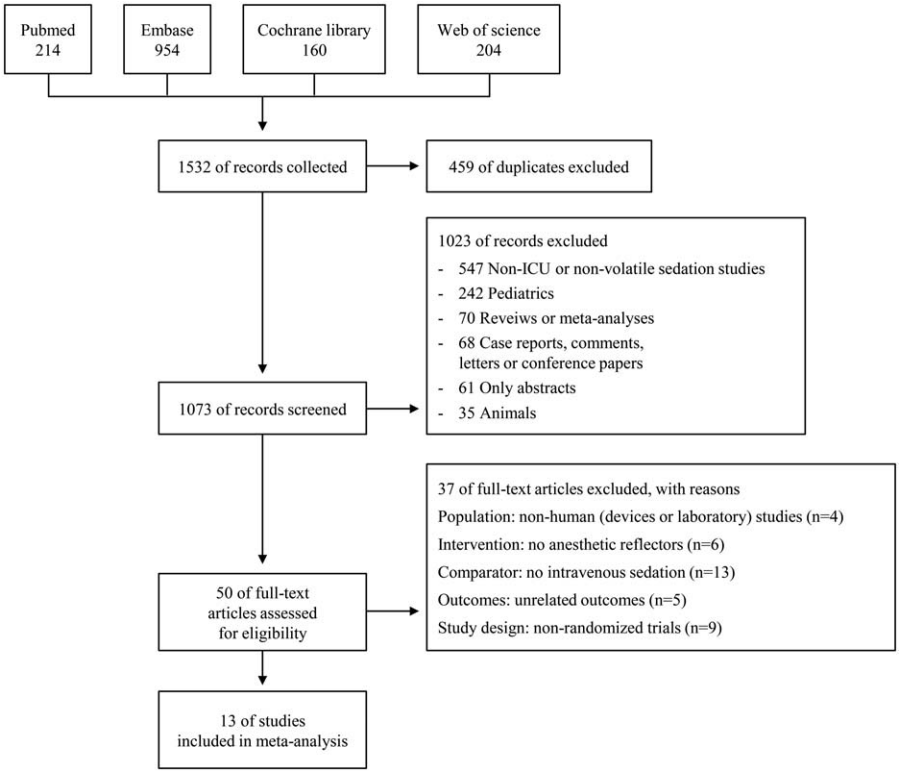

Figure 1. Flow diagram depicting the study selection process.

(n=547), pediatric patients (n=242), reviews or meta-analyses (n=70), case reports, comments, letters, or conference papers (n=68), abstracts only (n=61), and animal studies (n=35). Of the 50 potentially eligible studies, we excluded 37 because they did not meet the PICOS criteria. Ultimately, 13 RCTs published between November 2004 and May 2017 were included in the meta-analysis.

3.2. Characteristics of the included studies

Thirteen studies[26–38] were included in the analysis. Two sets of studies ([27,29] and [30,32]) were assumed to be the same trials based on their clinical trial numbers (http://www.clinicaltrials.gov). Because the outcomes overlapped in 2 of these studies,[27,29] outcomes were extracted from the study with the larger sample size.[29] Because 1 study[32] represented outcomes of continuous variables as medians and interquartile ranges without the first and third quartiles, these outcomes were excluded and only outcomes with categorical variables, such as the incidences of delirium and PONV, were included in our meta-analysis. Three studies were performed in mixed medical-surgical ICUs,[26,28,31] while the remaining 10 studies were performed in surgical ICUs consisting of only postsurgical patients.[27,29,30,32–38] Of the 10 studies performed in surgical ICUs, 1 study included patients who underwent major abdominal, vascular, or thoracic surgery,[29] while the other 9 studies only enrolled patients who underwent cardiac surgery.[27,30,32–38] All included studies used the AnaConDa device in the volatile sedation arm; there was no RCT using the Mirus device. Among the 13 included studies, 9 compared sevoflurane with propofol,[27,29,30,32–37] 3 compared isoflurane with midazolam,[26,28,38] and 1 compared sevoflurane with propofol and midazolam.[31] We did not consider the type of anesthetics used intraoperatively. The characteristics of the included studies are summarized in Table 1. The details on the sedation scales used in the included studies are listed in Table S1, Supplemental Content, http://links.lww.com/MD/B988.

3.3. Quality assessment

The 13 included studies were evaluated using the Risk of Bias tool (Fig. 2). Although 2 sets of studies were identified as being the same trials ([27,29] and [30,32]), the risk of bias in these studies was assessed independently because the included outcomes did not coincide. Detailed information on the risk of bias assessment is presented Table 2.

3.4. Primary outcomes

3.4.1. Awakening time. The 4 studies that examined awakening time included a total of 181 patients, with 86 in the volatile sedation arm and 95 in the IV sedation arm.[26,27,31,38] Our analysis using the random effects model showed that the awakening time was significantly shorter for volatile sedation than for IV sedation (MD, −80.1 minutes; 95% CIs, −134.5 to −25.6; $P=.004$; $I^2=95\%$; Fig. 3). Subgroup analyses were performed to explore possible sources of heterogeneity. In subgroup analyses, the pooled effect sizes were smaller in the short-term (≤24 hours) sedation group[29,38] (MD, −41.7 minutes, 95% CIs, −51.2 to −32.1; $P<.001$; $I^2=0\%$) than the long-term (>24 hours) sedation group[26,31] (MD, −133.1 minutes, 95% CIs, −170.7 to −95.5; $P<.001$; $I^2=54\%$) (Figure S1, Supplemental Content, http://links.lww.com/MD/B988). The pooled effect sizes between subgroups were significantly different ($P<.001$) using meta-regression.

Table 1

Characteristics of the included studies.

Study	Subjects	Intraoperative maintenance of anesthesia	Volatile group (n)	IV group (n)	Volatile agent dose	IV sedative dose	Mean sedation duration	Target sedation level	Included outcomes
Sackey et al[26]	18–80 yo mechanically ventilated patients expected to need >12 h sedation	No remark; medical patients were included	20	20	Isoflurane ET 0.5%	Midazolam 0.02–0.05 mg/kg/h	Maximum: 96 h Volatile: 52 h IV: 32 h	BBSS −1 to 1	Awakening time, extubation time
Hanafy [38]	16–80 yo, male patients undergoing elective on-pump CABG	Midazolam + fentanyl + sevoflurane	12	12	Isoflurane ET 0.5%	Midazolam 0.02–0.03 mg/kg/h	Maximum: 24 h	RSS 3–4	Awakening time, extubation time, ICU LOS, hospital LOS
Rohm et al[27]	18–80 yo, 50–120 kg, ASA 1–3 patients undergoing elective CABG	Sevoflurane + sufentanil; During CPB: midazolam	35	35	Sevoflurane ET 0.5–1%	Propofol 2–4 mg/kg/h	Volatile: 8.1 h IV: 8.4 h	RASS −4 to −3	Awakening time, extubation time
Sackey et al[28]	18–80 yo, mechanically ventilated patients expected to need >12 h sedation	No remark; medical patients were included	10	7	Isoflurane ET 0.5%	Midazolam 0.02–0.05 mg/kg/h	Maximum: 96 h Volatile: 44.2 h IV: 61.3 h	BBSS −1 to + 1	ICU LOS, delirium
Rohm et al[29]	18–80 yo, 50–120 kg, ASA 1–3 patients undergoing major abdominal, vascular, or thoracic surgery	Sevoflurane + fentanyl	64	61	Sevoflurane ET 0.5–1%	Propofol started at 2 mg/kg/h	Volatile: 9.2 h IV: 9.3 h	RASS −4 to −3	ICU LOS, hospital LOS, serum creatinine, delirium, PONV
Hellstrom et al[30]	Patients undergoing elective or subacute on-pump CABG	Sevoflurane + fentanyl; During CPB: propofol	50	50	Sevoflurane ET 0.5–1%	Propofol started at 2 mg/kg/h	Volatile: 2.93 h IV: 3.68 h	MAAS 2–3	Serum troponin, serum NT-proBNP, serum creatinine
Mesnil et al[31]	18–80 yo, 50–120 kg patients expected to need ≥24 h sedation	No remark; medical patients were included	19	14; 14	Sevoflurane ET 0.5%	Propofol 2 mg/kg/h; Midazolam 0.1 mg/kg/h	Volatile: 50 h Propofol: 57 h Midazolam: 50 h	RSS 3–4	Awakening time, extubation time, ICU LOS, delirium, serum creatinine
Hellstrom et al[32]	Patients undergoing elective or subacute on-pump CABG	Sevoflurane + fentanyl; During CPB: propofol	49	50	Sevoflurane ET 0.5–1%	Propofol 2 mg/kg/h	Volatile: 2.75 h IV: 3.08 h	MAAS 2–3	Delirium, PONV
Soro et al[33]	≥18 yo patients undergoing elective CABG, expected to need ≥4 h sedation	Volatile group: sevoflurane; IV group: Propofol; During CPB: midazolam + remifentanil	36	37	Sevoflurane ET 0.5–1%	Propofol 1–4 mg/kg/h	Minimum: 4 h	RASS −3 to −2	ICU LOS, hospital LOS, serum troponin, serum NT-proBNP
Steurer et al[34]	18–90 yo patients undergoing elective on-pump cardiac surgery, expected to need ≥4 h sedation	Propofol + remifentanil	46	56	Sevoflurane Age-adjusted 0.5 MAC	Propofol started at 2 mg/kg/h	Minimum: 4 h	Not mentioned	ICU LOS, hospital LOS, serum troponin, serum creatinine, PONV
Guerrero Orriach et al[35]	Off-pump CABG and EuroSCORE ≤7	Sevoflurane + remifentanil; Propofol + remifentanil	20	20; 20	Sevoflurane ET 0.5–0.7%	Propofol TCI 1–1.5 μg/mL	Extubation time: 4.25–6.3 h	BIS 60 to 70	Serum troponin, serum NT pro-BNP

(*continued*)

Table 1
(continued).

Study	Subjects	Intraoperative maintenance of anesthesia	Volatile group (n)	IV group (n)	Volatile agent dose	IV sedative dose	Mean sedation duration	Target sedation level	Included outcomes
Marcos-Vidal et al[36]	>18 yo patients undergoing on-pump coronary or mixed (coronary + valve) surgery	Sevoflurane	67	62	Sevoflurane ET 0.5–1%	Propofol 1–4 mg/kg/h	Volatile: 44.09 h IV: 46.76 h	BIS 60 to 80	ICU LOS, serum troponin, serum creatinine
Jerath et al[37]	Patients undergoing elective on- or off-pump CABG	Volatile group: sevoflurane or isoflurane; IV group: TIVA	67	74	Sevoflurane Age-adjusted 0.1–0.3 MAC	Propofol 0.6–1.5 mg/kg/h	Maximum: 14 h	RASS −1 to +1	ICU LOS, hospital LOS, PONV

ASA = American Society of Anesthesiologists, BBSS = Bloomsbury Sedation Scale, BIS = bispectral index, CABG = coronary artery bypass graft, CPB = cardiopulmonary bypass, ET = end-tidal fraction, EuroSCORE = European System for Cardiac Operative Risk Evaluation, ICU = intensive care unit, IV = intravenous, LOS = length of stay, MAAS = motor activity assessment scale, MAC = minimal alveolar concentration, PONV = postoperative nausea and vomiting, RASS = Richmond Agitation Sedation Scale, RSS = Ramsay Sedation Scale, TCI = target concentration infusion, TIVA = total intravenous anesthesia.

3.4.2. Extubation time. Although 6 studies presented the extubation time as an outcome,[26,27,31,32,37,38] 2 studies were excluded due to ambiguous start time measurements[37] and different data representation.[32] There were 181 patients (86 in the volatile sedation arm and 95 in the IV sedation arm) in the 4 included studies.[26,27,31,38] In the pooled analysis using the random effects model, volatile sedation significantly shortened the extubation time compared with IV sedation (MD, −196.0 minutes; 95% CIs, −305.2 to −86.8; $P < .001$; $I^2 = 90\%$; Fig. 4). In subgroup analyses, the short-term (≤24 hours) sedation group[29,38] showed a smaller effect on extubation time (MD, −108.5 minutes, 95% CIs, −125.2 to −91.9; $P < .001$; $I^2 = 52\%$) than the long-term (>24 h) sedation group[26,31] (MD, −284.4 minutes, 95% CIs, −388.9 to −179.9; $P < .001$; $I^2 = 54\%$) (Figure S2, Supplemental Content, http://links.lww.com/MD/B988). The pooled effect sizes between subgroups were also significantly different ($P = .006$) using meta-regression. Additional subgroup analyses according to whether or not the studies received financial support from a medical instrument or pharmaceutical company ($P = .911$) or which IV agent was used (propofol vs midazolam) ($P = .542$) did not show any significant differences using meta-regression, and heterogeneity remained high at >80%.

3.4.3. LOS in the ICU and hospital. A total of 658 patients (321 in the volatile sedation arm and 337 in the IV sedation arm) from 8 studies[28,29,31,33,34,36–38] were included in the analysis of LOS in the ICU. The pooled analysis using the fixed effects model did not show a significant difference between volatile and IV sedation in terms of LOS in the ICU (MD, −0.9 hours; 95% CIs, −3.6 to 1.8; $P = .513$; $I^2 = 0\%$; Fig. 5). For the analysis of LOS in the hospital, 465 patients (225 in the volatile sedation arm and 240 in the IV sedation arm) from 5 studies were identified.[29,33,34,37,38] The pooled effect sizes were comparable between both arms using the fixed effects model (MD, −0.5 hours; 95% CIs, −1.0 to 0.0; $P = .059$; $I^2 = 0\%$; Fig. 6).

3.5. Secondary outcomes

3.5.1. Myocardial and renal effects. Five studies with a total 464 patients used serum troponin T[30,34,36] or troponin I[33,35] levels as a marker of cardiac injury. Serum troponin I levels were converted to troponin T levels according to a predefined formula (Troponin T = Troponin I * 0.65/2). All of the patients in the eligible studies underwent cardiac surgery and were sedated with low-dose sevoflurane (end-tidal concentration 0.5–1%) or propofol (1–4 mg/kg/h) after admission to the ICU. Because each trial measured the serum troponin at different time points after ICU admission, we analyzed the data by dividing them into time intervals as follows: 0 to 6, 6 to 12, 12 to 24, and 24 to 48 hours after ICU admission. The serum troponin levels were significantly lower in the volatile sedation arm than the IV sedation arm at the 6 to 12, 12 to 24, and 24 to 48-hour intervals, but not at the 0 to 6-hour time interval (Fig. 7). The effect size was largest in the 12 to 24-hour time interval (MD, −0.27 μg/L; 95% CIs, −0.44 to −0.09; $P = .003$; $I^2 = 73\%$). Serum NT-proBNP on the first postoperative day was recorded in 3 studies[30,33,35] and was significantly lower in the volatile sedation arm than the IV sedation arm (MD, −711.6 pg/mL; 95% CIs, −904.9 to −518.3; $P < .001$; $I^2 = 90\%$, Fig. 8).

Renal effects of sedatives were assessed by measuring serum creatinine levels on the first postoperative day. The 5 included studies[29–31,34,36] consisted of 489 patients with 246 in the

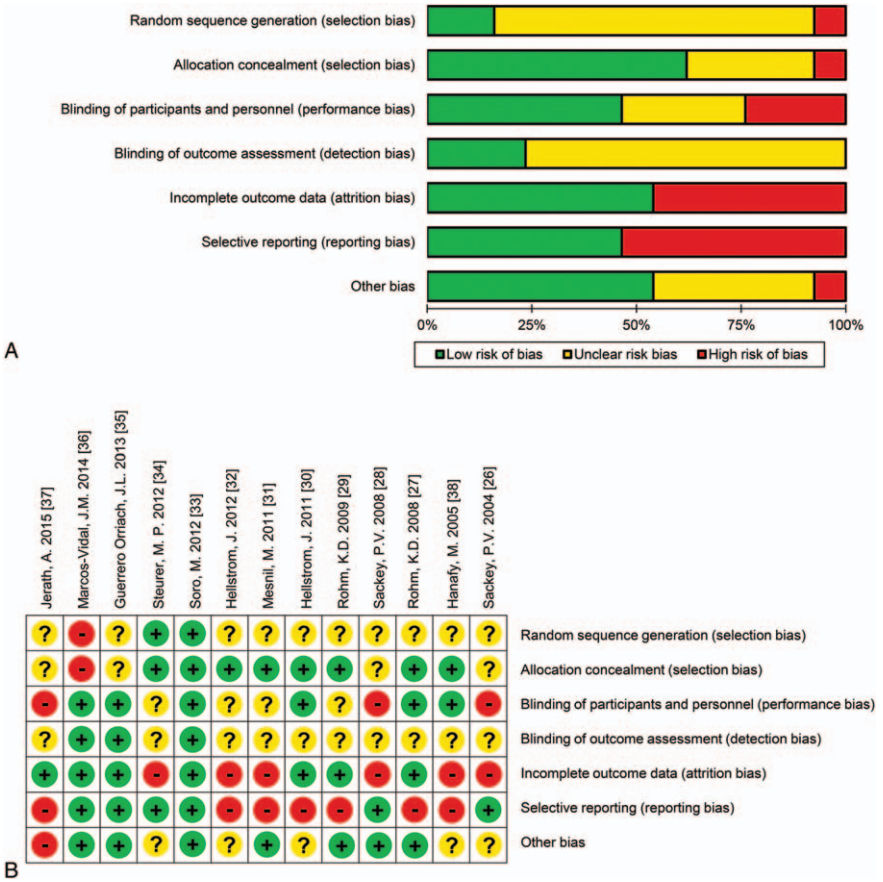

Figure 2. Risk of bias graph (A) and summary (B) of the included studies. + indicates a low risk of bias, − indicates a high risk of bias, and? indicates an unclear risk of bias.

sevoflurane arm and 243 in the propofol arm. Although no study showed a significant difference, the pooled analysis showed a lower serum creatinine level in the sevoflurane arm compared with the propofol arm (MD, −0.05 mg/dL; 95% CIs, −0.10 to −0.002; $P=.043$; $I^2=44\%$, Fig. 9).

3.5.2. Delirium and PONV. Four studies evaluated the incidence of delirium by clinician observations[29,31] or patient questionnaires.[28,32] A significantly lower incidence of delirium was identified in the volatile sedation arm (OR, 0.47; 95% CIs, 0.23–0.94; $P=.033$, $I^2=0\%$) compared with the IV sedation arm (Fig. 10). The incidence of PONV from 4 studies,[29,32,34,37] which compared sevoflurane sedation with propofol sedation in postsurgical patients, was comparable between the volatile and IV sedation arms (OR, 1.58; 95% CIs, 0.97–2.58; $P=.068$; $I^2=0\%$, Fig. 11).

3.6. Publication bias

Although the number of included studies for each outcome was small, we evaluated publication bias using the Egger regression test and a funnel plot. Adjustment using the trim and fill method was performed for the extubation time and incidence of delirium, which showed a positive publication bias. The extubation time

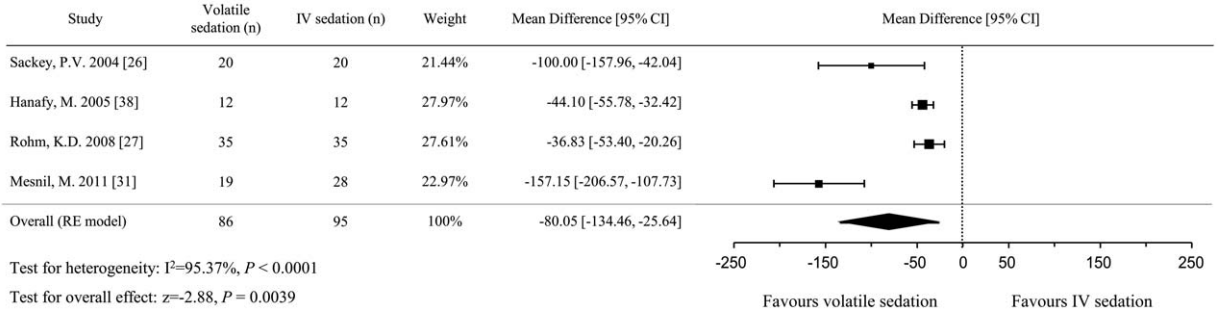

Figure 3. Forest plot of the mean differences and 95% confidence intervals (CIs) for awakening time (in min) in the volatile and IV sedation groups. Data were analyzed using a random effects model.

Table 2

Assessment of risk of bias.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Sackey et al[26]	? No remark	? No remark	H Only the patients were blinded. No definite criteria of ventilator weaning.	? No remark	H Study duration limited to 96 h after admission and only 50% of patients were extubated.	L All pre-defined outcomes were reported.	? Financial support by manufacturer
Hanafy [38]	? No remark	L Sealed envelopes	L Sedation stop and ventilator weaning were based on objective criteria, although only the patients were blinded.	? No remark	H Because the study duration was limited to 24 h after admission, this study was likely to have incomplete data.	H Pre-defined "serum creatinine" was not reported.	? The author did not reveal conflicts of interest
Rohm et al[27]	? No remark	L Sealed envelopes	L Sedation stop and ventilator weaning were based on objective criteria, although only the patients were blinded.	? No remark	L No missing outcome data.	H Only patients who underwent CABG were enrolled, unlike the protocol.	L None
Sackey et al[28]	? No remark	? No remark	H Only the patients were blinded. No definite extubation criteria.	? No remark	H Delirium was measured by a questionnaire at 6 mo after the ICU stay. The response rate for the questionnaire was only 59%.	L All pre-defined outcomes were reported.	L None
Rohm et al[29]	? No remark	L Sealed envelopes	? Sedation stop and ventilator weaning were based on objective criteria, although only the patients were blinded. However, because the methods of PONV and delirium assessments were not presented, a lack of blindness may have affected the outcome.	? No remark	L No missing outcome data.	H Extubation time was only presented in the methods section.	L None
Hellstrom et al[30]	? No remark	L Sealed envelopes	L Sedation stop and ventilator weaning were based on objective criteria, and cardiac and renal profiles were based on laboratory results, although only the patients were blinded.	? No remark	L All patients were analysed as an intention to treat analysis.	H Pre-defined 'ambient sevoflurane level' was not reported.	? Financial support by manufacturer
Mesnil et al[31]	? No remark	L Sealed envelopes	? Sedation stop and ventilator weaning were based on objective criteria, although only the patients were blinded. However, because the method of delirium assessment was not presented, a lack of blindness may have affected the outcome.	? No remark	H 12/40 patients were excluded in the IV group, while 1/20 were excluded in the volatile group	H Pre-defined "nausea" was not reported.	L None
Hellstrom et al[32]	? No remark	L Sealed letters	? Sedation stop and ventilator weaning were based on objective criteria, although only the patients were blinded.	? No remark	H Less than 50% response rate for the delirium questionnaire.	H Pre-defined "ambient sevoflurane level" was not reported.	? Financial support by manufacturer

(*continued*)

Table 2

(continued).

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
			Delirium was measured with a systematic questionnaire. However, because the method of PONV assessment was not presented, a lack of blindness may have affected the outcome.				
Soro et al[33]	L Random table generator	L Sealed, opaque envelopes	L Double-blinded. Sedation stop and ventilator weaning were based on objective criteria.	L Outcome assessors were blinded	L No missing outcome data.	L All pre-defined outcomes were reported.	L None
Steurer et al[34]	L Random table generator	L Sealed envelopes	? Sedation stop and ventilator weaning were based on objective criteria, although only the patients were blinded. However, because the methods of PONV and delirium assessments were not presented, a lack of blindness may have affected the outcome.	? No remark	H Patients were analysed as a per protocol analysis, not as an intention to treat analysis.	L All pre-defined outcomes were reported.	? Financial support by manufacturer
Guerrero Orriach et al[35]	? No remark	? No remark	L Sedation stop and ventilator weaning were based on objective criteria, and objective outcomes that were based on laboratory results were collected, although only the patients were blinded.	L Outcome assessors were blinded	L No missing outcome data.	L All pre-defined outcomes were reported.	L None
Marcos-Vidal et al[36]	H Alternative allocation	H Alternative allocation	L Sedation stop and ventilator weaning were based on objective criteria, and objective outcome data that were based on laboratory results were collected, although only the patients were blinded.	L Outcome assessors were blinded	L No missing outcome data.	L All pre-defined outcomes were reported.	L None
Jerath et al[37]	? No remark	? No remark	H Only the patients were blinded. Criteria for stopping sedation were not presented. The method of PONV assessment was not presented.	? No remark	L No missing outcome data.	H Pre-defined TnT was not reported.	H The level of sedation was different than in other studies

?=unclear risk, CABG=coronary artery bypass graft, H=high risk, ICU=intensive care unit, IV=intravenous, L=low risk, PONV=postoperative nausea and vomiting, TnT=troponin T.

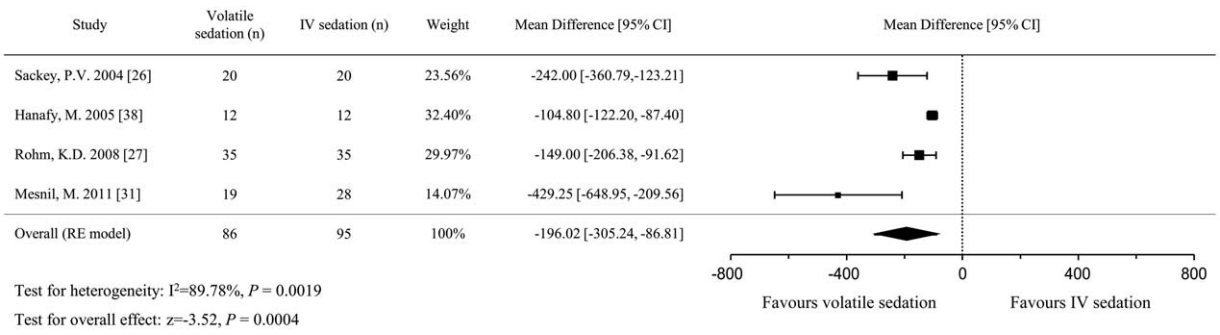

Figure 4. Forest plot of the mean differences and 95% confidence intervals (CIs) for extubation time (in min) in the volatile and IV sedation groups. Data were analyzed using a random effects model.

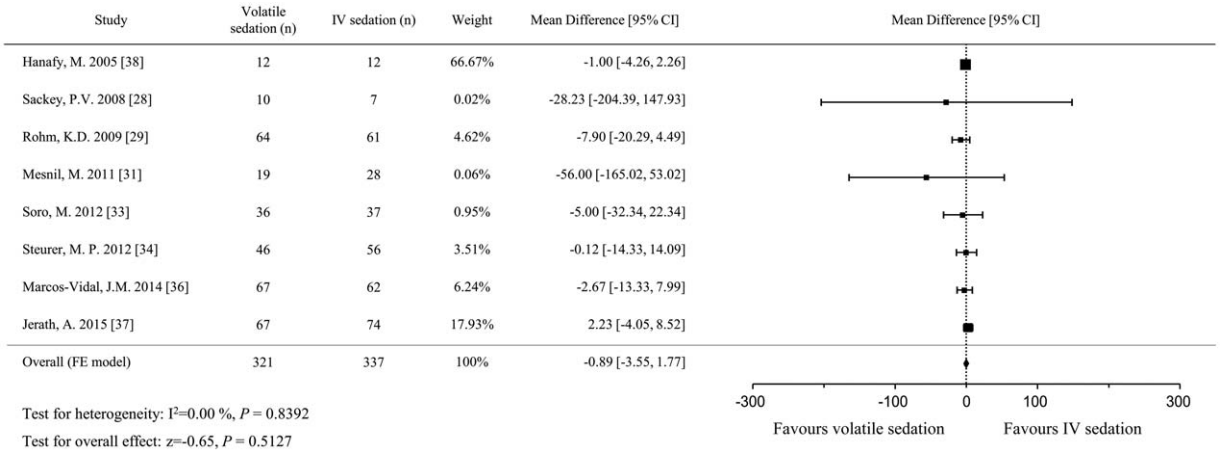

Figure 5. Forest plot of the mean differences and 95% confidence intervals (CIs) for length of stay (in h) in the intensive care unit in the volatile and IV sedation groups. Data were analyzed using a fixed effects model.

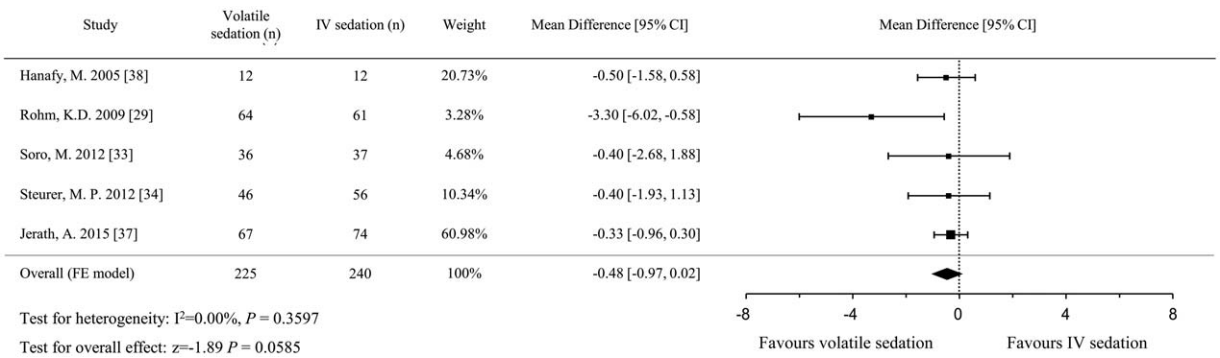

Figure 6. Forest plot of the mean differences and 95% confidence intervals (CIs) for length of stay (in d) in the hospital in the volatile and IV sedation groups. Data were analyzed using a fixed effects model.

after including 2 imputed studies to improve asymmetry still showed a significant reduction in the volatile sedation arm compared with the IV sedation arm (MD, −108.5 minutes; 95% CIs, −124.8 to −92.3; $P < .001$). The incidence of delirium after including 1 imputed study did not show any difference between the 2 arms (OR, 0.54; 95% CIs, 0.27–1.05; $P = .070$) after adjustment.

4. Discussion

Our systematic review and meta-analysis of 13 RCTs revealed that sedation in the ICU with volatile anesthetic agents compared with conventional IV sedatives, such as propofol or midazolam, shortened the awakening time by 80 minutes and the extubation

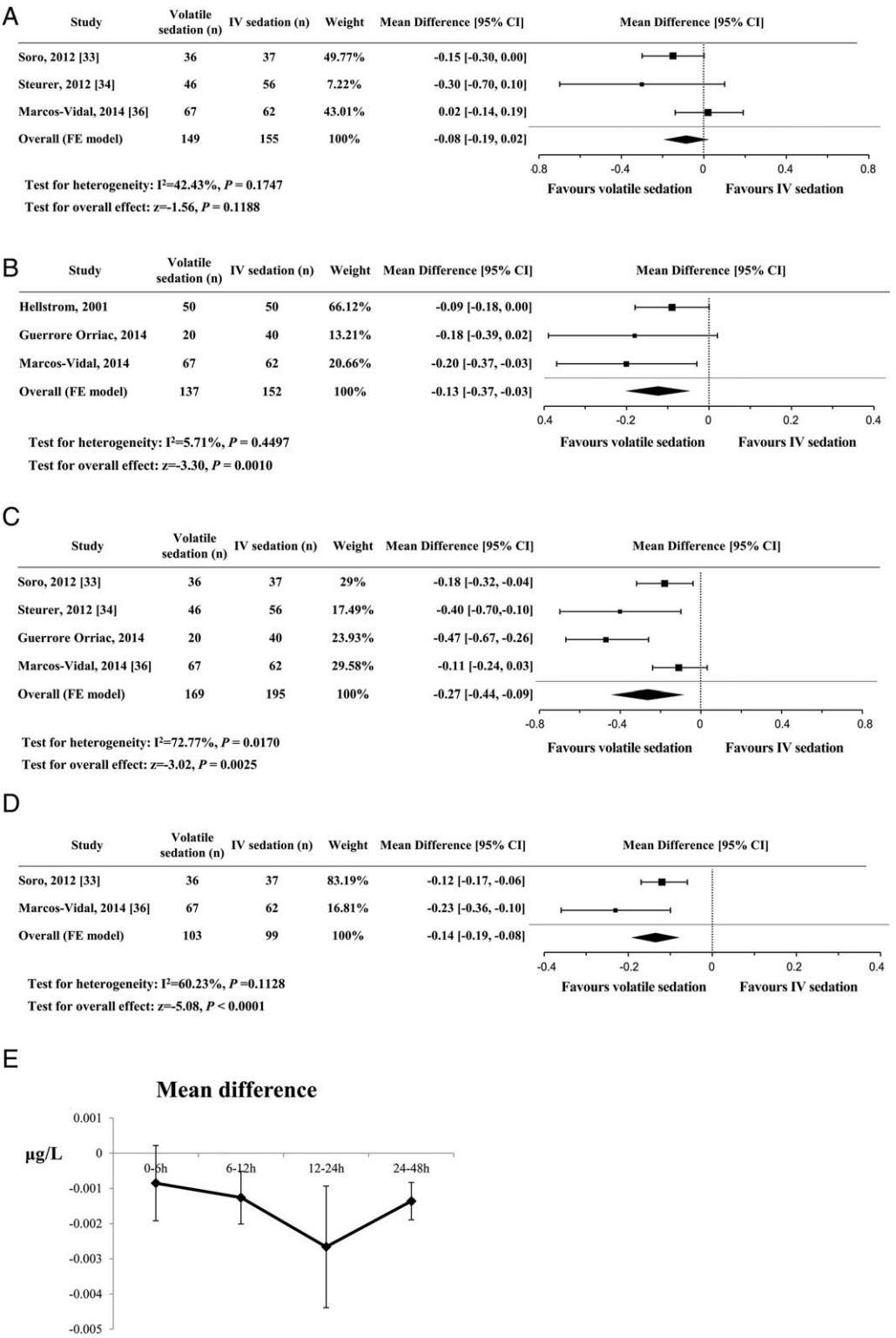

Figure 7. Forest plot of the mean differences and 95% confidence intervals (CIs) for serum troponin levels (μg/L) at different time points after ICU admission. The data were analyzed by dividing them into time intervals as follows: (A) 0–6 h, (B) 6–12 h, (C) 12–24 h, and (D) 24–48 h after ICU admission. (E) The line represents the difference in means and the vertical bar represents 95% confidence intervals for serum troponin levels (vertical axis) at different time points after ICU admission (horizontal axis).

time by 196 minutes. Despite these reductions in awakening and extubation times with volatile sedation, no reductions in the LOS in the ICU or hospital were noted. Compared with IV sedation, volatile sedation showed lower serum troponin and NT-proBNP levels, beginning around 6 hours after ICU admission, although cardiac function was not directly evaluated.

After the introduction of volatile sedation, there have been several recent meta-analyses in ICU patients[45,46] and

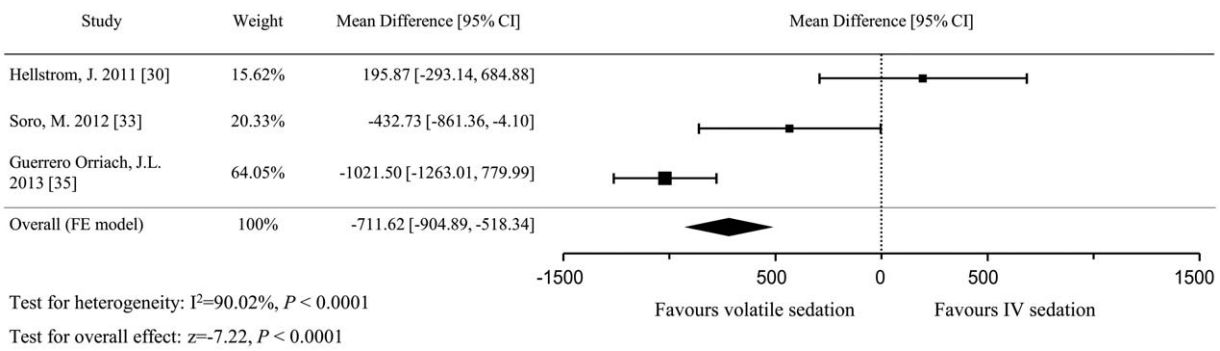

Figure 8. Forest plot of the mean differences and 95% confidence intervals (CIs) for serum N-terminal prohormone of brain natriuretic peptide levels (pg/mL) on the first postoperative day. Data were analyzed using a fixed effects model.

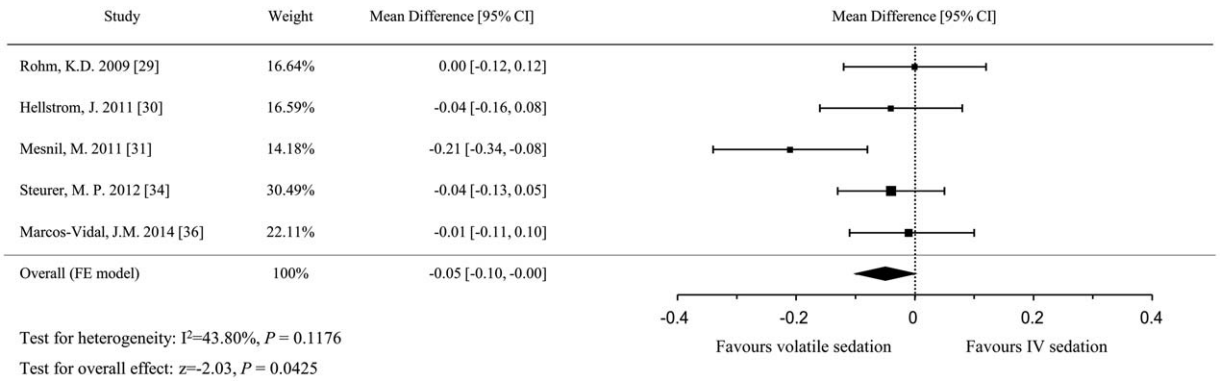

Figure 9. Forest plot of the mean differences and 95% confidence intervals (CIs) for serum creatinine levels (mg/dL) on the first postoperative day. Data were analyzed using a fixed effects model.

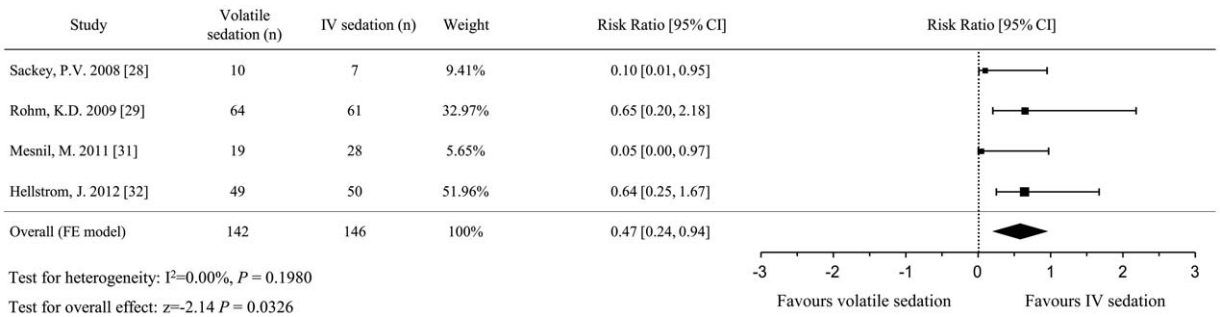

Figure 10. Forest plot of the risk ratio and 95% confidence intervals (CIs) for the incidence of delirium in the volatile and IV sedation groups. Data were analyzed using a fixed effects model.

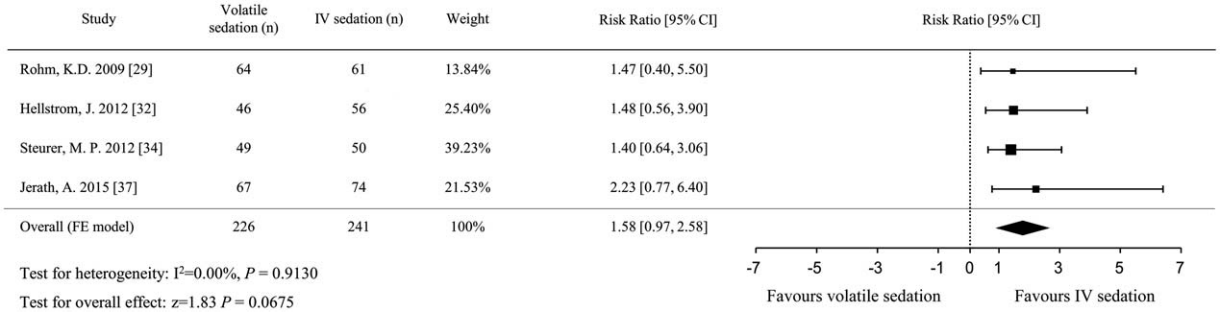

Figure 11. Forest plot of the risk ratio and 95% confidence intervals (CIs) for the incidence of postoperative nausea and vomiting in the volatile and IV sedation groups. Data were analyzed using a fixed effects model.

postcardiac surgical patients.[47] However, these meta-analyses included volatile sedation using a conventional vaporizer, which had significantly slow anesthetic wash-out times compared with the new anesthetic reflectors using the same fresh gas flow rates; this is because the conventional vaporizer could not be removed from the breathing circuit.[48,49] In addition, the time difference of more than 5 years between studies using conventional vaporizers versus the new anesthetic reflectors might have been influenced by changes in the sedation guidelines. Therefore, we selected only studies that used the new anesthetic reflectors. Because no RCT used the Mirus device, our meta-analysis included only RCTs using the AnaConDa device.

The results of our pooled analysis, as well as each included study, showed significantly shorter awakening and extubation times in the volatile sedation arm than in the IV sedation arm, regardless of whether propofol or midazolam was used as the conventional IV sedative. The rapid elimination of volatile anesthetics via pulmonary exhalation, lack of accumulation, and increased control of the drug concentration by monitoring end-tidal fractions are likely explanations for these results.[10,11] For the volatile agents, analgesic effects induced by N-methyl-D-aspartate antagonist activity[31] may have contributed to opioid-sparing effects and shorter awakening and extubation times. However, there was a lack of criteria for controlling pain. In addition, various types of analgesics such as acetaminophen, morphine, remifentanil, and sufentanil were used in this study. Therefore, further evaluations are needed to elucidate opioid-sparing effects of volatile agents.

Meanwhile, our pooled effect size in extubation time (196 minutes) was larger than was seen in previous meta-analyses, which showed pooled effect sizes of 52.7 minutes[45] and 76 minutes.[47] This result may be explained by the fact that we only included studies using the AnaConDa device and excluded 2 studies of extubation time from our analysis due to ambiguous time measurements[37] and different data representations.[30] Despite the more consistent selection of studies, however, substantial heterogeneity ($I^2 = 90\%$) remained. To identify sources of heterogeneity, we performed additional subgroup analyses in awakening and extubation times according to the sedation duration [short-term ($\leq$24 hours) vs long-term (>24 h)], patient type (cardiac surgical patients vs noncardiac surgical or medical patients), financial support (supported vs unsupported studies from a medical instrument or pharmaceutical company), and which IV agent was used (midazolam vs propofol). The subgroup analyses according to sedation duration and patient type showed reduced heterogeneity ($I^2 = 50$–52%), and the MD was greater in the long-term sedation (> 24 h) and noncardiac surgery groups than the short-term sedation ($\leq$24 hours) and cardiac surgery groups. Other subgroup analyses according to financial support and IV agents were comparable between the 2 sedation groups. However, all subgroup analyses should be cautiously interpreted due to the small number of included studies.

The correlation between the duration of mechanical ventilation (MV), LOS in the ICU, and complications such as increased ventilator dependency, ventilator-associated pneumonia, and ventilator-induced lung injury has been previously established.[50,51] A meta-analysis comparing ICU sedatives by Fraser et al[52] showed that non-benzodiazepine based sedation shortened the MV duration and LOS in the ICU compared with benzodiazepine-based sedation. Although volatile sedation shortened the MV duration in the present study, our meta-analysis did not indicate that volatile sedation shortened the LOS in the ICU. Before interpreting the results for LOS, we examined the length of sedation and MV duration. Here, the mean MV duration in all of the studies was within 3 days; this was different from the mean MV duration in the studies examined by Fraser et al,[52] which ranged from 3.7 to 8.4 days. Relatively short sedation periods in these studies that we included might be insufficient to reveal differences in LOS in the ICU. Therefore, additional studies with longer sedation periods and controlled conditions should be performed to examine the link between type of sedation and LOS in the ICU.

The end-organ protective effects of halogenated volatile agents have also been examined previously by numerous studies.[15–17,53–57] Among these, the most extensive studies focused on cardiac effects. Such studies confirmed that volatile agents reduce myocardial damage when administered immediately before an ischemic event (pre-conditioning) or during the early reperfusion period after an ischemic event (post-conditioning).[54,58] Several receptors and chemical mediators have been shown to play roles in the reduction of ischemia/reperfusion injury in hibernating and stunned tissue.[15] Because the optimal length of volatile agent administration for maximizing the post-conditioning effect is unknown, several studies investigated the cardioprotective effects using volatile agents as sedatives in the ICU.[30,33–36] Our pooled effect sizes from 5 cardiac surgical populations were 0.27 μg/L in troponin T (at the largest time interval; 12–24 hours after ICU admission) and 711 pg/mL in NT-proBNP. Considering the upper reference limits (0.014 μg/L in troponin T and 300 pg/mL in NT-proBNP) for diagnosing myocardial infarction and heart failure,[59,60] the pooled results suggest that even a late (postoperative) and subanesthetic dose (one-third of the dose used for general anesthesia) may have cardioprotective effects (Fig. 6). However, there were differences in intraoperative management and postoperative sedation durations. Unfortunately, we were unable to perform an analysis to calibrate the sedation duration, as not every study reported the exact sedation duration. Thus, further studies that can adjust for sedation duration are needed.

Several previous studies have also reported that volatile agents are renoprotective.[53,56,61] However, the risk of nephrotoxicity from inorganic fluoride, which forms when volatile agents such as sevoflurane are metabolized, is still a concern. Although our analysis identified differences in the serum creatinine levels on the first postoperative day, the pooled effect size of 0.05 mg/dL was too small to assess the effect on renal function if significant renal dysfunction was defined as an increase of 0.3 mg/dL over baseline.[62,63] Similarly, whether volatile agents have neuroprotective effects[55,64] or are neurotoxic and induce cognitive dysfunction[65,66] remains controversial. There was a difference in the incidence of delirium between the volatile and IV sedation arms; however, after adjusting for publication bias, both arms were comparable. Furthermore, delirium, which was used as a marker of cognitive dysfunction, was not measured using currently recommended tools (i.e., the Confusion Assessment Method for ICU or the Intensive Care Delirium Screening Checklist). Therefore, the data regarding the effects of sedative agents on the kidney and brain should be interpreted with caution.

One of the major concerns of using volatile agents is PONV.[18,67,68] When administering general anesthesia, volatile agents are known to be a potent risk factor of PONV.[19] In our analysis, the pooled OR of PONV did not show a significant difference between the volatile and IV sedation arms. However, the interpretation was limited due to variance among studies in terms of adjuvant opioid and anti-emetic usage.

The present study has several limitations. First, the number of included studies and sample sizes were small and the study durations were short. The largest study included only 141 subjects, and the mean sedation duration in all of the studies was less than 3 days. Thus, several outcomes may have been underpowered. Second, none of the included studies, except for one,[33] were double-blind; it is likely that this lack of blindness affected the observed findings. Third, these studies had multiple heterogeneities, including the group of patients examined (medical or surgical, cardiac or noncardiac surgical patients), intraoperative anesthesia (volatile anesthesia or total IV anesthesia), patient management (different methods of assessing sedation), and outcome measurement (different time points for measuring outcomes). These heterogeneities might have influenced outcomes by introducing many potential confounders. Fourth, all studies included were conducted in Europe except 1 Egyptian study.[38] Therefore, it is uncertain whether intercontinental differences in sedation practices might have affected outcomes. Fifth, we used laboratory values to evaluate end-organ protective effects and did not to directly measure organ function. Finally, we could not analyze other important factors such as cost-effectiveness, hemodynamic stability, or the effects of increased respiratory dead space and work of breathing.

Despite several limiting factors, our study provides the following new knowledge. First, volatile sedation using the only new anesthetic reflector had more reduction in awakening and extubation times than previous meta-analyses,[45–47] including studies using conventional ventilator and new anesthetic reflector together. In addition, the effect size was greater in long-term sedation (>24 hours) than short-term sedation (≤24 hours). Second, subanesthetic dose (one-third of the dose used for general anesthesia) of volatile sedation administered after cardiac surgery might have cardioprotective effects. Third, major concerns about volatile anesthetics (nephrotoxicity, nausea, and vomiting) were not proven at the sedation dose used in the present study.

A strength of our meta-analysis was that we only included RCTs; before-and-after and retrospective studies were excluded to minimize biases such as drug hangover effects. The fact that we only included studies where the AnaConDa device was used also reduced bias. To the best of our knowledge, this is the first meta-analysis to compare volatile sedation via the AnaConDa device with IV sedation in the ICU. Our results demonstrate that volatile sedation supports the current sedation practice emphasizing daily awakening and early extubation.[2] Especially, ICU patients requiring long-term sedation may benefit from volatile sedation due to rapid elimination of volatile anesthetics. In addition, postsurgical sedation after cardiac surgery may benefit from volatile sedation in term of myocardial protection.

In conclusion, the present meta-analysis found that volatile sedatives administered through the AnaConDa device in the ICU reduced awakening and extubation times compared with IV sedatives. Moreover, subanesthetic doses of volatile sedation administered after cardiac surgery might have cardioprotective effects. Given the technological advancements in volatile vaporizers, it is possible that volatile sedation will become the new standard of care in ICU sedation. However, because the included studies were small with high heterogeneity, additional large, high-quality prospective clinical trials are needed to validate these findings.

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