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Safety and effectiveness of inhaled sedation in critically ill patients: a systematic review and meta-analysis

Fang Feng[1*†], Huaxiong Kang[1†], Zhaohui Yang[1], Li Ma[1] and Yu Chen[1]

Abstract

Background Sedation is a landmark treatment in the intensive care unit; however, the disadvantages of intravenous sedative drugs are increasingly prominent. Volatile sedation is becoming increasingly popular in ICUs due to fewer technical issues with the development of anaesthesia reflectors.

Objective To explore the safety and effectiveness of inhaled sedation in critically ill patients.

Search methods We searched the PubMed, Embase, and Web of Science databases for all randomized trials comparing awakening and extubation times, ICU length of stay, and side effects of different inhaled sedative drugs using an anaesthetic-conserving device (ACD) with intravenous sedation.

Selection criteria The inclusion criteria were formulated in accordance with the PICOS: P, use of sedatives after admission to the ICU, aged > 18 years; I, intravenous sedatives; C, use of volatile sedatives (heptafluoride, sevoflurane, isoflurane, or desflurane) by AnaConDa or Mirus reflector; O, at least one primary outcome (awakening time, extubation time, ICU length of stay) or secondary outcome (postoperative nausea and vomiting, PONV) or incidence of delirium was reported; and S, RCT. The extubation time was defined as time from ICU admission to extubation.

Data collection and analysis Two researchers independently conducted literature screening, data extraction, and literature quality evaluation and reached a consensus after cross-checking.

Main results Fifteen trials with a total of 1185 patients were included, including 568 in the inhaled sedation group and 617 in the intravenous sedation group. Compared with intravenous sedation, inhaled sedation administered through an ACD shortened the awakening time and extubation time. There were no differences in the occurrence of postoperative nausea and vomiting (PONV) between the two groups.

Conclusion Inhaled sedation has advantages over intravenous sedation in terms of awakening time, extubation time, and ICU LOS (non-cardiac ICU); however, there is no significant difference in the incidence of PONV. Inhaled sedation may be safe and effective for critically ill patients.

Keywords Inhaled sedation, Sevoflurane, Intravenous sedation, Critically ill patients, Delirium

Background

Sedation is a landmark treatment in the intensive care unit (ICU), and approximately 85% of patients admitted to the ICU require sedation [1]. Sedative drugs can be used to help patients better tolerate endotracheal intubation, mechanical ventilation, and invasive operations, effectively control agitation, and prevent adverse

†Fang Feng and Huaxiong Kang contributed equally to this work.

*Correspondence:
Fang Feng
ldyy_fengf@lzu.edu.cn
[1] Intensive Care Unit, The Second Hospital & Clinical Medical School, Lanzhou University, LanZhou, Gansu 730000, China

events such as accidental extubation and falling out of bed [2]. Propofol and midazolam are two commonly used intravenous sedative drugs in the ICU [3, 4]. Most of these drugs are metabolized and eliminated by the liver and kidneys, so patients need to have no obvious impairment of liver or kidney function. At the same time, many such substances produce active metabolites. Critically ill patients often present with liver and kidney dysfunction, which delays the systemic clearance of drugs. This often leads to excessive sedation associated with high doses, which has been reported to occur in up to 60% of ICU patients [5]. Slow clearance of these drugs can lead to overdose, delay of physiological arousal, loss of airway reflexes, and delay of extubation. In addition, these intravenous sedative drugs often lead to the development of delirium [6].

Volatile sedation used in general anaesthesia is also used as sedatives because of their good pharmacokinetics, such as rapid elimination through pulmonary exhalation, almost complete bypass of the hepatic or renal system, and no accumulation effect [7]. Furthermore, perioperative organ-protective effects of volatile anaesthetic drugs, particularly on the heart, have been demonstrated through ischaemic pre- and postadaptation mechanisms [8]. Meantime, inhaled sedatives reduce lung inflammation that can lead to improved oxygenation in patients with lung injury [9]. A meta-analysis which included 68 randomized controlled trials with 7104 patients showed the following [10]: In cardiac surgery, as opposed to noncardiac surgery, general anaesthesia with volatile anaesthetics has been found to offer significant advantages in outcomes. These benefits include reduced mortality rates and a lower occurrence of pulmonary and other complications. This study included adult patients undergoing general anaesthesia for surgery, not the critically ill patients. And a meta-analysis conducted by Jerath in 2017 showed that in critically ill patients, volatile-based sedation demonstrates a reduction in time to extubation, with no increase in short-term adverse outcomes. However, the authors pointed out marked study heterogeneity was present, and the results show marked positive publication bias [11]. The use of volatile sedation in the ICU has been limited due to these reasons:

1) A lack of familiarity with these agents among intensivists and common complications such as postoperative nausea and vomiting (PONV) and inorganic fluoride-induced nephrotoxicity [12, 13]
2) Most importantly, the use of volatile sedation is limited by technical issues in the ICU, including the waste of volatile drugs from high-flow ICU ventilators and atmospheric contamination from open ventilator circuits [14].
3) Lack of knowledge regarding these agents among providers including physicians and nurses
4) Lack of means to deliver these drugs using conventional ICU ventilators, including lack of vaporizers and scavenging systems
5) Lack of relevant inhaled sedation protocols

The miniature vaporizers and scavenging systems address this shortcoming and enable safe delivery of these agents in the ICU. In addition to potentially improving clinical outcomes, this provides another way to sedate ICU patients that can be used when IV drug supplies in short supply, as was experienced during the recent COVID-19 pandemic [15].

Volatile sedation is becoming increasingly popular in ICUs due to fewer technical issues with the development of anaesthesia reflectors, such as AnaConDa (SEDANA Medical) and Mirus (Pall Medical, Dreieich, Germany), which reduce the waste of volatile agents. In the early days, several small RCTs compared the effects of volatile and conventional intravenous sedation drugs in the ICU [16–18]. However, due to the small sample size of the studies, they failed to receive clinical attention. With the continuous deepening of research and the exploration of sedative drugs in clinical work, inhaled sedation has become increasingly popular in the clinic.

We therefore conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) using these novel anaesthesia reflectors (AnaConDa and Mirus) to assess whether inhaled sedation is associated with improved outcomes compared with intravenous sedation in adult ICU patients. We have registered this study on the PROSPERO website with the registration number: CRD42024532523.

Materials and methods

Search strategy

As this study was secondary research, ethical approval was not needed. Two authors (F. F. and Y. C.) independently searched PubMed (1946–2023), Embase (1947–2023), and the Cochrane Central Register of Controlled Trials (from inception to 2023). The following search terms were used: (sevoflurane OR isoflurane OR desflurane OR & anaesthetic conserving device OR AnaConDa OR Mirus) AND sedation AND (critical care OR intensive care). See Additional file 1.

Literature inclusion and exclusion criteria

The inclusion criteria were formulated in accordance with the PICOS: P: use of sedatives after admission to the ICU, aged > 18 years; I: intravenous sedatives; C: use of volatile sedatives (heptafluoride, sevoflurane, isoflurane, or desflurane) by AnaConDa or Mirus reflector;

O: at least one primary outcome (awakening time, extubation time, ICU length of stay) or secondary outcome (postoperative nausea and vomiting, PONV) or incidence of delirium was reported; and S: RCT. The extubation time was defined as time from ICU admission to extubation.

The exclusion criteria were as follows: [1] duplicate publications reporting too little information or only abstracts, letters, and reviews and (2) invalid data or unknown descriptions.

Data extraction and quality evaluation

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart was used to record the study selection process (Additional file 2). Two researchers independently conducted literature screening, data extraction, and literature quality evaluation and reached a consensus after cross-checking. The full texts of the included studies were read, and the following information was extracted: the first author, the number of patients in the two groups, the basic information of the research subjects, and the research outcome indicators. Our bias risk assessment will be based on the Cochrane Risk of Bias tool—version 1 (RoB 1) as recommended in the Cochrane Handbook of Systematic Reviews of Interventions [19]. We will evaluate the methodology in respect of the following bias domains: Random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and researchers (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. For each item, the response options were "low risk", "high risk", and "unclear risk". The two researchers reached a consensus after discussion.

Data analysis

RevMan 5.3 software was used for the meta-analysis. Data expressed as medians, interquartile ranges, or ranges were converted into means and standard deviations by SPSS software, and continuous data with mean differences (MD) and 95% confidence intervals (95% CIs) were used for effect analysis. For binary data, odds ratios (ORs) and 95% CIs were used for effect analysis. The χ^2 test was used to determine whether there was heterogeneity between studies, and the I^2 value was used to determine the degree of heterogeneity. Since each study comes from a different population and the variability of each study is very large, we changed all the studies in the study to a random effect model. $P<0.05$ was used to indicate that the difference was statistically significant.

Results

Basic characteristics of the included studies

A total of 1989 relevant documents were initially retrieved, and 641 duplicate documents were excluded; 1293 irrelevant documents were eliminated by reading the titles and abstract (767 non-volatile sedation studies, 364 paediatrics, 101 reviews, 29 case reports or letters, and 32 animal studies), and after reading the full texts, 15 RCTs were ultimately included [9, 20–33]. Finally, 1185 patients were included, including 568 in the inhaled sedation group and 617 in the intravenous sedation group. The literature screening process is shown in Fig. 1; the basic characteristics of the included studies are shown in Table 1.

Risk of bias assessment of included studies

The included studies varied widely because the methodological sections of each study did not provide complete information. The included studies were evaluated using the Risk of Bias tool. In one of the included studies [25], all seven bias assessments were low risk, which was due to its rigorous design. However, there were also one set [34] in which only random sequence generation was low risk, and the rest were high risk or unknown. Included studies are highly heterogeneous (see Figs. 2 and 3).

Main outcome

Awakening time

Six studies reported the awakening time. There was heterogeneity between studies ($P<0.00001$, $I^2=96\%$). The analysis revealed a statistically significant difference in the recovery time between the two groups of patients ($MD=-64.31$ min, 95% $CI=-83.78\sim-41.24$, $P<0.00001$) (Fig. 4).

Extubation time

Nine studies provided extubation time outcomes, and there was heterogeneity among the studies ($P<0.00001$, $I^2=99\%$). Analysis revealed a statistically significant difference in extubation time between the two groups of patients ($MD=-124.78$ min, 95% $CI=-174.74\sim-74.81$, $P<0.0001$) (Fig. 5).

ICU length of stay

Eleven studies reported ICU length of stay, and there was heterogeneity among the studies ($P=0.03$, $I^2=50\%$). Analysis revealed no statistically significant difference in the ICU length of stay between the two groups of patients ($MD=-0.39$ days, 95% $CI=-0.77\sim-0.01$, $P=0.05$). We further conducted subgroup analysis, and the results showed that in cardiac ICU, there

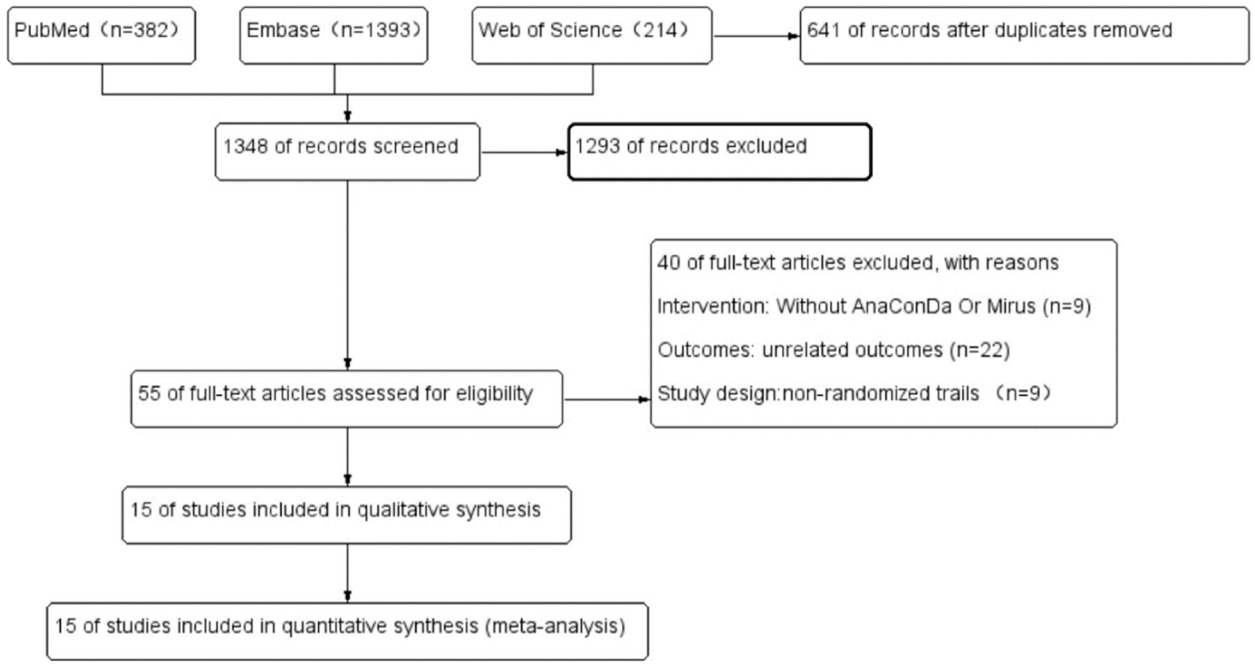

Fig. 1 Flow diagram of the study selection process

was no statistically significant difference in cardiac ICU ($MD = -0.16$ days, 95% CI $= -0.40 \sim 0.09$, $P = 0.22$). And there was a statistically significant difference in noncardiac ICU ($MD = -1.76$ days, 95% $CI -3.37 \sim -0.14$, $P = 0.03$); however, there was no statistically significant difference between the subgroups ($P = 0.06$) (Fig. 6).

Secondary outcomes

Incidence of delirium

Five studies reported the incidence of delirium, and there was no heterogeneity among the studies ($P = 0.43$, $I^2 = 0\%$). The analysis showed that there was a statistically significant difference in the incidence of delirium between the two groups ($OR = 0.55$, 95% $CI = 0.32 \sim 0.95$; $P = 0.03$) (Fig. 7).

Incidence of PONV

Five studies reported the incidence of PONV. There was no heterogeneity between studies ($P = 0.66$, $I^2 = 0\%$). The analysis revealed no statistically significant difference in the incidence of PONV between the two groups of patients ($OR = 1.31$, 95% $CI = 0.81 \sim 2.11$; $P = 0.27$) (Fig. 8).

Discussion

Intravenous sedation is currently the most commonly used sedation method in the ICU [35]. However, with the deepening of research on the pathophysiology of critically ill patients, the disadvantages of intravenous sedation have become increasingly apparent. Critically ill patients often suffer from multiple organ failure and require continuous renal replacement therapy (CRRT) making it impossible to accurately grasp the patient's depth of sedation. Inhalational anaesthetics have low solubility in the blood, and the concentration in the alveolar blood and the concentration in the inhaled air quickly reach equilibrium; therefore, the patient can be sedated quickly and awaken quickly [36]. Modern medical equipment can be used to easily monitor the minimum alveolar effective concentration (MAC), which is helpful for controlling the depth of sedation by inhaled sedation.

A total of 15 RCTs were included in this meta-analysis. Compared with intravenous sedation, the inhaled sedation resulted in a significantly shortened awakening time, significantly shortened extubation time, and significantly shortened ICU LOS. In previous studies, the inhaled sedation protocol used vacuum atomization, but the study we included used the AnaConDa device. There are currently no RCTs using Mirus, so this study included only AnaConDa.

Awakening time and extubation time

The studies included in this study showed that the awakening time and extubation time were significantly shorter in the inhaled sedation group than in the intravenous sedation group, and the difference was significant. In particular, the Mensil study showed that the awakening

Table 1 Information of the included studies

Study	ICU type/ patient population	Volatile group (n)	IV group (n)	Volatile agent	IV sedative	Duration sedation (h)	Target sedation level	Outcomes
Guerrero Orriach (2013) [32]	Cardiac surgery	20	20, 20	Sevoflurane	Propofol	4.4 (0.9)	BIS 60 to 70	Extubation time
Hanafy (2005) [33]	Cardiac surgery	12	12	Isoflurane	Midazolam	Not specified	RSS 3–4	Awakening time, extubation time, ICU LOS
Hellström (2012) [20]	Cardiac surgery	49	50	Sevoflurane	Propofol	2.8 (0.9)	MAAS 2–3	Awakening time, extubation time, delirium, PONV
Jabaudon (2017) [9]	Medical ICUs	25	25	Sevoflurane	Midazolam	Not specified	BIS 40 to 50	ICU LOS
Jerath (2015) [21]	Cardiac surgery	67	74	Sevoflurane	Propofol	Not specified	RASS − 1 to + 1	Awakening time, extubation time, PONV
Marcos-Vidal (2014) [31]	Cardiac surgery	62	67	Sevoflurane	Propofol	4.7 (2.4)	BIS 60 to 80	ICU LOS
Marina (2012) [25]	Cardiac surgery	36	37	Sevoflurane	Propofol	Not specified	RASS − 3 to − 2	ICU LOS
Mesnil (2011) [22]	Medical ICUs	19	14, 14	Sevoflurane	Propofol, midazolam	50 (23.7)	RSS 3–4	Awakening time, extubation time, ICU LOS delirium
Röhm (2008) [23]	Cardiac surgery	35	35	Sevoflurane	Propofol	8.1 (3.1)	RASS − 4 to − 3	Awakening time, extubation time, delirium, PONV, ICU LOS
Röhm (2009) [24]	Surgical ICUs	64	61	Sevoflurane	Propofol	9.2 (4.3)	RASS −4 to −3	Awakening time, extubation time, delirium, PONV, ICU LOS
Sackey (2004) [28]	MSICU	20	20	Isoflurane	Midazolam	52 (21)	BBSS − 1 to 1	Awakening time, extubation time
Sackey (2008) [30]	MSICU	17	12	Isoflurane	Midazolam	32 (23.3)	BBSS − 1 to 1	ICU LOS, delirium
Soukup (2023) [29]	Medical ICUs	36	33	Sevoflurane	Propofol	137 (93)	RASS − 3 to 0	Extubation time, ICU LOS
Steurer (2012) [26]	Cardiac surgery	46	56	Sevoflurane	Propofol	Not specified	Not mentioned	PONV, ICU LOS
Wasowicz (2018) [34]	Cardiac surgery	60	67	Isoflurane or sevoflurane	Midazolam or propofol	Not specified	BIS 40 to 60	Extubation time, ICU LOS

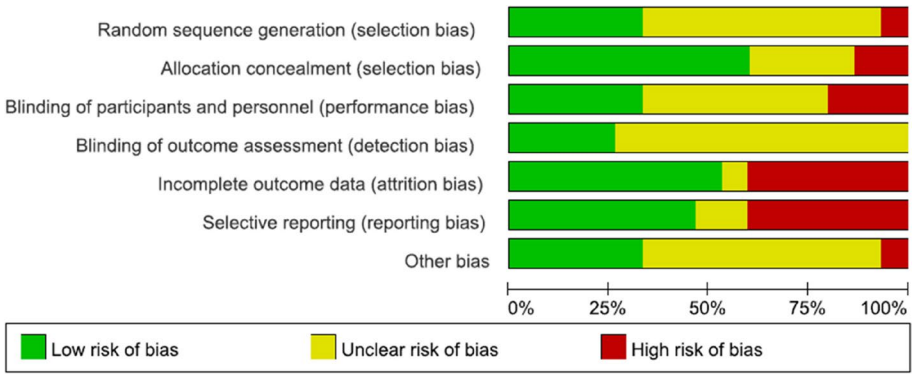

Fig. 2 Risk of bias summary of the included studies. (+) indicates a low risk of bias, (-) indicates a high risk of bias, and (?) indicates an unclear risk of bias

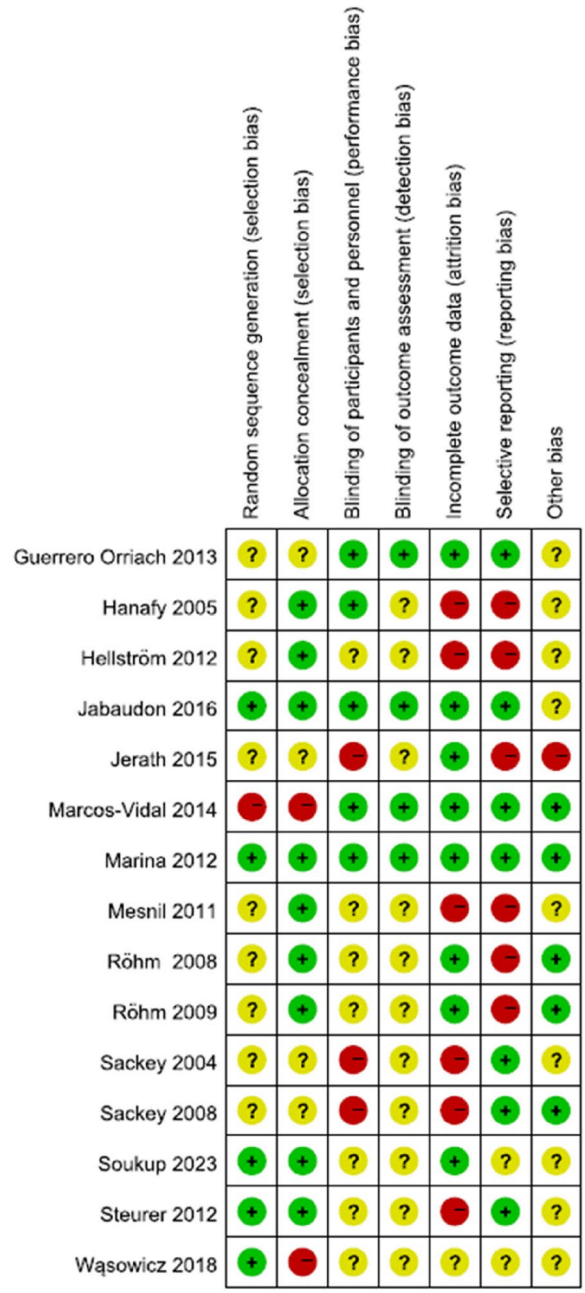

Fig. 3 Risk of bias graph of the included studies. (+) indicates a low risk of bias, (-) indicates a high risk of bias, and (?) indicates an unclear risk of bias

time of the inhaled sedation group was significantly shorter than that of the intravenous sedation group. The time to awakening in the intravenous sedation group was 260.2 min, but it was only 18.6 min in the inhaled sedation group. There was heterogeneity between the included studies ($P<0.00001$, $I^2=96\%$), but after analysing the patients included in the study, it was found that the heterogeneity was because the included patients were postcardiac surgery and noncardiac surgery patients. Because most postcardiac surgery patients have long procedures and difficult surgeries, the large amount of intravenous sedation medication required accounts for this heterogeneity. After further analysis, we found that nine of the studies we included involved patients in cardiac ICU. Although the patients included in Jabaudon's study were MICU patients, the included patients were severe ARDS patients and required longer time mechanical ventilation, which resulted in a prolonged awakening/extubation time. This might be a reason for the difference in awakening time and extubation time between the two groups.

ICU LOS

Our study also showed that the ICU LOS in the inhaled sedation group was shorter than that in the intravenous sedation group, with an average reduction of 0.39 days, but there was no statistically significant difference. Due to the heterogeneity among the included studies. We further conducted the subgroup analysis, and the results showed that in cardiac ICU, there was no statistically significant difference ($MD=-0.16$ days, 95% $CI=-0.40\sim-0.09$, $P=0.22$). And there was a statistically significant difference in noncardiac ICU ($MD=-1.76$ days, 95% $CI-3.37\sim-0.14$, $P=0.03$). And there was no statistically significant difference between the subgroups ($P=0.06$). This result showed that patients from different ICU sources might not be the source of heterogeneity. However, it should be noted that the number of patients included in the subgroup is small, and the results should be treated with caution.

Side effects

Our study revealed that the incidence of delirium in the inhaled sedation group was significantly lower than that in the intravenous sedation group ($OR=0.55$, $P=0.03$). Previous studies have shown that benzodiazepines can increase the incidence of delirium. Once delirium occurs, the ICU stay can be prolonged, and various complications can occur. PONV is a common complication of inhaled sedation. Under general anaesthesia, inhaled sedative drugs are considered a potential risk factor for PONV. Five of the included studies [11, 12, 17] reported PONV outcomes; there was no heterogeneity among the included studies, and there was no significant difference in the occurrence of PONV between the two groups of patients ($OR=1.31$, $P=0.27$).

Limitations

Our study has the following shortcomings: first, the number of included studies was small, and the

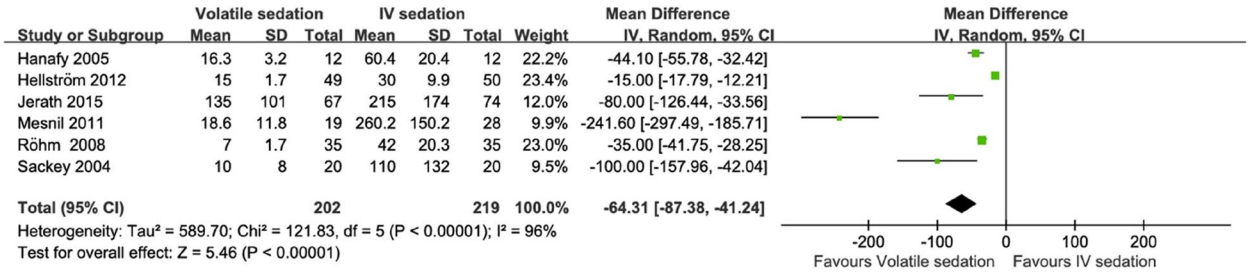

Fig. 4 Forest plot of awakening time (min) in the volatile sedation and IV sedation groups

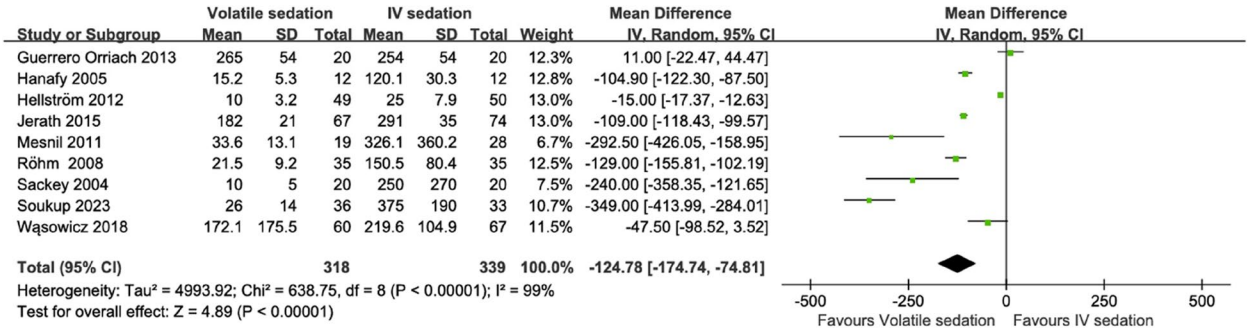

Fig. 5 Forest plot of extubation time (min) in the volatile sedation and IV sedation groups

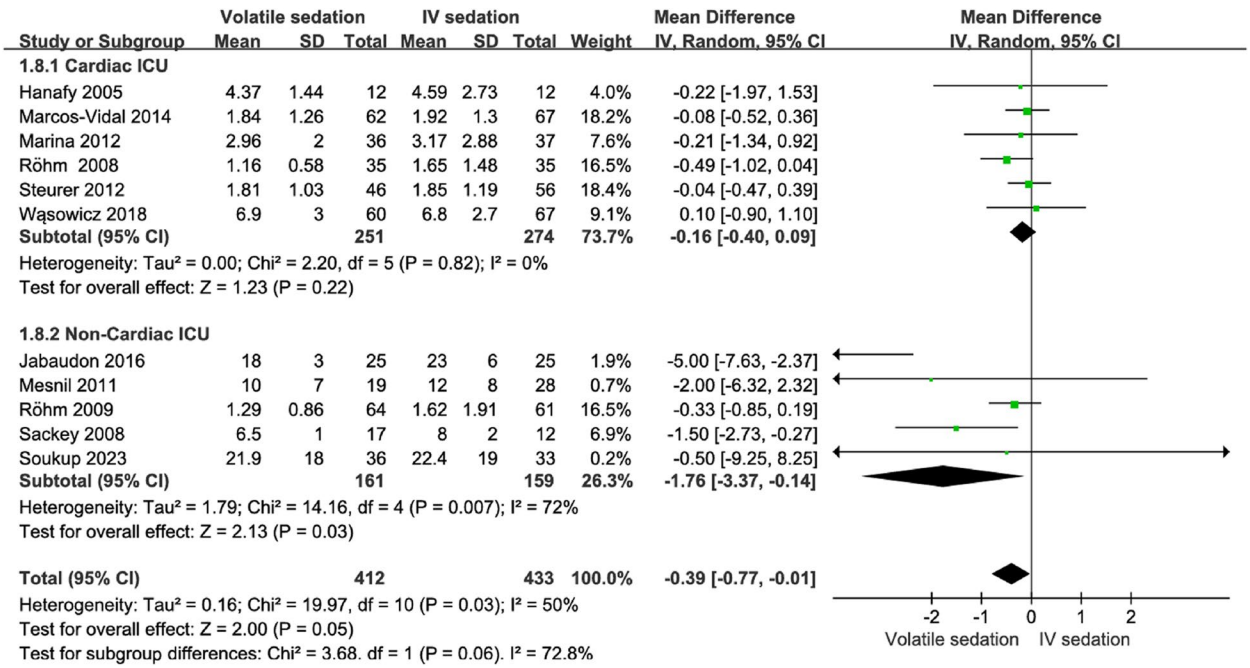

Fig. 6 Forest plot of ICU LOS (days) in the volatile sedation and IV sedation groups

largest study included only 141 patients. Second, in the included studies, patients came from different groups, including those who underwent postcardiac surgery, internal medicine, or noncardiac surgery. Therefore, there was a certain degree of heterogeneity. Third, in the included studies, different scales were used to determine the depth of sedation, and the use of different scales yields inconsistent results. Fourth, our study

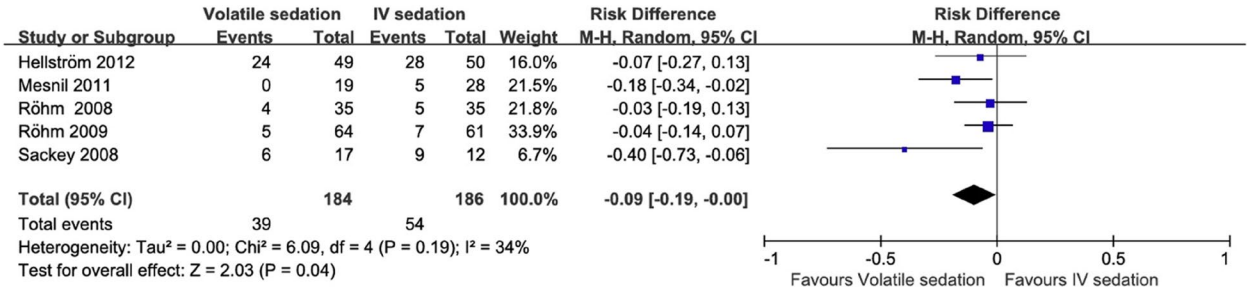

Fig. 7 Forest plot of the incidence of delirium in the volatile sedation and IV sedation groups

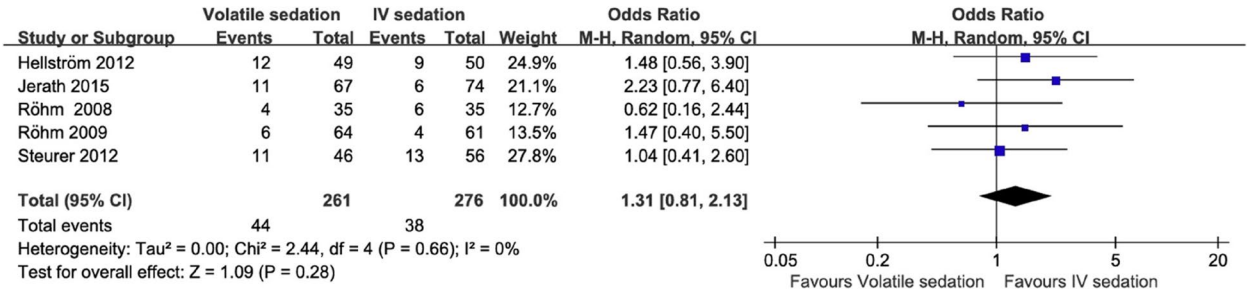

Fig. 8 Forest plot of the incidence of postoperative nausea and vomiting in patients receiving volatile sedation and IV sedation

was not pre-registered, and there may be a small bias, but we still strictly followed the steps of a systematic review. Last but not the least, our study showed that the incidence of delirium in the inhaled sedation group was significantly lower than that in the intravenous sedation group ($OR = 0.55$, $P = 0.03$), However, the meta-analysis conducted by Cuninghame showed that there was no difference in the incidence of delirium between inhaled sedation and intravenous sedation (95% *CI* 0.59 ~ 1.54) [36]. After careful screening, the studies conducted by Hellstrom (2012) and Mesnil (2011) which were included in our research that did not use standard delirium screening tools — this may explain the difference between the two SR/MAs. This may have had a certain impact on the results of our study. Despite the above shortcomings, this study still provides theoretical support for the application of inhaled sedation in ICU patients. Since only RCTs were included and retrospective studies were excluded in this study, the level of evidence was relatively high.

Conclusion

Inhaled sedation has advantages over intravenous sedation in terms of awakening time, extubation time, and ICU LOS (noncardiac ICU); however, there is no significant difference in the incidence of PONV between the two. The use of inhaled sedation may be safe and effective for critically ill patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-025-02791-6.

Additional file 1. Search strategy.

Additional file 2. PRISMA 2020 checklist.

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Authors' contributions
Conducted the study, YC and FF. Collected all data, ZY, HK, and LM. Performed the statistical analysis, YC and FF.

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Data availability
All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate.
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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